Canadian Tuberculosis Standards

7th Edition

Public Health Agency of Canada / Agence de la santé publique du Canada

THE LUNG ASSOCIATION™ / L'ASSOCIATION PULMONAIRE

CANADIAN THORACIC SOCIETY / SOCIÉTÉ CANADIENNE DE THORACOLOGIE

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PREFACE

The last 10 years have witnessed remarkable progress in our understanding of the pathogenesis, immunology and epidemiology of tuberculosis as well as the development of new diagnostic and therapeutic tools. This 7th edition of the *Canadian Tuberculosis Standards* (the *Standards*) has been extensively revised to incorporate much of this new information, building upon the six previous versions of the *Standards*, which were published in 1972 (with a pediatric supplement in 1974), 1981, 1988, 1996, 2000 and 2007.

As in the past, each chapter is written by authors from across Canada with expertise in the specific areas. Again, the *Standards* is jointly funded, edited and produced by the Canadian Thoracic Society (CTS) of the Canadian Lung Association (CLA) and the Public Health Agency of Canada (PHAC). However, it is important to note that the clinical recommendations in the *Standards* are those of the CTS.

This edition was also developed in close collaboration with the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada), whose expert representatives served as chapter authors and external reviewers.

In response to feedback from users of previous versions of the *Standards*, some sections have been expanded, while others have been reduced or eliminated. The document is intended to provide information to public health and clinical professionals and does not supersede any provincial/territorial legislative, regulatory, policy and practice requirements or professional guidelines that govern the practice of health professionals in their respective jurisdictions.The *Standards* does not replace consultations between clinical practitioners and public health authorities with respect to a particular patient or circumstance.

As with previous editions, the 7th edition of the *Standards* is based upon the best available scientific evidence. The authors of each chapter carefully reviewed all published evidence, particularly the most recent studies, and synthesized and rated this evidence as summarized below. Recommendations are considered strong or conditional on the basis of these ratings of evidence:

Quality of Evidence

Strong	Evidence from multiple randomized controlled trials (RCTs – for therapeutic evidence), or cohort studies (etiologic evidence) with strong designs and consistent results.
Moderate	Evidence from only one RCT or RCTs with an inadequate number participants or inconsistent results, or multiple observational studies of strong design providing consistent results.
Weak	Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients.
Very Weak	Evidence from published case series and/or opinion of the authors and other experts.

Strength of Recommendations

Strong	The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence.
Conditional	The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence.

Reference is made to specific tests, procedures and therapies throughout the *Standards*. For the most part generic terms are used rather than trade names or manufacturers' names. However, in a few instances when only a single manufacturer or product is available, a trade name may be mentioned. This is done only to enhance readers' understanding by providing a name with which they are more likely to be familiar. Use of trade names and commercial sources is for identification only and does not imply endorsement by PHAC, the CTS or CLA.

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- the provincial and territorial TB programs that provide non-nominal confidential case reports for national TB surveillance; and the members of the Canadian TB Laboratory Technical Network and their teams for participation in national TB drug resistance surveillance;
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Finally, the Canadian Thoracic Society, and all authors and editors wish to acknowledge the contribution to TB control, care and education made by Dr Jae Yang, Director of the TB clinic at St Michael's Hospital in Toronto, whose untimely death in November 2012 deprived the Canadian TB community of a great TB provider and teacher.

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CHAPTER 1

EPIDEMIOLOGY OF TUBERCULOSIS IN CANADA

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KEY MESSAGES/POINTS

- In Canada, the overall rate and annual number of cases of tuberculosis have continued to decline.
- However, disparities are pronounced in certain population groups and geographic regions; foreign-born individuals and Aboriginal peoples in particular are disproportionately affected by TB.

BACKGROUND

GLOBAL EPIDEMIOLOGY OVERVIEW

The World Health Organization (WHO) estimated that there were 8.8 million incident cases of TB worldwide in 2010, for an incidence rate of 128 cases per 100,000 population.[1] As a result of improvement in general living conditions and overall population health,[2] coupled with intensive efforts by the global Stop TB Strategy, the number of annual incident cases has been falling since 2006. Similarly, the incidence rate has been decreasing since it peaked at 141 cases per 100,000 population in 2002.[3] In 2010, one-eighth of incident cases were coinfected with HIV, 82% of whom were in the African Region of the WHO.[4] Furthermore, there were an estimated 1.4 million people who died as a result of TB in 2010, 25% of whom were coinfected with HIV.[4] The Stop-TB Partnership target of reducing mortality by 50% from 1990 to 2015 is likely to be met in all WHO regions except the African Region, but mortality rates continue to have a significant impact: nearly 10 million children were orphaned as a result of TB deaths in 2009 alone.

Of the 8.8 million estimated incident cases in 2010, 5.7 million were actually reported, for an estimated case detection rate of 65%.[4] Of cases detected in 2009, the treatment success rate for smear-positive cases was 87%, which is the highest success rate ever reported.[4] From 1995 through 2010, 46 million individuals were successfully treated, and an estimated 6.8 million deaths were averted in programs that adopted the DOTS (Directly Observed Treatment Short Course)/Stop TB Strategy.[4]

Multidrug-resistant (MDR) TB remains a significant challenge, 150,000 annual deaths being estimated in 2008 and 650,000 prevalent cases in 2010.[4] While it is estimated that 3.4% of new and 20% of retreatment cases starting treatment in 2010 had MDR-TB, only 16% of these cases were treated for the condition.[1] This can be attributed to the fact that less than 5% of new and previously treated TB patients were tested for MDR-TB in most countries.[1,4]

SURVEILLANCE OF ACTIVE TB IN CANADA

It is a requirement of local public health authorities to report all cases of TB to their respective provincial/territorial TB program. Provincial and territorial TB programs then voluntarily submit reports of TB cases that meet the case definition for national-level surveillance to the Canadian TB Reporting System (CTBRS). The CTBRS is managed by the Public Health Agency of Canada and maintains selected non-nominal information for each case of active TB, including, but not limited to, demographic, clinical, diagnostic, treatment and outcome details.

The most recent TB reports for Canada are available at:
http://www.phac-aspc.gc.ca/tbpc-latb/surv-eng.php

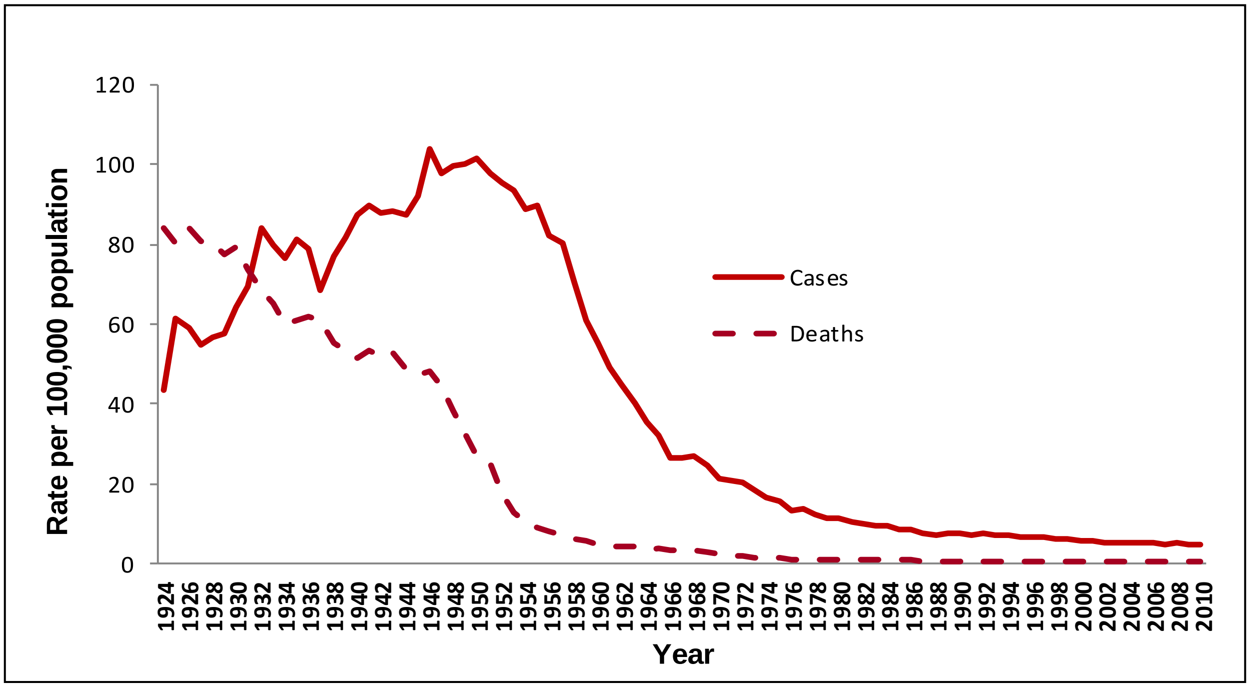
The most recent WHO reports on TB are available at:
http://www.who.int/tb/country/en/index.html

INCIDENCE AND MORTALITY

In the first half of the 20th century, TB was a major cause of morbidity and mortality in Canada. Historical data on the reported number of cases of TB and the number of deaths attributed to TB are available from 1924. As illustrated in Figure 1, deaths from TB appeared to outnumber new diagnoses each year during the 1920s. This may reflect incomplete reporting of all cases, or it may indicate that reported cases only reflected hospitalized cases, whereas deaths captured all terminal cases of TB whether they were hospitalized or not. Systematic reporting of TB cases was instituted on a national basis in 1933, providing a more accurate and complete record of the burden of TB in Canada through the century.

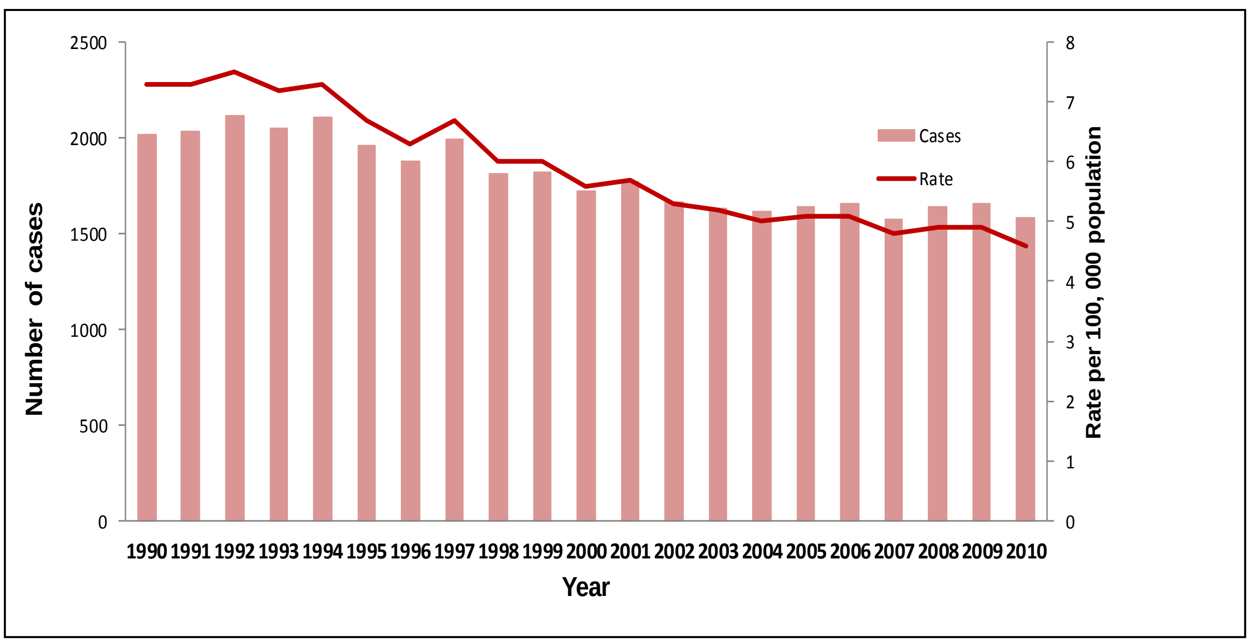
From the available reports, in 1926, 1 in 13 of all reported deaths in Canada was due to TB, a number slightly higher than the number of deaths reported for cancer.[5] As a result of improved living conditions and isolation of some infectious cases in sanatoria, incidence and mortality rates began to fall in subsequent years, and rates further declined with the introduction of effective antibiotic treatment in the mid-20th century (Figure 1).

Figure 1. Reported tuberculosis incidence and mortality rates in Canada, 1924-2010



Over the past two decades, both the number of reported TB cases and the overall Canadian incidence rate have continued to decline, albeit much more gradually than the drop observed between 1950 and 1990. In 1990, the rate was 7.0 per 100,000 population (Figure 2), which fell to an all-time low in 2010 of 4.6 per 100,000 population (1,577 cases reported for 2010).

Figure 2. Reported TB cases and incidence rates in Canada, 1990-2010

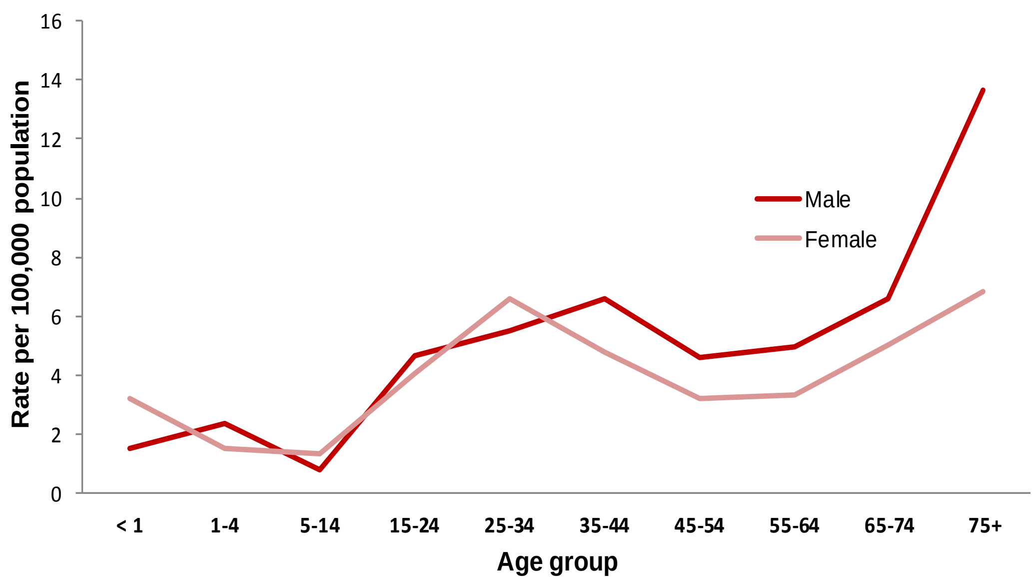


AGE AND SEX DISTRIBUTION

The reported TB incidence rate has always been higher among males than females in Canada; however, the differential has decreased over time. In 2010, the male to female ratio was 1:0.8.

Between 2000 and 2010, individuals in the 25-34 and 35-44 year age groups accounted for the largest number of cases relative to other age groups. However, the highest age-specific rate was found in the 75+ age group. For 2010, 35% of the cases were between the ages of 25 and 44, whereas the highest age-specific rate, at 9.6 per 100,000, occurred among those aged 75 years or older (Figure 3). Overall, by age and sex, males 75 years of age and over had the highest rate, at 13.6 per 100,000 population.

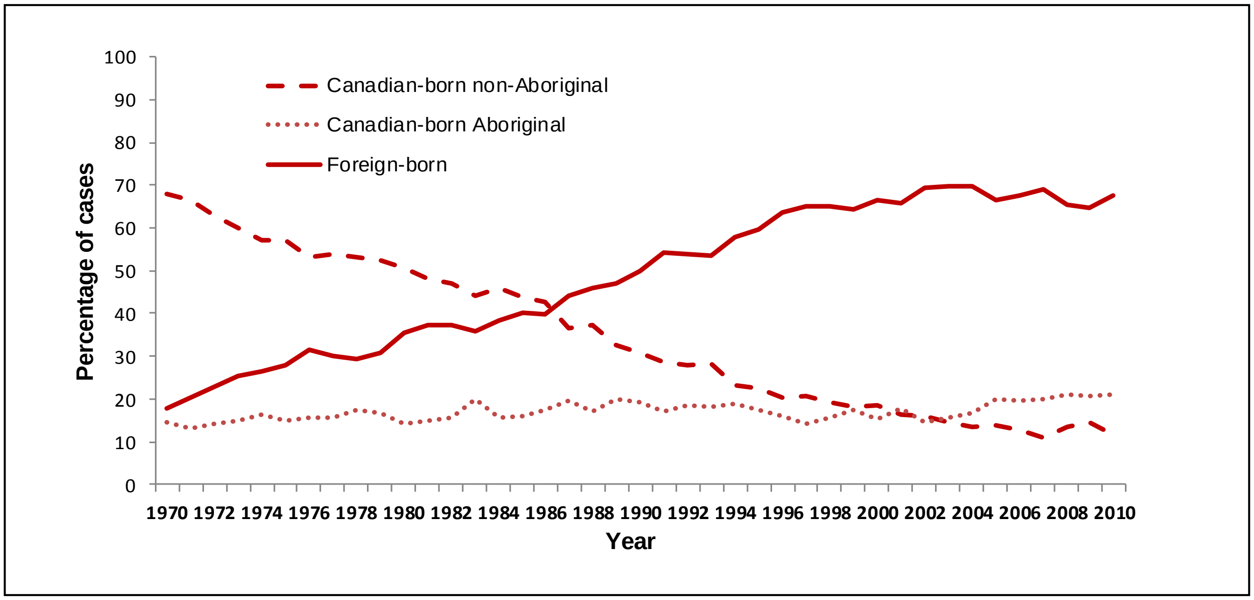
Figure 3. Reported TB incidence rate by sex and age group in Canada, 2010



DISTRIBUTION BY POPULATION GROUP AND PROVINCE/TERRITORY

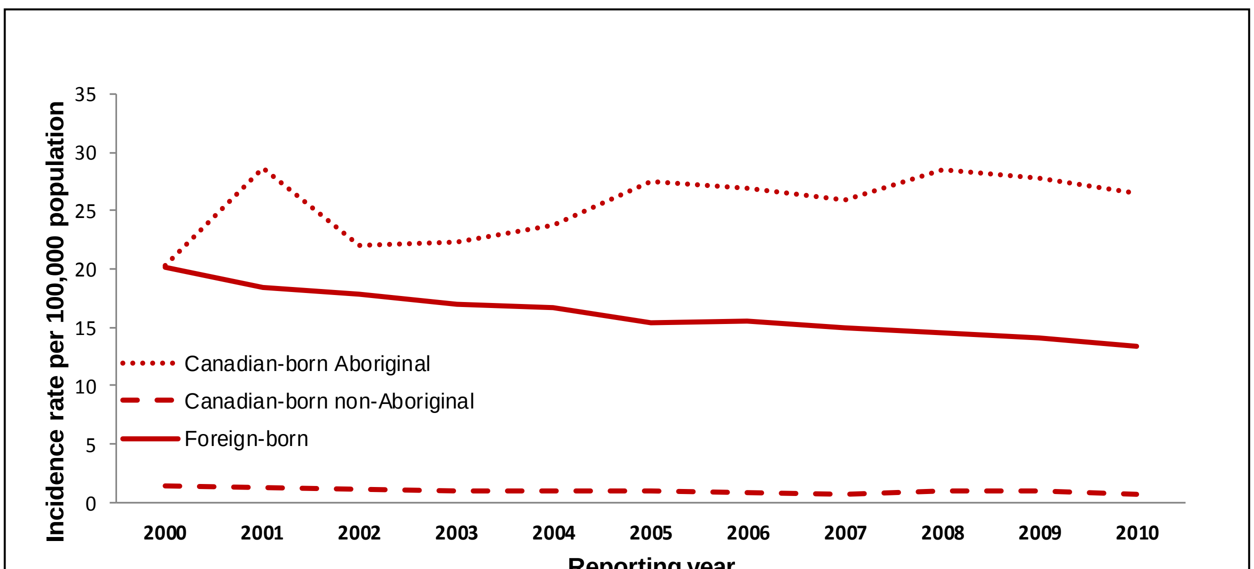
Although the overall rate in Canada continues to decline, the TB burden is not shared equally.[6] In particular, Canadian-born Aboriginal peoples and foreign-born individuals are disproportionately affected (Figure 4). From 1970 to 2010, the proportion of active TB cases in the Canadian-born non-Aboriginal population decreased significantly, from 67.8% to 11.8%. During the same period, the proportion among foreign-born individuals increased significantly, from 17.7% to 67.0%, and the proportion among Canadian-born Aboriginal peoples increased from 14.7% to 21.2%.

Figure 4. Percentage of reported TB cases by population group in Canada, 1970-2010



Cases among Canadian-born non-Aboriginal people continue to drop. In 2010, this population group had an incidence rate of 0.7 per 100,000 population (Figure 5).

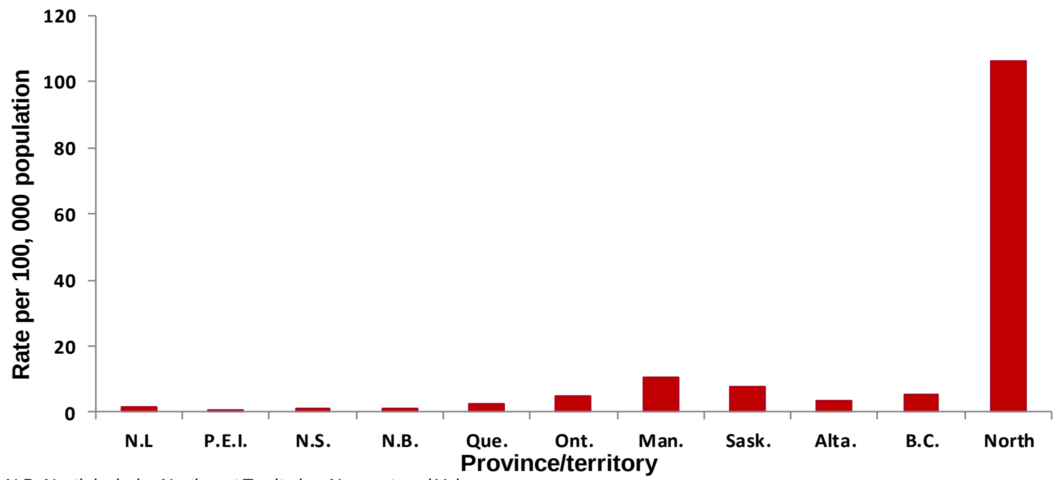
Figure 5. Reported TB incidence rate by population group in Canada, 2000-2010*



* Population denominators obtained from Statistics Canada

In addition to differential incidence rates by population group, TB case patterns also reveal pronounced disparities based on geographic region within Canada. In 2010, incidence rates ranged from a low of 0.7 per 100,000 population in Prince Edward Island to a high of 106.1 per 100,000 population in Northern territories combined (Figure 6). The three most populous provinces in Canada, namely British Columbia, Ontario and Quebec, with 75% of the popu-lation, accounted for 69% of all TB cases in 2010.

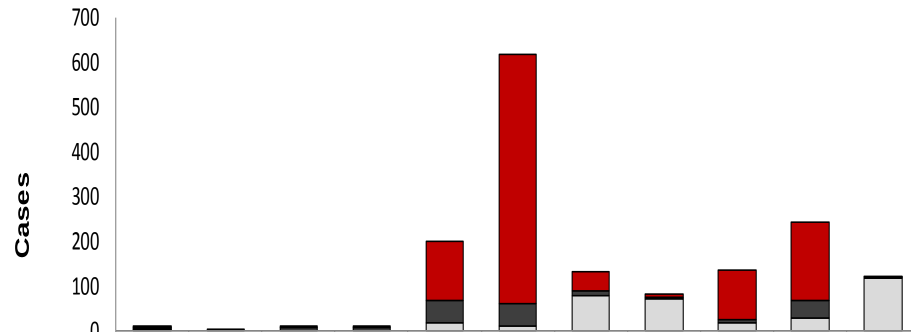
Figure 6. Reported TB incidence rates by province/territory, Canada, 2010



N.B. North includes Northwest Territories, Nunavut and Yukon
Population denominators obtained from Statistics Canada

Distribution of TB cases by population group also varies significantly by jurisdiction. As depicted in the graphs below (Figure 7), the majority of cases in Alberta, British Columbia, Ontario and Quebec occurred in foreign-born individuals, whereas in Manitoba, Saskatchewan and the Northern territories most cases occurred largely in Aboriginal people. These varied geographic patterns in part reflect differences in the populations among jurisdictions: there are more foreign-born individuals in Ontario, Quebec, British Columbia and Alberta in particular, whereas Aboriginal communities make up a higher proportion of the general population in the prairies and in the North.

Figure 7. Number of reported TB cases by population group and province/territory in Canada, 2010*



	N.L.	P.E.I	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	North
Foreign-born	2	1	5	5	135	557	43	7	109	175	1
Canadian-born non-Aboriginal	2	0	5	5	50	52	13	5	10	39	2
Canadian-born Aboriginal	4	0	0	0	15	8	76	70	15	27	115

Province/territory

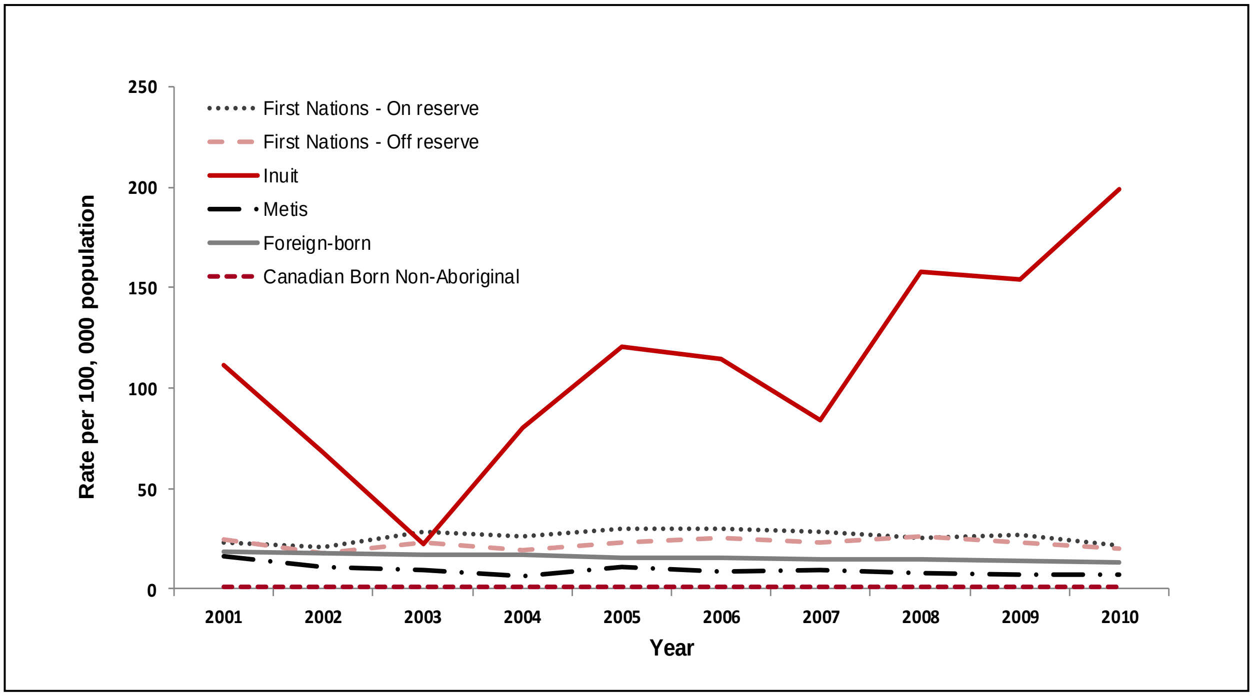
*Population denominators obtained from Statistics Canada

TUBERCULOSIS IN CANADIAN-BORN ABORIGINAL PEOPLES

While the greatest number of cases is reported among foreign-born individuals, the reported incidence rate has consistently been highest among Canadian-born Aboriginal individuals over the past decade (Figure 8).

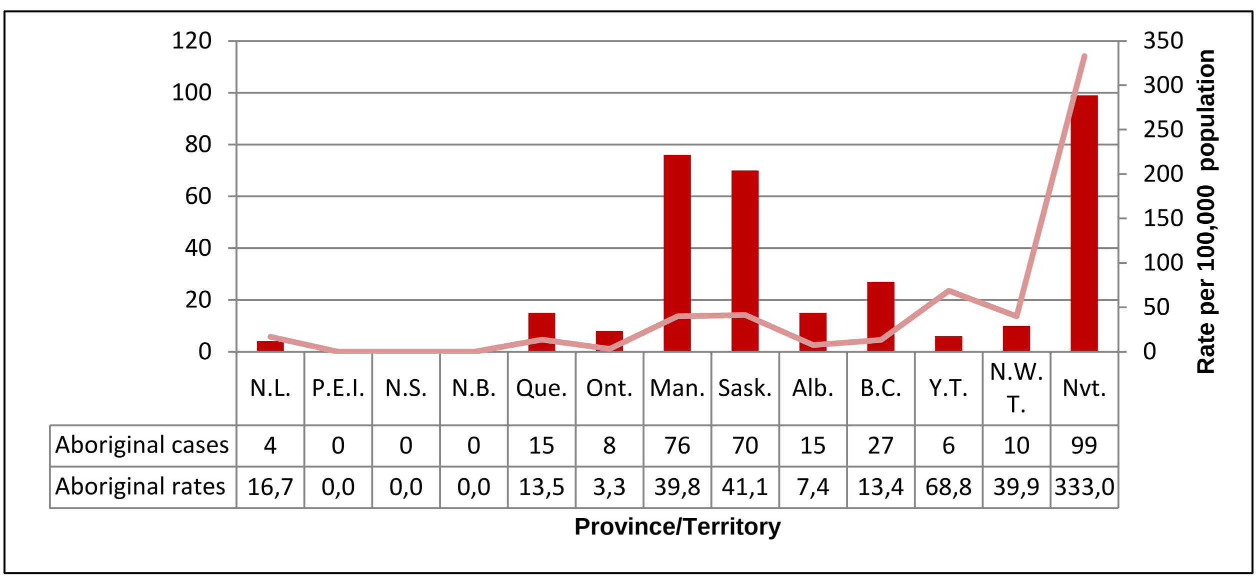
“The *Constitution Act* of 1982 recognizes three major groups of Aboriginal Peoples in Canada: Indian (more commonly referred to as First Nations), Inuit and Métis. First Nations (on- and off-reserve) and Inuit account for the vast majority of incident cases of TB in Aboriginal peoples in Canada.”[7] From 2001 to 2010, the rate of TB was highly variable in the Inuit population and peaked in 2010 at approximately 200 cases per 100,000 population. In contrast, the rates were relatively stable for First Nations (on- and off-reserve) and Métis (Figure 8).

Figure 8. Reported TB disease incidence rates in Canada by population group, 2001-2010



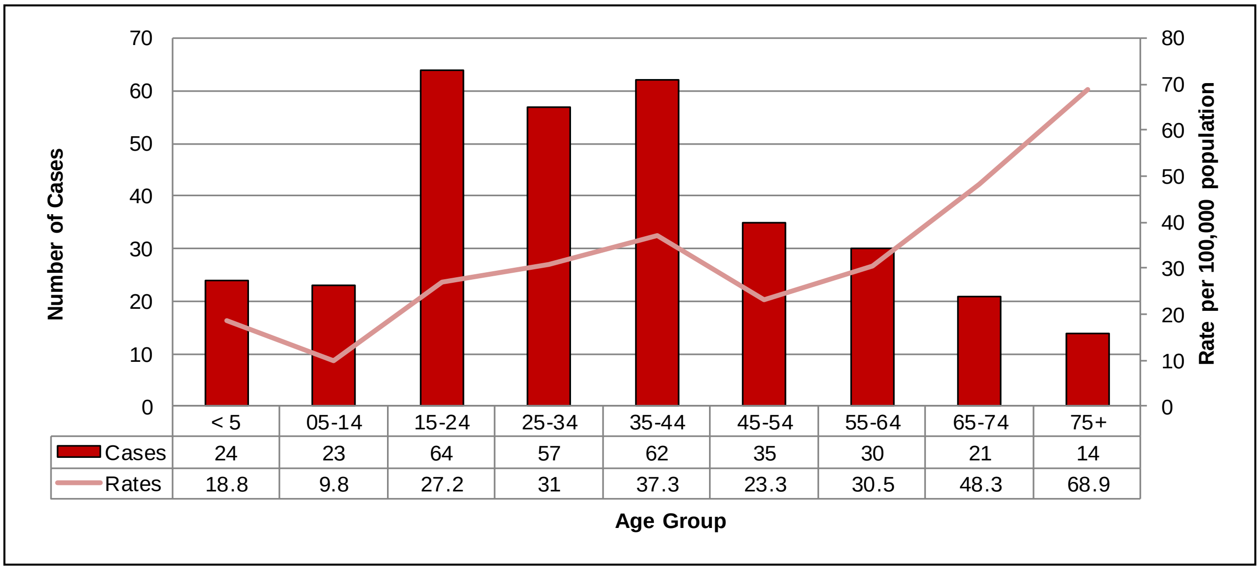
The burden of TB disease among Aboriginal populations varies by jurisdiction. In terms of both overall cases as well as rates, TB cases in Aboriginal individuals in 2010 were significantly higher in Nunavut, Saskatchewan and Manitoba (Figure 9).

Figure 9. Distribution of active TB cases and incidence rates for Aboriginal populations, 2010



	N.L.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alb.	B.C.	Y.T.	N.W.T.	Nvt.
Aboriginal cases	4	0	0	0	15	8	76	70	15	27	6	10	99
Aboriginal rates	16,7	0,0	0,0	0,0	13,5	3,3	39,8	41,1	7,4	13,4	68,8	39,9	333,0

Figure 10. TB cases and incidence rates among Canadian-born Aboriginal populations by age group, 2010

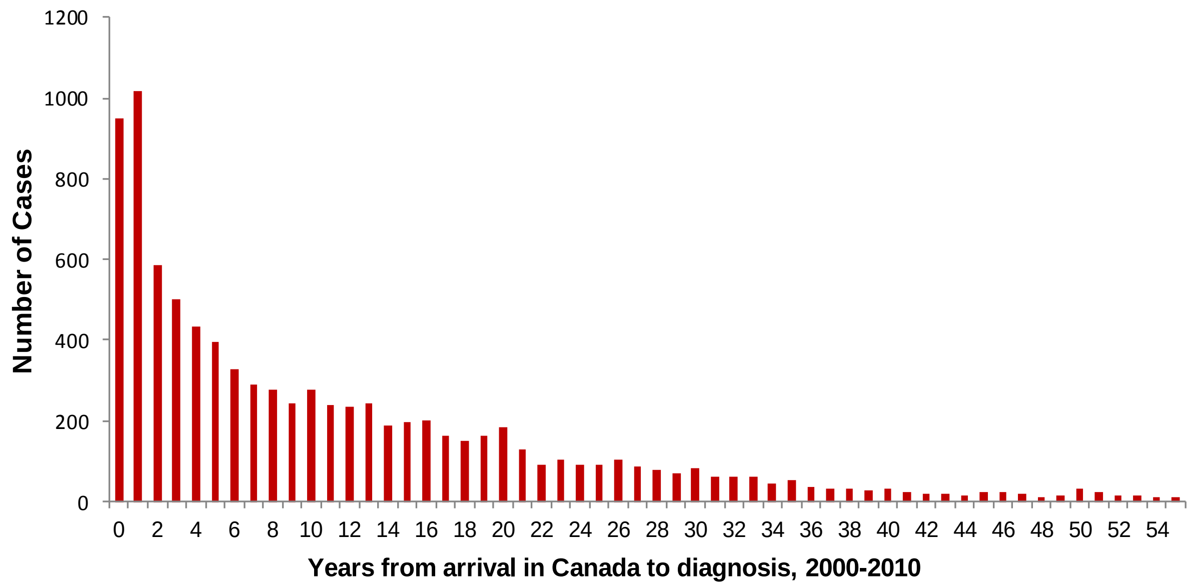


The majority of all cases in Aboriginal individuals were reported in adolescents and young adults in the 15-44 year age groups (Figure 10). A substantial number of cases in Canadian-born Aboriginal individuals were reported in children, and the incidence rate was much higher than that seen in other Canadian populations. This suggests ongoing transmission in some Aboriginal communities.

TUBERCULOSIS IN THE FOREIGN-BORN POPULATION

While the proportion of all TB cases in Canada among the foreign-born has increased significantly in the past 40 years, the annual number of reported cases has not changed substantially, averaging 1,000 cases per year. Over the past 11 years, however, the incidence rate has declined slowly but steadily, reaching 13.3 per 100,000 in 2010 (Figure 8). Of the foreign-born TB cases reported in Canada from 2000 to 2010 for which the date of arrival was known, 11% were reported within the first year of arrival, 22% within the second year of arrival and 44% within 5 years (Figure 11).

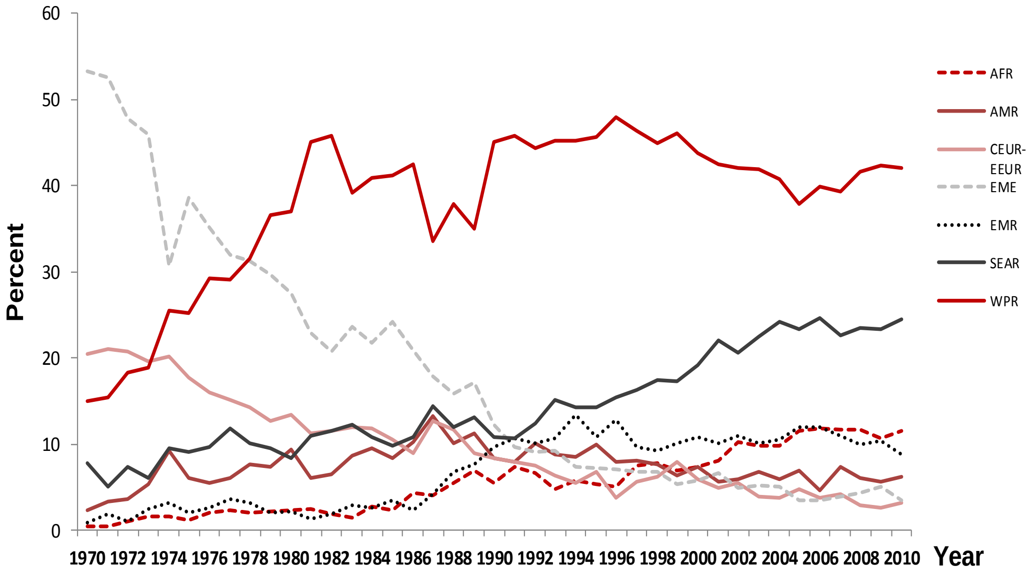
Figure 11. Reported foreign-born TB cases in Canada, 2000-2010: time from arrival in Canada to diagnosis, in years



Each foreign-born TB case was assigned to a WHO TB epidemiologic region[8] on the basis of the individual's country of birth. (These regions differ from the WHO's standard administrative regions.) Figure 12 depicts changes over time in the distribution of the region of origin of all foreign-born TB cases reported in Canada. During the period 1970 to 2010 the proportion of cases from established market economies[*§] decreased, whereas the proportion of cases reported from the Western Pacific and South-East Asia regions increased.

[§] "Established market economies" is defined by the WHO as including the following countries: Andorra, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Spain, Sweden, Switzerland, United Kingdom and the USA.

Figure 12. Percentage of reported foreign-born TB cases in Canada by WHO TB epidemiologic region, 1970-2010



N.B. WHO Regions: EME = Established Market Economies, WPR = Western Pacific, SEAR = South- East Asia, CEUR.EEUR = Central Europe. Eastern Europe, AMR = American Region - Latin American Countries, EMR = Eastern Mediterranean, AFR = Africa

Changing immigration patterns account for some of the changes to this distribution. In addition to increased migration to Canada of people from African, Asian and Pacific regions, these regions also have the highest TB incidence rates (Table 1), which results in a corresponding shift in Canada's distribution. Rates within Canada are calculated as the number of cases in Canada among people born in a certain region divided by the total population in Canada born in that region. Rates within Canada are significantly lower across people from all WHO regions compared with respective rates within the regions. People in Canada who emigrated from the two African Regions** (high and low HIV prevalence), as well as the South-East Asia Region and the Western Pacific Region, show the highest rates, mirroring patterns seen within the regions themselves. Almost one-half of TB cases typically occur within 5 years of arrival in Canada.

** A list of countries included in the WHO African Region can be found at: http://www.afro.who.int/en/countries.html.

Table 1. Comparison of reported foreign-born TB incidence rate in Canada by WHO TB epidemiologic region of birth (per 100,000 population) with WHO estimated TB incidence rate in the respective region

WHO region*	Reported rate in Canada. 2010	WHO estimated TB incidence rate in regions, 2010**
Africa, High HIV Prevalence	37.4	306.3
Africa, Low HIV Prevalence	21.5	194.4
American Region – Latin American Countries	7.0	42.9
Eastern Europe	4.9	93.4
Eastern Mediterranean	11.8	109.0
Established Market Economies and Central Europe	1.9	9.8
South-East Asia	30.3	194.1
Western Pacific	22.8	98.4
Overall	13.3	128.2

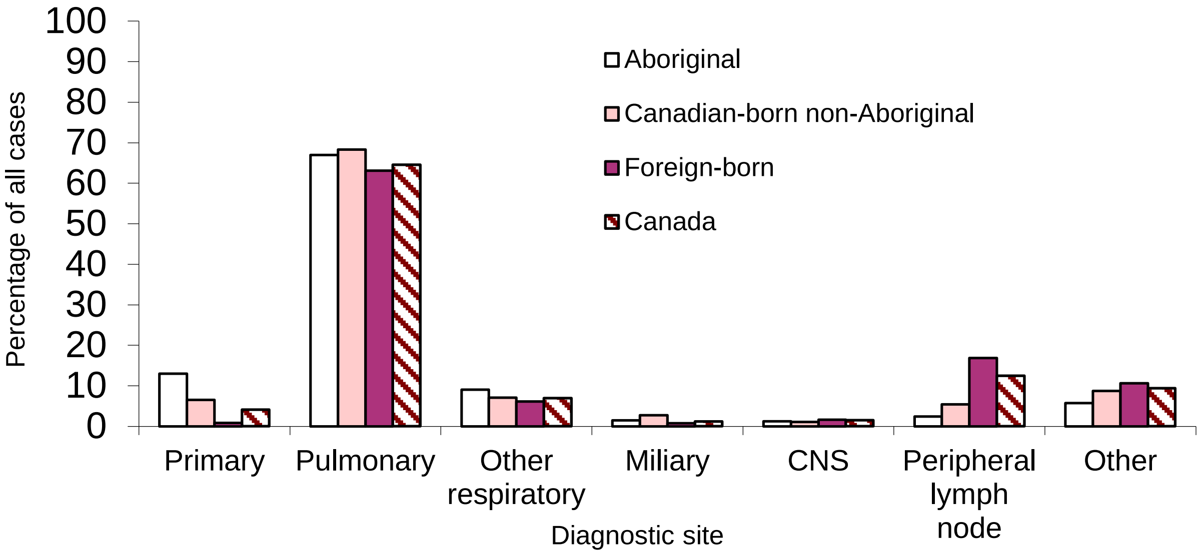
*Source: The Stop TB Partnership and World Health Organization. Global Plan to Stop TB 2006-2015. Geneva, World Health Organization, 2006 (WHO/HTM/STB/2006.35).

**Source: Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report 2011. Geneva, World Health Organization (WHO/HTM/TB/2011.16).

DISEASE SITE

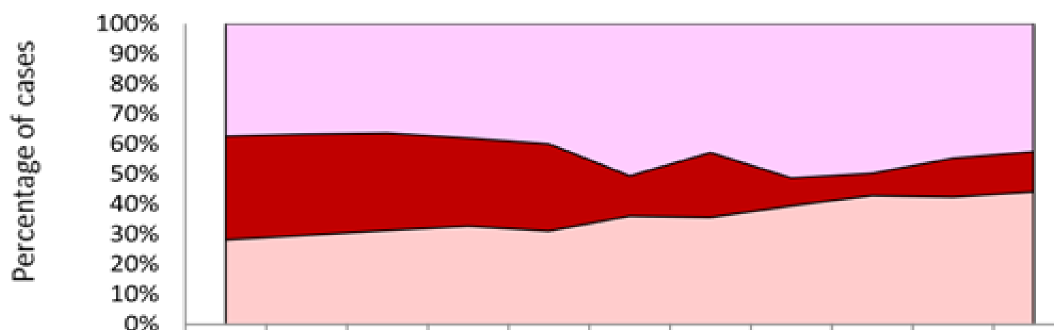
The majority of reported TB cases in 2010 (64%) were diagnosed as pulmonary TB. Peripheral lymph node was the second most commonly reported site, at nearly 13% of cases in the same year. Slight differences were observed when comparing the three origin groups. A greater proportion of cases in Aboriginal individuals were due to primary disease, and a greater proportion of foreign-born individuals received a diagnosis of peripheral lymph node TB (Figure 13).

Figure 13. Percentage of reported cases by diagnostic site and origin in Canada, 2010



The majority of TB cases in Canada are diagnosed by culture confirmation. In 2010, 1,261 (80%) were culture-confirmed. Figure 14 presents data on the proportion of pulmonary TB cases that were smear-positive (indicating a higher level of infectivity) and smear-negative, and the proportion of cases for which laboratory data were not reported. Between 2000 and 2010, an average of 41% of all reported pulmonary TB cases were smear-positive, 34% were reported as smear-negative, and for 25% laboratory microscopy results were not reported.

Figure 14. Percentage of pulmonary cases by sputum smear microscopy result: Canada, 2000-2010



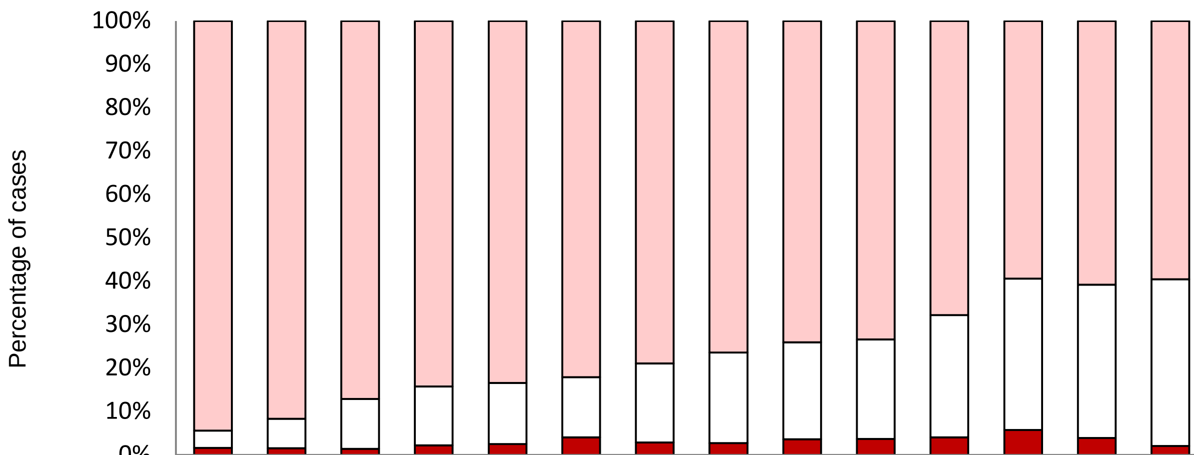
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Smear Positive	406	421	378	371	379	492	463	525	558	496	433
Smear Unknown	374	385	336	285	275	130	232	95	83	143	135
Smear Negative	305	339	324	318	294	350	384	403	480	469	448

Reporting year

TB-HIV COINFECTION

Canada's national HIV/AIDS and TB surveillance systems have their own limitations regarding their ability to estimate TB-HIV coinfection. However, information on HIV status is increasingly included in TB cases reported to the CTBRS. In 2000, HIV status was reported for only 16% of TB cases, but that figure had increased to 40% in 2010 (Figure 15). Among cases for which HIV status was reported, the coinfection rate in 2010 was 5%. This percentage is possibly biased towards HIV testing among those individuals with known risk factors for HIV infection. In the unlikely event that these were the only coinfected cases, the overall coinfection rate was 2%. The true coinfection rate probably lies somewhere in the 2%-5% range. The WHO has estimated the Canadian rate in 2007 to be 5.7%.[9] Underreporting imposes serious limitations on the interpretation of HIV-TB coinfection in Canada.

Figure 15. Percentage of reported TB cases by HIV status, Canada, 1997-2010



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Unknown	94,4	91,7	87,1	84,2	83,5	82,1	78,9	76,4	74,0	73,4	67,8	59,4	60,8	59,5
Negative	4	6,8	11,5	13,6	14,1	13,9	18,3	20,9	22,4	22,9	28,2	34,9	35,3	38,4
Positive	1,6	1,5	1,4	2,1	2,5	4,0	2,8	2,7	3,6	3,7	4,0	5,7	3,9	2,0

Reporting year

DRUG RESISTANCE

Data and trends on TB drug resistance in Canada are detailed in Chapter 8, Drug-Resistant Tuberculosis.

TREATMENT AND CASE OUTCOMES

Of 1,658 cases of active TB disease diagnosed in 2009, 1,599 (96%) had a treatment outcome. Of these, 1,399 (87%) were deemed cured or treatment completed, 129 (8%) died before or during treatment, and 31 (2%) transferred out of Canada at some point during their treatment with final outcome unknown. Of the remaining 3% of cases reporting an outcome, 18 absconded and were lost to follow-up, 1 had a treatment failure, and treatment was discontinued for 1 case because of adverse reactions to the medications. For the 4% of the total number of reported cases in 2009 for which treatment was not completed, treatment was ongoing in 42 cases and was unknown at the time of writing in the remaining 17 cases.

Drug regimen was reported for 1,249 reported cases in 2009. Of these, 89% were reported to have received three or more drugs. Fifty-nine percent of the individuals were reported to have received directly observed therapy (DOT), 32% self-administered therapy and 8% unspecified or other.

Between 2000 and 2009, 8.6% of diagnosed cases were reported to have died before or during treatment. TB was reported to have been the cause of death in 18% of these cases and contributed to but was not the underlying cause of death in an additional 41% of the cases. TB was reported not to have contributed to death but was an incidental finding in 28% of cases. For 12% of cases, the cause of death was not reported. However, it is important to note that identification of the precise cause of death can be inaccurate, and the WHO recommends that the most important indicator is death (of any cause) during treatment.

Between 2000 and 2009, of those individuals with a diagnosis of active TB disease, 1,429 were reported to have died before or during treatment. Males accounted for 63% of these deaths and had a median age of 73 years at the time of death. Females accounted for 37% and had a median age of 74 years at the time of death. Ten percent had had a previous episode of TB disease. HIV status was known for 17% of all deaths during this period; of these, 39% were HIV-positive. Of the 1,429 TB-attributed deaths reported, 170 (12%) were found to have TB on post-mortem examination.

SUMMARY OF SALIENT TRENDS

Both the overall rate and annual number of reported cases of TB continue to slowly decline in Canada. Nevertheless, pronounced disparities are observed in certain population groups and in several geographic regions. The high proportion of cases in foreign-born individuals presents unique challenges, in particular because of changing demographic patterns. Also of concern are the continued high rates observed among Aboriginal peoples born in Canada, particularly in Inuit communities.

CONCLUSIONS

TB partners in Canada aim to reduce the national TB incidence rate, and in particular to reduce the burden of TB disease among Canadian-born Aboriginal peoples and the foreign-born. In order to achieve reduction in these key populations, prevention and control interventions should target those determinants of health that contribute to the disease. The public health community has long recognized that economic, social, cultural and environmental factors play a role in TB infection and disease. As detailed in this chapter, certain Canadian populations experience greater risk of TB than others. In addition to foreign-born and Aboriginal communities in Canada, those who are incarcerated or homeless also show higher rates, as outlined in subsequent chapters of the *Standards*. There are numerous determinants of health that relate to TB, which include education, employment, physical environment, social support, access to health care, personal health practices and culture.[7] Addressing the underlying determinants of health is universally recognized by TB experts as being an integral component of the response, both in Canada as well as globally.[10,11]

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CHAPTER 2

PATHOGENESIS AND TRANSMISSION OF TUBERCULOSIS

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KEY MESSAGES/POINTS

- Infection with *Mycobacterium tuberculosis* is acquired by inhalation of bacilli-containing droplet nuclei small enough (diameter 1-5 microns) to reach the alveoli.
- Through innate immune mechanisms, alveolar macrophages eradicate the bacteria in some individuals; in others, the bacteria are able to replicate and establish tuberculosis (TB) infection. Bacterial factors and host genetic factors that promote or limit acquisition of infection are not well understood.
- After infection with *M. tuberculosis*, early primary TB disease develops in 5% of people unless they first receive treatment for latent infection. Rapid progression to primary active TB is most frequent in infants and young children, and in people with immune compromise.
- In another 5% of infected people there is later development of reactivation TB in the absence of treatment for latent TB infection (LTBI). Risks are much higher for people with immune compromise, notably HIV infection.
- In the remaining 90% progression to active disease never occurs.
- Intact cell-mediated immunity (CMI) is required to control and contain *M. tuberculosis* infection. Beyond evident clinical and radiographic risk factors, it is impossible to predict which infected people will ultimately develop active TB.
- Transmission of *M. tuberculosis* occurs, with very few exceptions, via droplet nuclei, which can then be inhaled by those who are exposed. For this reason, only those with active pulmonary and/or laryngeal TB are likely to be contagious.
- The probability of transmission increases with the following:
  - bacterial burden (smear positivity), cavitary and upper lung zone disease, and laryngeal disease;
  - amount and severity of cough in the source case;
  - duration of exposure;
  - proximity to the source case;
  - crowding and poorer room ventilation;
  - delays in diagnosis and/or effective treatment.
- The most effective way to reduce transmission is to diagnose and treat patients with active TB disease as soon as possible.

PATHOGENESIS

The pathogenesis and transmission of TB are inter-related. *M. tuberculosis* is almost exclusively a human pathogen. How it interacts with the human host determines its survival. From the perspective of the bacterium a successful host-pathogen interaction is one that results in pathogen transmission. Initial infection is usually self-limited and followed by a variable period of latency, which ultimately, in a proportion of those infected, results in infectious pulmonary TB. Transmission from a case of infectious pulmonary TB is by the airborne route in minute droplets of moisture that become increasingly reduced by evaporation, creating “droplet nuclei”.[1]

EVOLUTION OF INITIAL INFECTION AND HOST RESPONSE

At the time of initial infection, the distribution of inhaled droplet nuclei in the lung is determined by the pattern of regional ventilation. It thus tends to follow the most direct path to the periphery and to favour the middle and lower lung zones, which receive most of the ventilation.[2] In immunocompetent hosts, it is theorized that alveolar macrophages ingest the *M. tuberculosis* organisms and may or may not destroy them, depending on the degree to which phagocytosing cells are nonspecifically activated, on host genetic factors and on resistance mechanisms in the bacteria.[3] If bacteria are successfully cleared, then test results will remain negative on the tuberculin skin test (TST) or interferon gamma release assay (IGRA).

When innate macrophage microbicidal activity is inadequate to destroy the initial few bacteria of the droplet nucleus they replicate logarithmically, doubling every 24 hours until the macrophage bursts to release the bacterial progeny.[3] New macrophages attracted to the site engulf these bacilli, and the cycle continues. The bacilli may spread from the initial lesion via the lymphatic and/or circulatory systems to other parts of the body. After a period lasting from 3 to 8 weeks the host develops specific immunity (cell-mediated immunity [CMI] and delayed-type hypersensitivity [DTH]) to the bacilli, and individuals typically show positive results on the TST or IGRA. The resulting *M. tuberculosis*-specific lymphocytes migrate to the site of infection, surrounding and activating the macrophages there. As the cellular infiltration continues, the centre of the cell mass, or granuloma, becomes caseous and necrotic. Radiographically demonstrable fibrocalcific residua of the initial infection include a Ghon focus (a calcified granuloma in the lung) alone or in combination with a calcified granulomatous focus in a draining lymph node (Ghon complex).[4,5] Infection and immune conversion are usually asymptomatic; any symptoms that do occur are self-limited. In a small proportion of those infected, erythema nodosum (a cutaneous immunologic response to an extracutaneous TB infection) or phlyctenular conjunctivitis (a hypersensitivity reaction) may develop.

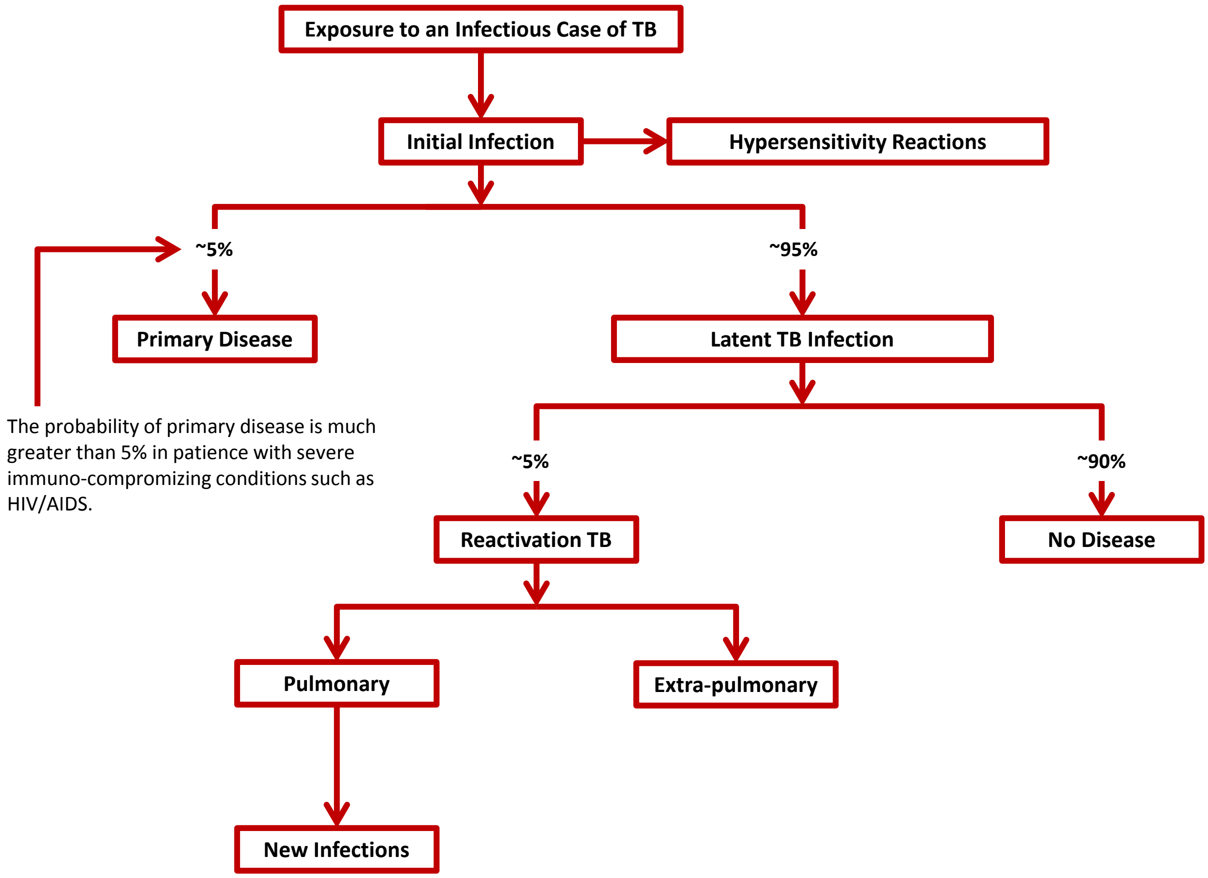
EARLY DISEASE PROGRESSION (PRIMARY TB)

A proportion of those who are recently infected are unable to contain the infection despite the stimulation of CMI and DTH, and there is progression to disease in a matter of months. Such early disease progression is a function of age and immunologic response, disease being especially likely to occur in young children and the immunocompromised. A progressive Ghon focus, disseminated (miliary) disease and central nervous system disease may occur as early as 2 to 6 months after infection in infants and the severely immunocompromised.[6,7] Uncomplicated and asymptomatic lymph node disease (hilar or mediastinal lymphadenopathy without airway involvement) may also occur in the first 2-6 months of infection, although there is debate about whether this should be called active disease (see Chapter 9, Pediatric Tuberculosis).[6,8]

At 4-12 months after infection, early disease manifestations include complicated lymph node disease (airway compression, expansile caseating pneumonia, infiltration of adjacent anatomic structures), pleural disease (most commonly a lymphocyte-predominant exudative effusion) and peripheral lymphadenitis (usually in the neck).[6] In immune competent children and adolescents early disease is more likely to manifest as intrathoracic adenopathy and in adults as a unilateral pleural effusion. In severely immunocompromised people of any age (e.g. those with advanced HIV or AIDS), early disease may manifest as intrathoracic adenopathy.[9,10] Rarely, in newly infected people who are 10 years of age or older (pubertal) adult-type pulmonary disease (see below) or other types of extrapulmonary TB (for example bone and joint TB) may develop within the first 24 months of infection.[11]

While early disease progression may or may not result from lympho-hematogenous spread, late disease progression (see below) is almost always the result of the lympho-hematogenous spread of bacilli. Recent infection with early disease progression probably accounts for many cases of TB in recently arrived immigrants.[12] For purposes of disease reporting, everyone with a diagnosis of TB made within 18-24 months of infection is considered to have "primary" disease (on balance about 5% of those infected). Those newly infected people in whom TB does not develop within this period of time will either be left with LTBI and will never experience disease (on balance about 90% of those infected) or, after a variable period of latency, they will develop late disease progression (on balance about 5% of those infected, see Figure 1).

Figure 1. The Pathogenesis of Tuberculosis in the Infected Host
(Adapted from the 6th Edition of the *Canadian TB Standards*)



LATENT TUBERCULOSIS INFECTION (LTBI)

In the classical concept of LTBI, *M. tuberculosis* bacteria are believed to survive for years in Ghon foci and complexes and in the small granulomas or solid caseous material of lympho-hematogenously seeded foci. Presumably, local conditions, an intact CMI or the presence of inhibitors result in conditions unfavourable to replication. Recent mapping of the complete genome sequence of the bacterium demonstrates that the organism has the potential to synthesize enzymes involved in anaerobic metabolism.[13] Although rapid death and autolysis occur after abrupt depletion of oxygen, the organism can shift into a state of dormancy if allowed to settle through gradual reductions in oxygen tension.[14,15] Therefore, although *M. tuberculosis* thrives in an aerobic environment, it possesses the genetic and biochemical capability of anaerobic survival and can persist experimentally in oxygen-depleted media. Tubercle formation, with its oxygen-depleted environment, is a defining characteristic of TB. LTBI is usually identified by a positive TST or IGRA in the absence of active disease (see Chapter 4, Diagnosis of Latent Tuberculosis Infection).

More recently LTBI and active TB have been considered as two ends of a spectrum of states ranging from asymptomatic infection to overt disease.[16,17] In this more nuanced concept, patients whose LTBI progresses to overt disease may pass through a continuum of asymptomatic intermediate states with detectable manifestations indicative of disease.[16] Such asymptomatic disease states frequently remain undiagnosed, and their manifestations and duration are mostly dependent on host immune response. Defining these intermediate states in concrete terms is considered to be important for pragmatic reasons, as they might have an impact upon the performance of TB biomarkers or other diagnostic measures and could also present targets for therapeutic interventions.[16,18]

REINFECTION

The elegant studies of Ferguson strongly suggest that it takes up to 18 months after the initial infection for CMI to mature.[19] During this period of time a reinfection carries the same risk of disease as the initial infection, perhaps explaining why disease is much more common in newly infected close contacts of smear-positive cases than it is in newly infected close contacts of smear-negative cases – the former having a greater likelihood than the latter of repeated exposure and reinfection.[20-22] Reinfection of immunocompetent hosts that occurs 18 months or more after the initial infection carries a much lower risk of progression to TB disease, estimated to be 21% of the risk of an initial infection progressing to disease.[22] It is not known whether this is because prior infection without development of overt disease is simply a marker for people who are less susceptible to disease development or better able to overcome it once it has developed. Nevertheless, in highly endemic areas the majority of TB cases occurring in those with prior LTBI may be due to reinfection rather than reactivation; in Canada, where repeat exposure is much less common, most active TB reflects reactivation and not reinfection.[23-25] In the severely immunocompromised host, reinfection and initial infection carry a similarly high risk of disease regardless of when the reinfection occurred (see Chapter 6, Treatment of Latent Tuberculosis Infection).

LATE DISEASE PROGRESSION (REACTIVATION TB)

In Canada, most TB is understood to be "reactivation" TB, i.e. occurring 18-24 months or more after the initial infection. It usually presents as adult-type pulmonary disease (upper lung zone fibrocavitary disease – previously referred to as postprimary TB – beginning in small foci that are the result of remote lympho-hematogenous spread), although it may also present as extrapulmonary TB. As mentioned earlier, adult-type pulmonary TB may on occasion be a manifestation of primary TB or a reinfection. In any population group, reactivation of LTBI, leading to reactivation TB, is much more likely to occur in people who are immune compromised.

There are a number of theories, most of them speculative, as to why adult-type pulmonary TB tends to localize in the upper lung zones. These are described elsewhere.[2,5] People with a history of untreated or inadequately treated pulmonary TB or a "high-risk" lung scar (upper lung zone fibronodular abnormality) on chest radiograph are understood to have a higher bacillary burden than those without such a history/radiograph, and to be at increased risk of reactivation TB.[26,27]

From the standpoint of public health and the organism's survival as a species, adult-type pulmonary TB is the most important phenotypic expression of the disease. Patients with adult-type pulmonary TB are much more likely to show lung cavitation, created when caseous material liquefies (possibly related to hydrolytic enzymes released from inflammatory cells during their destruction and DTH to tuberculin-like proteins) and erodes into the bronchi.[28] Within the unique extracellular environment of cavities, host defences are ineffectual, and bacteria multiply in large numbers. Because cavities are open to, and discharge their contents into, nearby bronchi these same bacteria are directly communicable to the outside air when the patient coughs. Transmission from patients with adult-type pulmonary TB is facilitated by the concurrent involvement of both the airways and their contiguous pulmonary blood supply at sites of disease in the lung. This minimizes the respiratory limitation experienced by the patient, extending the life of the host within the community and creating further opportunities for transmission before the patient either seeks medical attention or succumbs.[29]

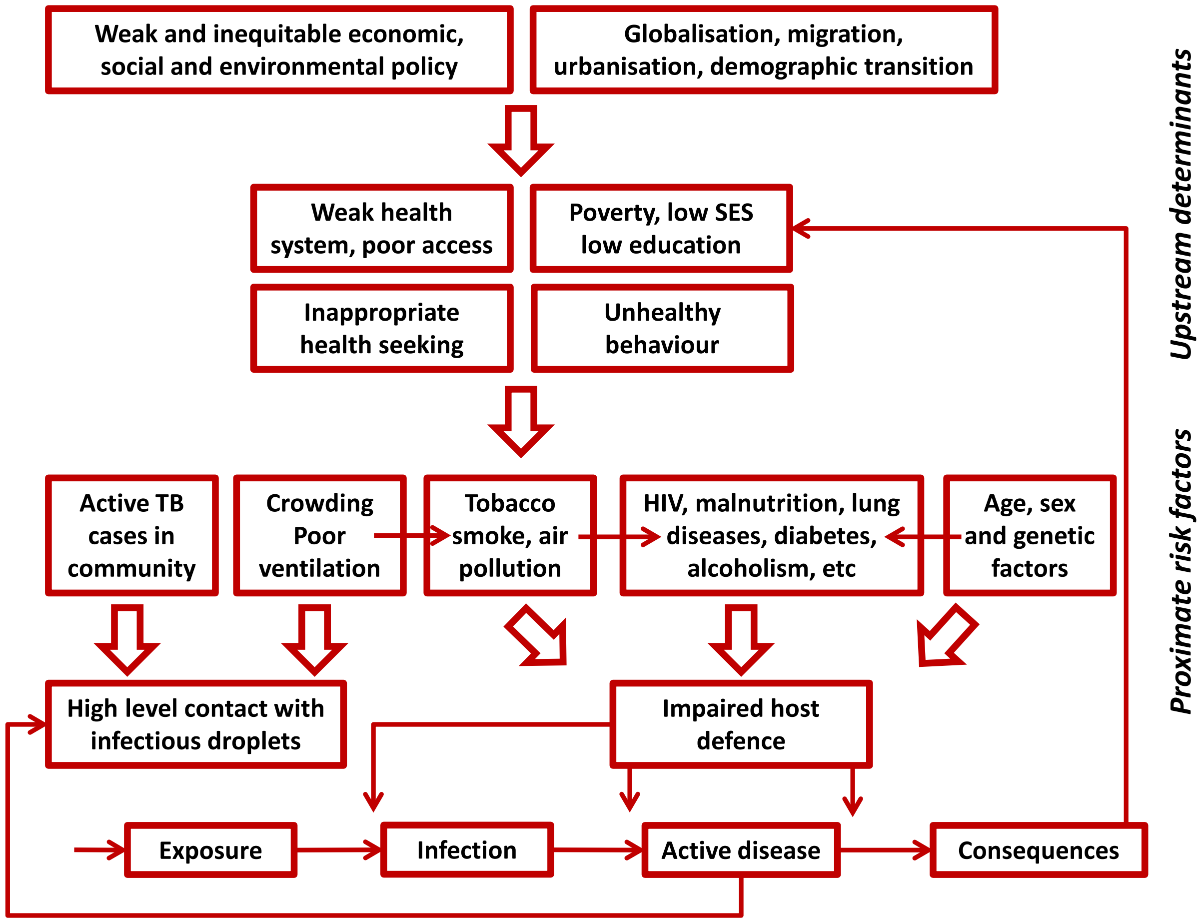
EXTRAPULMONARY TB

Outside of the extrapulmonary sites of disease alluded to in the section Early Disease Progression and cases of bone and joint TB, whose timeline from infection to disease in children may be as short as a year, most extrapulmonary TB is reactivation disease. Extrapulmonary TB or combined pulmonary and extrapulmonary TB is more common in those who are severely immunocompromised; in those coinfected with HIV the occurrence of extrapulmonary TB increases as the CD4 count decreases (see Chapter 7, Non-respiratory Tuberculosis).[9,10]

RISK FACTORS FOR PROGRESSION FROM INFECTION TO DISEASE

The risk of transition from LTBI to active TB, primary or reactivation, is largely dependent on the immune competency of the host. Age and sex appear to directly affect the immunologic response and the risk of disease: morbidity is greater among young children (<5 years of age), especially infants, among young adults, especially females, and among older adults, especially males. In high-burden countries, the population attributable fraction of undernutrition for TB is 27% according to the WHO.[30] The seasonality of TB (with the highest incidence in spring and early summer) has been attributed to reduced sunlight and vitamin D deficiency during the winter months in some studies but not in others.[31-33] Ethnic differences have been offered as factors determining host immune response, with some support,[34] but differences among ethnic groups in all clinical forms of TB are probably best explained as phase differences in an epidemic wave.[35] All races initially exposed in an epidemic as a group are equally susceptible, but eventually death and survival outcome select out people who are relatively more resistant. A growing body of evidence suggests that host genetic factors are important in determining susceptibility to TB.[36-38] Most important from a clinical perspective are the many medical conditions that are well known to affect host immunologic response and increase the risk of progression from LTBI to active TB disease. These are reviewed in detail in Chapter 6, Treatment of Latent Tuberculosis Infection. To identify entry points for interventions aimed at addressing TB risk factors as well as social determinants, Lönnroth and colleagues developed a framework for proximate risk factors and upstream determinants of TB (see Figure 2).[39]

Figure 2. Framework for proximate risk factors and upstream determinants of TB[39]



TRANSMISSION[40-43]

M. tuberculosis is communicable from one human to another mainly by the aerosol route and rarely through ingestion or percutaneous inoculation (e.g. through laboratory or hospital accident). Bovine TB, which in the past was caused by ingestion of milk heavily infected by *M. bovis* that then penetrated the mucosa of the oropharynx or the gastrointestinal tract, has been largely eradicated as a result of the pasteurization of milk and the tuberculin testing of cattle, followed by the slaughter of animals found to be infected.

The reservoir for *M. tuberculosis* is humans. Other animals, in particular primates, may be infected but are rarely a source of infection.[40-43] Droplet nuclei, sometimes referred to as "the quanta of contagion", are created by forceful expiratory efforts, such as coughing, sneezing, singing, playing wind instruments and even speaking. Before droplets reach the airspace of a room and have had an opportunity to evaporate down to a “droplet nucleus” their numbers can be reduced by wearing a simple gauze (surgical) mask or covering the mouth and nose during coughing. Certain procedures, for example, bronchoscopy, sputum induction, processing of specimens, autopsy and even irrigation or other manipulation of tuberculous abscesses, may also produce infectious aerosols. The droplets have an extremely slow settling rate (0.5 mm per second or less), which permits their transport by air currents, duct systems or elevator shafts for significant distances from the source case. Large particles settle quickly and are either not inhaled by contacts or, if inhaled, are trapped in the mucus of the upper airway.

If the organism reaches the trachea and bronchi it is usually swept back to the larynx by ciliary action and cough, and then swallowed. For practical purposes, only the droplet nuclei in the size range 1 to 5 microns reach the terminal air spaces or alveoli; each is understood to contain only a few bacteria. In most instances only one such droplet nucleus is believed to be responsible for establishing infection in the host. Bacteria that are lodged on fomites (linen, furniture, books, floors) do not constitute a significant source of infection: most die quickly through the action of drying, heat or sunlight.[5,40-43]

The rate of transmission can be measured by the percentage of close contacts (household and non-household) whose TST or IGRA responses are converted from negative to positive or in whom active TB disease develops. The percentage will depend on the number of infectious droplet nuclei per volume of air (infectious particle density) and the length of time that the uninfected individual spends breathing that air. In the past, drug susceptibility patterns and phage typing of *M. tuberculosis* isolates have helped to confirm the transmission between source case and contact. More recently, DNA fingerprinting of *M. tuberculosis* isolates has greatly refined the identification of this relation.[44]

Because of the highly variable latency period of *M. tuberculosis* infection it is difficult to precisely document transmission using currently available tools. People found to have positive TSTs and/or IGRAs during contact investigation may have been infected in the past (remotely) rather than by the recent source case of concern, though for contact management and public health purposes these contacts are treated as if recently infected if there is no way to determine the duration of infection. DNA fingerprinting techniques will only detect transmission to the small group of people in whom active disease develops following transmission. If most TB disease in a community reflects recent/ongoing transmission, the first priority for public health authorities should be to prevent further transmission. On the other hand, if most TB reflects reactivation of remotely acquired infection, the priority should shift to identification and treatment of people with LTBI, notably those with risk factors for reactivation.

PATIENT, PATHOGEN AND ENVIRONMENTAL DETERMINANTS OF TRANSMISSION

Several patient, pathogen and environmental factors determine whether transmission occurs, largely by affecting the number of infectious droplet nuclei per volume of air (see Table 1). Although the probability of being infected after contact with an infectious source decreases with decreasing duration and decreasing closeness of contact, the absolute number of casual contacts infected may exceed the number of infected close contacts, since the former may far outnumber the latter.[45] DNA fingerprint data have highlighted the limits of contact tracing in settings where there is exposure of a large number of people unknown to source cases and in settings where social connections are tenuous at best.[46,47] At this point very little is known about what, if any, host determinants influence the acquisition of initial infection after inhalation of a droplet nucleus. Some individuals are able to achieve complete or "sterile" elimination of *M. tuberculosis* bacteria rather than developing latent infection.[48] Observational studies suggest that BCG vaccination in infancy offers some protection against infection with *M. tuberculosis* as detected by an IGRA.[49-52]

Table 1. Patient, pathogen and environmental factors affecting transmission

Patient	Pathogen	Environment
Disease type	Strain variability	Indoor/outdoor
Pulmonary Smear-positive/smear-negative Cavitary/non-cavitary on CXR* Typical/atypical on CXR Laryngeal		Air circulation/ventilation Sunlight
Extrapulmonary		Proximity to the source case
Symptomatology		Duration of exposure
Delayed diagnosis		
Treatment		

*CXR = chest radiograph

PATIENT FACTORS

With rare exception (e.g. transmission related to an inadequately sterilized bronchoscope or a needle stick injury), transmission requires that a TB patient be able to produce airborne infectious droplets.[41-43] This most often limits the potential for transmission to adolescent or adult patients with adult-type pulmonary TB. Younger children can on occasion be infectious,[53] but as a general rule they have few bacilli in their lesions, often do not produce sputum and rarely have communicable disease.[54] Of patients with TB involving the respiratory tract not all are equally efficient at transmission.

1. Sputum smear status

Patients with smear-positive/culture-positive pulmonary TB are more infectious than patients with smear-negative/culture-positive pulmonary TB, and the latter are more infectious than patients with smear-negative/culture-negative pulmonary TB (see Table 2 for a summary of the epidemiologic studies on the risk of infection in household [close] contacts grouped according to the bacteriologic status of the source cases).[55-62] Sputum that is smear-positive contains 5,000 or more organisms per millilitre of sputum.[57,58,63,64]

Patients with smear-positive bronchoalveolar lavage fluid are considered just as infectious as those with smear-positive sputum.[65] Smear-positive induced sputum is for practical purposes considered to indicate the same degree of contagiousness as smear-positive spontaneously expectorated sputum, though there are currently no data that prove this assertion.[55] With the use of molecular epidemiologic tools the relative transmission rate of smear-negative compared with smear-positive patients has been determined to be 0.17-0.22 or roughly one-fifth the likelihood of transmission.[66,67] In addition to the greater infectivity of smear-positive cases, as mentioned in the section Pathogenesis, the risk of disease after infection from a smear-positive case is greater, by virtue of the higher probability of repeated infection, than it is after infection from a smear-negative case.

Table 2.* Risk of infection among household (close) contacts according to bacteriologic status of index case (pulmonary TB only)

Ref no.	Year of survey	Location	Contacts		Number and % infected contacts by bacteriologic status of index case						General population % positive PPD†
					S+C+		S-C+		S-C-		
			Age	Total no.	N	%+	N	%+	N	%+	
56	1949-56	England	0-14	545	262	63%	126	21%	157	18%	13%
57	1950-53	England	0-14	823	374	65%	228	27%	221	18%	22%
58	1963-64	Holland	all ages	858‡	391	20%	467	1%	–	–	<<1%
20	1966-71	Canada-Whites	0-19	2406	1210	38%	655	12%	541	10%	2%
		Canada-Aboriginals	0-19	1168	592	45%	377	31%	199	27%	NA
59	1967-69	Rotterdam	0-14	134	40	50%	43	5%	51	8%	1%
60	1969	USA	all ages	130	88	44%	14	21%	28	14%	NA
61	1971-74	USA	all ages	761	504	46%	257	28%	–	–	NA
62	1975-77	USA	all ages	541	368	40%	173	27%	–	–	NA

*Adapted from reference number 55

† Taken from the same reference, i.e. a comparable reference population.

‡ In this study contacts were considered infected only if tuberculin conversion and/or primary TB had been documented.

S = smear, C = culture, PPD = purified protein derivative

2. **Disease type on plain chest radiograph**

Pulmonary TB patients with cavitation on chest radiograph are more infectious than pulmonary TB patients without cavitation after bacteriologic findings have been taken into account.[68-70] Pulmonary TB patients with "typical" chest radiographic findings (upper lung zone disease, with or without cavitation, and no discernable intrathoracic adenopathy) are more infectious than pulmonary TB patients with "atypical" chest radiographic findings (all others).[71]

3. **Laryngeal disease**

Patients with laryngeal TB are more infectious than those with pulmonary TB.[72] Most patients with laryngeal TB (hoarseness associated with inflammation and ulceration of the vocal cords) have far advanced pulmonary disease upstream from the larynx.[73]

4. **Symptomatology**

In general, normal breathing produces few infectious particles, a bout of coughing or five minutes of speaking in a normal tone produce many more, and a sneeze produces the most.[74,75] The likelihood that household contacts will be infected increases with the frequency of cough in the source case.[60] When the aerial infectivity of the droplets from smear-positive patients was evaluated by artificially atomizing sputum and exposing guinea pigs to a standard dose, there was marked variability in the infectivity of aerosolized sputum, perhaps explaining the extraordinary heterogeneity of infectiousness among patients with smear-positive pulmonary TB.[76-78] Thus, although patients may appear to have an equal number of bacteria in their sputum, the physical and chemical properties of their sputum, as well as their effectiveness as an aerosolizer, may determine whether they produce a large or small number of droplet nuclei. The role of smoking, allergy or coincidental viral upper respiratory tract infection in aerosol formation is unknown.[79]

5. **Delayed diagnosis**

The number of contacts and the duration of exposure of each contact may increase as time to diagnosis increases. The longer the duration of symptoms in the source case the greater the risk of transmission.[65]

6. **Treatment**

Effective treatment (see Chapter 5, Treatment of Tuberculosis Disease) appropriate to the drug susceptibility test results rapidly reduces cough frequency and sputum bacillary counts.[60,80] Even faster than the rate of decrease of the latter is the rate of decrease of bacillary counts in cough-generated aerosol cultures.[81] With treatment those bacteria that continue to be expectorated may be expected to be less metabolically active and/or are inhibited by the drugs, two effects that may decrease the chances of the organism establishing an infection in the host.[76,82] However, in theory, any residual viable bacteria in respiratory secretions can be transmitted, although the chances of this occurring decrease rapidly with effective treatment.[83] Given the frequency of drug resistance, the determination that treatment is effective in reducing the infectiousness of a given patient should reflect objective clinical, radiographic and/or microbiologic improvement, and not simply time elapsed since treatment initiation.

PATHOGEN FACTORS

Data are emerging to suggest that one or more virulence properties of *M. tuberculosis* may affect its ability to be transmitted.[84] For example, one strain may be better suited than another to overcoming the innate resistance of the host. Although drug-resistant strains have shown reduced virulence in animal models,[85] clinical evidence of their transmissibility is compelling,[86-89] and for practical purposes they should be considered just as transmissible as drug-susceptible strains. Beijing/W strains have been reported to be hypervirulent, but indices of transmission have been found to be no greater in patients with these strains than in those without them.[90]

ENVIRONMENTAL FACTORS

Outdoor exposures are very unlikely to result in transmission unless the source and the susceptible person are in talking distance. Bacillary dispersion is immediate, and sunlight rapidly kills any viable bacilli.[91,92] For practical purposes outdoor exposures are not investigated during a contact tracing exercise.

1. Air circulation and ventilation

Given a defined number of bacteria expelled into the air, the volume of air into which the bacteria are expelled determines the probability that a susceptible individual breathing that air will become infected. A high concentration of viable bacteria in the inhaled air of the contact is favoured by indoor exposure, poor ventilation or recirculation of air, and little sunlight (ultraviolet rays). Ventilation dramatically dilutes the concentration of infectious droplet nuclei (see Chapter 15, The Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for further information on clearance times).

2. Proximity to the source case

Proximity to the source case is also a determinant of transmission. Related to this is overcrowding: if, as a result of there being many people in a room, an individual is forced into close proximity with an infectious case his or her risk of infection is likely to increase.

3. Duration of exposure

Because of the dilution of infected air and the low concentration of infectious droplet nuclei, the duration of exposure required to ensure that transmission occurs is commonly prolonged (days, months or even years), and yet reports have confirmed that exposures as short as a few minutes may be sufficient to infect a close contact. The latter would appear to be supported by the high proportion of active cases that deny any history of exposure.

MEASURES TO PREVENT TRANSMISSION

The highest priority should be given to early diagnosis and prompt, effective treatment of the source case together with isolation of the patient when necessary. The insidious development of symptoms in most cases of TB commonly results in a delay of weeks or months before the patient presents for diagnosis. At that point, when the patient is often at his or her most infectious, any further delay caused by the physician, nurse or system allows unnecessary transmission to others. Maintaining an appropriate awareness of TB among health care providers is thus critical to reducing transmission and initiating early prevention and treatment. Administrative and engineering controls that aim to reduce exposure in health care and other congregate settings complement—but cannot replace—prompt diagnosis and appropriate therapy. Methods once thought to be important in preventing the transmission of TB – disposing of such personal items as cloths or bedding, sterilizing fomites, using caps and gowns, gauze or paper masks, boiling dishes and washing walls – are unnecessary, because they have no bearing on airborne transmission.

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CHAPTER 3

DIAGNOSIS OF ACTIVE TUBERCULOSIS AND DRUG RESISTANCE

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KEY MESSAGES/POINTS

- Testing for active tuberculosis (TB) is indicated in everyone with signs and symptoms of TB or considered to be at high risk of TB disease.
- Every effort should be made to obtain a microbiological diagnosis, which requires demonstration of acid-fast bacilli on smear microscopy and/or culture of *Mycobacterium tuberculosis*, or requires amplification and detection of *M. tuberculosis* complex (MTBC) nucleic acids using nucleic acid amplification tests (NAATs).
- Chest radiography is an integral part of the TB diagnosis algorithm but is not specific for the diagnosis of pulmonary TB. Chest radiography cannot provide a conclusive diagnosis on its own and should be followed by microbiological tests for TB disease.
- At least three sputum specimens should be collected and tested with microscopy as well as culture.
- Where feasible, three sputum specimens (either spontaneous or induced) can be collected on the same day, a minimum of 1 hour apart.
- Everyone with suspected TB should undergo testing with at least three concentrated fluorescent smears.
- Every specimen that is sent for smear microscopy should be set-up for culture in one solid medium and one liquid medium.
- At least one respiratory sample should be tested with a Health Canada approved or validated in-house NAAT in all new, smear-positive cases. In addition, NAA testing may be performed in smear-negative patients upon request by the physician or the TB control program. NAAT results are not recommended for monitoring TB treatment response.

- In settings where there is currently no on-site capacity for routine smear microscopy and culture, an automated cartridge-based NAA test can be used to make rapid decisions on TB treatment and isolation while routine smear and culture results are awaited. All such NAAT results should be confirmed by routine smears and cultures. In particular, all positive rifampin (RMP) resistance results should be interpreted cautiously, given the very low prevalence of multidrug-resistant (MDR)-TB in Canada and the likely low positive predictive value of RMP resistance results from the automated cartridge-based NAA assay.
- The use of serologic, antibody-based TB tests is not recommended for TB diagnosis.
- The use of tuberculin skin test (TST) or interferon gamma release assay (IGRA) for the diagnosis of active TB in adults is not recommended.
- Phenotypic drug susceptibility testing (DST) should be routinely performed for all first positive culture isolates obtained from each new TB case. While the agar proportion method is considered the gold standard for DST, a broth method is the recommended standard of practice in North America.
- Rapid molecular tests for DST should be reserved for patients with a high pretest probability of MDR-TB. **The use of these tests does not eliminate the need for conventional culture and DST,** which are recommended to confirm initial results and also detect resistance to drugs other than RMP and isoniazid (INH).

DIAGNOSIS OF RESPIRATORY TB DISEASE

In Canada, respiratory TB includes primary TB, pulmonary TB, tuberculous pleurisy (nonprimary) and TB of the intrathoracic lymph nodes, mediastinum, nasopharynx, nose (septum) and sinus (any nasal). Pulmonary TB refers to TB of the lungs and conducting airways, which includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia, tuberculous pneumo-thorax, isolated tracheal or bronchial TB and tuberculous laryngitis. The diagnosis of nonrespiratory TB is described in Chapter 7, Nonrespiratory Tuberculosis; the diagnosis of nontu-berculous mycobacterial infections is described in Chapter 11, Nontuberculous Mycobacteria.

CLINICAL PICTURE OF PULMONARY TB

EPIDEMIOLOGIC RISK GROUPS

As summarized in Chapter 1, Epidemiology of Tuberculosis in Canada, foreign-born individuals, particularly those from countries with high TB incidence, Aboriginal Canadians, the elderly (particularly elderly males) and close contacts of infectious TB cases are at increased risk of TB disease.[1]

SYMPTOMS

The classic symptom of pulmonary TB disease is a chronic cough of at least 2-3 weeks' duration. This cough is initially dry but after several weeks to months will become productive. Cough of 2 weeks duration is a more sensitive criterion, but cough of 3 weeks duration will be more specific. Selection of 2 or 3 weeks as the criterion depends on the local experience and epidemiology of TB. Fever and night sweats are common but may be absent in the very young and the elderly. Hemoptysis, anorexia, weight loss, chest pain and other symptoms are generally manifestations of more advanced disease.[1,2]

SIGNS

The most common physical finding in pulmonary TB is a totally normal examination**,** even in relatively advanced cases. Bronchial breathing, rales or crepitations will be found in more advanced cases. It is important to examine for signs of extrapulmonary disease, such as lymphadenopathy, pleural effusion and abdominal or bone and joint involvement, as these may be present concomitantly, particularly in HIV-infected individuals.[1,2]

RECOMMENDATIONS

- **Testing for active TB is indicated in everyone with signs and symptoms of TB or considered to be at high risk of TB.**

  (Strong recommendation, based on moderate evidence)

- **Every effort should be made to obtain a microbiological diagnosis, which requires demonstration of acid-fast bacilli on smear microscopy and/or culture of *Myco-bacterium tuberculosis*, or requires amplification and detection of MTBC nucleic acids using NAATs. It is important to note that NAAT results are not confirmatory; they are pre-sumptive, and confirmation by culture is recommended.**

  (Strong recommendation, based on strong evidence)

ACTIVE TB TESTING ALGORITHM FOR TB SUSPECTS

In Canada, the standard testing algorithm for active TB includes the following tests:[1]

- chest radiography;
- sputum smear microscopy;
- mycobacterial culture and phenotypic DST;
- NAATs.

CHEST RADIOGRAPHY

Chest radiography (posterior-anterior and lateral views) is the usual first step in evaluation of an individual with pulmonary symptoms.[1] However, it is important to be aware that chest radiography has substantial limitations in the diagnosis of pulmonary TB disease.[1]

1. **Typical findings: a triad of classic findings is seen in immunocompetent adults.[3]**

   - Position – infiltrates in the apical-posterior segments of upper lobes or superior segment of lower lobes in 90%.
   - Volume loss – this is a hallmark of TB disease as a result of its destructive and fibrotic nature.
   - Cavitation – this is seen at a later stage and depends upon a vigorous immune response. Therefore, it often is not seen in immunocompromised individuals.

2. **Atypical features**

   These will be seen in patients with immunocomprising conditions such as HIV infection, diabetes, renal failure or long-term use of corticosteroids and other immunosuppressive agents.[3]

   - Hilar and mediastinal lymphadenopathy, particularly in HIV-infected individuals
   - Non-cavitary infiltrates and lower lobe involvement.

3. **Radiographic signs of complications[3]**

   - Endobronchial spread of disease. TB may spread via the airways to the ipsilateral and contralateral lower lobes. This results in irregular, poorly defined, small nodular shadows, which represent acinar shadows. These will slowly enlarge and coalesce to form TB pneumonia, formerly known as "galloping consumption."
   - Pleural effusion can be seen concomitant with pulmonary disease and may represent TB empyema.
   - Pneumothorax can rarely occur as a result of erosion of a caseous focus into a bronchus and simultaneously into the pleural space, causing a bronchopleural fistula.

LIMITATIONS OF CHEST RADIOGRAPHY

1. **Sensitivity:**

   Chest radiography will have a sensitivity of only 70% to 80% for the diagnosis of active TB based on the abnormalities listed above. If any abnormality is considered, it will have more than 95% sensitivity.4 Approximately 10% of HIV-positive people or close contacts with active culture-confirmed pulmonary disease will have normal x-rays.[4]

2. **Specificity:**

   This is relatively poor, in the range of 60% to 70%. If the sensitivity were improved (any abnormality considered possible TB), then the specificity would be much lower.[4]

3. **Inter-reader variability:**

   One of the greatest problems of chest x-ray reading is that the interpretation is highly variable.[4] There is very poor agreement among readers regarding the presence of cavitation, hilar lymphadenopathy and the likelihood of active disease.[4]

RECOMMENDATIONS

Chest radiography is an integral part of the TB diagnosis algorithm but is not specific for the diagnosis of pulmonary TB. Chest radiography cannot provide a conclusive diagnosis on its own and should be followed by microbiological tests for TB disease (described below).

(Strong recommendation, based on strong evidence)

MICROBIOLOGY

The role of the mycobacteriology laboratory is to detect, isolate, identify and perform susceptibility tests on clinically significant mycobacteria from clinical specimens. Mycobacterial culture, using both solid and liquid media, is considered the gold standard for diagnosis, and the use of broth-based culture methods for DST is the standard of practice in North America.[2,5,6] The most widely used rapid test is the examination of smears of sputum or other respiratory specimens after staining for acid-fast organisms (AFB smear). However, molecular-based techniques (NAATs) for the detection and identification of mycobacterial species are now widely available, enabling rapid identification of individuals with disease due to MTBC. Appendix D provides more information on TB laboratory standards.

COLLECTION OF RESPIRATORY SPECIMENS FOR MICROBIOLOGY

Given the critical importance of microbiology for TB diagnosis, it is important to ensure that respiratory specimens are correctly collected and processed to achieve valid results. All specimens should be collected in sterile, leak-proof, laboratory-approved containers and accompanied by a carefully completed requisition form providing the patient's demographic data, the physician's name, the date and time of collection, and the specimen type and site. As much as possible, specimens collected for initial diagnosis should be obtained before the initiation of anti-TB therapy.[1,2]

Once collected, specimens should be transported to the laboratory promptly. If processing within 1 hour is not possible, samples should be refrigerated at 4 ^{o}C (not frozen) and protected from light. Clinical specimens should be handled, processed and transported in an environment in which biosafety procedures are in place. Appendix D on TB laboratory standards provides more details on biosafety and the transportation of samples.

Sputum

At least three sputum specimens of 5-10 mL each should be collected and tested with microscopy as well as culture. While available evidence shows that the yield of the third sputum smear is only about 2%-5%,[7] the yield of the third culture may be as high as 5%-10%, especially in HIV-infected people.[8,9] Thus, it is important to collect at least three specimens for smears and cultures, especially in a low-incidence setting such as Canada, where smear-negative TB is the most common presentation.[1]

While it is conventional to collect sputum specimens using the standard spot-morning-spot (SMS) scheme, it is well known that this scheme is inconvenient to patients, and drop-outs during diagnosis are common. Recently published research has focused on the “same-day” or “frontloaded” diagnosis of TB using specimens collected on the same day in order to reduce patient drop-out, which is likely to happen if patients are asked to come back daily for sample collection.[10]

A multicentre clinical trial of 6,627 adults with cough of ≥2 weeks' duration compared the sensitivity/specificity of two sputum samples collected “on the spot” (one hour apart) during the first visit plus one sputum sample collected the following morning (spot-spot-morning [SSM]) versus the standard SMS scheme.[11] The centres participating in the study were randomly assigned each week for a year to use either the SMS or the SSM sample collection scheme. Compared with mycobacterial culture, the sensitivities of the SSM and SMS schemes were 70.2% and 65.9% respectively. Similarly, the specificity of SSM (96.9%) was not inferior to that of SMS (97.6%). Importantly, the sensitivity of diagnosis using just the first two samples collected in the SSM scheme was also noninferior to the sensitivity of diagnosis using the first two samples collected in the SMS scheme (63.6% versus 64.8%). Finally, patients tested using the SSM scheme were more likely to provide the first two samples than patients tested using the SMS scheme (98% versus 94.2%).[11] This large trial informed a recent World Health Organization (WHO) policy on same-day diagnosis.[10]

The findings of this trial were confirmed by a meta-analysis published in 2012 of eight research studies (involving 7,771 patients) comparing the accuracy of same-day microscopy and standard sputum smear microscopy for the diagnosis of culture-confirmed pulmonary TB.[12] Compared with the standard approach of examination of two smears with Ziehl-Neelsen microscopy over 2 days, examination of two smears taken on the same day had much the same sensitivity (64% [95% confidence interval 60% to 69%] for standard microscopy vs 63% [58% to 68%] for same-day microscopy) and specificity (98% [97% to 99%] vs 98% [97% to 99%]).

Thus, same-day sample collection with an interval of as little as 1 hour between sample collection may be especially helpful to reduce patient drop-out and make faster decisions about TB infection control and discharge from respiratory isolation (please see chapter 15, Prevention and Control of Tuberculosis Transmission in Healthcare and Other Settings).

RECOMMENDATIONS

- **At least three sputum specimens should be collected and tested with microscopy as well as culture.**

  (Conditional recommendation, based on moderate evidence)

- **Where feasible, three sputum specimens (either spontaneous or induced) can be collected on the same day, at least 1 hour apart.**

  (Conditional recommendation, based on moderate evidence)

Induced sputum

A recent meta-analysis of 17 studies evaluated the sensitivity of sputum induction and found that this procedure detects approximately 75% of culture-positive TB cases under study conditions among children and adults, regardless of the HIV prevalence, although the estimates varied across studies.[13] Another recent systematic review of 23 studies reported that the overall success of sputum induction was high, ranging from 76.4% to 100%, while adverse events associated with sputum induction were infrequent and mild. The sensitivity of microscopy compared with culture on induced sputum samples ranged from 0% to 100%. Yield was generally higher for sputum induction than nasopharyngeal aspiration and gastric lavage.[14]

It is important that sputum induction be performed with large volumes of 3% hypertonic saline. For best results, an ultrasonic nebulizer should be used that can administer 5 to 6 mL per minute over 15 minutes.[1] With the use of this, virtually all patients will produce sputum, and a single sputum induction will have equivalent or better yield than fibreoptic bronchoscopy.[15] Sputum induction has been performed successfully in very young children[16] (please see Chapter 9, Pediatric Tuberculosis). It is important to indicate on the requisition that the sputum was induced, because the resulting specimen often appears watery. However, it can be handled in the laboratory in the same way as spontaneously expectorated sputum.[2,17]

Bronchoscopy

Bronchoscopy may be used to facilitate the diagnosis of TB when spontaneous sputum and induced sputum are unavailable, or all samples are smear-negative.[17] Bronchoscopy is very useful if other pulmonary diseases, such as lung cancer, are also suspected. However, for the diagnosis of active TB it entails risk and discomfort for the patient, is expensive and can contribute to nosocomial spread of TB if not performed in an appropriate environment with protection of staff. In addition, the overall yield of bronchoscopy in prospective series of patients is only 77%.[18-21] If bronchoscopy is done, post-bronchoscopy sputum should be sent for AFB testing, as this has a yield similar to that of bronchial washings and lavage.[2,17]

Gastric aspirate

This technique was introduced more than 70 years ago and is still used in some centres.[22] The primary indications are investigation of possible TB in children who cannot expectorate sputum or, for the same reason, elderly demented patients. A recent systematic review of the accuracy of gastric aspiration (GA) and gastric lavage (GL) for TB diagnosis in children reported that GA/GL microscopy was positive in 0%-21% (median 7%), and culture was positive in 0%-75% (median 20%) of children with a clinical diagnosis of likely TB.[23] Culture isolation rates depended on the clinical criteria used to define TB.

The technique is relatively simple and is described in Chapter 9, Pediatric Tuberculosis. However, it is uncomfortable and unpleasant for patients, and may be difficult to implement because it needs to be performed immediately upon the patient awakening.[24] This often means that he or she has to be kept overnight in hospital, although it can be done for outpatients.[24]

Smear Microscopy

Sputum smear microscopy is the most widely used test for TB disease.[2,17] Two stains are widely used: 1) the traditional Ziehl-Neelsen or Kinyoun staining, which requires a light or bright field microscopy and 2) the auramine stain, which requires fluorescence microscopy. In most high-income countries (including Canada), fluorescence microscopy is standard practice (see Appendix D, Tuberculosis and Mycobacteriology Laboratory Standards: Services and Policies). Everyone with suspected TB should undergo testing with at least three concentrated auramine smears. Spontaneous or induced sputum specimens can be used.

Smear microscopy is rapid, inexpensive and identifies the most infectious TB patients.[1,2] However, the test has well known limitations:

- Sensitivity is modest and variable (20%-80%) depending upon the type of specimen, patient population, stain used and the experience of the microscopist.[25-27] Thus, multiple sputum smears are recommended to increase the overall sensitivity and yield. Sensitivity is higher for respiratory than for nonrespiratory specimens, particularly body fluids.
- In low TB incidence settings, smear microscopy has lower specificity – a positive smear could be due to nontuberculous mycobacteria (NTM).
- Smear microscopy has lower sensitivity in childhood TB and extrapulmonary disease, especially in HIV-infected people.
- Smear microscopy cannot be used to determine drug resistance.

Specimens need to be homogenized and then concentrated. The fluorochrome stain auramine is the most widely used staining method for initial acid-fast bacilli (AFB) smears because it can be read at a lower magnification than the classical Ziehl-Neelsen or Kinyoun stain, and thus slides can be read more quickly.[5] Fluorescence microscopy can be performed by conventional mercury vapour fluorescence microscopes or newer, light-emitting diode microscopes, which have many practical advantages[28] and have been endorsed by the WHO.[29] The sensitivity of all staining methods is inferior to that of culture. The threshold of detection of AFB in concentrated specimens using a fluorochrome stain is 5,000-10,000 bacteria/mL of sputum and is 100,000 bacteria/mL using the Ziehl-Neelsen stain. The threshold of detection in unconcentrated smears is 10-fold higher, resulting in much lower sensitivity.

This is important to remember, since often "Stat" smears are unconcentrated. In contrast, as few as 10-100 viable bacteria can be detected by culture.[2,5]

The specificity of the AFB smear is high for mycobacteria, but it is important to remember that all NTM will be AFB-positive. Other organisms, such as *Nocardia* and other actinomycetes, can be weakly acid-fast, but these are less common. Therefore, a positive AFB smear almost always indicates the presence of mycobacteria, but not necessarily *M. tuberculosis*.[5]

When acid-fast organisms are seen, the number of bacteria is reported semi-quantitatively, as shown in Table 1. Although there are different scales in use, North American laboratories use the Association of Public Health Laboratories recommended semi-quantitative system[5] (Table 1).

Table 1. Number of bacteria seen on microscopy and laboratory interpretation[5]

Number of AFB seen by staining methods		
Fuchsin stain (Ziehl-Neelsen) (1,000-fold magnification)	**Fluorochrome (250-fold magnification)**	**Semi-quantitative grading system**
0 in 300 fields	0 in 30 fields	Negative
1-2 per 300 fields	1-2 per 30 fields	Inconclusive, repeat
1-9 per 100 fields	1-9 per 10 fields	1+ (rare)
1-9 per 10 fields	1-9 per field	2+ (few)
1-9 per field	10-90 per field	3+ (moderate)
>9 per field	>90 per field	4+ (numerous)

RECOMMENDATION

- **Everyone with suspected TB should undergo testing with at least three concentrated fluorescent smears. Spontaneous or induced sputum specimens can be used. Smear microscopy is performed routinely on all specimens submitted to the mycobacteria laboratory for testing.**

  (Conditional recommendation, based on moderate evidence)

Mycobacterial Culture

Mycobacterial culture is the most sensitive and the current gold standard method for the detection of active TB disease.[2,5,17] In Canada, every specimen that is sent for smear microscopy is submitted for culture on one solid medium and one liquid medium. The use of culture remains necessary for the definitive diagnosis of smear-negative TB. The benefits of culture include identification, DST and further use of culture isolates for molecular epidemiology using DNA fingerprinting.[17] Culture can be performed on all specimen types, but typically sputum is used for the diagnosis of pulmonary TB.[17] Standards for TB culture are described in Appendix D.

Culture results typically take 2-8 weeks, depending on the culture method used and the number of MTBC bacteria in the inoculum. Solid culture typically uses either Lowenstein–Jensen media or Middlebrook 7H10 or 7H11 agar media for the isolation of MTBC and DST is performed using either Middlebrook 7H10 or 7H11 agar media. MTBC typically has a faster growth rate in liquid media than on solid agar. Also, liquid cultures are about 10% more sensitive than solid cultures, although more prone to contamination.[30] Three automated liquid culture systems are approved by Health Canada: Beckton-Dickinson (Bactec960 MGIT [mycobacterial growth indicator tube]), bioMérieux (BacT/ALERT) and Trek Diagnostic Systems Inc. (Myco-ESP culture System II). These are fully automated systems that use either fluorometric or colorimetric detection of mycobacterial growth and can be used for the isolation of MTBC and for DST.[31] Automated systems permit a higher throughput of specimens for testing, and DST results are often available within 7 days from the time of DST set-up.[5]

Culture for *M. tuberculosis* is considered the gold standard in diagnosis.[2,5,17] For pulmonary TB, the sensitivity of three sputum cultures exceeds 90%, although six specimens are required to achieve 100% sensitivity.[4] Three sputum cultures are recommended, as this represents the best balance between high sensitivity and efficiency.[5] A single positive culture for *M. tuberculosis*, in general, is considered definitive for active disease. However, it is important to remember that cultures occasionally can be falsely positive, which may be due to cross-contamination within the laboratory. A report of a single positive culture, especially with a long detection time and/or few colonies, when clinical suspicion is low should raise the possibility of a false-positive result. The laboratory reporting this culture should investigate and review all positive cultures initially processed on the same day or within proximity to the culture, ideally performing DNA fingerprinting on the isolate.[5]

All culture isolates should be subject to species identification using methods recommended in TB laboratory standards (Appendix D).

RECOMMENDATION

- **Every specimen that is sent for smear microscopy should be submitted for culture on one solid medium and one liquid medium.**

  (Strong recommendation, based on strong evidence)

Nucleic Acid Amplification Tests (NAAT)

The amplification of nucleic acids for the diagnosis of TB or to detect drug resistance is a sensitive method and produces a much faster result than conventional culture methods.[32,33] Polymerase chain reaction (PCR) is the most common method of amplification. In addition to commercial assays, there are many protocols for so-called “home brew” or in-house molecular assays. Unlike standardized, commercial NAATs, in-house NAATs can produce inconsistent results.[33] It is therefore recommended that validation studies be conducted before implementation and that the tests be used in accredited laboratories with quality assurance systems in place. Please see Appendix D for reporting standards for in-house NAAT results.

The sensitivity of commercial NAATs to detect TB is high (>95%) in sputum smear-positive samples.[32,34] The sensitivity of NAATs is lower (50%-70%) when smear-negative/culture-positive specimens are tested.[32-35] The sensitivity of NAATs is also lower in extrapulmonary specimens.[36-38] Thus, it is recommended that a negative NAAT result should not be used to rule out TB, especially in paucibacillary forms of TB (i.e. smear-negative and extrapulmonary TB). However, the specificity of the commercial NAAT is very high in all specimens (90%-100%).[32,34]

In general, NAATs require sophisticated laboratory infrastructure and highly skilled technicians. The risk of contaminating the test site with amplified DNA also requires stringent quality control procedures and a specific infrastructure to limit contamination. Please see Appendix D.

The following assays are commercially available and Health Canada approved: Roche (COBAS®Taqman® MTB; real-time-PCR), Becton Dickson (BD ProbeTec®, strand displacement amplification [SDA]), Gen-Probe (Amplified *Mycobacterium tuberculosis* Direct [AMTD], transcription mediated amplification [TMA]), Hain Lifescience (GenoType® Mycobacteria Direct, PCR) and Cepheid (Xpert MTB/RIF®, automated cartridge-based nested PCR).The COBAS® Taqman® MTB, AMTD, and Xpert MTB/RIF tests are approved for direct testing on sputum specimens.

In 2010, the WHO published a policy on a new NAAT – the Xpert MTB/RIF© test (Cepheid Inc, Sunnyvale, CA), a cartridge-based, automated, nested, real-time PCR test utilizing the GeneXpert© platform, which can detect MTBC for diagnosis and can detect RMP resistance, a marker of MDR-TB, in less than 2 hours with minimal hands-on technical time.[39,40] This assay was approved by Health Canada in 2012 as a laboratory-based technology.

Unlike conventional NAATs, the Xpert MTB/RIF test is completely automated and self-contained, and is not dependent on reference laboratories or a high degree of technical expertise.[41] Sample processing steps are minimized to less than 5 minutes of hands-on time, and the use of a sample preparation reagent effectively inactivates the specimen with more than an 8-log decrease in viability, posing virtually no biosafety risk.[42] Currently, Xpert MTB/RIF is the only fully automated, cartridge-based NAAT on the market and the only product in its class.[40]

A recently completed Cochrane systematic review on the accuracy of Xpert MTB/RIF identified 18 published studies.[43] The majority were performed in low/middle-income countries. In 17 of the 18 studies, Xpert was performed by trained technicians in reference laboratories. In the meta-analyses for MTBC detection, pooled median sensitivity and specificity estimates (95% confidence intervals) were as follows: overall (15 studies, 7,517 participants), pooled median sensitivity and specificity were 88% (83%, 92%) and 98% (97%, 99%) respectively; in direct comparisons (15 studies), pooled median sensitivity was 98% (97%, 99%) for smear-positive, culture-positive TB and 68% (59%, 75%) for smear-negative, culture-positive TB; in direct comparisons (four studies), pooled median sensitivity was 80% (67%, 88%) in people living with HIV and 89% (81%, 94%) in people without HIV infection. In the meta-analysis for RMP resistance detection (11 studies, 2,340 participants), pooled median sensitivity and specificity were 94% (87%, 97%) and 98% (97%, 99%) respectively. When used as an add-on test following smear microscopy (15 studies), Xpert yielded a 25% higher sensitivity over smear. Xpert could distinguish between MTBC and NTM in clinical samples with high accuracy (of 139 specimens with NTM, cross-reactivity was observed in only one specimen).[43]

Overall, the available evidence shows high accuracy for TB detection, but this evidence is mostly from high-burden countries and involves the use of spontaneous sputum samples. Similar data from low-incidence settings and with the use of induced sputum samples are lacking. The data, although limited, also suggest that Xpert MTB/RIF can significantly reduce the time to diagnosis and treatment.[44] The predictive value for RMP resistance will depend on the prevalence of drug-resistant TB in a given setting. In a low MDR-TB prevalence setting such as Canada, false-positive RMP results are a major concern. Thus, all Xpert results should be confirmed by conventional culture methods.

Because the Xpert technology is simple and can be implemented in peripheral laboratories, this test may be potentially useful in remote settings (for example, hospitals in northern regions of Canada serving Aboriginal populations) where there is currently limited on-site capacity for routine smear microscopy and cultures, and where smear and culture results may sometimes be delayed. In such settings, if the Xpert test is performed by trained laboratory technicians the results could be available within hours and used to inform rapid decisions on TB treatment and isolation pending routine smear and culture results. This could potentially help reduce diagnostic delays, especially in the context of the ongoing high rates of TB in Nunavut and Nunavik (Northern Quebec) (see Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples). **However, it is important to note that the use of Xpert in these settings should not replace conventional smears and cultures**. All Xpert MTB/RIF results should be confirmed by routine smears and cultures. In particular, all positive RMP resistance results should be interpreted cautiously, given the very low prevalence of MDR-TB in Canada[45] and the expected low positive predictive value of RMP resistance results from the Xpert MTB/RIF assay in this setting.[43] Because NAATs can amplify nonviable AFB, the Xpert result, as with any other NAAT, is not recommended for use in monitoring TB treatment response.[2]

RECOMMENDATIONS

- At least one respiratory sample should be tested with a Health Canada approved or validated in-house NAAT in all new, smear-positive cases. In addition, NAA testing may be performed in smear-negative patients upon request by the physician or the TB control program. NAAT results are not recommended for monitoring TB treatment response.

  (Conditional recommendation, based on moderate evidence)

- In settings where there is currently no on-site capacity for routine smear microscopy and culture (for example, hospitals in the North serving Aboriginal populations), an automated, cartridge-based NAA test can be used to make rapid decisions on TB treatment and isolation pending routine smear and culture results. All Xpert MTB/RIF results should be confirmed by routine smears and cultures. In particular, all positive RMP resistance results have to be interpreted cautiously, given the very low prevalence of MDR-TB in Canada and the low positive predictive value of RMP resistance results from the Xpert MTB/RIF assay in this setting. The Xpert result is not recommended for monitoring TB treatment response.

  (Conditional recommendation, based on moderate evidence)

Role of Immune-based Methods (Serology, TST and IGRAs)

For decades, researchers and the industry had pinned their hopes on serologic antibody-detection methods for point-of-care test development. Indeed, dozens of serologic rapid (lateral flow assays) and ELISA (enzyme-linked immunosorbent assay) tests were commercialized, even though no international guideline recommended their use.[46,47] Today, these tests are on the market in at least 17 of the 22 countries with the highest TB burden, and millions of patients in the private sector undergo serologic testing.[48,49] Unfortunately, TB serologic tests are neither accurate nor cost-effective,[47,50] prompting the WHO to issue a strong negative recommendation against their use.[51]

As described in Chapter 4 (Diagnosis of Latent Tuberculosis Infection), neither the TST nor IGRA can separate latent TB infection from active TB disease and therefore have no value for active TB detection in adults.[52] A recent WHO policy on IGRAs has discouraged their use for active TB diagnosis.[53] In children, TST and/or IGRAs are useful as an indicator of TB infection and can be used to support a diagnosis of TB disease, along with clinical data, radiologic and microbiological investigations (refer to Chapter 9, Pediatric Tuberculosis).

RECOMMENDATIONS

- The use of serologic, antibody-based TB tests is not recommended for TB diagnosis.
  (Strong recommendation, based on strong evidence)
- The use of TST or IGRA for the diagnosis of active TB in adults is not recommended.
  (Strong recommendation, based on strong evidence)

DIAGNOSIS OF DRUG RESISTANCE

The diagnosis of drug-resistant TB can be made using two approaches: 1) phenotypic and 2) genotypic (molecular) methods (although molecular methods should be used in conjunction with phenotypic testing).[2,5,6,31]

Phenotypic DST should be routinely performed for all first positive culture isolates obtained from each new TB case.[5,6] While the agar proportion method is considered the gold standard for DST, a broth method is the recommended standard of practice in North America for DST[6] (See Appendix D). Set-up of first-line DST should provide phenotypic results within 4 to 14 days for first-line drugs and 4 to 21 days for second-line drugs.[5,6]

Genotypic methods involve NAATs, which amplify and detect mutations that confer drug resistance. Two genotypic methods are endorsed by the WHO for rapid diagnosis of drug-resistant TB: 1) line-probe assays (LPAs) and 2) the Xpert MTB/RIF test. In addition, other validated in-house NAATs may be used, as described earlier.

In patients with a high pretest probability of MDR-TB, rapid molecular tests can help make quick decisions on appropriate second-line TB therapy, while conventional DST results are awaited.[54,55] In patients with a low pretest probability of MDR-TB, rapid molecular tests will have low positive predictive value and should be interpreted very cautiously.[43]

LPAs have been developed and evaluated to perform DST from smear-positive sputum samples directly or to perform rapid DST on culture isolates. Two LPA tests are commercially available: the Inno-LiPARif.TB line probe assay (Innogenetics, Belgium) and the GenoType MTBDR*plus* assay (Hain Lifescience, Germany). The GenoTypeMTBDR*plus* assay is approved by Health Canada. It is performed in reference level facilities with dedicated rooms for preparation and a containment level 2 (CL2) laboratory for processing sputum, or a containment level 3 (CL-3) laboratory if manipulation of MTBC culture is needed.

A meta-analysis showed that the GenoType MTBDR*plus* assay has a pooled sensitivity of 98.1% and specificity of 98.7%.[56] The accuracy for INH was variable, with lower and inconsistent sensitivity (84.3%) and high specificity (99.5%).[56] LPAs are endorsed by the WHO for rapid diagnosis of INH and RMP resistance from sputum smear-positive samples.[57] However, the use of LPAs does not eliminate the need for conventional culture and DST capability; culture is recommended for definitive diagnosis of TB in smear-negative patients, while conventional DST is recommended to diagnose extensively drug-resistant TB.[57]

As previously described, the Xpert MTB/RIF assay can rapidly diagnose RMP resistance in under 2 hours with a sensitivity of about 94% and a specificity of 98%.[43] However, these estimates are from high-burden settings. The predictive value for RMP resistance will depend on the prevalence of drug-resistant TB in a given setting. Thus, all positive RMP resistance results on the Xpert assay should be interpreted cautiously, given the very low prevalence of MDR-TB in Canada[45] and the expected low positive predictive value of RMP resistance results from the Xpert MTB/RIF assay in this setting.

RECOMMENDATIONS

- Phenotypic DST should be routinely performed for all first positive culture isolates obtained from each new TB case. While the agar proportion method is considered the gold standard for DST, a broth method is the recommended standard of practice in North America for DST.

  (Strong recommendation, based on moderate evidence)

- Rapid molecular tests for DST should be reserved for patients with a high pretest probability of MDR-TB. The use of these tests should not eliminate the need for conventional culture and DST, which are recommended to confirm initial results and also detect resistance to drugs other than RMP and INH.

  (Strong recommendation, based on moderate evidence)

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CHAPTER 4

DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

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KEY MESSAGES/POINTS

- The goal of testing for latent tuberculosis infection (LTBI) is to identify individuals who are at increased risk for the development of active tuberculosis (TB) and therefore would benefit from treatment of LTBI.
- Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.
- There are two accepted tests for identification of LTBI: the tuberculin skin test (TST) and the interferon gamma release assay (IGRA).
- When interpreting a positive TST, it is important to consider much more than simply the size of the reaction. Rather, the TST should be considered according to three dimensions: size of induration, positive predictive value and risk of disease if the person is truly infected.
- As with the TST, IGRAs are surrogate markers of *Mycobacterium tuberculosis* infection and indicate a cellular immune response to *M. tuberculosis*.
- In general, IGRAs are more specific than the TST in populations vaccinated with Bacille Calmette-Guérin (BCG), especially if BCG is given after infancy or multiple times.
- Neither the TST nor IGRAs can separate LTBI from TB disease and therefore have no value for active TB detection. Both tests have suboptimal sensitivity in active TB, especially in HIV-infected people and children.
- Both tests appear to correlate well with the gradient of exposure. Both tests are associated with nonspecific variations and reproducibility issues, and borderline values need careful interpretation.
- Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs might reduce the number of people considered for preventive treatment.

MAJOR RECOMMENDATIONS

Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated, with preferences and exceptions noted below.

1. **Situations in which neither TST nor IGRAs should be used for testing**

    - Neither the TST nor the IGRA should be used for testing people who have a low risk of infection and a low risk that there will be progression to active TB disease if they are infected. However, low-risk individuals are commonly tested before exposure, when repeat testing is likely. In this situation TST is recommended (see recommendation 3 below); if the TST is positive then an IGRA may be useful to confirm a positive TST result to enhance specificity.
    - Neither TST nor IGRA should be used for active TB diagnosis in adults (for children, see recommendation 4).
    - Neither TST nor IGRA should be used for routine or mass screening for LTBI of all immigrants (adults and children).
    - Neither TST nor IGRA should be used for monitoring anti-TB treatment response.

2. **Situations in which IGRAs are preferred for testing but a TST is acceptable**

    - People who have received BCG as a vaccine after infancy (1 year of age) and/or have received BCG vaccination more than once.
    - People from groups that historically have poor rates of return for TST reading.

3. **Situations in which TST is recommended for testing but an IGRA is NOT acceptable**

    - The TST is recommended whenever it is planned to repeat the test later to assess risk of new infection (i.e. conversions), such as repeat testing in a contact investigation or serial testing of health care or other populations (e.g. corrections staff or prison inmates) with potential for ongoing exposure.

4. **Situations in which both tests can be used (sequentially, in any order) to enhance sensitivity**

    Although routine dual testing with both TST and IGRA is not recommended, there are situations in which results from both tests may be helpful to enhance the overall sensitivity:

    - When the risks of infection, of progression to disease and of a poor outcome are high.
    - In children (under age 18 years) with suspected TB disease, IGRAs may be used as a supplementary diagnostic aid in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute for, or obviate the need for, appropriate specimen collection. A negative IGRA (or TST) does not rule out active TB at any age and especially not in young children.
    - In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline or invalid, and a reason for testing persists.

INTRODUCTION: DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

While diagnosis and treatment of individuals with active TB is the first priority for TB control, an important second priority is identification and treatment of individuals with LTBI. In most individuals, *M. tuberculosis* infection is contained initially by host defences, and infection remains latent. However, latent infection can develop into active disease at any time. Identification and treatment of LTBI can substantially reduce the risk of development of disease (see Chapter 6, Treatment of Latent Tuberculosis Infection) and so have the potential to protect the health of the individual as well as the public by reducing the number of possible sources of future transmission.

There are two tests for identification of LTBI: the TST and the IGRA. Both tests evaluate cell-mediated immunity, and neither test can distinguish between LTBI and active TB disease.[1] The TST consists of the intradermal injection of a small amount of purified protein derivative (PPD) from *M. tuberculosis* bacteria. In a person who has cell-mediated immunity to these tuberculin antigens, a delayed hypersensitivity reaction will occur within 48 to 72 hours. The reaction will cause localized swelling and will be manifest as induration of the skin at the injection site.[2]

IGRAs are *in vitro* blood tests of cell-mediated immune response; they measure T cell release of interferon gamma (IFN-gamma) following stimulation by antigens specific to *M. tuberculosis*.[1,3] Previous Advisory Committee Statements (ACSs) have provided guidance on the use of IGRAs in Canada.[4-6] This chapter supersedes these statements and serves as the updated guideline on the use of both IGRAs and TST in Canada.

INDICATIONS FOR LTBI TESTING AND GOAL OF TESTING

The goal of testing for LTBI is to identify individuals who are at increased risk for the development of active TB and therefore would benefit from treatment of latent TB infection (formerly termed preventive therapy or prophylaxis). Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive. This means that screening for LTBI in people or groups who are healthy and at low risk of active disease development is discouraged, since the positive predictive value of TST or IGRA is low and the risks of treatment will often outweigh the potential benefits. Moreover, screening for LTBI should be undertaken only when there is an *a priori* commitment to treatment or monitoring should test results be positive.[7]

In general, testing for LTBI is indicated when the risk of development of disease, if the patient is infected, is increased. The specific populations targeted for LTBI testing and the risk categories are described in Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, and Chapter 6, Treatment of Latent Tuberculosis Infection.

TUBERCULIN SKIN TESTING

The only internationally recommended method of tuberculin skin testing is the Mantoux technique, which consists of intradermal injection of tuberculin material into the inner surface of the forearm. It has been adapted and reproduced,[2,7] as described below.

ADMINISTRATION

Handling the tuberculin solution

- Tubersol® 5 tuberculin units (5-TU) of PPD-S (purified protein derivative – standard) is recommended in Canada. Use of one tuberculin unit (1-TU) is not recommended as it leads to too many false-negative reactions. Use of 250-TU is not recommended as this is associated with a very high rate of false-positive reactions.[8]
- Store at 2° to 8° C, but do not freeze. Discard the solution if frozen.
- Remove the tuberculin solution from the vial under aseptic conditions. A little more than 0.1 mL of PPD solution should be drawn into the TB syringe. Hold the syringe upright and lightly tap out the air, then expel one drop. Check that a full 0.1 mL remains in the syringe.
- Do not transfer the solution from one container to another (the potency of the PPD may be diminished).
- Draw up the solution just before injecting it. Do not preload syringes for later use as the potency of the PPD may be diminished.
- The solution can be adversely affected by exposure to light. PPD should be stored in the dark except when doses are actually being withdrawn from the vial.
- Discard the solution if the vial has been in use for longer than 1 month or for an undetermined amount of time (the potency of the solution may be diminished).
- Use the solution within 1 month after opening. Label each bottle with the discard date when it is opened.

Preparing the person to be tested

- Seat the person comfortably, and explain the procedure.
- Use the inner aspect of the forearm, preferably the nondominant arm (where administration and reading of the reaction is easiest), about 10 cm (4 inches) below the elbow; avoid areas with abrasions, swelling, visible veins or lesions. If there is a localized rash, a burn or localized eczema, avoid this area.
- If neither forearm is suitable, use the outside of the forearm or the upper arm. In this case mark the location clearly in the record.
- Cleanse the area to be injected with an alcohol swab and let it dry.
- Do not use EMLA® cream (or similar local anesthetic cream), as application of this cream has been reported to cause localized edema, which could easily be confused with a positive TST result.[7]

Injecting the PPD tuberculin solution

- Use a 0.6 to 1.3 cm (¼ to ½ inch), 26- or 27-gauge needle with a disposable plastic tuberculin syringe.
- Position the bevel of the needle so that it opens facing up.
- While holding the skin of the inner aspect of the forearm taut, insert the needle at a 5°-15° angle to the skin without aspirating. The tip of the needle will be visible just below the surface of the skin. The needle is inserted until the entire bevel is covered (see Figure 1).
- Administer the PPD by the slow intradermal injection of 0.1 mL of 5-TU.
- A discrete, pale elevation of the skin (a wheal) 6-10 mm in diameter should appear. The wheal will typically disappear in 10-15 minutes. The size of the wheal is not completely reliable, but if a lot of liquid runs out at the time of injection and there is no wheal, then repeat the injection on the opposite forearm, or on the same forearm as before, but at least 5 cm from the previous injection site.
- A drop of blood may be seen – this is normal. The person tested should be offered gauze to remove the blood but should be advised not to massage the site in order to avoid squeezing out the PPD and disrupting the test.
- Do not cover the site with a bandage.
- Tell the patient that he or she should not scratch the site but may perform all normal activities, including showering or bathing.
- Place uncapped disposable needles and syringes in appropriate puncture-resistant containers immediately after use.
- If the TST is accidentally given as a subcutaneous or an intramuscular injection, this should not pose a serious problem. It is possible that tuberculin-sensitive people would have localized inflammation, which should be self-limited. It would not be possible to take a measurement of or clinically interpret any such reaction, so the TST should be administered again *but using proper intradermal technique* on the volar surface of the forearm. This should be done immediately (as soon as it is realized that the injection was too deep).

Figure 1. Technique of administration of TST

Record the following:

- date of injection;
- dose of PPD (5 TU, 0.1 mL);
- PPD manufacturer;
- PPD lot number;
- expiration date of the PPD reagent;
- site of injection;
- person administering the TST.

PRECAUTIONS

- Acute allergic reactions, including anaphylaxis, angioedema, urticaria and/or dyspnea, have been very rarely reported following skin testing with Tubersol®, see "Risk of Serious Allergic Reactions Following Tubersol® [Tuberculin Purified Protein Derivative (Mantoux)] Administration" (available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14373a-eng.php).
- These reactions may occur in people without a history of a TST.
- Epinephrine hydrochloride solution (1:1000) and other appropriate agents should be routinely available for immediate use in case an anaphylactic or other acute hypersensitivity reaction occurs. Health care providers should be familiar with the current recommendations of the National Advisory Committee on Immunization on monitoring the patient for immediate reactions over a period of at least 15 minutes after inoculation and for the initial management of anaphylaxis in non-hospital settings (http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-03-eng.php).

The following people should not receive a TST:

- Those with positive, severe blistering TST reactions in the past or with extensive burns or eczema present over TST testing sites, because of the greater likelihood of adverse reactions or severe reactions.
- Those with documented active TB or a well-documented history of adequate treatment for TB infection or disease in the past. In such patients, the test is of no clinical utility.
- Those with current major viral infections (e.g. measles, mumps, varicella).
- Those who have received measles or other live virus immunization within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results. Note that only measles vaccination has been shown to cause false-negative TST results, but it would seem prudent to follow the same 4-week guideline for other live virus immunizations – mumps, rubella, varicella (chickenpox) and yellow fever. However, if the opportunity to perform the TST might be missed, the TST should not be delayed for live virus vaccines since these are theoretical considerations. (NOTE that a TST may be administered before or even on the same day as the immunizations but at a different site.)

The following people can receive a TST:

- Those with a history of receiving BCG vaccination(s);
- Those with a common cold;
- Those who are pregnant or are breastfeeding;
- Those immunized with any vaccine on the same day;
- Those immunized within the previous 4 weeks with vaccines other than the ones listed earlier;
- Those who give a history of a positive TST reaction (other than blistering) that is not documented;
- Those taking low doses of systemic corticosteroids, <15 mg prednisone (or equivalent) daily. It generally takes a steroid dose equivalent to ≥15 mg prednisone daily for 2-4 weeks to suppress tuberculin reactivity.[9,10]

MEASURING INDURATION

- The TST should be read by a trained health professional. Individuals without experience in reading a TST may not feel slight induration, and the TST would be mistakenly recorded as 0 mm.
- Self-reading is very inaccurate and is strongly discouraged.[11]
- Reading should be performed 48 to 72 hours after administration, as maximum induration can take up to 48 hours to develop, but after 72 hours it is difficult to interpret a reaction. Reactions may persist for up to 1 week, but for as many as 21% of individuals with a positive reaction at 48 to 72 hours the reaction will be negative after 1 week.[12] If the TST cannot be read within 72 hours because of unforeseen circumstances, it should be repeated at an

injection site far enough from that of the previous test that the reactions do not overlap. No minimum wait is required before the repeat test.

- The forearm should be supported on a firm surface and slightly flexed at the elbow. Induration is not always visible. Palpate with fingertips to check whether induration is present. If there is induration, mark the border of induration by moving the tip of a pen at a 45° angle laterally toward the site of the injection (Figure 2). The tip will stop at the edge of the induration, if present. Repeat the process on the opposite side of the induration. This pen method has the advantages of being as reliable as the traditional palpation method (which relies entirely on fingertips) among experienced readers and of being easier for new readers to learn and use.
- Using a caliper, measure the distance between the pen marks, which reflects the diameter of the induration at its widest transverse diameter (at a right angle to the long axis of the forearm). A caliper is recommended because readings will be more precise and, most important, if the reader has to set the caliper and then read the diameter the rounding error is reduced. If a caliper cannot be found a flexible ruler could be used.
- Disregard and do not record erythema (redness). Approximately 2%-3% of people tested will have localized redness or rash (without induration) that occurs within the first 12 hours. These are minor allergic reactions, are not serious and do not indicate TB infection. They are not a contraindication to future TSTs.[13]
- Blistering, which can occur in 3% to 4% of subjects with positive tests, should be recorded.
- Record the result in millimetres (mm). Record no induration as “0 mm.” Recordings of positive, negative, doubtful, significant and non-significant are not recommended.
- Do not round off the diameter of the induration to the nearest 5 mm. as this can interfere with determining whether TST conversion has occurred in the event of a future TST. If the measurement falls between demarcations on the rules, the smaller of the two numbers should be recorded.

Figure 2. Ball-point method for reading transverse diameter of TST induration

Record the following:

- dates the induration was read;
- measurement of the induration, if any, in millimetres (mm);
- any adverse reactions, e.g. blistering;
- name of the individual reading the test.

Provide a record of the TST result to the individual tested.

INTERPRETATION OF A NEGATIVE TST RESULT

False-negative reactions

False-negative reactions can be caused by technical or biologic reasons (see Table 1 on next page).

Table 1. Potential causes of false-negative tuberculin tests[2,14-16]

Technical (potentially correctable)
Tuberculin material: - Improper storage (exposure to light or heat) - Contamination, improper dilution, or chemical denaturation **Administration:** - Injection of too little tuberculin or injection made too deeply (should be intradermal) - Administration more than 20 minutes after drawing up into the syringe **Reading:** - Inexperienced or biased reader - Error in recording
Biologic (not correctable)
Infections: - Active TB (especially if advanced) - Other bacterial infection (typhoid fever, brucellosis, typhus, leprosy, pertussis) - HIV infection (especially if CD4 count <200) - Other viral infection (measles, mumps, varicella) - Fungal infection (South American blastomycosis) **Live virus vaccination: measles, mumps, polio** **Immunosuppressive drugs:** **corticosteroids, tumour necrosis factor (TNF) inhibitors, and others** **Metabolic disease:** **chronic renal failure, severe malnutrition, stress (surgery, burns)** **Diseases of lymphoid organs:** **lymphoma, chronic lymphocytic leukemia, sarcoidosis** **Age: infants <6 months, the elderly**

MANAGEMENT OF A POSITIVE TST RESULT

Management of a positive TST should occur in two distinct steps:

STEP 1 – Deciding that a TST is positive

The health professional reading the TST should decide whether the test is positive. This is based on the size, using the criteria listed in Table 2. Once a TST is considered positive, the individual should be referred for medical evaluation. There is no clinical utility in performing a TST in the future once a test is considered positive, as long as the TST was properly performed and read.[2,7]

STEP 2 – Medical evaluation

This should include assessment of symptoms suggestive of possible active TB, risk factors for TB, such as contact history or other medical illnesses, as well as chest radiography. In the presence of symptoms or abnormal chest x-ray, sputum for acid-fast bacteria smear and culture should be taken. In subjects without evidence of active TB, a recommendation should be made regarding therapy for LTBI, based on interpretation of the TST.[2,7]

INTERPRETATION OF A POSITIVE TST

When interpreting a positive TST, it is important to consider much more than simply the size of the reaction. Rather, the TST should be considered according to three dimensions:[17]

1. size of induration;
2. positive predictive value; and
3. risk of disease if the person is truly infected.

A web-based interactive algorithm,[17] The Online TST/IGRA Interpreter (Version 3.0), which incorporates all three dimensions, is available (http://www.tstin3d.com) to assist in TST and IGRA interpretation (Figure 3).

FIRST DIMENSION – Size of induration

This dimension (Table 2) is the easiest to understand (but the least important).[17] A criterion of 5 mm for a diagnosis of LTBI has a sensitivity of >98%, but the specificity is lower. This criterion is used when maximum sensitivity is desirable because the risk of development of active disease is high. A criterion of 10 mm has a sensitivity of 90% and specificity of >95%, and is recommended for most clinical situations. A criterion of 15 mm or more has sensitivity of only 60%-70% but has high specificity (>95%) in most parts of the world. However, this criterion is not appropriate for use in Canada, because specificity is not much higher than with 10+ mm, yet the sensitivity is reduced considerably.[2,7]

Figure 3. Screenshot of the Online TST/IGRA Interpreter (Version 3.0)

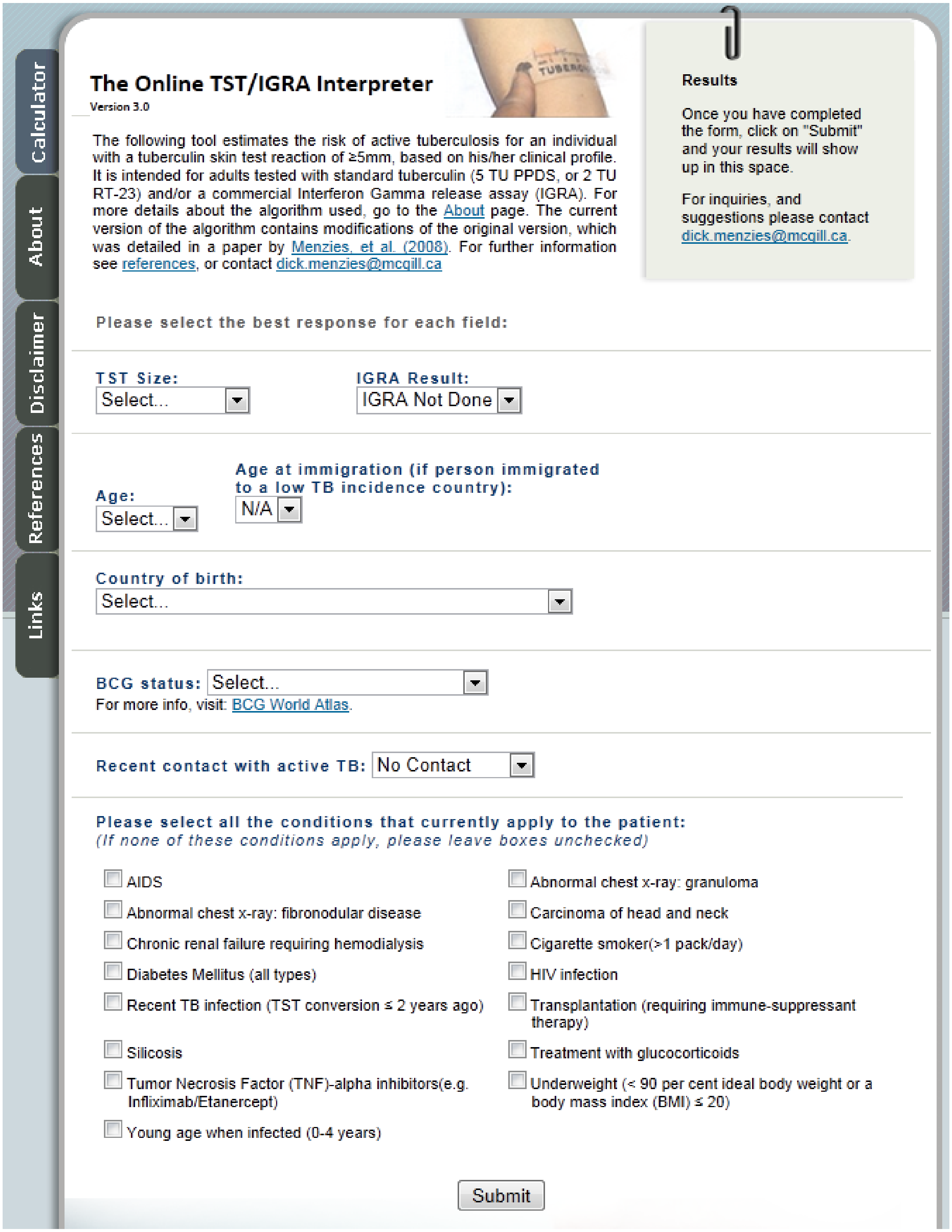


Table 2. Interpretation of tuberculin skin test results and cut-points in various risk groups[2,7]

TST result	Situation in which reaction is considered positive*
0-4 mm	In general this is considered negative, and no treatment is indicated.
	Child under 5 years of age and high risk of TB infection
≥5 mm	HIV infection
	Contact with infectious TB case within the past 2 years
	Presence of fibronodular disease on chest x-ray (healed TB, and not previously treated)
	Organ transplantation (related to immune suppressant therapy)
	TNF alpha inhibitors
	Other immunosuppressive drugs, e.g. corticosteroids (equivalent of ≥15 mg/day of prednisone for 1 month or more; risk of TB disease increases with higher dose and longer duration)
	End-stage renal disease
≥10 mm	All others, including the following specific situations: - TST conversion (within 2 years) - Diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day) - Silicosis - Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g. head and neck)

*The goal of testing for LTB is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of LTB. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive (see text).

SECOND DIMENSION – Positive predictive value

The positive predictive value of the TST is the probability that a positive test result represents the true presence of TB infection. This differs from the TST sensitivity, which reflects the probability of a positive TST result in the presence of known TB infection. Positive predictive value is primarily influenced by the pretest probability or prevalence of TB infection, as well as the specificity of the TST. Thus, the positive predictive value is low and the utility of the TST is limited in populations at low risk of TB infection, those with previous exposure to nontuberculous mycobacteria (NTM) or those with a previous BCG vaccination, each of which can reduce the specificity of the TST.[18]

NTM: In parts of the world with tropical, subtropical or warm, temperate climates NTM are frequently found in soil and water, and most adults will have evidence of exposure and sensitization to some NTM antigens. Because the antigens of NTM are similar to those of *M. tuberculosis*, in people who are sensitized to NTM antigens there will be cross-reactivity with PPD-S, causing small tuberculin reactions, most of 5-9 mm and some of 10-14 mm, although almost none of 15+ mm. In most of Canada, sensitivity to NTM antigens is uncommon and is not an important cause of TST reactions of 10 mm or greater.[19] A study in Quebec demonstrated that less than 5% of all reactions of 10 mm or greater to standard PPD were due to this cross-reactivity.[20,21] This is why, in Canada, 10 mm remains the standard cut-point to determine whether TB infection is present.[7]

BCG vaccination: Several population groups in Canada are likely to have received BCG vaccination. These include immigrants from many European countries and most developing countries.[22] In Canada, many Aboriginal Canadians have been vaccinated, as have people born in Quebec and Newfoundland and Labrador between the 1940s and the 1970s (see the Public Health Agency of Canada's website for a summary of the provincial and territorial usage of BCG vaccine over time: http://www.phac-aspc.gc.ca/tbpc-latb/bcgvac_1206-eng.php).

Studies conducted in Canada and several other countries show that if BCG was received in infancy (the first year of life) only 1% had a TST result of ≥10 mm if tested >10 years later.[18] Therefore, a history of BCG vaccination received in infancy can be ignored in all people aged 10 years and older when interpreting an initial TST reaction of 10 mm or greater.[18,23-26]

If the BCG vaccination was received after 12 months of age, 42% had a false-positive TST of ≥10 mm after 10 years. If the vaccine was received between the ages of 1 and 5 years, persistently positive TST reactions were seen in 10%-15% of subjects up to 25 years later.[26] Of subjects vaccinated at the age of 6 years or older, up to 40% had persistent positive reactions. BCG-related reactions may be as large as 25 mm or even greater.[27,28] Therefore, if BCG vaccination was received after 12 months of age, it can be an important cause of false-positive TST reactions, particularly in populations whose expected prevalence of latent TB infection (i.e. true positive reactions) is less than 10%.

In summary, BCG vaccination can be ignored as a cause of a positive TST under the following circumstances:[2,7]

- BCG vaccination was given in infancy, and the person tested is now aged 10 years or older;
- there is a high probability of TB infection: close contacts of an infectious TB case, Aboriginal Canadians from a high-risk community or immigrants/visitors from a country with high TB incidence;
- there is high risk of progression from TB infection to disease.

BCG should be considered the likely cause of a positive TST under the following circumstances:[2,7]

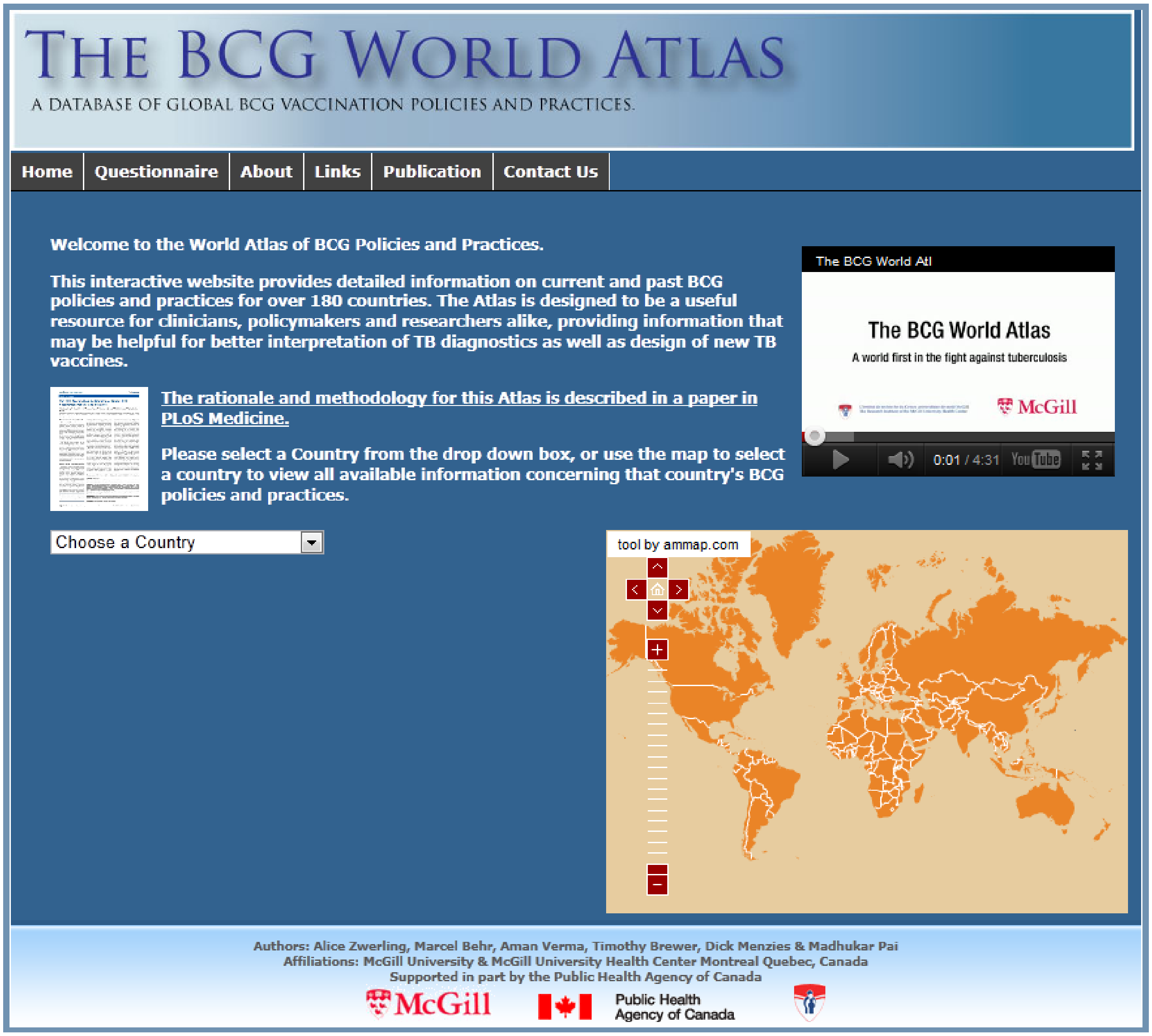
- BCG vaccine was given after 12 months of age AND
  - There has been no known exposure to active TB disease or other risk factors AND
    - the person is either Canadian-born non-Aboriginal OR
    - an immigrant/visitor from a country with low TB incidence.

International TB incidence rates are available at: http://www.phac-aspc.gc.ca/tbpc-latb/itir-eng.php.

“Recognition of BCG (versus smallpox) scars” offers some tips on identifying BCG scars and may be viewed at: http://www.phac-aspc.gc.ca/tbpc-latb/pdf/recognition-bcg-scars_e.ppt

BCG vaccination policies in different countries can be found in the *BCG World Atlas*[22] at http://www.bcgatlas.org (Figure 4).

Figure 4. Screenshot of the *BCG World Atlas*



THIRD DIMENSION – Risk of development of active TB disease

After primary TB infection, the lifetime cumulative risk for the development of active TB is generally estimated to be 10%. Half of these cases will occur in the first 2 years after infection. Certain factors increase the risk of TB reactivation because of diminished local or systemic immunity, as summarized in Chapter 6, Treatment of Latent Tuberculosis Infection.

Many medical illnesses and therapies can increase the risk of reactivation, but the strongest risk factor is HIV infection.[2,7] The other problems have in common a reduction or suppression of immune function and include diabetes, renal failure, malnutrition, certain cancers, alcohol overuse and cigarette smoking. Medical therapies that suppress immune function, described in Chapter 6, are increasingly important indications for LTBI treatment.

Example of three-dimensional interpretation

As an example, consider a young woman aged 20, referred because of apical fibronodular scarring as observed on her chest x-ray. This is unchanged from previous chest radiographic results obtained 6 months earlier. She was vaccinated with BCG as an infant, recently (a year ago) immigrated to Canada from the Philippines, a country with high TB incidence, and is asymptomatic. The TST reaction is measured as 8 mm. Using the Online TST/IGRA Interpreter (www.tstin3d.com) algorithm, her annual risk of development of active tuberculosis disease is estimated to be about 1%, and the likelihood that this is a true positive test (PPV) is estimated as 77%. After consideration of the likelihood of a true- versus false-positive TST result and the risk of disease development, the prescription of isoniazid (INH) may or may not be indicated, depending on the balance between the risk of disease and the risks of therapy (see Chapter 6, Treatment of Latent Tuberculosis Infection).

INTERPRETATION WHEN SERIAL (REPEATED) TST IS PERFORMED

Nonspecific variation

Because of differences in the technique of administering or reading the TST or because of biologic differences in response, there may be differences in the same individual from test to test of as much as 5 mm in reaction size. Therefore, 6 mm has been selected as the criterion to distinguish a real increase from nonspecific variation.[29]

Conversion

The most helpful guide in distinguishing conversion from the booster effect described in the next section is the clinical situation. If there has been recent exposure, such as close contact with an active case or occupational TB exposure, then conversion will be more likely than when there has been no exposure. Conversion is defined as a TST of 10 mm or greater when an earlier test resulted in a reaction of less than 5 mm. If the earlier result was between 5 and 9 mm, the definition of conversion is more controversial.

There are at least two criteria in use, although neither have strong supportive evidence:

1. An increase of 6 mm or more – this is a more sensitive criterion, which is suggested for those who are immune compromised with increased risk of disease or for an outbreak;
2. An increase of 10 mm or more – this is a less sensitive but more specific criterion.
   In general, the larger the increase, the more likely that it is due to true conversion.[29]

All available experimental and epidemiologic evidence consistently shows that TST conversion occurs within 8 weeks of exposure.[29] Therefore, adopting 8 weeks as the maximum interval for conversion following exposure allows newly infected contacts to be identified a month sooner. It is also more practical for casual contacts who can be tested once only after 8 weeks, and it results in fewer problems of interpretation because of the booster effect.

Two-step TST and the booster effect

A single TST may elicit little response yet stimulate an anamnestic immune response, so that a second TST at any time from 1 week to 1 year later will elicit a much greater response.[29] This phenomenon is important to detect, as it could be confused with TST conversion. The booster effect was first described in older people in whom it was felt to show LTBI acquired many years before (remotely) with subsequent waning of immunity.[30] It has also been described in people with prior BCG vaccination or sensitivity to nontuberculous mycobacterial antigens.[21,31,32]

Indications for 2-step tuberculin testing

A two-step TST should be performed if subsequent TSTs will be conducted at regular intervals or after exposure to an infectious TB case, for instance among health care or correctional service workers.[29] This is to reduce the chance of a false-positive TST conversion when the TST is repeated. One controversial area is whether travellers should be given two-step TST before and/or after travel to a region with high TB incidence. Please refer to Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, for recommendations.

The two-step protocol needs to be performed ONCE only if properly performed and documented. It never needs to be repeated. Any subsequent TST can be one step, regardless of how long it has been since the last TST.[2,7]

Repeat TST in a contact investigation: In a contact investigation, a single TST should be performed as soon as possible after the diagnosis has been made in the source case and the contact is identified. If this first TST is negative and it was performed less than 8 weeks after contact with the source case was broken, then a second TST should be performed no sooner than 8 weeks after the contact was broken. This is done to detect very recent infection that occurred just before contact was broken, since it will take anywhere from 3 to 8 weeks for the TST to become positive after new infection.[2,7]

Technique[2,7,29]

The same material and techniques of administration and reading should be used. The second test should be performed 1 to 4 weeks later. Less than 1 week does not allow enough time to elicit the phenomenon, more than 4 weeks allows the possibility of a true TST conversion to occur. Both tests should be read and recorded at 48 to 72 hours. In some centres, to reduce the total number of visits required to three, the first TST is read at 1 week, so that people with a negative TST can have a second TST immediately. However, reading performed at 1 week is less accurate and is not recommended.

Interpretation

The only two longitudinal studies of the risk of TB following a booster reaction defined the reaction simply as a second TST result of 10 mm or more induration.[16,33] Therefore, it is recommended that a second TST result of 10 mm or more should be considered significant and the patient referred for medical evaluation and chest radiography.

In the elderly, a significant booster effect most likely represents remotely acquired LTBI. In longitudinal studies, subjects with a second TST response of 10 mm or more had a risk of TB that was approximately half that of subjects in whom the first TST response was 10 mm or more.[33] Therefore, it is recommended that individuals with a reaction of 10+ mm on a second TST should be considered to have a risk of TB disease that is intermediate between individuals with initial positive and individuals with initial negative TST results from the same population group.

Management

All subjects with a reaction of 10+ mm on the second TST of a two-step TST do not need a TST in the future. There is no clinical utility.[2,7] They should be referred for medical evaluation, as performed for those with a positive first TST. Since the risk of TB is about half that of patients whose initial TST result is positive, the decision to give INH should be individualized.

A common question is how to manage a person in whom first TST measured 5-9 mm and the second test measured 10+ mm but increased by less than 6 mm from the first test. This should be managed as a positive TST, meaning referral for medical evaluation and no further TSTs. While appropriate epidemiologic data are lacking, it seems reasonable to suggest that the risk of active TB development would be lower than in people whose second TST increased by at least 6 mm. The decision to give INH should be individualized.

INTERFERON GAMMA RELEASE ASSAYS (IGRAS)

The development of IGRAs is a new advance in the diagnosis of LTBI. IGRAs are *in-vitro* blood tests of cell-mediated immune response; they measure T cell release of interferon gamma (IFN-gamma) following stimulation by antigens specific to *Mycobacterium tuberculosis* – early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These antigens are encoded by genes located within the region of difference 1 (RD1) segment of the *M. tuberculosis* genome.[1] They are more specific for *M. tuberculosis* than PPD because they are not shared with any BCG vaccine strains or most species of nontuberculous mycobacteria other than *M. marinum*, *M. kansasii*, *M. szulgai* and *M. flavescens*.[1]

TYPES OF ASSAYS

Two IGRAs are available in many countries: the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom). Both tests are approved by Health Canada and the United States Food and Drug Administration (FDA).

The QFT-GIT assay is an ELISA (enzyme-linked immunosorbent assay)-based, whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10 and TB7.7) in an in-tube format. The result is reported as quantification of IFN-gamma in international units (IU) per millilitre. An individual is considered positive for *M. tuberculosis* infection if the IFN-gamma response to TB antigens is above the test cut-off (after subtracting the background IFN-gamma response in the negative control, see Appendix D, Tuberculosis and Mycobacteriology Laboratory Standards: Services and Policies).

The T-SPOT.TB is an enzyme-linked immunospot (ELISPOT) assay performed on separated and counted peripheral blood mononuclear cells; it uses ESAT-6 and CFP-10 peptides. The result is reported as number of IFN-gamma producing T cells (spot-forming cells). An individual is considered positive for *M. tuberculosis* infection if the spot counts in the TB antigen wells exceed a specific threshold relative to the control wells (see Appendix D).

IGRAs require laboratories with adequate equipment and trained personnel to perform the assays. In addition, IGRAs require fresh blood samples: pre-analytical steps and transportation delays can affect test performance.[34] Blood specimens for the QFT assay should be collected and shaken as per the manufacturer's instructions. They should be placed in an incubator as soon as possible and within 16 hours of blood collection. For the standard T-SPOT.TB assay, blood should be processed within 8 hours of collection. However, if the T-Cell Xtend® reagent is used, whole blood can be stored overnight prior to processing in the T-SPOT.TB assay.[35] Test kits should be transported and stored in optimum conditions to prevent exposure to excessive heat. Strict quality assurance is necessary to detect unusual patterns in results (such as a spike in the number of indeterminate results due to low mitogen response or high negative control responses), and it is important to run both positive and negative controls with each assay. The appendix on TB laboratory standards provides technical information on how to perform and interpret IGRA results, and how to achieve high quality.

In the recommendations that follow, both commercial IGRAs (QFT and T-SPOT.TB) are treated as acceptable alternatives, acknowledging that these assays differ in terms of laboratory expertise required, cost, pre-analytical steps and ease of use (see Appendix D). The decision regarding which commercial IGRA to offer is left to the discretion of provincial, commercial and hospital laboratories in Canada.

SENSITIVITY AND SPECIFICITY OF IGRAs

When measured using active TB as a surrogate reference standard, IGRAs have a specificity of >95% in the diagnosis of LTBI, and specificity is not affected by BCG vaccination.[36,37] The sensitivity for T-SPOT.TB appears to be higher than for QFT-GIT or TST (approximately 90%, 80% and 80% respectively).[37] TST specificity is high in populations not vaccinated with BCG (97%). In populations administered BCG it is much lower, although variable (approximately 60%).[37]

Because IGRAs are not affected by BCG vaccination status, they are useful for evaluating LTBI in BCG-vaccinated individuals, particularly in settings in which BCG vaccination is administered after infancy or when multiple (booster) BCG vaccinations are given. In contrast, as discussed previously, the specificity of TST varies depending on the timing of BCG and whether repeated (booster) vaccinations are given.[18]

Further, although the finding is based on limited evidence, IGRAs appear to be unaffected by most infections with nontuberculous mycobacteria, which can cause false-positive TSTs. However, two nontuberculous mycobacteria that affect humans, *Mycobacterium marinum* and *Mycobacterium kansasii*, contain gene sequences that encode for ESAT-6 or CFP-10, antigens used in the new IGRAs. Infection with either of these NTMs has been shown to produce positive results in IGRAs using these antigens, as with the TST.[38,39]

IGRA sensitivity is diminished by HIV infection.[40,41] Lower CD4 counts have been associated with higher rates of indeterminate IGRA results; this is especially the case with QFT-GIT.[40,41] T-SPOT.TB appeared to be less affected by immunosuppression than QFT-GIT, likely because the testing procedure requires that an adequate number of peripheral blood mononuclear cells are placed in each test well, even if the overall peripheral blood lymphocyte count is low. An "indeterminate result" implies that the test cannot produce a valid result; often this is because of immune suppression, which leads to lack of T-cell response to the positive control. The likelihood of indeterminate results increases as CD4 count levels decrease in HIV-infected individuals. An indeterminate IGRA result should be repeated to make sure there are no technical or laboratory flaws. If the repeat result is also indeterminate, then the clinician cannot rely on IGRA for clinical decision-making. Other tests, risk factors and clinical information will be informative.[42]

EVIDENCE BASE ON IGRA PERFORMANCE IN VARIOUS SUBGROUPS

A large number of studies have evaluated IGRAs, and these have been summarized in several systematic reviews and guidelines (See Table 3 on next page). As with the TST, IGRAs are surrogate markers of *M. tuberculosis* infection and indicate a cellular immune response to *M. tuberculosis*. IGRAs (like the TST) cannot distinguish between latent infection and active TB disease.

Table 3. Key findings of recent systematic reviews of IGRAs

Subgroup or focus of the review	Key findings	Reference
Active TB (pulmonary as well as extrapulmonary TB)	IGRAs have limited accuracy in diagnosing active TB. Their sensitivity is not high enough to rule out TB disease, and since they do not distinguish active from latent TB, specificity for active TB is low and cannot be used as a "rule in" test.	43,44
Children	TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children. Both tests have similar correlations with exposure gradient in children. However, the ability of either TST or IGRAs was suboptimal to "rule in" or "rule out" active TB.	45,46
HIV-infected people	Current evidence suggests that IGRAs perform similarly to the TST in identifying HIV-infected individuals with LTBI. Both tests have modest predictive value and suboptimal sensitivity. Although T-SPOT appeared to be less affected by immunosuppression than QFT-GIT and the TST, overall, differences among the three tests were small or inconclusive.	40,41,47
Immune-mediated inflammatory diseases (IMID)	Current evidence does not clearly suggest that IGRAs are better than TST in identifying individuals with IMID who could benefit from LTBI treatment. To date, no studies have been done on the predictive value of IGRAs in IMID patients. Among patients receiving biologic therapy, in regions of moderate or high TB prevalence, or in patients with TB risk factors there is some evidence that a dual testing strategy of TST and IGRA improves sensitivity.	48-50
Health care workers (HCWs)	The use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in settings of low TB incidence. However, when the manufacturer's cut-offs are used, IGRAs had high rates of conversions (2%-5%), which were frequently much higher than the rates of TST conversions and higher than the annual risk of TB infection expected in these low-incidence settings. IGRAs also had high rates of spontaneous reversions, which ranged from about 20%-40% in most studies.	51,52
Predictive value for progression to active TB disease	Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment.	53
Reproducibility, within-person variation of IGRA results, and boosting effect of TST on IGRA results	Although the finding was based on limited data, within-subject variability was present in all studies, but the magnitude varied (16%-80%) across studies. A TST-induced ''boosting'' of IGRA responses was demonstrated in several studies and although more pronounced in IGRA-positive (i.e. sensitized) individuals it also occurred in a smaller but not insignificant proportion of IGRA-negative subjects.	54
Use of IGRAs for monitoring response to anti-TB therapy	Monitoring changes in IGRA response during anti-TB treatment has no utility in adults. Data in children are limited but are in line with results reported in adults.	55

IGRAS FOR ACTIVE TB DIAGNOSIS

For the diagnosis of active TB, IGRA sensitivity and specificity are poor, particularly in people from settings with high TB incidence.[43] Specificity is poor because these populations (e.g. recent immigrants) will have a high prevalence of LTBI, and the immune-based tests cannot distinguish between active disease and latent infection.[43] Sensitivity is reduced because of the temporary anergy of the acute illness. A positive IGRA result may not necessarily indicate active TB, and a negative IGRA result may not rule out active TB. Therefore, IGRAs should not be used for diagnosis of active TB in adults.[43]

CHILDREN

Available data from systematic reviews suggest that the TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children.[45,46] Both tests have similar correlations with exposure gradients in children. However, the ability of either the TST or IGRAs was suboptimal to "rule in" or "rule out" active TB, reinforcing the appropriate use of these tests as adjuncts (rather than isolated tests) in the clinical diagnosis of active TB. In children with suspected active TB, every effort should be made to collect appropriate clinical specimens for microbiological testing, and IGRAs should be used with other clinical data (e.g. TST results, chest radiographic findings, history of contact) to support a diagnosis of active TB.[56]

HIV-INFECTED PERSON

Systematic reviews show that in HIV-infected people with active TB (a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous but higher for T-SPOT.TB (72%; 95% confidence interval [CI] 62%-81%) than for QFT-GIT (61%; 95% CI 47%-75%) in low-/middle-income countries.[5] However, neither IGRA assay was consistently more sensitive than the TST in head-to-head comparisons. Although T-SPOT.TB appeared to be less affected by immunosuppression than QFT-GIT and the TST, overall, differences among the three tests were small or inconclusive. Thus, current evidence suggests that IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI, and both tests have suboptimal sensitivity for active TB.[5,6,47]

REPRODUCIBILITY

A systematic review published in 2009 found limited data on reproducibility but reported that within-subject variability was present in all studies, the magnitude varying (16%-80%) across studies.[54] More recent studies have confirmed this finding and expanded the type of evidence on test reproducibility.

There are now studies that show five important sources of variability in IGRA results:

1. pre-analytical steps (e.g. tube shaking, time to incubation, actual incubation time);[34]
2. test-retest variation (i.e. same sample tested twice);[57]
3. within-person variations over time (i.e. same person tested on separate days with separate samples);[58]
4. interlaboratory variations (i.e. same sample tested in different laboratories);[59]
5. TST-induced variations in QFT results (i.e. effect of a prior PPD placement on subsequent IFN-gamma values).[60]

The importance of pre-analytical factors, such as the time lapse between blood collection and sample processing and/or incubation at 37° C, was brought out by a recent study in the United States.[34] Compared with immediate incubation, 6- and 12-hour delays resulted in positive-to-negative reversion rates of 19% (5/26) and 22% (5/23) respectively.

A recent large US study on the repeatability of QFT performed multiple IGRA tests using leftover stimulated plasma.[57] This study reported substantial variability in TB response when QFT tests were repeated using the same patient sample. The normal expected range of within-subject variability in TB response upon retesting included differences of +/–0.60 IU/mL for all individuals (coefficient of variation [CV]) 14%) and +/–0.24 IU/mL (CV 27%) for individuals whose initial TB response was between 0.25 and 0.80 IU/mL. The authors recommended that test results should be interpreted cautiously among individuals with a positive IFN-gamma value of less than 0.59 IU/mL.[57]

Another recent study compared results from the same subjects when QFT ELISAs were performed in different laboratories in the United States.[59] This study reported substantial within-subject interlaboratory variability in QFT interpretations and IFN-gamma measurements when blood samples collected from the same person at the same time were tested in three different laboratories. Of the 97 subjects tested in three laboratories, 11% had discordant QFT interpretations based on the original reported data. A portion of the variability in test interpretation was associated with manual data entry errors.[59]

All of these studies have argued for a borderline zone (conceptually similar to the interpretation of a TST result of 5 to 9 mm) for the interpretation of IGRAs, rather than a simplistic negative/positive interpretation. Currently, the FDA- and Health Canada-approved versions of QFT Gold In-Tube do not provide a borderline zone, and laboratories do not routinely report absolute values of IFN-gamma or spot-forming cells.

There is currently no consensus on the exact borderline zone that should be used, and this an active area of debate and research. Until more definitive evidence and consensus emerges, on the basis of existing literature it appears that IFN-g values of 0.20-1.00 IU/mL for QFT should be interpreted cautiously, as nonspecific and reproducibility issues can easily result in false conversions and reversions if the initial value fell in this borderline zone. If results do fall in this borderline zone, care providers could choose to repeat the test, depending on the clinical context and other information available (e.g. on risk factors). To facilitate the interpretation of such values, laboratories should provide quantitative results in addition to the dichotomous (positive/negative) results. This is particularly critical for interpretation of repeated IGRA results (see Appendix D).

Laboratories should also ensure that there is standardization of pre-analytical procedures such as tube shaking, time interval between the drawing of blood and incubation, and exact duration of incubation. If portable incubators are used, it is important to make sure that such incubators can accurately stabilize the temperature at 37° C. Laboratories should avoid manual entry of results to avoid additional variability and errors (see Appendix D).

HEALTH CARE WORKERS AND OTHER GROUPS THAT MIGHT BENEFIT FROM SERIAL TESTING

Serial (repeated) testing for TB infection is indicated in specific populations, such as HCWs in high-risk settings, prison inmates and staff, and close contacts.

Several studies have evaluated the use of IGRAs in HCWs, and these have been summarized in systematic and narrative reviews.[52,55,61] In settings of low TB incidence the pooled prevalence of positive IGRA in HCWs was significantly lower than for a positive TST. However, in high-incidence settings there were no consistent differences in the prevalence of positive tests. IGRAs showed good correlation with occupational risk factors for TB exposure in low-incidence settings. Only 10 studies assessed the use of IGRA for serial testing, and all showed large variation in the rates of conversions and reversions, with no data suggesting that IGRAs are better than the TST at identifying the incidence of new TB infection.[51]

Thus, the use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in settings of low TB incidence. However, when simple negative/positive changes were used as cut-offs, IGRAs had high rates of conversions (2%-15%), which were frequently higher than the rates of TST conversions and higher than the annual risk of TB infection expected in these low-incidence settings. IGRAs also had high rates of reversions, which ranged from about 20% to 40% in most studies.[52] Thus, the use of IGRAs for serial testing is complicated by lack of data on optimum cut-offs for serial testing, issues with reproducibility, and unclear interpretation and prognosis of conversions and reversions.[61]

On the basis of a growing number of serial IGRA testing studies, several observations can be made:[44]

- IGRAs are inherently dynamic in a serial testing context, and this is reflected in the literature, which consistently shows high rates of both conversions and reversions.
- This dynamic pattern is seen in settings of low, intermediate and high TB incidence, suggesting that at least some of the observed variations may be intrinsic to the assay, independent of the risk of exposure. These include nonspecific variations due to biological reasons as well as assay reproducibility issues (reviewed earlier)
- While IGRAs are not prone to the subjectivity that adversely affects the reading of TST, other factors affect their reproducibility, including pre-analytical delays (e.g. time to incubation and length of incubation), procedures such as tube shaking (for QFT), and test-retest and inter-laboratory variations.
- When the manufacturer’s cut-offs are used for conversions, the result will likely be conversion rates that are incompatible with what is epidemiologically expected for a given setting.

- IGRA reversions are highly likely to occur among those with interferon gamma values (or spot counts) just above the diagnostic threshold (i.e. borderline zone), and reversion rates can exceed 40%-50% in some settings. Reversions can occur spontaneously, even in the absence of treatment.
- While a previous IGRA will not boost the results of the subsequent IGRA result, a previous TST can boost the subsequent IGRA result, and this is mostly seen among those who are already sensitized to mycobacteria (i.e. TST positive) but is not due to BCG.
- When tests are repeated more frequently on the same individuals, more complex patterns or phenotypes are seen, including stable and unstable (transient) conversions, persistent positives and negatives, and other complex patterns that defy description.
- There are no longitudinal data on the prognosis of such phenotypes, and it is unclear which subgroup should be targeted for preventive therapy.

Overall, routine implementation of IGRAs in serial testing programs offers some benefits (e.g. higher specificity and easier logistics) but also poses significant challenges in the interpretation of test results – for the individual and for the health care provider. This is evident from recent experiences of North American hospitals that began implementing IGRAs for employee screening after publication of the 2005 Centers for Disease Control and Prevention guide-lines.[62-64] Similar findings have been reported from Canadian hospitals.[65]

There is limited evidence on the timing of IGRA conversions. Available evidence suggests that most IGRA conversions occur within 4 to 7 weeks after TB exposure.[66,67] However, in some cases conversion may be delayed longer than 3 months; agreement between TST and IGRA show a better concordance after this window period.

PREDICTION OF ACTIVE DISEASE

As shown in a recent systematic review, neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment (because of higher specificity).[53] Several longitudinal studies show that incidence rates of active TB, even in IGRA-positive individuals in countries with a high burden of TB, are low, suggesting that in a vast majority (>95%) of IGRA-positive individuals there is no progression to TB disease during follow-up. This is similar to the TST. Compared with test-negative results, IGRA-positive and TST-positive results were much the same with regard to the risk of TB (pooled incidence rate ratios in the five studies that used both was 2.11 [95% CI 1.29-3.46] for IGRA versus 1.60 [0.94-2.72] for TST at the 10 mm cut-off).[53]

Only one study has evaluated the risk of progression to TB associated with an IGRA conversion.[68] This study, conducted among adolescents in South Africa, compared the incidence rate of TB disease following recent QFT conversion with the incidence among non-converters. Recent QFT conversion was indicative of an approximately 8-fold higher risk of progression to TB disease (compared with non-converters) within 2 years of conversion in a cohort of adolescents. For QFT converters, the TB incidence rate (all cases) was 1.46 cases per 100 person years. A significantly lower TB incidence rate (0.17 cases per 100 person years) was observed for QFT non-converters.[68] It is noteworthy that even among QFT convertors, the overall TB incidence was about 3% within 2 years of conversion. This is consistent with other studies showing that in a vast majority of IGRA- or TST-positive individuals there is no progression to TB disease. Thus, further research is needed to identify biomarkers that are highly predictive and can identify latently infected individuals who are at highest risk of disease progression.[69]

TREATMENT MONITORING

A recent systematic review on the use of IGRAs for monitoring TB treatment found that reversion from positive to negative IGRA occurred in a minority of treated patients and monitoring IGRA changes over time had no clinical utility in adults.[55] Data in children were limited but in line with results reported for adults.

REVISED RECOMMENDATIONS FOR USE IN CANADA

Available evidence suggests that both the TST and IGRAs are acceptable, but imperfect, tests for LTBI. In general, IGRAs are more specific than the TST in BCG-vaccinated populations, especially if BCG is given after infancy or multiple times. Neither test can distinguish LTBI from TB disease and therefore has no value for active TB detection in adults. Both tests have suboptimal sensitivity in active TB, especially in HIV-infected people and children. Both tests appear to correlate well with gradient of exposure. Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for LTBI treatment. IGRAs do offer some improvements over the TST, but the improvement is incremental rather than transformational.[70]

In 2010, the Canadian Tuberculosis Committee issued an updated Advisory Committee Statement on IGRAs,[4] which recommended the use of IGRA as a confirmatory test when false-negative or false-positive TST results are suspected. The following new recommendations will supersede the previous ACS:

Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated, with preferences and exceptions noted below.

NEW RECOMMENDATIONS

1. Situations in which neither TST nor IGRAs should be used for testing

- Neither the TST nor the IGRA should be used for testing people who have a low risk of infection and a low risk that there will be progression to active TB disease if they are infected. However, low-risk individuals are commonly tested before exposure, when repeat testing is likely. In this situation TST is recommended (see recommendation 3); if the TST is positive then an IGRA may be useful to confirm a positive TST result to enhance specificity.

- Neither TST nor IGRA should be used for active TB diagnosis in adults (for children, see recommendation 4).
- Neither TST nor IGRA should be used for routine or mass screening for LTBI of all immigrants (adults and children).
- Neither TST nor IGRAs are useful tools for monitoring anti-TB treatment response.

  (Strong recommendations, based on strong evidence)

Rationale

The goal of testing for LTBI is to identify individuals who are at increased risk for the development of active TB and therefore would benefit from treatment of LTBI. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive. This is the rationale for not using either TST or IGRA for screening low-risk individuals. However, in some settings, low-risk individuals might get tested with TST. In such situations, it may be helpful to rule out a false-positive TST result by performing an IGRA test. This strategy will improve the overall specificity of the testing process in low-risk individuals and may also be cost-effective, as shown in a Canadian study.[71]

Neither the TST nor the IGRA can distinguish latent infection from active TB disease, and therefore these tests should not be used for adults with suspected active TB.[43] In children with suspected active TB disease, every effort must be made to collect specimens for microbiological testing. IGRAs can be used as a supplementary diagnostic aid, along with TST and other investigations and clinical data (e.g. chest radiography, history of contact) to support a diagnosis of TB in children.[56]

Neither the TST nor IGRAs are useful tools for monitoring anti-TB treatment response, and their use for this purpose should be avoided.[55]

2. Situations in which IGRAs are preferred for testing but a TST is acceptable

- People who have received BCG as a vaccine after infancy (1 year of age) and/or have received BCG vaccination more than once.
- People from groups that historically have poor rates of return for TST reading.

  (Conditional recommendations, based on moderate evidence)

Rationale

Among people with a history of post-infancy BCG vaccination or of multiple BCG vaccinations, the specificity of the TST is likely to be poor. IGRAs are therefore the preferred tests, although a TST can still be used. In populations that are known to have poor rates of return for TST reading (e.g. homeless individuals and injection drug users), use of IGRAs can help achieve a higher rate of test completion and follow-up, although completion of LTBI treatment may still be challenging in these populations.

3. **Situations in which TST is recommended for testing but an IGRA is NOT acceptable**

- The TST is recommended whenever it is planned to repeat the test later to assess risk of new infection (i.e. conversions), such as repeat testing in a contact investigation, or serial testing of health care or other populations (e.g. corrections staff or prison inmates) with potential for ongoing exposure.

  (Conditional recommendation, based on moderate evidence)

Rationale

IGRAs are not recommended in these situations because serial testing studies have shown high rates of conversions and reversions, unrelated to exposure or treatment. There is no consensus on the appropriate cut-offs or borderline zones for deciding on IGRA conversions and reversions, although the literature suggests that IFN-gamma values of 0.20-1.00 IU/mL for QFT should be interpreted cautiously, as nonspecific and reproducibility issues can easily result in false conversions and reversions if the initial value fell in this borderline zone. If results do fall in this zone, care providers could choose to repeat the test, depending on the clinical context and other information available (e.g. risk factors). To facilitate the interpretation of such borderline values, laboratories should provide quantitative results in addition to the dichotomous (positive/negative) results.

4. **Situations in which both tests can be used (sequentially, in any order) to enhance sensitivity**

Although routine dual testing with both TST and IGRA is not recommended, there are situations in which the results from both tests may be helpful to enhance the overall sensitivity:

- When the risk of infection, of progression to disease and of a poor outcome are high. See Chapter 6, Treatment of Latent Tuberculosis Infection.
- In children (under age 18 years) with suspected TB disease, IGRAs may be used as a supplementary diagnostic aid in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute, or obviate the need, for appropriate specimen collection. A negative IGRA (or TST) does NOT rule out active TB at any age and especially not in young children.
- In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline or invalid and a reason for testing persists.

  (Conditional recommendations, based on moderate evidence)

In these situations, it is recommended that health care providers use either a TST or IGRA as the initial test and if it is negative consider a second test using the alternative format. If the initial test is positive, then no second test is required.

For example, if the initial TST is positive, then the testing process stops because LTBI is diagnosed. If the initial TST is negative, then an IGRA test can be performed (or vice-versa, if testing was started with an initial IGRA).

IMPORTANCE OF CONSIDERING THE CLINICAL CONTEXT

The results of both TST and IGRA should be interpreted with other relevant clinical information, such as age, BCG status, history of contact with active TB and factors that increase the risk of progression to active disease. An online TST/IGRA algorithm (www.tstin3d.com) has been developed to facilitate the three-dimensional interpretation of these tests. All individuals with positive TST or IGRA results should undergo evaluation to determine whether they have LTBI or active TB disease and be managed according to the recommendations in Chapters 5, Treatment of Tuberculosis Disease and 6, Treatment of Latent Tuberculosis Infection.

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CHAPTER 5

TREATMENT OF TUBERCULOSIS DISEASE

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KEY MESSAGES/POINTS

- Treatment of active TB should include two effective drugs at all times, and in the initial phase (first 2 months) at least three effective drugs are recommended.
- Treatment should be guided by the results of drug sensitivity testing, which should be performed for all patients with culture-confirmed disease.
- All patients with active TB in Canada should be treated with a regimen of isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB) initially. If the isolate causing disease is fully susceptible to all first-line drugs, the EMB can be stopped, and PZA should be given for the first 2 months. After that it is recommended that only INH and RMP be given for the remainder of therapy – usually another 4 months.
- Therapy is prolonged to 9 months if there are risk factors for relapse. These include persistent presence of cavity on the chest x-ray after 2 months or at the end of effective anti-TB therapy, persistent smear and/or culture positivity after 2 months of therapy, or HIV coinfection.
- Providers who are initiating TB therapy should provide comprehensive, patient-centred care and be able to monitor that 100% of prescribed doses are taken. Directly observed treatment (DOT) is one method to achieve this and is recommended at a minimum for patients with risk factors for non-adherence, or population groups with historically increased rates of treatment failure or relapse or with inadequate rates of treatment completion, defined as default rates of 5% or greater. It is recommended that all jurisdictions across Canada have the capacity to provide DOT.
- Therapy can be given 5 days per week in the initial 2 months, then three times per week if DOT is used, to facilitate treatment supervision. Therapy that is self-administered should be taken daily.
- Fixed-dose combination (FDC) preparations of multiple TB medications are not recommended.
- Treatment of active disease in pregnant or breastfeeding women should be the same as the standard regimen.
- The same drugs, dosing and duration as in the standard regimen are recommended for treatment of active disease in patients with renal insufficiency. However, prolonged dosing intervals are recommended for PZA and EMB from daily to three times per week.

- Therapeutic drug monitoring (TDM) is not available in Canada but is available in the United States. The impact of TDM on important outcomes is unknown. Nevertheless, TDM should be considered for patients with renal or hepatic insufficiency, HIV coinfection or known malabsorption.
- Treatment of drug-resistant, HIV-associated, extrapulmonary and pediatric TB is described in separate chapters.

FUNDAMENTALS OF TREATMENT OF TB DISEASE

These fundamentals are discussed in a number of other excellent sources, and interested readers are referred to these references.[1-6]

OBJECTIVES OF TREATMENT OF DISEASE

There are three fundamental objectives of treatment of active TB. It is useful to understand these objectives, as each one is achieved by different TB drugs or combinations of drugs:

1. Rapid killing of TB bacilli, to produce rapid improvement in the clinical condition of the patient and thereby prevent complications (reduce morbidity), prevent death (reduce mortality) and prevent transmission (reduce contagiousness).
2. Prevent the emergence or worsening of drug resistance.
3. Prevent the relapse of disease after completion of therapy and achieve long-lasting cure.

PRINCIPLES OF TREATMENT OF DISEASE

Therapy is given in two phases: initial intensive, and continuation.

In the initial phase multiple effective drugs are used in combination to achieve the first and second objective. On the basis of results of randomized trials, this phase should last 2 months, and the drugs should preferably be given daily.

The second objective is addressed by the continuation phase, during which only two drugs are usually given. The length of this phase is variable, depending on indicators of risk of relapse, on the drugs given in the initial phase and on the results of pre-treatment drug susceptibility testing. Therapy can be daily or intermittent.

Optimal therapy to achieve all three treatment objectives for patients of all ages, with disease at any site, should be guided by the results of drug susceptibility testing. This reinforces the importance of microbiologic confirmation of the diagnosis of TB disease. Patients with suspected active TB should always have multiple specimens sent for microbiologic investigation before treatment is started. (See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.)

It is recommended that at least two effective drugs should be used at all times. If drug susceptibility testing results are pending then more drugs may be needed to ensure that at least two are likely to be effective.

In the initial intensive phase, particularly when bacillary load is high (see below), three likely effecttive drugs should be used to prevent emergence of drug resistance.

A decision to initiate TB treatment implies a commitment to ensure that therapy is not interrupted or irregular at any time, until the planned date of treatment completion. Therefore, it is recommended that all necessary measures be taken to avoid patient drop-out or loss to follow-up, or interruption of drug supply. If patients experience adverse events, an alternative therapy should be initiated promptly. Practitioners who cannot guarantee adequate monitoring and supervision of therapy should refer the patients immediately to centres where this can be assured.

PREVENTION OF DRUG RESISTANCE

Drug resistance is discussed in detail in Chapter 8, Drug-Resistant Tuberculosis. However, to understand the rationale for many of the principles above it is useful to understand how drug resistance develops. In brief, all patients with active disease harbour at least a few bacilli which have undergone spontaneous mutations to produce resistance to each anti-TB drug.[7,8] The mutation rate for each TB drug has been established from *in-vitro* experiments.[7,8] Therapy with a single drug will lead to the uninhibited growth of bacilli carrying the mutation to this drug while all other bacilli are eradicated.[9] This means that within 2-3 months of the start of monotherapy all bacteria will carry this mutation, and clinically the patient will be fully resistant to that drug.[10] Fortunately, the mutations to different drugs are independent, so treatment with two drugs will usually mean that the mutants with resistance to one drug are killed by the other drug, unless the total number of bacilli is very high.[9]

Experimental studies have established the total number of bacilli present with each type of TB lesion or extent of disease.[7] Using this, and the spontaneous mutation rate, it is possible to calculate the probability that treatment with one, two or three drugs will lead to the emergence of drug resistance as a result of natural or spontaneous mutations, even in a patient who takes all doses properly. As seen in Table 1, monotherapy will not lead to the emergence of resistance in a patient with latent TB but is very likely to do so with minimal active TB. On the other hand, two effective drugs will be adequate for many patients with active TB but not for patients with more extensive disease.

Table 1. Probability of drug resistance emerging if TB with different bacillary loads is treated with different numbers of drugs[9]

Number of TB bacilli (TB infection/disease state)	Probability of resistance by number of drugs in treatment		
	1 drug	2 drugs	3 drugs
10^3 (latent infection)	0	0	0
10^4 (latent infection)	0	0	0
10^6 (smear-negative culture-positive)	50%	0	0
10^8 (single cavity)	100%	50%	0
10^{10} (several cavities)	100%	100%	0
10^{12} (very extensive disease)	100%	100%	1%

DRUGS USED IN TREATMENT

Anti-TB drugs are divided into two broad groups.

First-line drugs (FLD)

Four drugs are classified as FLD in Canada, because all are effective, can be taken orally and are well tolerated (or at least better tolerated than the second-line drugs).

Second-line drugs (SLD)

The SLD include the fluoroquinolones, all injectables and many "older" TB drugs that were used in the 1950s and 1960s but were abandoned because of relatively poor efficacy and/or greater toxicity.[4]

Evidence about the action and the role in therapy of each drug comes from *in-vitro* and animal studies as well as from multiple randomized trials. Table 2 summarizes the doses, with daily or thrice weekly schedules, of the four FLD and the most commonly used SLD.

Table 2. Recommended drug doses for daily and intermittent therapy in adolescents and adults[1,6]*

	Daily		Thrice weekly	
	By weight	Max (mg)	By weight	Max (mg)
First-line drugs				
INH	5 mg/kg	300	10 mg/kg	600
RMP	10 mg/kg	600	10 mg/kg	600
PZA	20-25 mg/kg	2000	30-40 mg/kg	4000
EMB	15-20 mg/kg†	1600	25-40 mg/kg	2400
Second-line drugs				
Fluoroquinolones‡ – moxifloxacin, levofloxacin		400 750-1000		¶ ¶
Injectables – amikacin§	15 mg/kg as single dose	**		¶

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol

*For doses in children see Chapter 9.

†EMB dosing: optimal dosing is unclear. It is clear that eye toxicity is dose dependent, and its risk is higher at 25 mg/kg than at 15 mg/kg.

‡Fluoroquinolones: gatifloxacin is not recommended in Canada because of dysglycemia problems. This drug has been used in recent trials and is still used in some countries.

§Amikacin: Of the injectables amikacin is preferred for use in Canada because of the ready availability of the drug, familiarity with its use by clinicians, nurses and pharmacists, and the ability to measure serum drug concentration in many facilities. Streptomycin (SM) is not available in Canada but may be preferred in some low- and middle-income countries as rates of toxicity are similar and costs may be lower.

¶There are inadequate data from randomized trials on the use of fluoroquinolones or injectables as part of intermittent regimens. If these drugs are needed because of intolerance or resistance to first-line drugs, daily therapy is suggested

**Initial dosage if renal function is normal. Dosing should be adjusted based on peak and trough serum levels in consultation with a pharmacist.

Isoniazid (INH)

This agent was first introduced in 1952 and is still a cornerstone of modern TB therapy. It has very powerful early bactericidal activity, meaning that it is highly effective in rapid killing of bacteria in the first few days. Hence, the drug is important in achieving Objective 1, above. It is also effective in preventing the emergence of resistance, although its role in preventing relapse is unclear. If INH is not given for the full duration of therapy, then therapy should be prolonged. If INH is not given at all, therapy should be for at least 12 months. Pyridoxine (vitamin B6) should routinely be added for patients with diabetes, renal failure, malnutrition, substance abuse or seizure disorders or for women who are pregnant or breastfeeding, because of the increased risk of symptoms related to pyridoxine deficiency in these patients. A pyridoxine dose of 25 mg is sufficient; higher doses may interfere with INH activity.

Rifampin (RMP)

This drug, introduced in 1968, is the most potent anti-TB drug available. Its use allows shortening of the regimen to a total of 9 months (or less if PZA is also used). The drug has good bactericidal activity (Objective 1), prevents acquired drug resistance (Objective 2) and is very important in preventing relapse (Objective 3). Current doses are based on studies performed in the 1960s, when the lowest effective dose was used because of the high cost of the drug. Case series have reported low RMP drug concentrations in 40%-50% of patients taking standard doses[11,12] and in patients with poor treatment outcomes.[13,14] This has given rise to the hypothesis, being tested in ongoing trials, that RMP at higher doses would be more effective. When the results of these trials are available it is possible that RMP dosing recommendations will change.

If RMP is not given for the full duration of therapy, then therapy should be prolonged. If RMP is not given at all, therapy should be for at least 18 months.

Rifabutin (RBT)

This rifamycin has similar activity *in vitro* against *M. tuberculosis* as RMP but causes much less upregulation of the cytochrome p450 system and so results in fewer drug interactions. Hence, RBT is commonly used for HIV-infected or transplant patients, as the regimens they are often taking may be profoundly affected by RMP, but not by RBT. Hematologic toxicity is more common with this drug.

Rifapentine (RPT)

This rifamycin has a half-life that is 5 times longer than RMP, which allows the drug to be given only once a week. However, in randomized trials, HIV-infected patients who received the drug, plus INH, once weekly in the continuation phase had significantly higher rates of failure, relapse and acquired drug resistance.[15] Hence, it is not recommended for use in the treatment of active TB at this time. In addition, RPT is available in Canada only through application for the treatment of an individual patient by means of the Special Access Program (at: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php).

Pyrazinamide (PZA)

This drug is also bactericidal but appears to provide benefit only in the first 2 months of therapy (Objective 1). In randomized trials, use of PZA in the continuation phase did not reduce relapse rates,[5,6] and the drug appeared to offer no protection against the development of resistance.[5]

If PZA is not given for the entire first 2 months, the total duration of therapy should be 9 months.

Ethambutol (EMB)

This is the least effective of the four FLD for bactericidal activity (Objective 1) or prevention of relapse (Objective 3), but it is effective in preventing the emergence of drug resistance (Objective 2). If a previously untreated patient has unrecognized INH resistance and is given only INH, RMP and PZA for the first 2 months then RMP resistance could emerge, given the inability of PZA to protect against the emergence of resistance. Hence, EMB is added in the initial phase whenever there is any suspicion of initial drug resistance and while the results of drug susceptibility testing (DST) are pending. In Canada EMB is recommended as part of standard initial therapy if the prevalence of INH resistance in the population group to which the patient belongs is 4% or more.

If the strain is fully susceptible, the duration of therapy is no different whether EMB is given or not.

Fluoroquinolones (FQN)

Currently these drugs are still considered second-line drugs, i.e. they are alternative medications for TB rather than part of standard first-line treatment, even though they are highly efficacious for TB,[16,17] are taken orally and are well tolerated. Indications for the use of FQN include drug resistance or intolerance of FLD. A number of ongoing trials are testing the use of FQN as part of first-line therapy to reduce the total duration of therapy. When the results are available, recommendations for use of the drugs as first-line therapy may change.

Injectables

The injectables include streptomycin, amikacin, kanamycin and capreomycin. SM is still used as part of first-line therapy in a few countries, but the inconvenience and pain of daily injections, plus higher rates of toxicity, have relegated SM to second- line drug status. This drug is not available in Canada. On the basis of expert opinion, the Canadian Thoracic Society suggests that of all the injectables amikacin is preferred for use in Canada, because it is available in most hospitals, providers (including pharmacists) are familiar with the drug, and drug concentrations are readily available, reducing risk of toxicity.

THERAPEUTIC REGIMENS

These regimens and the underlying evidence are discussed in more detail in two other excellent publications.[4,6]

STANDARD REGIMEN

RECOMMENDATION

As summarized in Table 3, standard therapy for patients with drug-sensitive TB or expected drug-sensitive TB (while DST results are pending) is INH, RMP, PZA and EMB for the first 2 months followed by INH and RMP for 4 more months.

(Strong recommendation, based on strong evidence)

EMB may not be needed if the likelihood of INH monoresistance or other forms of resistance is less than 4%. There are few situations in which one can confidently predict such a low likelihood of any resistance, especially since the prevalence of resistance has risen steadily over the last 40 years in all populations with access to treatment. EMB could be avoided in some Aboriginal populations and elderly Canadians who acquired TB infection during the pre-antibiotic era, as they usually have such a low prevalence of drug resistance. EMB can be discontinued as soon as DST results are available if the organisms are shown to be fully susceptible.

Table 3. Treatment regimens recommended by the Canadian Thoracic Society for adults with fully susceptible (or expected to be fully susceptible) disease

	Initial phase (first 2 months)	Continuation phase
Standard		
Regimen 1	INH RMP PZA EMB* daily (or 5 days/week)	INH RMP for 4 months daily (or 3 times/week)†
Regimen 2	INH RMP EMB* daily (or 5 days/week)	INH RMP for 7 months daily (or 3 times/weekly)
Elderly (>65) or other risk factor for hepatotoxicity		
	INH RMP EMB* daily (or 5 days/week)	INH RMP for 7 months daily (or thrice weekly)
Pregnant		
	INH RMP PZA EMB† or INH RMP EMB* daily (or 5 days/week),	INH RMP for 7 months *if PZA not used and for 4 months if PZA used in first 2 months* daily (or thrice weekly)

*EMB can be stopped as soon as the DST results are available if pan sensitive. PZA is continued for the full 2 months.

†Three times weekly preferred over twice weekly for programmatic reasons. If patients miss a single dose while receiving thrice weekly therapy they effectively receive twice weekly therapy, which is still adequate. If they miss a dose of twice weekly therapy they effectively receive once weekly therapy which is inadequate. HIV-negative patients with minimal disease (e.g. initially smear-negative but culture-positive) or known to be reliable with DOT may be considered for twice weekly therapy in the continuation phase.

ROUTES OF ADMINISTRATION

Therapy for TB is effective and most readily administered by the oral route. When necessary, all of the oral forms of anti-TB medication can be administered by means of nasogastric or feeding tube. The tablets can be crushed and mixed with water, or suspensions of the medications can be prepared to make delivery easier. Only INH, RMP, the injectable agents and the FQN are available for parenteral administration. In patients for whom parenteral medications are needed, consultation with a TB specialist is recommended.

PROLONGING THE CONTINUATION PHASE

In a recent meta-analysis, among patients with initially fully susceptible strains, relapse was less than 1% following treatment with RMP-containing regimens lasting 8 months or more, compared with 4% following 6-month regimens.[18] To prolong therapy in all patients in order to achieve a 3% reduction in relapse would expose many patients needlessly to prolonged therapy. However, risk factors for relapse have been identified. These include having more extensive disease and/or cavities on a chest x-ray in the first 2 months of therapy,[19] being culture-positive after 2 months of therapy[19] or having a cavity on chest x-ray at the end of treatment.[20]

RECOMMENDATION

In patients with any of the above risk factors, the continuation phase should be prolonged from 4 to 7 months, to provide a total of 9 months of therapy.

(Strong recommendation, based on moderate evidence)

There is also evidence from a recent meta-analysis that among HIV-infected individuals not taking antiretroviral therapy, relapse rates are significantly lower with 9 months of anti-TB therapy than 6 months[21] (see Chapter 10, Tuberculosis and Human Immunodeficiency Virus).

INTERMITTENT THERAPY

Many randomized trials have demonstrated that intermittent regimens have excellent results in patients with drug-sensitive TB.[5,9] Intermittent therapy should be used only with DOT, which it facilitates by reducing the number of times that patients need to be observed taking medications. If therapy is self-administered, all drugs should be taken daily.[6]

Findings from a recent systematic review and meta-analysis of randomized trials of RMP-containing regimens[18] and related recommendations from the World Health Organization (WHO)[6] are summarized on the following page.

1. No randomized trials have evaluated the efficacy of RMP-containing regimens given twice weekly from the outset or after an initial 2 weeks of daily therapy.

   These regimens are not recommended.

   (Strong recommendation, based on strong evidence)

2. RMP-containing regimens given three times weekly from the outset or after an initial 2 weeks of daily therapy had somewhat higher failure and relapse rates, and significantly higher rates of acquired drug resistance in a pooled meta-analysis of randomized trials. This finding has also been seen in cohort studies.[22,23]

   - **In the initial intensive phase daily therapy is recommended.**
     This can be given 5 days per week, if therapy is given by DOT.

     (Strong recommendation, based on moderate evidence)

   - **When daily DOT in the initial phase is difficult, patients may be treated with thrice weekly therapy if they are HIV-uninfected, have a low bacillary load (i.e. have non-cavitary, smear-negative disease initially) and have demonstrated excellent adherence to their DOT in the first 2 weeks.**

     (Conditional recommendation, based on moderate evidence)

3. Many studies have evaluated different schedules of therapy in the continuation phase, after daily therapy for the first 2 months. These have included daily as well as once, twice or thrice weekly schedules.

   - **Once weekly regimens are inadequate and should not be used.**

     (Strong recommendation, based on strong evidence)

   Treatment outcomes were similar with all other schedules of drug administration.

   - **If DOT is used, then thrice weekly therapy is preferred in the continuation phase.[6]**

     (Conditional recommendation, based on moderate evidence)

   This is based mostly on practical considerations: if a patient given a twice weekly regimen misses a single dose, then effectively he or she will receive once weekly therapy, which is inadequate. If a patient receiving thrice weekly intermittent therapy misses a single dose they are effectively receiving twice weekly therapy, which is still acceptable.

   - **When thrice weekly DOT in the continuation phase is difficult, patients may be treated with twice weekly therapy if they are HIV-uninfected and have demonstrated excellent adherence to their DOT to date.**

     (Conditional recommendation, based on moderate evidence)

   - **Intermittent therapy is not recommended for HIV-infected people** (following WHO guidelines, see Chapter 10, Tuberculosis and Human Immunodeficiency Virus).

FIXED-DOSE COMBINATION (FDC)

Fixed-dose combination tablets containing two or more of the first-line drugs have been manufactured for over 30 years, and the WHO recommends their use.[6] A combination of INH/RMP/PZA is available in Canada. In theory these formulations should prevent monotherapy – from physician or patient error, or patient selection of only some of their medication. Since there are many fewer tablets with FDCs than separate formulations in the initial phase (see Figure 1) they may be preferred by patients.

Figure 1. Typical number of tablets taken for active TB treatment with FDCs (on left) or separate drug formulations (on right)

A recent systematic review and meta-analysis of 15 randomized trials comparing FDCs with separate formulations found no significant differences in rates of failure, relapse, acquired drug resistance, treatment completion or adverse events.[24] None of the five studies that assessed patient adherence favoured FDCs. Patient satisfaction was assessed in only two of the 15 studies and was significantly better with FDCs in one of these two studies, but not the other.

On the basis of this evidence, use of FDCs is not recommended.

(Strong recommendation, based on strong evidence)

TREATMENT OF ACTIVE TB IN THE ELDERLY (AND OTHERS AT MODERATE TO HIGH RISK OF HEPATOTOXICITY)

PZA is the most toxic of the standard first-line drugs and the most common cause of drug-induced hepatotoxicity in patients treated for TB disease.[25,26] Therefore, it may be better to avoid PZA in patients at risk of hepatotoxic effects, such as the elderly or patients with pre-existing mild-moderate liver dysfunction.

(Conditional recommendation, based on moderate evidence)

If PZA is not given in the first 2 months then the total duration of therapy should be a minimum of 9 months. If the risk of non-adherence is judged to be low, the lower risk of toxicity may justify the longer therapy.

TREATMENT OF ACTIVE TB IN THOSE WITH SEVERE LIVER DISEASE

In patients with severe liver disease, use of RMP, or INH or PZA is risky, because any of these three drugs can cause drug-induced hepatotoxicity and dramatically worsen the patient's condition. All three should be avoided if possible, although because RMP is such a potent and effective drug and hepatotoxicity is rare with RMP alone,[25,26] its use may be considered in people with more extensive disease (smear-positive and/or cavitary disease) or more serious forms of extrapulmonary disease.

A suggested regimen is an FQN plus EMB plus an injectable (amikacin) for the first 2 months followed by an FQN and EMB for a total of 18 months.

(Conditional recommendation, based on weak evidence)

As above, RMP may be added but with careful monitoring of liver enzymes and function.

TREATMENT OF ACTIVE TB WITH RENAL INSUFFICIENCY AND DIALYSIS

In patients with creatinine clearance that is impaired but above 30% of normal, the need for adjustment of drug dosing or frequency is unclear. It is suggested that all drugs can be given in normal doses and frequency, but with careful monitoring for toxicity. If creatinine clearance is less than 30% of normal then, as summarized in Table 4, EMB and PZA can be used but at reduced doses because they are excreted by the kidney.

It is preferable to reduce the frequency of administration of these drugs rather than reduce the doses, as the peak serum concen-trations are key to their bactericidal effects. Visual toxicity from EMB is more common in patients with renal insufficiency. Monitoring serum concentrations will be very useful to ensure that adequate, yet safe, doses are given. INH and RMP are safe to give in the usual doses since these drugs are metabolized mostly by the liver. The use of injectables (streptomycin, amikacin, kanamycin and capreomycin) should be avoided if possible in patients with impaired renal function, as these drugs are excreted by the kidney and may cause worsening renal function as well as other toxicities.[1,6]

In patients undergoing dialysis, INH and RMP may be given in the usual doses since they are not appreciably affected by dialysis. EMB and PZA are dialyzable and should be given in standard doses three times per week after dialysis (see Table 4). Ideally, all medications could be given together (including INH and RMP) right after dialysis; this facilitates DOT. When uncertainties arise, the patient should be referred to a TB specialist.

Peritoneal dialysis

There are no data on the pharmacokinetic characteristics of first-line TB drugs in patients receiving peritoneal dialysis. Hence, the standard dosing and schedule are recommended, but patients should be closely monitored, and therapeutic drug monitoring (i.e. measurement of serum drug concentrations) should be considered.

Table 4. Recommended doses of TB drugs in renal failure[1,6]

	Clearance by kidney	Normal dose	Creatinine clearance <30%* or hemodialysis†
INH	No	5 mg/kg daily	No change
RMP	No	10 mg/kg daily	No change
PZA	Metabolites	20-25 mg/kg daily	25-35 mg three times per week
EMB	Yes	15-20 mg/kg daily	15-25 mg three times per week
Levofloxacin	Partial	750-1000 mg/daily	Give usual dose, but only three times/week‡
Amikacin	Yes	15 mg/kg daily	12-15 mg two or three times per week

*Insufficient data if creatinine clearance >30% but <60%. Give standard doses, but monitor closely.

†No data on pharmacokinetics if patient is undergoing peritoneal dialysis. Give doses as for hemodialysis but monitor closely.

‡Renal clearance of moxifloxacin is less, but dosing interval is not established.

TREATMENT OF ACTIVE TB IN PREGNANCY AND BREASTFEEDING

The risk of untreated active TB to a pregnant woman and her fetus is far greater than the risk of the toxic effects of the drugs used in its treatment. In a pregnant woman with active TB it is recommended that effective therapy be administered promptly. TB is not an indication for the termination of pregnancy.[6]

RECOMMENDATION

INH, RMP and EMB are considered safe in pregnancy, so all three should be used as initial treatment.

(Strong recommendation, based on strong evidence)

Pyridoxine (vitamin B6) should be given.[1,6] The WHO recommends use of PZA in pregnancy,[6] although there remains some uncertainty about its safety in pregnancy.[1] To date there have been no reports of teratogenicity even though this drug has been given to millions of pregnant women worldwide.

RECOMMENDATION

Hence, PZA can be given in women with extensive disease and/or women who do not tolerate any of the other FLD.

(Conditional recommendation, based on moderate evidence)

Most second-line agents are not considered safe in pregnancy,[4] either because of known teratogenicity or inadequate data indicating safety. FQN are best avoided during pregnancy and breastfeeding. The use of injectables (streptomycin, amikacin, kanamycin and capreomycin) is contraindicated because of the effects on the fetus, including eighth cranial nerve palsies, deafness and teratogenic effects.[4] These drugs should only be considered for use in specific instances after consultation with a TB specialist.

Specific information regarding the effects of anti-TB drugs in breastfed children is available at the Drugs and Lactation Database, LactMed, of the United States Library of Medicine's Toxicology Data Network: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. Mothers receiving treatment for TB can safely breastfeed but should be given pyridoxine (vitamin B6) supplements. At most, 3% of the maternal dose is excreted in breast milk.[27] The resulting amounts ingested by the newborn baby will not produce toxic effects. It is important to remember that the amount ingested in maternal milk would not constitute an effective dose for treatment or prophylaxis in a nursing infant, even in a newborn.[27]

INTERACTIONS OF TB MEDICATIONS WITH OTHER DRUGS AND FOOD

Significant interactions may occur between TB medications and other medications. The absorption of some TB drugs may be adversely affected by food. A list of significant interactions is available from the Heartland National TB Center, Texas, at: http://www.heartlandntbc.org/products/tuberculosis_medication_drug_and_food_interactions.pdf.

The most important cause of interactions with other medications is RMP, which causes upregulation of cytochrome p450 hepatic metabolism. Most of these drug interactions can be managed by adjusting the dosage according to measured drug concentrations (e.g. phenytoin), by monitoring the clinical effect of these drugs (e.g. international normalized ratio for warfarin) or by substituting certain drugs (e.g. antiretroviral regimens, see Chapter 10, Tuberculosis and Human Immunodeficiency Virus). In some patients the drug interactions are not manageable or could result in serious consequences, such as a patient receiving immune suppressive therapy following solid organ transplantation. In these patients, RBT may be used in place of RMP, although it should be remembered that RBT has a higher rate of adverse events than RMP, particularly hematologic events.[1]

ADJUNCTIVE USE OF CORTICOSTEROIDS

Corticosteroids should be used only when adequate anti-TB therapy is also being administered. In randomized trials adjunctive use of corticosteroids improved survival in patients with TB meningitis[28,29] and improved survival and reduced the need for pericardiectomy in patients with TB pericarditis.[30] Two reviews suggest that prednisone in doses of 40-80 mg/day for 6-12 weeks is likely to be effective,[31,32] but the optimal dose and duration of treatment are not well defined. Corticosteroids, in replacement doses, may also be of clinical value in cases of TB-caused adrenal insufficiency and in cases of life-threatening disseminated disease if there is concern about adrenal insufficiency. In a meta-analysis of three small randomized trials of patients with tuberculous pleurisy, corticosteroids resulted in more rapid resolution of symptoms and pleural fluid, but there was no evidence of long-term benefits.[33]

RECOMMENDATION

Adjunctive corticosteroids (in addition to effective anti-TB therapy) are recommended for patients with TB meningitis and TB pericarditis.

(Strong recommendation, based on strong evidence)

RECOMMENDED FOLLOW-UP DURING TREATMENT AND MANAGEMENT OF ADVERSE EVENTS

HOSPITALIZATION

Although frequently diagnosed in hospital, TB is largely managed in the outpatient setting. With increasing age, patients with TB are more likely to have severe disease or to require additional medical services not directly related to TB and thus require hospital treatment.

TB patients should be hospitalized in facilities capable of providing adequate airborne isolation and staffed by experienced personnel knowledgeable in the management of TB (see Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings).

INDICATIONS FOR HOSPITALIZATION

- Investigation and/or treatment of symptoms, i.e. fever, life-threatening hemoptysis, malaise/cachexia.
- Establishment of an acceptable therapeutic regimen in patients with significant drug-related adverse events or with known/suspected drug resistance.
- Drug desensitization.
- Management of associated medical conditions complicating the diagnosis of TB, i.e. congestive heart failure, HIV infection, respiratory failure.
- Provision of airborne isolation if this cannot be effectively provided as an outpatient.
- Involuntary admission when other measures such as DOT are unsuccessful.

ROUTINE OUT-PATIENT FOLLOW-UP

There is no published evidence regarding the impact of follow-up on patient outcomes. Hence, the following is suggested by the Canadian Thoracic Society (CTS), based on expert opinion.

Follow-up during active TB treatment should be at least monthly, to assess adherence and response to therapy, and to detect adverse events: response to treatment should be gauged clinically, radiographically and microbiologically. Of these methods, microbiologic monitoring is considered the most reliable.[9] Patients who are sputum direct smear AFB positive should have one weekly smear examination to assess response to therapy and contagiousness (see Chapter 15) until smear-negative. When sputum direct smears are AFB negative, one culture should be done at the end of the second month of therapy to assess risk of relapse, then again towards the end of therapy. If a patient is suspected of failing therapy, two sputum smears and cultures (with DST if culture-positive) should be done. Chest radiography should be performed after 2 and 6 months of therapy to assess response, potential complications and risk of relapse.

ACHIEVING COMPLETION OF THERAPY AND DIRECTLY OBSERVED TREATMENT (DOT)

Poor adherence to prescribed anti-TB therapy is the most common cause of treatment failure and is difficult to predict, although some risk factors have been identified.

> **The decision by a care provider to initiate treatment of active TB implies a commitment to ensure that all the recommended doses are taken without interruption. The goal of active TB treatment is to take 100% of prescribed doses. This is best done by providing a comprehensive, patient-centred treatment program.[34]**
>
> *(Conditional recommendation, based on weak evidence)*

This means not only careful monitoring of adherence and response to the treatment regimen but also providing multi-disciplinary support for all problems facing the patients.[35] Key elements include use of incentives and enablers, nursing care, coordinating care for other medical problems, social service support such as for child care, housing assistance, referral for treatment of substance abuse and providing transportation where possible. For patients receiving self-administered therapy this would also include monitoring and reinforcement of adherence through measures such as detailed inquiry, reinforcement of prompts to take the medications at every follow-up visit, use of tick-off calendars, linking medication taking to a specific event in the daily routine, routine pill counts or daily cell phone text reminders. Adequate resources are needed to achieve this. In many jurisdictions the public health department can and does play an important role in monitoring and enhancing adherence to treatment.

DOT is one method to monitor and enhance adherence to therapy and has been the subject of considerable debate. In its simplest form DOT involves watching the patient swallow each dose of medication to support higher completion rates. This can be achieved through paid TB program staff at a health facility or outreach workers, or through volunteers such as family or friends. Many studies, including randomized trials, cohort and ecologic studies, have examined this question. Six high-quality trials have directly compared treatment completion in all patients with TB disease randomly assigned to self-administered or directly observed treatment.[36-41] Pooled treatment success with DOT was 68% (95% confidence interval 61%, 76%) compared with 67% (62%, 72%) with self-administered therapy. Treatment completion was significantly superior with DOT compared with self-administered therapy in only one study, in which DOT was supervised by a family member.[36] In one of the remaining negative trials, completion rates were substantially, but not significantly, greater in the arm with community-based DOT.[40] In three of the six trials DOT was facility-based (i.e. patients had to travel to a clinic daily to get their medications).

The majority of the published cohort[42-54] and ecologic[55-61]studies, including a recent Canadian study,[62] have reported an association of improved treatment outcomes, or other TB control parameters, with use of DOT. Many of these studies reported on DOT programs that were community-based (rather than facility-based), used non-family members to supervise/support treatment, included outreach to locate patients who were lost to follow-up and had high completion rates – over 90%. However, confounding and other sources of bias were major limitations of these observational studies.

The studies that are considered to have the strongest designs provide reasonably consistent evidence that the use of DOT for all patients adds little to enhance treatment completion. However, only one of these trials was conducted in a high-income country, none involved North American style DOT programs, none of the trials involved children or adolescents, and the completion rates were all suboptimal with respect to current standards of treatment in Canada. Hence, the generalizability of these results to Canadian settings may be questioned, particularly with respect to children or adolescents. Taken together, the CTS believes that the overall evidence supporting the use of DOT for all patients in all settings (universal DOT) should be considered weak.

RECOMMENDATION

Close supervision and monitoring of medication is considered essential for all TB patients. It is recommended that all jurisdictions have the capacity to provide DOT. The need for DOT should be considered for each patient. An additional advantage of DOT is the closer monitoring of side-effects for all patients. At a minimum, individuals with known risk factors for non-adherence[63] and/or whose TB has major individual and public health implications if they fail treatment should be considered for DOT throughout their treatment.

Individual risk factors:

- disease due to multidrug-resistant organisms;
- treatment failure or documented relapsed disease;
- injection drug use/other substance abuse;
- homelessness or unstable housing;
- suspected non-adherence or previous non-adherence;
- major mental illnesses; and
- children and adolescents.

As well, routine use of DOT should be strongly considered in populations with previously documented high rates of non-completion. This is defined as a benchmark of 5% or more of patients who had outcomes of default, lost to follow-up, transfer out without known outcomes or were otherwise not accounted for. If this benchmark is not met, then the CTS suggests that programs strongly consider adoption of universal DOT for their population in addition to other program enhancements to provide comprehensive care.

THERAPEUTIC DRUG MONITORING

There are several clinical situations in which the monitoring of serum concentrations of TB drugs might be helpful. These include coinfection of patients with gastrointestinal disease or HIV (in whom malabsorption of drugs is common),[64] liver or renal dysfunction (resulting in reduced excretion) or drug-resistant TB (for which optimization of every available drug is crucial). At the present time there is no laboratory in Canada that offers this service. Serum samples must be sent to the Florida Infectious Disease Pharmacokinetics Laboratory (http://idpl.cop.ufl.edu) or the National Jewish Health in Denver, CO (http://www.nationaljewish.org/). Information about the timing of blood draws, processing and shipping of samples is available from the websites of the two laboratories offering this service.

A systematic review of 66 studies of therapeutic drug monitoring, which involved 2,938 patients, has recently been completed. It found 27 studies with 1,025 patients that reported RMP concentrations; these were low in 63% (95% confidence interval 51%, 74%). Twenty-seven studies with 812 patients reported INH concentrations, which were low in 38% (27%, 50%) of patients. Of the 66 studies, none evaluated the impact of monitoring on patient outcomes, and only three evaluated the impact on patient management (J Minion, personal communication).

On the basis of this evidence, therapeutic drug monitoring is suggested for patients with risk factors for altered drug absorption or metabolism and excretion.

(Conditional recommendation, based on weak evidence)

ADVERSE EVENTS

Recognition and appropriate management of adverse drug reactions is an essential part of the treatment program. Physicians and nurses responsible for the treatment of TB should be well acquainted with these reactions (Table 5). Any possible adverse event should be carefully evaluated in order to identify other potential causes or to identify the responsible drug, which is not easy with multiple-drug regimens. It is very important to avoid unnecessary cessation of a first-line drug, as the efficacy of the treatment will be less, the duration longer and the toxicity of a replacement drug possibly worse than that of the drug that was stopped. Once a serious adverse reaction is clearly attributed to any anti-TB drug, the patient should not receive this agent again.

Table 5. Adverse events of first- and second-line drugs[6]

	Common adverse events	Uncommon but important adverse events	Rank for probability of hepatitis*	Rank for probability of rash
First-line drugs				
INH	Rash, hepatitis, neuropathy	CNS toxicity, anemia	2	3
RMP	Drug interactions, rash	Hepatitis, 'flu-like illness, neutropenia, thrombocytopenia	3	1
PZA	Hepatitis, rash, arthralgia	Gout	1	2
EMB	Eye toxicity	Rash	4	4
Second-line drugs				
Fluoroquinolones	Rash	Tendonitis, tendon rupture, QT interval prolongation		
Amikacin	Nephrotoxicity, ototoxicity			

CNS = central nervous system

*1 = most likely / 4 = least likely

Serious adverse reactions (death, life-threatening event, hospitalization, disability) associated with any anti-TB drug should be reported to local public health departments and to Health Canada's Canadian Adverse Drug Reaction Monitoring Program. To report these on-line, see http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php and follow the links.

INH

INH may produce liver dysfunction ranging from asymptomatic, mild elevation of the serum transaminases to liver failure. Risk factors for hepatotoxicity include older age,[26,65] daily alcohol consumption[64] and pre-existing liver disease,[26,66] particularly hepatitis C.[65] INH may interfere with pyridoxine metabolism and cause peripheral neuropathy or other significant reactions (i.e. psychotic episodes). Rash may also occur, as may nausea and vomiting, especially with intermittent regimens administered in combination with RMP. Finally, patients may also note fatigue, drowsiness, headaches or mild hair loss.

RMP

The most important adverse reactions with RMP are hypersensitivity reactions and drug interactions. Hypersensitivity reactions to RMP include skin rash, fever, abdominal pain, thrombocytopenia and a rare hypotensive reaction similar to anaphylactic shock. RMP induces hepatic microsomal enzymes and accelerates the clearance of many drugs metabolized by the liver. These include estrogens, coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonylureas, theophylline, cyclosporin, methadone and ketoconazole. Women using hormonal contraceptives should be advised to use alternative forms of birth control while receiving RMP.

RMP alone is rarely hepatotoxic,[67,68] but combined with INH there is a slightly increased incidence of liver toxicity than with either drug alone.[69] Patients receiving RMP should be informed that their saliva and urine may become orange/red in color but that this is of no significance. Those wearing soft contact lenses should be advised that the drug may lead to permanent discoloration of the lenses from pigmented tears.

PZA

PZA is the most common cause of drug-induced hepatotoxicity and rash in patients taking standard initial therapy.[25] In up to 11% of people taking PZA arthralgias will develop; these can be very painful but are easily managed with non-steroidal anti-inflammatory drugs. Almost invariably PZA will cause elevation of serum uric acid levels, but acute gout is rarely seen except in patients with pre-existing gout. Gastrointestinal upset may also occur with PZA.

EMB

Visual impairment manifested by decreases in visual acuity, visual fields or colour vision is the most significant adverse effect of EMB. Risk factors include higher doses (e.g. 25 mg/kg), older age and renal impairment. In a recent review, incidence was 2 per 1,000 patients taking 15-25 mg/kg for 2-8 months.[70]

Patients should be advised to report any change in vision immediately. Patients who will take EMB for longer than just the initial phase should be referred to an ophthalmologist for periodic assessment of visual acuity, colour vision and visual fields. Monthly nursing assessment of visual acuity and red-green colour discrimination is recommended. EMB-related optic neuritis is usually reversible if the drug is stopped promptly, although resolution can take several months. EMB should be used with caution in children who are too young for monitoring, although a recent review suggests that its use is safe in children.[71] Other side effects, such as rash may also occur.

SUGGESTED MANAGEMENT OF COMMON ADVERSE REACTIONS

Appropriate management of adverse reactions is complicated. If there is uncertainty, consultation with a TB specialist is recommended.

Management of presumed TB drug-induced rash

All of the TB drugs may cause rash, although some cause rash more frequently than others. Mild itching or slight rash may be treated symptomatically without changing TB treatment. It is important to remember that failure and relapse rates are higher with alternative regimens; hence, any decision to stop the first-line drugs should never be made lightly. However, if the rash is generalized, particularly if associated with involvement of mucous membranes, wheezing, hypotension etc, then the following are suggested (based entirely on expert opinion).

RECOMMENDATION

(All conditional recommendations, based on very weak evidence)

- Stop all current drugs, and immediately start at least two alternative TB medications: a fluoroquinolone plus an injectable or an oral second-line agent.
- Review the history carefully, especially with regard to other possible causes of rash, such as food allergies or other drugs taken, including over-the-counter and herbal remedies.
- When rash has resolved restart one TB drug. Give the drug judged least likely responsible but also one of the most effective TB drugs. If history is unclear (which is the norm) give INH.
- Wait 2 to 3 days to verify if rash recurs with INH before starting the second drug – RMP.
- If there is no rash after 2-3 days of RMP give EMB.
- If there is no rash with EMB, assume that the rash was due to PZA. The decision to rechallenge with PZA depends on the need for PZA and the severity of the initial allergic reaction.

If the rash recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust the regimen according to which drug was permanently stopped.

MANAGEMENT OF PRESUMED TB DRUG-INDUCED HEPATITIS

Drug-induced hepatitis can be caused by PZA, INH or RMP, in that order of probability. Diagnosis may be difficult, as symptoms are nonspecific. A feeling of being unwell may be the first sign of impending hepatitis. If the serum transaminase level (aspartate aminotransferase or alanine aminotransferase [ALT]) exceeds five times the upper limit of normal or clinical jaundice develops then the following are suggested (based on entirely on expert opinion).

RECOMMENDATIONS

(All conditional recommendations, based on very weak evidence)

- Stop PZA, INH and RMP, and immediately start at least two alternative TB medications: an FQN plus an injectable, or an FQN plus an oral second-line agent.
- Review the history carefully, especially with regard to other possible causes of hepatotoxicity, such as alcohol or other drugs taken, including over-the-counter and herbal remedies. Check viral serologies (hepatitis A, B and C).
- When transaminases have returned to normal restart one of the three TB drugs stopped earlier. Give RMP, as this drug is the least likely to be responsible and is the most effective TB drug.
- Wait 2 weeks to verify that transaminases remain normal with RMP before starting INH. If initial hepatotoxicity was very severe (ALT >1,000 U/L) it may be wiser not to rechallenge with PZA or with INH; fatalities have been reported with INH rechallenge in this situation. This depends on the need for these two drugs. Consult with a TB specialist.
- If RMP and INH are restarted and transaminases remain normal, assume that the hepatitis is due to PZA. Do NOT rechallenge with PZA.

If hepatitis recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust regimen according to which drug was permanently stopped.

FOLLOW-UP AFTER TREATMENT

As a general rule, patients who have completed treatment and are judged to be cured do not need follow-up after treatment. For patients with HIV/TB or drug-resistant TB, or in whom adherence was at all questionable, regular follow-up every 6 months for 2 years is suggested. All patients should be told to return at any time in the future for evaluation of symptoms that suggest disease relapse, such as persistent cough or fever, hemoptysis or unexplained weight loss.

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CHAPTER 6

TREATMENT OF LATENT TUBERCULOSIS INFECTION

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KEY MESSAGES/POINTS

- Treatment of latent TB Infection (LTBI) can provide important individual and public health benefits – if given to people at high risk of developing active TB. This benefit has been demonstrated only in those with a positive tuberculin skin test (TST).
- Before treatment of LTBI is started, active disease must be excluded carefully by means of history, physical examination and chest radiography. Sputum samples should be sent for smear and culture, or other appropriate investigations should be performed if active disease is considered possible.
- The decision to treat LTBI should be individualized, with consideration of the risks of therapy from adverse events, such as hepatotoxicity, balanced against the risk of development of active disease.
- The current standard for treatment of LTBI is self-administered isoniazid (INH) taken daily for 9 months (9INH), as this shows the best evidence of efficacy.
- Acceptable alternatives include daily self-administered INH for 6 months (6INH), and daily self-administered INH and rifampin (RMP) for 3-4 months.
- Recent publications have reported good efficacy of a new regimen of 12 doses of INH and rifapentine (RPT) taken once weekly under direct observation. However, RPT is only available in Canada through the Special Access Program. If RPT is obtained through this program, clinicians should be aware that further evaluations of the regimen are needed, as adverse events are common, may be serious and are not well understood.
- Directly observed intermittent INH is an acceptable option in settings or populations in which completion rates of daily self-administered INH have been poor. The efficacy of this regimen is unclear although better than placebo in randomized trials. Use of other regimens, given intermittently, has not been studied adequately.
- Because of greater risk of hepato-toxicity in the post-partum period, treatment of LTBI should be deferred in pregnant women until 3 months postpartum unless they are at very high risk of disease (HIV-infected, close contacts, documented TST conversion). Treatment can be safely given to women who are breastfeeding.

- Contacts of patients with INH resistance (but not RMP resistance) should be treated with 4 months daily RMP (4RMP). Contacts of patients with RMP resistance (but not INH resistance) should be treated with 9INH. Contacts of patients with both INH and RMP resistance (but not fluoroquinolone resistance) can be offered therapy with levofloxacin or moxifloxacin daily for 9 months.

GENERAL CONSIDERATIONS

INTRODUCTION

After infection with *Mycobacterium tuberculosis* the risk of active tuberculosis (TB) development is influenced by the time since infection occurred, and the age and other medical conditions or therapies that affect the immune system of the person infected. Risk is highest in the first 1-2 years after infection. Risk is also high in very young children and declines rapidly in the first 5 years of life (see also Chapter 9, Pediatric Tuberculosis). In children, adolescents and adults a number of medical conditions that result in diminished immunity will increase risk of reactivation of latent infection.

The concept that mono-therapy with INH could successfully treat LTBI and prevent TB disease was first reported by Ferebee.[1] This was subsequently confirmed in more than 15 randomized trials involving more than 100,000 patients.[1] In these trials INH was effective, and excess toxicity was not detected. Because INH is also inexpensive it has become the standard first-line treatment of LTBI globally.[2-4]

RISK FACTORS FOR REACTIVATION OF ACTIVE DISEASE FROM LTBI

As summarized in Table 1, there are a large number of conditions that increase the risk of reactivation of active TB from LTBI. Many medical illnesses and therapies can increase the risk of reactivation, but the strongest risk factor is HIV infection. The other problems have in common a reduction or suppression of immune function and include diabetes, renal failure, malnutrition, certain cancers, alcohol overuse and cigarette smoking. Medical therapies that suppress immune function, listed in Table 1, are increasingly important indications for LTBI treatment.

Table 1. Risk factors for the development of active tuberculosis among people with a positive tuberculin skin test (presumed infected with *Mycobacterium tuberculosis)*

Risk factor	Estimated risk for TB relative to people with no known risk factor	Reference number
High risk		
Acquired immunodeficiency syndrome	110 - 170	5
Human immunodeficiency virus infection	50 - 110	6, 7
Transplantation (related to immune-suppressant therapy)	20 - 74	8 - 12
Silicosis	30	13, 14
Chronic renal failure requiring hemodialysis	7 - 50	15 – 18, 46, 47
Carcinoma of head and neck	11.6	19
Recent TB infection ($\leq$2 years)	15.0	20, 21
Abnormal chest x-ray – fibronodular disease	6 - 19	22 - 24
Moderate risk		
Tumour necrosis factor alpha inhibitors	1.5 - 5.8	25, 26, 43
Diabetes mellitus (all types)	2 - 3.6	27 - 29
Treatment with glucocorticoids ($\geq$15mg/d prednisone)	4.9	30
Young age when infected (0-4 years)	2.2 - 5	31
Slightly increased risk		
Heavy alcohol consumption ($\geq$3 drinks/day)	3 - 4	32, 33
Underweight (<90% ideal body weight; for most people, this is a body mass index $\leq$20)	2 - 3	34
Cigarette smoker (1 pack/day)	1.8 - 3.5	35 - 38
Abnormal chest x-ray – granuloma	2	24, 39
Low risk		
Person with positive TST, no known risk factor, normal chest x-ray ("low risk reactor")	1	40
Very low risk		
Person with positive two-step TST (booster), no other known risk factor and normal chest x-ray	0.5	Extrapolated from 40 and 1

TRANSPLANTATION

The immune suppression associated with prevention of rejection confers a risk of progression to active TB nearly as great as HIV infection, with an estimated incidence of over 500/100,000 annually in a Spanish cohort undergoing solid organ transplantation (crude risk ratio [RR] 26.6 compared with the general population).[8] Some clinicians may elect to initiate treatment under close supervision before liver transplantation in candidates with compensated cirrhosis, according to limited safety data.[41]

ANTI-TUMOUR NECROSIS FACTOR (ANTI-TNF) AGENTS

Anti-TNF agents currently licensed in Canada include adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®) and infliximab (Remicade®). Etanercept is a soluble TNF receptor, which binds competitively with circulating TNF; the other agents are monoclonal anti-TNF antibodies.

These agents are used for the treatment of autoimmune, inflammatory conditions, notably rheumatic diseases such as rheumatoid arthritis and inflammatory bowel disease.

Since the initial report of 70 patients in whom active TB developed after infliximab treatment[25] laboratory investigation has demonstrated that anti-TNF agents interfere with both innate and adaptive immune responses essential to containment of LTBI in granulomas.[42] The incidence of active TB appears to be markedly elevated in patients with rheumatoid arthritis (RA) who are administered these medications.[26] Comparing subjects who were receiving vs. those who were not receiving an anti-TNF agent, the RR of active TB after adjustment for age, sex, other comorbidities and other anti-rheumatic drug use was 1.5 (95% confidence interval [CI] 1.1-1.9) . However, a Spanish registry study comparing RA patients who received vs. those who did not receive an anti-TNF agent estimated a crude incidence rate ratio of 5.8 (95% CI 2.5-15.4).[43] It is clear that patients who begin anti-TNF treatment are at higher risk of TB disease than the general population. There are also limited observational data that suggest systematic screening and treatment of LTBI in these individuals successfully reduces the risk of active TB.[43]

CORTICOSTEROIDS

Systemic corticosteroids are administered for a variety of inflammatory conditions, either transiently for flares (as in asthma) or as long-term maintenance treatment (e.g. for rheumatic diseases). As with the anti-TNF agents, systemic corticosteroid use substantially increases the risk of active TB; the risk increases with the amount taken daily and with duration/cumulative dose. For example, patients receiving a daily dose of <15 mg prednisone had an adjusted odds ratio (AOR) of 2.8 (95% CI 1.0-7.9) for development of active TB compared with non-users, and for those taking a highest daily dose of ≥15 mg the AOR was 7.7 (2.9-21.4).[30] Although subjects received systemic corticosteroids for varying durations, risk was clearly elevated with even a single prescription. In another pharmacoepidemiologic study, the adjusted RR for active TB with systemic corticosteroid use (any dosage) was 2.4 (95% CI 1.1-5.4) among RA patients. Similar risks were observed in patients who were new users, defined as 90 days or less since first prescription.[44]

Use of inhaled corticosteroids is associated with more modest risk of active TB (adjusted rate ratio 1.48, 95% CI 1.11-1.97), although this finding was dose related, with an adjusted rate ratio of 1.97 (1.18-3.30) for the highest dose, i.e. ≥1,000 micrograms fluticasone equivalent daily.[45]

As with anti-TNF agents, everyone who is started on a regimen of systemic corticosteroids at daily doses of ≥15 mg prednisone equivalent for 1 month or longer should first be tested for LTBI. However, given the more modest effect of inhaled corticosteroids, screening for LTBI among users is not recommended.

CHRONIC RENAL FAILURE AND HEMODIALYSIS

Patients with end-stage renal disease receiving hemodialysis are at substantially elevated risk of active TB, with cited relative risks ranging from 7-50 times the background incidence.[46] A recent Greek study estimated an RR of over 30 after adjustment for age, body mass index and diabetes.[47] This relates to impaired immunity in the context of chronic uremia.

RADIOGRAPHIC SCARRING

Individuals with fibronodular scarring on chest radiography are at substantially increased risk of TB reactivation, in the absence of previous treatment. Estimated RRs range from 6 to 19.[22,24]

DIABETES

With the growing frequency of obesity and overweight in Canada, the prevalence of diabetes is increasing. It is estimated that over 2 million people in Canada carry the diagnosis of diabetes (over 6% of the Canadian population). Prevalence increases with age, particularly after age 40; the estimated prevalence now exceeds 20% in the 75-79 age group.[50] In addition, the prevalence of diabetes may be elevated in some immigrant and some Aboriginal populations, which also have a higher prevalence of TB infection (see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, and Table 1 in Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations). For example, in a population-based Ontario study, immigrants from South Asia had an adjusted RR of diabetes of 3-4 compared with Canadian-born residents; among those from Latin America, the Caribbean and sub-Saharan Africa the RR was approximately 2.0.[51] A meta-analysis by Jeon and Murray estimated that active TB was 3 times more likely in diabetics than non-diabetics, after adjustment for age.[52] A more recent meta-analysis by Baker and colleagues estimated relative risks ranging from 1.7 to 5 for treatment failure, relapse and death among diabetics.[53]

CANCER

In a recent systematic review and meta-analysis of 18 studies of the risk of active TB development in patients with cancer, the risk compared with the general population was high (incidence rate ratio [IRR] 11.6; 95% CI 7.0-19.2).[19] The relative risk of active TB was markedly increased for all types of cancer although not significantly increased for solid tumours: risk for hematologic malignancies (IRR = 29.6 [11.6-75.7]), solid tumours (IRR = 17 [0.7-391]) and stem cell transplants for hematologic malignancies or hematologic disorders (IRR = 5.3 [2.6-10.9]). The risk of TB in patients with head and neck cancer is difficult to quantify as the studies describing this relationship were not comparable with each other or with other studies included in the review, and the reported cumulative incidence took place over variable periods of time rather than being an annual risk of disease.[54-56]

On the basis of these findings, patients with all types of hematologic malignancies and bone marrow transplant for hematologic malignancy should be offered screening for LTBI, but there is insufficient evidence to offer LTBI screening and treatment to patients with solid tumours.

TOBACCO AND ALCOHOL

Tobacco smoking is associated with increased risk of LTBI (estimated RR 1.7-1.9), active TB disease (RR 2.0-2.7) and death from TB (RR 2.6), according to two recent meta-analyses.[35-37] Another recent meta-analysis suggested that heavy alcohol use (>40 g/day) is also associated with an increased risk of active TB (RR 2.9, 95% CI 1.9-4.6).[57]

INDICATIONS FOR TREATMENT OF LTBI

For consideration of LTBI treatment in an individual patient the risk factors reviewed above and listed in Table 1 are important, as the degree of risk will determine the potential benefit from LTBI treatment. There are two categories of indications for LTBI treatment: recent infection and increased risk of reactivation. Reactivation risks have been considered above; recent infection is common in contacts of patient with active contagious TB (see also Chapter 12). This is also seen in people with documented TST conversion from negative to positive (see Table 2; see also Chapter 4, Diagnosis of Latent Tuberculosis Infection), such as health care workers.

Table 2. Tuberculin skin test cut-points for treatment of latent TB infection

TST result	Indication*
0-4 mm	In general this is considered negative and no treatment is indicated.[†]
	Close contacts in children less than 5 years of age should be treated pending results of repeat skin test 8 weeks after exposure.[‡]
≥5 mm	HIV infection
	Contact with infectious TB within the past 2 years
	Fibronodular disease on chest x-ray (healed TB and not previously treated)
	Organ transplantation (related to immune suppressant therapy)**
	TNF alpha inhibitors
	Other immunosuppressive drugs, e.g. corticosteroids (equivalent of ≥15 mg/day of prednisone for 1 month or more; risk of TB disease increases with higher dose and longer duration)
	End-stage renal disease
≥10 mm	TST conversion (within 2 years)
	Diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day)
	Silicosis
	Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g. head and neck)

*Age ≥35 years is *not* a contraindication to treatment of LTBI if the risk of progression to active TB disease is greater than the risk of serious adverse reactions to treatment.

[†]Treatment with INH of people with HIV infection who were TST negative (0-4 mm) and/or anergic was of no benefit in several randomized trials. Other authorities suggest this treatment may be considered in the presence of HIV infection or other cause of severe immunosuppression AND high risk of TB infection (contact with infectious TB, from high TB incidence country or abnormal chest x-ray consistent with prior TB infection). Hence any decision to give treatment should be individualized in consultation with a TB expert.

[‡]If first TST is negative, begin treatment immediately. Repeat TST 8 weeks after exposure to infectious TB case ended. Treatment can be stopped in a healthy child if repeat TST is negative (<5 mm induration). In children <6 months of age, the immune system may not be mature enough to produce a positive TST, even if the child is infected (See Chapter 9, Pediatric Tuberculosis).

**LTBI therapy is often given to people in whom transplantation is planned but before the actual transplantation.

However, if considered from a public health perspective, treatment of some of these high-risk conditions will have little impact at a population level. This is because the total number of cases attributable to each of these conditions is determined by not only the risk but also the prevalence of the condition. As summarized in Table 3, the World Health Organization has estimated that some widely prevalent conditions contribute more cases than HIV infection to the global burden of TB.[58] Hence, if LTBI treatment of everyone who is malnourished, has diabetes or smokes cigarettes were possible, then this would have the greatest public health impact.

Table 3. Impact of risk factors on the global burden of tuberculosis
(adapted from Lonnroth et al.[58])

Risk factor	Relative risk (compared with healthy person)	Population attributable fraction
HIV infection	35-110	11%
Malnutrition	2-3	27%
Diabetes	3-4	8%
Alcohol abuse	2-3	10%
Cigarette smoking	2-2.5	16%

LTBI TREATMENT IF IMMUNE COMPROMISED AND TST IS NEGATIVE

Multiple randomized trials have compared INH with placebo in HIV-infected individuals who are TST positive or TST negative. Five of these trials were summarized in a meta-analysis. The pooled estimate of reduction in disease compared with placebo was 14% in HIV-infected individuals who were initially TST negative and more than 60% in those who were initially TST positive; the latter finding was significant.[59] These findings were recently confirmed in a large-scale trial in Botswana, in which benefit of INH for 36 months was demonstrated only in those with initial TST of 5 mm or greater (positive).[60] Two trials have compared rate of disease following INH or placebo in HIV-infected individuals who had no response to tuberculin antigens (i.e. were TST negative) or to a panel of common antigens (i.e. were anergic).[61,62] In both trials there was no significant benefit of INH treatment.

Hence, based on these studies, LTBI therapy is not indicated for individuals who are immune compromised and TST negative. In certain circumstances a severely immune compromised patient may be considered at such a high risk of infection and subsequent disease that LTBI treatment may be given presumptively, even with a negative TST or in the absence of a TST. Such treatment should be carefully considered by balancing the risks and benefits on an individual basis.

ADVERSE EVENTS OF THE DRUGS USED TO TREAT LTBI

(See Chapter 5, Treatment of Tuberculosis Disease.)

RECOMMENDATIONS FOR TREATMENT

Recommendations for LTBI treatment are summarized in Table 4. The evidence, from randomized trials, in support of these recommendations is summarized in Table 5.

STANDARD REGIMEN

The standard regimen of first choice is 9 months of daily self-administered INH (9INH).

(Strong recommendation, based on strong evidence)

INH is still considered the standard first-line therapy, given its long history of use, well- known safety profile and demonstrated efficacy in multiple randomized trials conducted in HIV-infected[59,80] and HIV-uninfected populations[1,81] in many settings.

INH is usually self-administered daily. The optimal duration based on a reanalysis by Dr. George Comstock of data from trials among Alaskan Inuit appears to be 9 months.[71] In this reanalysis, protective efficacy against reactivation of TB progressively increased with longer duration of INH, up to a maximum of 90% with 9 months' therapy; there was no further improvement in efficacy with longer duration of therapy.[71]

Pyridoxine (vitamin B6) should be given to minimize the risk of neuropathy in people with risk factors for pyridoxine deficiency (such as malnourished or pregnant individuals) or for neuropathy (patients with diabetes or renal insufficiency). B6 supplements are not routinely needed otherwise.[3]

INH treatment is associated with two major problems. The first is toxicity, particularly hepatotoxicity, which can be fatal. The second problem is the long duration. These two problems result in poor acceptance of this therapy by patients and providers, and poor completion rates by patients. As a result there has been substantial interest and research in shorter regimens that are safer than and at least as effective as INH.

SHORTER ALTERNATIVE REGIMENS

Six months of daily, self-administered INH (6INH) is an acceptable alternative.

(Strong recommendation, based on strong evidence)

This regimen has been documented to achieve better completion rates but has a protective efficacy of only 67%[73] or 69%.[63] In Canada 6INH should be considered a regimen of second choice, even if this regimen is recommended by authorities elsewhere.[4]

Three or 4 months of daily, self-administered INH and RMP (3-4INH/RMP) is also an acceptable alternative.

(Strong recommendation, based on strong evidence)

A number of randomized trials have compared the efficacy and safety of daily self-administered INH and RMP taken together for 3-4 months. These results have been summarized in a recent systematic review meta-analysis, which found that the efficacy and safety of this regimen was similar to 6 to 9 months of INH.[82]

Three months of once weekly, directly observed INH and RPT (3INH/RPT) has acceptable efficacy, but because of high rates of poorly understood hypersensitivity reactions should be used only with very close monitoring.

(Conditional recommendation, based on moderate evidence)

RPT is a rifamycin with a half-life that is 5 times longer than that of RMP. Hence, it can be given as infrequently as once weekly.[69] The 3INH/RPT regimen has been assessed in three randomized trials. In these trials every dose was directly observed, whereas the comparator regimen of INH was self-administered daily. The first, conducted in Brazil, found that this regimen was slightly but not significantly worse than 6 months of INH in preventing active disease among close contacts, with similar toxicity.[79] The second, published in 2011, was conducted in South Africa and reported similar efficacy and toxicity but better completion than 6INH.[74] The third and largest trial involved more than 8,000 mostly HIV-uninfected individuals in the United States, Canada and Spain. In this trial the 3INH/RPT regimen was as efficacious as 9INH, with significantly better completion rates and significantly less hepatotoxicity.[69] Interestingly, the overall rate of serious adverse events was actually higher with the 3INH/RPT regimen because of an excess occurrence of hypersensitivity reactions.[69]

In summary, the evidence to date indicates that this is a very promising regimen that is well accepted, has high completion rates and shows efficacy that is similar to that of 9 months of INH. However, every dose should be directly observed, which can be difficult to organize in some practice settings or populations. More importantly, the occurrence of hypersensitivity reactions, which can be severe, is unexplained. Until this problem is better understood the regimen should be used ONLY under carefully monitored circumstances; patients who are prescribed this regimen should be questioned carefully, before administration of each dose, about any problems that were related to the preceding dose. Therefore, the regimen is not recommended at this time for general use. It is hoped that these adverse reactions will be better understood with more use of the regimen, allowing them to be prevented and/or managed more easily. A second barrier is that RPT is only available in Canada through the Special Access Program (http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php).

Four months of daily, self-administered RMP (4RMP) can be used as an alternative, given excellent safety but uncertain efficacy.

(Conditional recommendation, based on moderate evidence)

In the United States and Canada 4RMP has been recommended as an alternative regimen since 2000.[2,3] Experience with the regimen under program conditions has been good; completion rates have been substantially and significantly better than for 9INH with very low toxicity, particularly hepatotoxicity.[83,84] Two randomized trials have demonstrated superior completion and lower adverse event rates.[68,77] To date, a single randomized trial has evaluated the efficacy of this regimen:[13] 3 months of RMP were compared with 6 months of INH , 3 months of INH/RMP, and placebo. A 63% reduction in disease was achieved with 3RMP, better than the other two regimens and significantly better than placebo.[13] There are no published data on the efficacy of 4RMP, although a large-scale international trial comparing the efficacy of 4RMP and 9INH is ongoing; the results will only be available in 2016. It is anticipated that the efficacy of 4RMP should be better than that of 3RMP, making it close to that of 9INH. Given the consequences of RMP resistance, careful exclusion of active TB is even more important if this regimen is used.

Two months of daily, self-administered rifampin/pyrazinamide (2RMP/PZA) should NOT be used.

(Strong recommendation, based on strong evidence)

In 1989 this regimen was reported to be highly effective in a mouse model of LTB.[85] Several randomized trials were subsequently conducted comparing this regimen with placebo or INH (with varying duration) in HIV-infected populations.[61,73,75] The 2RMP/PZA regimen had efficacy and toxicity similar to those of the comparator INH regimens. Following recommendations for the use of 2RMP/PZA[3] the regimen was adopted enthusiastically by providers and patients. Within a year numerous reports were published of severe, even fatal, hepatotoxicity with use of 2RMP/PZA.[86,87] This led to revised recommendations to restrict its use.[88,89] The regimen is not recommended in Canada.

INTERMITTENT REGIMENS

To enhance the feasibility of directly observed therapy, intermittent LTBI regimens have been assessed in a few randomized trials. Given twice weekly, 6INH resulted in significant reduction of disease compared with placebo in two trials in HIV-infected individuals.[75,76] In the only published trial that has directly compared intermittent with daily INH, thrice weekly 6INH was somewhat less effective than daily 6INH in HIV-infected children.[91] This difference was not significant, but statistical power was limited because the trial was stopped early as a result of a very high rate of disease in the placebo arm. Twice weekly directly observed INH and RMP for 6 months was significantly superior to daily self-administered INH for 12 months in a non-randomized observational study in Saskatchewan.[91]

On the basis of this limited evidence it appears that intermittent regimens with INH offer some benefit relative to nothing (placebo control), but their efficacy relative to daily INH has not been adequately assessed.

Hence, intermittent, directly observed regimens with INH or INH/RMP should be considered alternative regimens and used in selected circumstances or populations where daily, self-administered regimens have had limited success.

(Conditional recommendation, based on weak evidence)

As with active TB, all doses of intermittent regimens for LTBI should be directly observed.

Table 4. Summary of recommended regimens for LTBI treatment

Drug(s)*	Duration	Schedule	Mode of administration	Level of evidence†
Standard regimen				
INH	9 months	Daily	SAP	1
Acceptable alternative regimens				
INH	6 months	Daily	SAP	1
INH/RMP	3 months	Daily	SAP	1
INH/RPT‡	3 months	Once weekly	DOP	1
RMP	4 months	Daily	SAP	2
INH	6-9 months	Twice weekly	DOP	2
INH/RMP	3 months	Twice weekly	DOP	2

INH = isoniazid, RMP = rifampin, RPT = rifapentine, SAP = self-administered prophylaxis, DOP = directly observed prophylaxis.

*For doses of these drugs see Chapter 5.

†Evidence for each regimen is summarized in Table 5. Level 1: multiple randomized trials; Level 2: single randomized trial and/or multiple observational (cohort) studies.

‡Use this regimen with careful monitoring for hypersensitivity reactions – these can be severe. RPT is only available in Canada through the Special Access Program.

Table 5. Summary of evidence to support recommendations
(data taken only from published randomized trials)

Regimen	Duration	Completion	Adverse events	Efficacy*
INH (Daily)	12 months	68%[63] 69%[64] 85%[65]	5.2%[63] 6.1%[64]	67%[66] 93%[63]
	9 months	57%[67] 60%[68] 62%[63] 69%[69] 86%[70]	0[†70] 3.7%[69] 4.0%[68]	90%[71]
	6 months	63%[61] 65%[72] 73%[13] 75%[73] 78%[63] 84%[74]	0.6%[73] 1.9%[74] 2.8%[61] 3.6%[63] 7%[72] 8%[13]	67%[63] 68%[73]
INH (Twice weekly)	6 months	55%[‡75] 72%[‡76]	0[75] 3%[76]	Eq2RMP/PZA[75] 40%[76]
RMP (Daily)	4 months	76%[13] 80%[68] 86%[77]	0[13] 1.5%[68]	63%[13]
INH/RMP (Daily or twice weekly)	3 months	63%[67] 69%[72] 75%[73] 76%[13] 95%[‡74] 97%[78]	0[‡70] 2.3%[73] 3.8%[74] 5%[13] 7%[78] 10%[67] 18%[72]	64%[73] Eq6INH[13,72,74] Eq9INH[67] Eq12INH[78]
INH/RPT** (Once weekly)	3 months	82%[‡69] 95%[‡79] 96%[‡74]	1.0%[79] 1.8%[74] 4.9%[69]	Eq 2RMP/PZA[79] Eq 6INH[74] Eq 9INH[69]

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, RPT = rifapentine, Eq = equivalent to,
12INH = 12 months INH, 9INH = 9 months INH, 6INH = 6 months INH, 2RMP/PZA = 2 months RMP & PZA

*Efficacy estimated from placebo controlled trials or listed as (EqNx), meaning equivalent to the comparator regimen. Estimates shown are for TST-positive patients if these results are provided.

†Study in children

‡Halsey et al.:[75] half of the doses were supervised. Mwinga et al:[76] fully supervised treatment (DOPT).

**RPT available in Canada only through Special Access Program, see text.

OLDER AGE AND LTBI TREATMENT

There is a well-recognized relationship between older age and greater risk of adverse events, particularly hepatotoxicity, during treatment with INH. This relationship was noted in the 1970s[92,93] and in more recent studies.[94,95] In one of the earliest surveillance studies mortality from INH hepatitis was reported only in individuals over the age of 35.[93] This well-known but post-hoc analysis has resulted in the common misconception that only patients under 35 should be treated. However, there is no age at which there is zero risk – hepatotoxicity has been reported in young children,[96] although this is rare (<1 per 1,000). In a recent study patients over the age of 50 had increased rates of hospitalization attributable to liver toxicity from INH.[95] In patients 65 and older, 2.6% were hospitalized for INH-associated hepatotoxicity. The greatest risk of hepatotoxicity was in the elderly with comorbidities; those without comorbidities under the age 65 had low rates of hepatotoxicity that were not age dependent.[95]

As shown in Table 6, the number of patients needing to be treated before harm, rather than good, is caused is more than 100 in those aged under 35, but falls within the range of 9-15 in the elderly.

Patients who are under 65 years old and have no comorbidities should be offered LTBI treatment if they are at moderate or higher risk.

(Conditional recommendation, based on moderate evidence)

However, the risks and benefits should be considered very carefully in people over the age of 65, although therapy may be reasonable in those at high risk of reactivation and without comorbidities. At any age the risk of toxicity should be weighed against the benefit of therapy. In older people with greater risk of toxicity, therapy is indicated only if the risk of disease is high, meaning that they must have recent infection or medical risk factors for reactivation. As an example, a 25-year-old healthy individual with no risk factors for reactivation (detected through pre-employment screening) may be considered for LTBI treatment, but the risks might exceed the benefits if, instead, they were 45 years old. However, the benefits of INH therapy will exceed the risks of toxicity at almost any age in an HIV-infected individual. The reader is referred to a useful on-line tool that may assist in the assessment of likely risk of disease and adverse events in an individual (see: http://www.tstin3d.com).

Table 6. Estimated number needed to harm with isoniazid treatment for LTB, with increasing risk of INH hepatotoxicity (derived from published toxicity estimates)

Age range	Incidence of hepatotoxicity (%)	Number*	95% Confidence interval
<20 yr	0.10	268	69-2513
	0.20	134	35-1256
20-34 yrs	0.25	107	28-1005
35-49 yrs	0.5	54	14-503
	0.75	36	9-335
50-64 yrs	1.0	27	7-251
	1.25	21	6-201
	1.50	18	5-168
	1.75	15	4-144
≥65 yrs	2.0	13	3-126
	2.25	12	3-112
	2.5	11	3-101
	2.75	10	3-91
	3.0	9	2-84

Risk of hepatotoxicity increases with age:
<20 yr: 0.1%-0.2%[97-103]
20-34 yr: 0.3%[104-106]
35-49 yr: 0.5%[104-106]
50-64 yr: 1%-3%[104-106]
≥65 yr: 2%-5%[95,107,108]

* Number of patients needing to be treated before harm, rather than good, is caused.

PREGNANCY OR BREASTFEEDING AND LTBI TREATMENT

INH and RMP are considered safe in pregnancy, although the mother should be given pyridoxine (vitamin B6) supplements.

(Strong recommendation, based on moderate evidence)

An increased risk of hepatotoxicity from INH has been reported in women treated during the first 3 months postpartum.[109]

Hence, deferral of treatment of LTBI until 3 months after delivery is recommended unless there is very high risk of development of disease, such as HIV infection or recent infection.

(Conditional recommendation, based on weak evidence)

Breastfeeding is considered safe for mothers taking INH or RMP, and they should also take pyridoxine (vitamin B6) supplements. Approximately 3% of the maternal dose is excreted in breast milk.[110] This means that even a newborn will not be exposed to a significant dose of INH.

DURATION OF THERAPY (IN HIV-INFECTED INDIVIDUALS)

In settings with a very high incidence of TB disease and accordingly high rates of transmission of TB infection, the benefits of INH therapy for LTBI have not extended far beyond the end of therapy in HIV-infected people. Several trials have examined a longer duration of INH. In Botswana, TST-positive, HIV-infected individuals were randomly assigned to 36 months of INH (36INH) or 6INH followed by 30 months of placebo.[60] The 36INH regimen was associated with substantially and significantly lower rates of disease, but only in subjects who were initially TST positive.[60] In a second study in South Africa, lifelong INH in TST-positive, HIV-infected people was more efficacious than 6INH.[74] However, adverse events were much more common, and compliance fell progressively over time.[74] In Canada such high transmission rates are rarely, if ever, encountered (see: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbcan10pre/index-eng.php).

Prolonged therapy with INH, beyond the standard 9 months, is not recommended in Canada.

(Strong recommendation, based on moderate evidence)

TREATMENT OF PRESUMED DRUG-RESISTANT LTBI

(See also Chapter 8, Drug-Resistant Tuberculosis.)

The question of how to treat presumed drug-resistant (DR) LTBI usually arises in patients who are close contacts of index cases with known drug-resistant TB. There have been no randomized trials of treatment of contacts of any form of DR-TB. Hence, all the recommendations in Table 7 are based on expert opinion rather than evidence of efficacy.

Table 7. Recommended regimens for contacts of drug-resistant index cases

Drug resistance pattern of index case	Recommended regimen*	Level of evidence†
PZA and/or EMB	9INH	1
Mono INH	4RMP	2
Polydrug resistance including INH	4RMP	1
Mono RMP resistance (INH susceptible)	9INH	1
MDR (INH and RMP resistant)	9 FQN: levofloxacin or moxifloxacin	4

PZA = pyrazinamide, EMB = ethambutol, INH = isoniazid, RMP = rifampin, 9INH = 9 months daily INH, 4RMP = 4 months daily rifampin, 6FQN = 6 months daily fluoroquinolone

*All regimens are suggested to be self-administered and taken daily.

†Level of evidence: 1 = multiple randomized trials, 2 = single trial and multiple observational studies, 4 = expert opinion only.

Simply stated, contacts of patients with INH resistance (but not RMP resistance) should be treated with 4RMP.

(Conditional recommendation, based on weak evidence)

Contacts of patients with RMP resistance (but not INH) should be treated with 9INH.

(Strong recommendation, based on strong evidence)

For contacts of patients with multidrug-resistant (MDR) TB, a combination of a later generation fluoroquinolone (FQN) and pyrazinamide (PZA) has been recommended.[3] However, two case series reported very high rates of toxicity and intolerance, and very poor completion rates with this regimen, possibly as a result of the effects of PZA.[111,112]

Daily use of levofloxacin or moxifloxacin for 9 months (*conditional recommendation, based on very weak evidence*) **is recommended**, based on evidence that later generation FQN are generally well tolerated and can adequately replace INH in active TB therapy.[113] However, the tolerability and safety of long-term use of FQN are not well known; patients should be advised of this and monitored closely for adverse events.

Contacts presumably infected with an MDR-TB isolate should be thoroughly educated about symptoms and signs of TB, and the need for immediate medical evaluation if symptoms occur. Because of the limited amount of information about the efficacy of preventive therapy in individuals likely to be infected with an MDR-TB strain, contacts should be followed closely for the 2 years immediately after infection. Contacts of MDR-TB patients who do not accept or tolerate TB preventive therapy or in whom there is no preventive therapy (the source case isolate is resistant to all first- and second-line drugs) should be carefully followed over a period of 2 years (e.g. at 6, 12 and 24 months) for the appearance of signs and symptoms of active disease.

THERAPY IF THERE IS RENAL OR LIVER DISEASE

Therapy for LTBI with INH or RMP does not need to be adjusted for renal insufficiency.[2,3]

Mild hepatic dysfunction is a relative contraindication for INH therapy. In such patients, RMP may be a better choice than INH in view of its lower hepatotoxicity in randomized trials[13,68] and observational studies.[83,84] In patients with severe hepatic dysfunction, INH, RMP and RPT should be avoided altogether. Instead, daily levofloxacin or moxifloxacin for 9 months may be used on the basis of evidence that these agents can replace INH in therapy of active TB;[113] their efficacy for LTBI is unknown. Generally, these agents are very well tolerated, although in a recent report their use was associated with an incidence of hepatotoxicity of approximately 4 per 100,000.[114]

FOLLOW-UP AND MONITORING DURING LTBI THERAPY

For patients receiving self-administered treatment of LTBI the prescription for medication should not exceed a 1-month supply of doses. Exceptions can be made, such as if a patient is travelling.[2,3]

There are two main objectives of follow-up during LTBI therapy: (i) early detection and management of adverse events; and (ii) monitoring and enhancing compliance. Practice varies widely, but contact with patients is recommended every month, at least by telephone if not in person.[2,3] Monitoring of liver function tests is controversial, but the consensus of expert opinion is reflected in Table 8 (all the recommendations in Table 8 are conditional, based on expert opinion, i.e. very weak evidence). If liver transaminases increase beyond 5 times the upper limit of normal (or 3 times in the presence of symptoms) the LTBI regimen should be stopped. (Detailed suggestions for management of adverse events are found in Chapter 5: Treatment of Tuberculosis Disease.)

Adherence can be monitored in several ways. Patients' self-report is notoriously unreliable, as is health care provider assessment.[115] Pill counts are somewhat more reliable, although patients can discard pills rather than swallow them. Urine tests can be performed to detect INH or RMP metabolites. Devices that monitor each time that doses are withdrawn from pill bottles are the most reliable,[116,117] but expensive; simple, reliable devices are still under development. At present there is no perfect way to monitor adherence.

It has been observed that there are large differences in rates of completion of LTBI therapy between programs. Programs with higher rates of completion emphasize patient-centred care, with close follow-up, frequent reminders of the importance of therapy and constant encouragement to complete therapy.[3]

Although rare, severe hepatotoxicity requiring transplantation or leading to death has occurred during INH treatment of LTBI.[118] Therefore, it is recommended that patients receiving INH therapy should be provided with a clear written plan of action, including contact telephone numbers, should symptoms arise. This plan, which should be reinforced by the prescribing health care provider, should recommend that patients contact their health care provider *immediately* if they have symptoms such as anorexia, nausea, vomiting, abdominal discomfort, unexplained fatigue, dark-coloured urine, scleral icterus or jaundice. If they cannot reach their provider they should stop the

INH until they have been seen and evaluated. Evaluation should include a physical examination and investigation of liver transaminase values and bilirubin levels.

Table 8. Suggested follow-up schedule for patients receiving 9INH latent TB treatment*
(Conditional recommendations, based on very weak evidence)

Actions	Start of treatment	1 month	2 month	3 month	4 month	5 month	6 month	7 month	8 month	9 month
Medical evaluation	X	X	X	If needed	X	If needed	X	If needed	X	If needed
Telephone call to patient				X		X		X		X
Compliance assessment		X	X	If needed	X	If needed	X	If needed	X	If needed
Chest radiography	X									
Bilirubin, transaminases										
Age <35	If clinical suspicion of liver disease	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed
Age 35-50	X	X	If needed		If needed		If needed		If needed	X
Age >50 or other risk factors†	X	X	X	X	X	X	X	X	X	X

*Schedule is for treatment with 9INH. If alternative regimen is used, suggest same schedule until end of therapy. All recommendations in this table are based solely on expert opinion.

†These include pregnancy or first 3 months postpartum, history of previous drug-induced hepatitis, current cirrhosis or chronic active hepatitis of any cause, hepatitis C, hepatitis B with abnormal transaminases, daily alcohol consumption or concomitant treatment with other hepatotoxic drugs (e.g. methotrexate). HIV infection is not an independent risk for drug-induced hepatitis.

DOCUMENTATION OF TREATMENT OF LTBI

The drug, dosage, interval (daily, 2x/wk, 3x/wk), mode (directly observed or self-administered), start date, end date and total number of doses taken should be recorded.

FOLLOW-UP AFTER LTBI TREATMENT AND MANAGEMENT FOLLOWING RE-EXPOSURE

There is no need for routine follow-up after completion of LTBI treatment. If a patient refuses or does not complete therapy, then he or she should be instructed carefully regarding the principal symptoms of active TB and instructed to return for evaluation if those symptoms arise. Routine chest radiography has very low yield and is not recommended (see Chapter 3: Diagnosis of Active Tuberculosis and Drug Resistance).

If patients are re-exposed through contact with a case of active contagious TB, there is no value in repeating the tests for LTBI infection ("once positive = no longer useful"[119]).

In immunocompetent people there is evidence that a first episode of TB infection provides approximately 80% protection against development of disease following re-exposure.[120] This benefit is similar to that achieved with 9 months of INH therapy.[71]

Hence, a second course of LTBI treatment is not recommended, even if the re-exposure was close/intense and even if exposure was to a drug-resistant case.

(Conditional recommendation, based on very weak evidence)

However, if there is uncertainty that a previous course of LTBI therapy was taken adequately, then it may be prudent to recommend the patient take a full course of LTBI therapy.

(Conditional recommendation, based on very weak evidence)

In immune compromised individuals, such as HIV-infected people or very young children (under 5), there may not be any effective immunity conferred by prior TB infection.

Therefore, it is recommended that these individuals could be considered for a second course of LTBI treatment.

(Conditional recommendation, based on very weak evidence)

However, this recommendation is not based on any published evidence that such treatment is effective, nor is there broad consensus on the benefits of retreatment of LTBI following re-exposure. Further considerations include how well the individual tolerated previous LTBI treatment, likely adherence to another course of treatment and probable public health consequences if active TB develops.

DOES TREATMENT OF LTBI CREATE DRUG RESISTANCE?

This is a commonly asked question, particularly when dealing with a population with historically low rates of LTBI treatment completion. A systematic review of 13 randomized trials found that the rate of disease with INH-resistant strains was somewhat but not significantly higher in those assigned to INH than to placebo.[121] In a subsequently published trial among HIV-infected people, those assigned to 36 months of INH had a similar rate of INH-resistant TB as the group assigned to 6 months of INH.[60] As well, a large cohort study in the United States found no evidence of increased INH resistance, simply that INH was ineffective in preventing INH-resistant TB.[122] In all studies disease was most likely to develop in those who did not complete INH; hence, the evidence is consistent that INH therapy of LTBI, even when inadequately taken, does not lead to the emergence of resistance. Of course, in all these studies active disease was carefully excluded before mono-INH was begun.

PROGRAM INDICATORS

The ideal LTBI treatment delivery program will achieve, at a minimum, 80% acceptance of treatment among people with LTBI in whom treatment is indicated, and at least 80% of those starting will complete the required number of doses.[2,3]

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CHAPTER 7

NONRESPIRATORY TUBERCULOSIS

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KEY MESSAGES/POINTS

EPIDEMIOLOGY

- Nonrespiratory tuberculosis accounted for 25% of cases of tuberculosis (TB) in Canada in 2010.
- Isolated nonrespiratory TB is more commonly seen in females and foreign-born people.
- Disseminated disease (concurrent involvement of at least two non-contiguous organ sites of the body or the involvement of the blood or bone marrow) is associated with immune-deficiency.

DIAGNOSIS

- Diagnosis of nonrespiratory TB often requires biopsy of the affected organ, and samples must be sent for acid-fast bacteria (AFB) smear and culture.
- All suspected cases of nonrespiratory TB should be assessed for concomitant respiratory TB to determine whether the case is infectious and to assist with diagnosis.

TREATMENT

- In life-threatening nonrespiratory TB disease (meningitis, miliary, pericardial) it is suggested that empiric treatment be commenced while appropriate diagnostic samples are being obtained.
- Six months of standard anti-tuberculous medical therapy is considered adequate for most forms of nonrespiratory TB.
- Given the severity of disease in disseminated and meningeal TB, and the lack of randomized controlled studies comparing different treatment durations, treatment is commonly extended to12 months.
- Adjuvant corticosteroids are recommended in meningeal TB and pericardial TB.

DEFINITION

The terms non-respiratory TB and extra-pulmonary TB are often used interchangeably. In Canada, extra-pulmonary TB refers to everything but pulmonary TB (TB of the lungs and conducting airways, and includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia and tuberculous pneumothorax, isolated tracheal or bronchial TB and tuberculous laryngitis), whereas respiratory TB includes pulmonary TB, plus TB of the pleura, the intrathoracic or mediastinal lymph nodes, nasopharynx, nose or sinuses. Nonrespiratory TB, reviewed in this chapter, refers to all other disease sites not part of respiratory TB.[1]

When comparing data among countries and reviewing the literature it is important to recognize the distinction between respiratory and nonrespiratory TB (as listed above), and pulmonary (disease limited to the lung parenchyma) and extrapulmonary TB.[1-4]

This chapter will review the epidemiology, diagnosis and treatment of nonrespiratory TB disease as defined in Canada.

EPIDEMIOLOGY

Canadian data from the early 1970s indicated that approximately 17% of all TB cases involved primarily a nonrespiratory site.[5,6] The genitourinary system and lymph nodes were the most common nonrespiratory sites of involvement. Both sites of disease were more common in the foreign-born: genitourinary TB was more common among those born in Europe and TB lymphadenitis among those born in Asia.[7]

More recent US data have shown young age and female sex to be independent risk factors for extrapulmonary TB.[8,9] It is important to note that any cause of significant immune suppression (e.g. HIV, tumour necrosis factor (TNF) alpha inhibitors, end-stage renal disease) has been shown to predispose to disseminated TB.[2,10-13]

In 2010, 25% of TB cases in Canada were nonrespiratory (Table 1), of which 50% were in the superficial lymph nodes.[14]

The number of reported cases of respiratory TB in Canada has decreased steadily since the 1980s, whereas the number of nonrespiratory cases decreased by a lesser extent. As a result, the proportion of total cases that were nonrespiratory rose.[2] Similar trends have been reported in the United States.[11] The smaller decline in nonrespiratory cases over recent years is not fully understood. Part of the explanation may be the increasing proportion of TB cases in Canada that are foreign-born, reflecting the shift in immigration from countries with low TB incidence (Western Europe) to those with high TB incidence (Africa, Asia, Central and South America, Eastern Europe).[15] Foreign-born people are significantly more likely to have nonrespiratory than respiratory TB compared with Canadian-born people (Table 1).[14] This may reflect the fact that respiratory, and not nonrespiratory, disease is actively screened for in new immigrants to Canada. Another possibility is the impact of HIV infection on TB morbidity. The incidence of HIV-TB coinfection is higher in certain foreign-born cohorts than among Canadian-born individuals.[16,17] TB patients with HIV infection are more likely to have nonrespiratory TB alone or concurrent with respiratory TB.[10-13]

Table 1. Anatomic site of disease and population groups of patients with TB, Canada 2010

Disease site	Aboriginal*		Canadian-born (other)		Foreign-born		Unknown		Total	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Respiratory[†]	270	81.8	144	78.7	660	63.6	14	53.7	1,088	69.0
Nonrespiratory	36	10.9	33	18.0	310	29.9	10	38.4	389	24.7
Both	24	7.3	6	3.3	68	6.6	2	7.7	100	6.3
TOTAL	330	100	183	100	1038	100	26	100	1,577	100

*****Includes Status and Non-Status Indians, Métis and Inuit.

[†]Includes primary, pulmonary, pleural and "other" respiratory TB.

DIAGNOSTIC CONSIDERATIONS

A high index of suspicion is paramount to the rapid diagnosis of nonrespiratory TB. Any delay in diagnosis could increase the risk of morbidity and mortality for the at-risk patient.[18] Delays in diagnosis of nonrespiratory TB are common, especially when it is present in unusual sites. Symptoms may be nonspecific (e.g. fever, night sweats, weight loss), or an organ-specific presentation may not be considered to be related to TB in the presence of a normal chest radiograph and negative sputum assessment for AFB. When evaluating at-risk patients with fever of unknown origin and site-specific signs and symptoms or patients with biopsy-proven granulomatous inflammation, appropriate steps should be taken to confirm the diagnosis of TB, including repeat sampling if mycobacterial cultures were not obtained.

Whenever practical, every effort should be made to obtain clinical samples for both mycobacteriologic (AFB smear and culture) and histopathologic tests.[7,19,20] Drug susceptibility testing can only proceed with a viable culture, the results of which can have important treatment implications.[7,19,20]

(Strong recommendation, based on strong evidence)

This point cannot be overemphasized: with the rising incidence of resistant *M. tuberculosis*, especially in the foreign-born, it is difficult to provide appropriate treatment when mycobacterial cultures and drug susceptibility test results are not available. A positive tuberculin skin test result supports the diagnosis, but its absence does not rule out the diagnosis and should never be relied on to exclude TB.

The clinical specimens obtained for diagnostic purposes will depend upon the suspected anatomic site of involvement. In general, tissue biopsy yields positive culture results more often than fluid aspiration; both are superior to swabs (please see Table 2 for diagnostic yield estimates). Biopsy material for mycobacterial culture should be submitted fresh or in a small amount of sterile saline.[19,20] Histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further culture confirmation.[19,20] Common histopathologic findings include necrotizing and non-necrotizing granulomatous inflammation, giant cells or epithelioid cells and may rarely demonstrate AFB (see Table 2). Loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas.[88] The utility of nucleic acid amplification (NAA) in nonrespiratory specimens remains incompletely defined. Its major advantage is a rapid diagnosis, generally within 48 hours, and its greatest promise is the early diagnosis of life-threatening disease such as meningeal TB.[35-37] The World Health Organization has not recommended the use of automated polymerase chain reaction (PCR) tests for the diagnosis of nonrespiratory TB to date, but this is an area of active research and thus the recommendation may change in the future.[21,89,90]

Every presumed case of nonrespiratory TB should be assessed for pulmonary TB. How infectious the possible case is depends upon respiratory involvement. Pulmonary involvement in patients with nonrespiratory TB disease can range from 10% to 50%, thus it may be possible to secure a diagnosis of TB with sputum assessment and avoid the need for more invasive sampling.[20]

(Strong recommendation, based on strong evidence)

A diagnosis of nonrespiratory TB, as with all cases of respiratory TB, should prompt an HIV test.

Table 2. Sensitivity and Specificity of Diagnostic Tests in Non-Respiratory Tuberculosis, Low HIV-prevalence

Site	Specimen-Type	Culture	Direct Stain (ZN)	GeneXpert		Histopathology and/or cytology	Fluid ADA		CXRAY	Percentage with Active Pulmonary TB	References
		SN	SN	SN	SP	SN	SN	SP	Percent Abnormal		
TB Lymphadenitis	Sputum	0.05-0.14	0.04	nsr			n/a	n/a	14-42	5.0-15%	26,35-40,
	FNA	0.62-0.79	0.26-0.35	0.60-.77	0.92-.96	0.52-0.83					185-191
	Exisional biopsy	0.71-0.88	0.35-0.53	nr		0.85-1.00					
CNS-Meningitis	Sputum	0.24-0.29	0.02	nsr		n/a	n/a	n/a	30-50	22-24%	22-24,26,155,161-163,189-191
	CSF	0.40-0.80	0.05-0.20	0.29-.85	0.98	n/a	0.79	0.91			
CNS - Tuberculoma	FNA			nsr		0.85-0.92	n/a	n/a			
	Exisional biopsy	0.8	0.33			1	n/a	n/a			
Abdominal TB	Sputum	0.28-0.50	0.05	nsr		n/a	0.95	0.93	50-64% in colonic; 38% in peritoneal	28-50% for colonic; 21% for peritoneal	20,26,127,131-137
	Feces	0.5	0	1	1						
	Ascitic Fluid	0.20-0.80	0.0-0.06	0.05-.57	0.99						
	Peritoneal Biopsy	0.38-0.92	0.05-0.20	nsr		0.9					
	Colon Biopsy	0.36-0.40	0.03-0.14			0.3					
GU TB - Renal	Urine	0.80-.90	0.15-0.30	0.67-.85	1	0.88	n/a	n/a	32-45	13-53% for renal TB; 3% for female genital tract; 25% male genital tract	20,26,55,58,64-75,79-83,189-191
	FNA/Biopsy	1	0.44	Nsr							
GU TB - Scrotal	Urine	0.63-0.93	0.24	0.67-.85	1	0.95					
	Biopsy	0.8	0.25-0.75	Nsr							
GU TB - Female Tract	Menstrual Fluid	0.06	0.05			0.05-0.12					
	Endometrial Biopsy	0.08	0.05								
	Surgical Biopsy	0.08-.11	0.05								
Bone TB	FNA Bone	0.50-0.83	0.30-0.36	0.5	1	0.56-0.89	n/a	n/a	7	7%	20,26,107-109,114-116,189-191
	Synovial Fluid	0.64-0.79	0.19	0.71	1	n/a					
	FNA Paraspinal Fluid	0.9	nr	0.8	1	n/a					
Pericardial TB	Sputum	0.10-0.11		nsr	nsr		n/a	n/a	30	10-11%	20,170-174,192-194
	Pericardial Fluid	0.25-0.77	0.01				0.89-.94	0.68-.89			
	Pericardial Biopsy		0.04			0.34-0.70	n/a	n/a			
Disseminated TB	Sputum	0.53-0.90	0.31-0.37	nsr	nsr	n/a	n/a	n/a	90%	n/a	20,90-94
	Bronchial Wash	0.07-0.27	0.20-0.55			n/a					
	Lung biopsy	0.42-0.54	0.25-.43			0.63					
	Liver biopsy	0.33-.50	0.4			0.88					
	Bone Marrow	0.21-0.25	0.25			0.67					
	Urine	0.33-0.67	0-0,18			n/a					

ZN= Ziehl-Neelsen, ADA = adenosine deaminase, CXRAY = chest radiography, SN = sensitivity, SP = specificity, FNA = fine-needle aspiration, nsr = no significant results, CNS = central nervous system, CSF = cerebrospinal fluid, GU TB = genitourinary TB

CLINICAL PRESENTATIONS

PERIPHERAL TB LYMPHADENITIS

Almost all forms of TB involve regional lymphatics and nodes. Intrathoracic lymph nodes are commonly involved in primary disease, in advanced pulmonary disease and in patients with HIV/AIDS. Intrathoracic nodes may be the major site of TB lymphadenitis seen in TB patients, but this section will focus on extrathoracic lymph nodes and specifically peripheral TB lymphadenitis. Peripheral TB lymphadenitis accounted for 12% of all cases of TB in Canada in 2010 (Table 3), and cervical lymph node TB is the most commonly affected nonrespiratory site.[14]

Table 3. Number of TB cases and incidence per 100,000 population by main diagnostic site, Canada 2010

Disease site	Cases		Incidence per 100,000
	n	(%)	population
Respiratory	1,088	(70.0)	3.2
Nonrespiratory	389	(24.7)	1.1
Peripheral lymph nodes	196	(12.4)	0.50
Miliary/disseminated	16	(1.0)	0.04
Meninges/central nervous system	22	(1.4)	0.06
Abdominal	39	(2.5)	0.1
Bones and joints	39	(2.5)	0.1
Genitourinary	24	(1.5)	0.07
Other*	53	(3.4)	0.16
Both	100	(6.3)	0.19
Total	1,577	100	4.64

*Includes 8 cases with more than one nonrespiratory site identified.

Tuberculous involvement of the lymph glands can be secondary to infection from *M. tuberculosis* as well as other nontuberculous mycobacteria.[91] Nontuberculous mycobacteria (NTM) are most commonly isolated from the cervical lymph nodes and submandibular glands of young (<5 years) Caucasian children.[92] Peripheral TB lymphadenitis has been identified at the anterior and posterior triangles of the neck, supraclavicular and axillary regions, as well as a variety of other nodal sites (Table 2).[10,14,93] Presentation can be at a single nodal site or in multiple sites. A study of TB lymphadenitis in Manitoba found that 18% of cases also had a concurrent diagnosis of TB elsewhere in the body.[93] In general, the disease is most often indolent, and the patient usually presents with an isolated, unilateral, nontender neck mass. The term "scrofula" has been used historically to describe tuberculous involvement of a cervical lymph node with sinus tract formation or ulceration of the overlying skin. Non-nodal symptoms are rare except in individuals infected with HIV/AIDS.[11,12,17] Peripheral lymphadenitis is particularly common among immigrants to Canada from Asian countries such as China, Viet Nam and the Philippines.[93,94] Among these immigrants, young women are especially prone to isolated lymph node involvement.[93,95] High rates of tuberculous lymphadenitis in the foreign-born are well documented in high-income countries.[17,95-97] In Manitoba, the highest incidence of peripheral lymphadenitis has been reported among older Aboriginal women.[93] The reasons for this age-, sex- and ethnicity-related organotropism are unknown.

Fine-needle aspiration (FNA) biopsy of affected lymph nodes is a useful initial procedure with a reported sensitivity of 77%, specificity of 93% and diagnostic accuracy of 62% (see Table 2).[22-27,98,99] If it is non-diagnostic, the highest-yield procedure is an excisional lymph node biopsy, which has a sensitivity of 80%. Incisional biopsies are discouraged because of the risk of sinus tract formation at the biopsy site. Swabs are discouraged because of the limited material obtained and because the hydrophobic nature of the mycobacterial cell wall inhibits the transfer of organisms from the swab to the culture media.[100]

As stressed earlier, specimens must be submitted for both mycobacteriologic and histopathologic analysis. Differentiation of *M. tuberculosis* from the *M. avium* complex (MAC) is important, as treatment of the two conditions is different. *M. tuberculosis* of the superficial lymph nodes should be treated with anti-tuberculous medication, whereas treatment of MAC lymphadenitis may be cured with surgery alone, medical therapy alone or a combination of both approaches, or it may undergo spontaneous resolution without intervention (please see Chapter 11, Nontuberculous Mycobacteria, for details).[101,102]

Medical treatment of tuberculous lymphadenitis results in the uneventful resolution of the condition in up to 80% of patients.[30] The suggested duration of treatment is 6 months.[103-108]

(Strong recommendation, based on strong evidence)

It is important to note that in up to 30% of patients, nodes can appear afresh or enlarge during treatment, possibly as an immune response, but this usually resolves without change in regime or additional therapy and should not be considered evidence of treatment failure.[109] At the end of treatment, 10% of patients may be left with residual nodes, and if after treatment the nodes enlarge or reappear afresh this is usually transient.[109] Such events do not necessarily imply relapse, but repeat FNA for mycobacterial culture can be performed to assess this possibility.[110]

Surgical procedures, other than diagnostic, should be reserved for the relief of discomfort caused by enlarged nodes or tense, fluctuant nodes.[111]

GENITOURINARY TB

Genitourinary TB accounted for 1.5% of all cases of TB in Canada in 2010 (Table 3).[14] The incidence of genitourinary TB has been decreasing over the last two decades in Canada.[7,14] Urinary tract disease is more commonly seen in men and those with end-stage renal disease requiring dialysis.[50]

URINARY TRACT

At the time of primary infection, or in the case of dissemination associated with reactivation, *M. tuberculosis* seeds the vascular renal cortex. Healed granulomatous lesions in the glomeruli can rupture into the renal tubule and become mechanically caught up at the loop of Henle; here granulomatous progression, necrosis and cavitation is likely to ensue in the medullary portion, which has poor host defense. Although both kidneys are usually seeded, severe renal involvement is often asymmetric or unilateral (25%), so that renal failure is uncommon.[51,112,113] Subsequently, through descending infection, the infundibulum, ureter, bladder, prostate, epididymis and testes may be involved.[20,50] A combination of upper and lower tract disease is highly suggestive of TB. Granulomatous lesions, usually in the upper or lower third of the ureter, can cause narrowing of the collecting system and strictures that can progress despite treatment.[50]

Most often, onset of the disease is insidious, and patients present with asymptomatic sterile pyuria, gross hematuria, frequency and dysuria.[114] Back pain or flank pain resembling acute pyelonephritis often reflects calyceal or ureteral obstruction, though renal colic is uncommon. Bladder involvement (with resultant diminished bladder capacity) may present with complaints of an inability to empty the bladder and may be associated with the development of a secondary bacterial bladder infection. It is important to obtain historical information regarding the prior administration of intravesical BCG for the treatment of bladder cancer, as in 1% of patients receiving this treatment local genitourinary disease will develop and in 0.4% disseminated BCG disease.[115]

Ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are useful diagnostic modalities for the assessment of genitourinary TB and are replacing an intravenous pyelogram as the primary method of radiologic investigation. Radiologic abnormalities associated with genitourinary TB are distorted or eroded calyces, overt papillary necrosis, renal parenchymal scarring and calcification (all of which can mimic the changes seen in chronic pyelonephritis).[116-118]

In patients with urinary tract disease, 80% to 90% will have positive urine cultures confirming the diagnosis. Three to six first-void morning urine specimens should be collected for AFB smear and culture to give the highest yield (only 30% to 40% of single specimens are positive).[52-56,113] Antibiotics, such as fluoroquinolones, used to treat superimposed bacterial infection may compromise the laboratory's ability to recover *M. tuberculosis* in urine samples and therefore should be stopped more than 48 hours before urine specimens are collected for mycobacteriologic assessment.[55] Occasionally, FNA of the kidney under ultrasound guidance may be indicated if radiologic assessment is suggestive of renal TB and urine mycobacterial cultures are negative[56,57] (see Table 2 for diagnostic yield).

GENITAL TRACT

Genital tract TB may follow from a renal focus, therefore the diagnosis of genital TB should lead to a search for urinary tract disease. However, disease involving the female genital tract or the seminal vesicles in males is most often due to hematogenous or direct spread from neighbouring organs.[20]

Female

Any site in the female genital tract may be involved; however, for reasons that are unknown, 90% to 100% of patients with pelvic TB have fallopian tube infection, and both tubes are usually involved with resultant high rates of infertility.[112] Pelvic TB is most commonly diagnosed during a work-up for infertility or during evaluation of abnormal uterine bleeding, pelvic pain or adnexal masses. Other less common sites of involvement in the female genital tract include cervical or vulvovaginal, which frequently presents as abnormal vaginal bleeding or ulcers. The diagnosis of female genital TB requires a combination of microbiologic, histologic and radiologic techniques.[59-61] Findings on hysterosalpingography may suggest TB, though, as with renal TB, imaging is often nonspecific and characteristic findings are typically seen only with more advanced disease. Cultures of *M. tuberculosis* can be obtained from several sources, including menstrual fluid, peritoneal fluid, endometrial biopsy or biopsy of abnormal tissue identified during laparoscopy.[59-63,119,120] The sensitivity of these tests for the diagnosis of female genital tract TB is difficult to determine given the lack of a gold standard (see Table 2). Even with adequate treatment for genital TB, subsequent fertility rates range between 10% and 30%.[61,119,121]

Male

As with the female genital tract, any site of the male genital tract can be involved. Epididymo-orchitis is the most common presentation.[112] Penile and prostatic involvements are rare. Male genital TB usually presents with scrotal swelling, sometimes with rectal or pelvic pain and less commonly with epididymitis, hydrocele or, in advanced cases, a discharging sinus ("watering can" perineum).[112] On examination, the epididymis can be rubbery or nodular, and the prostate can be thickened with hard nodules. Between 50% and 75% of patients have palpable thickening of the vas deferens. Urine and discharge from draining sinuses should be sent for AFB smear and culture.[64,65,120,121] If this is non-diagnostic, biopsies (FNA or excisional) should be performed for diagnosis (see Table 2).

Treatment with standard 6-month therapy is usually adequate in genitourinary TB *(conditional recommendation, based on moderate evidence)*. Surgery is not indicated except for symptom relief, complications or failure to respond to appropriate antituberculous therapy.[50,68]

There are high rates of associated pulmonary disease described in renal TB and male genital TB, thus assessment for associated pulmonary disease is recommended.[7,20,50,51,66-68,112,113]

MILIARY/DISSEMINATED TB

The term miliary TB was originally a pathologic and then radiologic description of the clinical disease caused by the widespread hematogenous dissemination of bacteria to most organs of the body.[122] Bacteria enter the bloodstream at the time of primary infection before the host's immune system has fully responded, or later, during reactivation of latent infection.[123] The disease may be manifest as a miliary pattern on the chest radiograph, which is characterized by 1-5 mm nodules, or, among those without a miliary pattern on chest radiograph, as a bone marrow aspirate/biopsy or a blood culture positive for *M. tuberculosis*, or as generalized TB at postmortem examination.[20,122] For this discussion, the terms miliary and disseminated are interchangeable.

Only 16 cases of miliary TB were reported in Canada in 2010 (Table 3). While the incidence in Canada has remained relatively stable for the last decade it has risen in the United States, largely because of HIV/AIDS. When the incidence of TB is high, disseminated TB occurs most commonly in childhood (especially <1 year of age). When the incidence of TB is low, it is mainly a disease of adults, especially people who are elderly, malnourished or HIV-infected or who have other conditions associated with impaired cell-mediated immunity, such as solid organ transplantation, renal failure, TNF alpha inhibitor use and steroid use. Fever, night sweats, anorexia, weight loss and weakness are common, respiratory or other organ-specific symptoms less so. A significant proportion present with fever of unknown origin, and the findings on chest radiography and tuberculin testing may be negative.[123] Choroidal tubercles seen on fundoscopy are very suggestive of the diagnosis. Most often, the presentation is subacute or chronic, though acute fulminant presentations can occur, with shock and acute respiratory distress syndrome.[124] The nonspecific and often variable presentation frequently leads to a delay or lack of diagnosis and a high mortality rate.[125]

Diagnosis of miliary TB is difficult, and a high index of suspicion with institution of therapy before a diagnosis is confirmed is recommended to prevent morbidity and death.[126]

(Strong recommendation, based on moderate evidence)

Laboratory findings are nonspecific, though hematologic abnormalities are common. Up to one-third of cases do not have the classic discrete micronodular or "miliary" pattern on chest radiograph. High-resolution CT is more sensitive though not necessarily specific for miliary TB.[127] Prompt examination by AFB smear and culture of clinical specimens from multiple sites increases the probability of a positive result and may obviate the need for more invasive testing.[20,83-87] Biopsy of lung if the imaging is abnormal (transbronchial, thoracoscopic or surgical), biopsy of liver (highest yield >90%) and biopsy of bone marrow will frequently demonstrate caseating granulomas or AFB on special stains, justifying the early commencement of anti-tuberculous therapy[20,83-87] (see Table 2). In children, gastric washings may be positive. Blood cultures may be positive (especially in those with HIV coinfection), however the mean time to culture positivity is 24.7 days, once again highlighting the importance of empiric treatment in these patients pending confirmation of TB diagnosis.[128] The yield of mycobacterial blood cultures increases in inverse proportion to the absolute CD4 count, and cultures may be positive in up to 50% of HIV-positive patients with CD4 counts less than 100×10^6/L. Liquid culture media specifically designed for the growth of *M. tuberculosis* should be used; these are different from the blood culture bottles used for the isolation of other bacteria.[128]

Standard anti-tuberculous treatment regimens should achieve microbiologic and clinical cure, but longer therapy (i.e. 12 months) can be considered for children and the immune compromised (e.g. those with HIV/AIDS), as well as patients with a slow response to treatment or with drug-resistant disease.[20,129]

(Conditional recommendation, based on weak evidence)

Despite appropriate treatment, mortality from miliary TB remain as high as 20%.[84,86] Negative prognostic indicators include meningeal disease, hematologic abnormalities, late presenta-tion, concomitant diseases, cachexia and anergy.[84,86]

BONE AND JOINT (OSTEOARTICULAR) TB

Bone and joint TB made up approximately 2.5% of all reported cases of TB in Canada in 2010 (Table 3), a proportion that has not changed significantly for decades.

SPINAL/VERTEBRAL DISEASE

Spinal or vertebral TB (Pott's disease) involvement is noted in approximately 50% of bone and joint TB cases.[20] Vertebral bodies remain highly vascular into adulthood, which explains the propensity for bone and joint TB to develop at this site. Infection often starts in the anterior-inferior aspect of a vertebral body, spreads beneath the anterior longitudinal ligament and can lead to disease in adjacent vertebral bodies. The lower thoracic and upper lumbar vertebrae are most often affected in spinal tuberculosis. Thoracic disease is more commonly seen in children, and lumbar disease is more commonly seen in adults.[20,130-132]

Most patients present with slowly progressive back pain. Fever and constitutional symptoms are not common unless in conjunction with extraspinal or disseminated disease. Complications include paraspinous fluid collections that have a typical fusiform appearance on imaging and that can progress to psoas muscle abscesses. Advanced disease may lead to spinal cord or nerve root compression with resulting neurologic deficits.[130-132]

Radiographic findings can be helpful in suggesting the diagnosis but are nonspecific and should not be used to make a definitive diagnosis.[20] White blood cell scans and bone scans will be positive in osteoarticular TB, suggesting infection and activity. CT and MRI findings suggestive of vertebral TB include anterior vertebral involvement of thoracic or lumbar vertebrae adjacent to the endplate with evidence of marrow edema with minimal sclerosis; discitis of intervening discs with preservation of the disc until late in disease; and large paraspinal abscesses (calcification being very suggestive of TB). MRI is very helpful in investigating spinal cord involvement or damage.[133-139]

As in all other forms of nonrespiratory TB, it is best to confirm the diagnosis microbiologically with AFB smear microscopy and TB culture. Culture and specifically sensitivity data are very important to obtain, given the difficulty in following and documenting cure in bone and joint TB. A CT-guided needle biopsy is the recommended first approach to obtain tissue for assessment when bone TB is being considered. The specimen should be sent for histopathologic assessment, microbiologic assessment (to assess for pyogenic infections) and AFB smear and culture.[69,70] If that assessment is non-diagnostic, a surgical biopsy should be performed for definitive diagnosis and to assess for etiologies other than tuberculosis osteomyelitis. It is important to review the patient for other manifestations of TB disease, as a recent study demonstrated that one-third of patients with spinal TB had evidence of TB elsewhere, and the diagnosis of TB disease was made in one-quarter of patients by obtaining extraspinal specimens (see Table 2).[69,70]

A recent Cochrane review has suggested that early surgical intervention for all cases of spinal TB is not required, and this is consistent with previous literature.[145,146] Surgical treatment of spinal TB should be considered in those with neurologic deterioration and in those less than 15 years of age with significant kyphosis.[145,146]

(Strong recommendation, based on strong evidence)

JOINT/ARTHRITIS TB

Tuberculous arthritis is usually a mono-arthritis affecting large, weight-bearing joints such as the hip or knee. Symptoms can include swelling, pain and loss of function. Focal signs typically associated with septic arthritis, such as local erythema and warmth, are invariably missing, as are constitutional symptoms. Cartilage erosion, deformity and draining sinuses have been associated with late presentation. *M. tuberculosis* has also been associated with prosthetic joint infections. Osteomyelitis affecting other sites in the skeleton is uncommon but has been described. Multifocal presentations can occur in 15%-20% of patients, often in immune-suppressed individuals, and can be misinterpreted as metastases.[71,140]

Radiologic findings suggestive of TB in joints primarily demonstrate the signs of synovial disease with thickening of the synovium and effusions, usually affecting only one joint. Differentiation of tuberculous arthritis from other arthritic conditions can be difficult. MRI changes suggestive of TB include moderate but uniform thickening of the synovium, as compared with the larger and more irregular synovial thickening seen in rheumatoid arthritis. Adjacent soft-tissue abscesses and bony erosions can be seen in tuberculous, pyogenic or rheumatoid arthritis, but the more numerous the abscesses (two or more) the more likely the arthritis is due to TB. Adjacent fasciitis and cellulitis can be seen in both TB and pyogenic arthritis but are more indicative of a pyogenic arthritis.[133,141-143]

Synovial fluid assessment is a reasonable first step in obtaining a diagnosis of tuberculous arthritis. Synovial fluid microscopy for AFB has a low yield (19%), but mycobacterial cultures have been reported as positive in 79% of cases.[70,140,142,143] Synovial biopsy with mycobacterial culture has a reported sensitivity of 94% and may be required if synovial fluid assessment is non-diagnostic (see Table 2).[72-74,134,140,143]

Standard anti-tuberculous treatment regimens will frequently achieve microbiologic and clinical cure. Six months of treatment is recommended when using isoniazid- and rifampin-based regimens.[144]

(Conditional recommendation, based on moderate evidence)

A recent literature review demonstrated the risk of relapse with these regimens in osteoarticular TB of 1.35% with 6 months of treatment, 0.86% with 6-12 months of treatment and 0.5% with treatment regimens longer than 12 months.[144] Increased risk of failure has been associated with extensive disease at the outset of treatment and evidence of sclerotic bony disease.[144] The definition of cure is difficult in bone and joint TB, and follow-up samples are not routinely obtained to demonstrate lack of mycobacterial growth. Alternative definitions of cure have used radiologic markers; however, plain x-rays may never return to baseline, and recent studies in spinal TB have shown that 50% of patients will have MRI evidence of tuberculous activity even at the end of 12 months of treatment.[136,137] Further research into osteoarticular TB may help determine the optimum treatment duration and cure definition. With these concerns, some physicians may extend treatment to 9 to 12 months in complicated patients with osteoarticular TB.

ABDOMINAL TB

Abdominal TB made up approximately 2.5% of all reported cases of TB in Canada in 2010 (Table 3). It was the second most frequent site of nonrespiratory TB involvement in 2010.[14] Abdominal TB includes disease of the intestines, peritoneum and mesenteric glands. The intestines and peritoneum are involved with similar frequency. The pathogenesis of abdominal TB has been attributed to direct infection through swallowing of infected sputum, ingestion of contaminated milk, hematogenous spread from initial primary foci in the lung or later dissemination of reactivated disease, and/or contiguous spread from adjacent organs. Both intestinal and peritoneal TB often present in association with enlarged mesenteric lymph nodes, but occasionally mesenteric adenitis is the only finding.[147,148]

GASTROINTESTINAL

Gastrointestinal involvement usually occurs in the ileocecal, jejunoileal or anorectal area but has been described in the esophagus, stomach and duodenum. Hepatosplenic, biliary tract and pancreatic TB are described but are comparatively rare. Patients with ileocecal TB may present with clinical and radiographic features that are indistinguishable from those of Crohn’s disease, such as chronic abdominal pain (up to 90%), constitutional symptoms and a right lower quadrant mass (25% to 50%).[147,148]

Radiologic investigations for enteric TB can include barium assessment, CT scan and abdominal MRI studies. Radiographic features of enteric TB are nonspecific and difficult to differentiate from inflammatory bowel disease. Associated involvement of the peritoneum and mesenteric lymph nodes is more commonly seen in TB than in inflammatory bowel disease. It is important to assess for pulmonary involvement when considering the diagnosis of enteric TB, as up to 50% of patients with intestinal TB have evidence of active or inactive pulmonary TB on chest radiography.[149-152]

The diagnosis of enteric TB should include stool assessments for AFB smear and culture (up to 50% yield). This should be specifically considered in HIV-positive individuals who are also at risk of gastrointestinal involvement with *Mycobacterium avium/ intracellulare*. Given that the main differential diagnosis of ileocecal TB is that of Crohn’s disease, the next investigative step in diagnosis should be colonoscopy with biopsy for histopathology, as well as AFB smear and culture (up to 80% diagnostic yield) (see Table 2).[42,152-156]

Histopathology findings on colonic biopsy suggestive of TB include the findings of multiple, confluent granulomas with caseous necrosis and ulcers lined with epithelioid histiocytes.[42,153,154] TB PCR assessments of colonoscopy biopsy specimens have been troubled by poor sensitivity and lack of gold standard comparison.[155] If colonoscopy is non-diagnostic, laparoscopy/laparotomy can be considered for definitive diagnosis, as can an empiric trial of anti-TB treatment with the usual concerns regarding empiric therapy.[20,154,155]

PERITONEAL

In those with primarily peritoneal involvement, common presenting symptoms are abdominal swelling, abdominal pain, fever, weight loss and diarrhea.[43,156] Patients with cirrhosis and those undergoing continuous ambulatory peritoneal dialysis are at increased risk. The peritoneum becomes studded with tubercles that leak proteinaceous fluid, clinically identified as ascites. Late presentations of TB peritonitis can be "dry" with predominant fibro-adhesive features ("doughy abdomen") and minimal ascitic fluid.[20,43,156]

Radiologic assessment can be helpful but is not diagnostic. An abnormal chest radiograph can be seen in 38% of patients with peritoneal TB. Ultrasound assessment often demonstrates peritoneal fluid with fine mobile strands. CT scan assessment demonstrates ascites fluid with high attenuation values (20-45 HU) with a thickened and nodular peritoneum. "Dry" TB peritonitis is characterized by omental masses and a hypervascular peritoneum. The commonly associated mesenteric adenopathy can be seen with both modalities.[150,151]

Assessment of ascitic fluid demonstrates an exudative pattern with a predominance of lymphocytes, although when TB peritonitis complicates chronic peritoneal dialysis, neutrophils may predominate.[44,45]Ascitic fluid is rarely smear positive (3%) but can demonstrate positive cultures in up to 80% of samples.[44-46] If ascitic fluid sampling is non-diagnostic, peritoneal biopsy (diagnostic image-guided or laporascopic) for definitive diagnosis should be considered as its diagnostic yield is higher than that of ascitic fluid sampling (see Table 2).[20,44-49]

Ascitic fluid adenosine deaminase (ADA) has shown reasonable sensitivity and specificity for the diagnosis of peritoneal TB in a recent meta-analysis;[157] however, with the low prevalence of tuberculous peritonitis in Canada this test is more helpful in ruling out the disease (negative predictive value) than ruling in the disease (positive predictive value). In addition, a diagnosis based on ADA does not yield the organism or the drug susceptibility profile of the organism, potentially affecting treatment. It is also important to recognize that tuberculosis peritonitis is associated with an elevation in serum CA 125 level, and there are multiple case reports of incorrect diagnosis of metastatic ovarian cancer in the setting of tuberculosis peritonitis when this tumour marker is relied on for a diagnosis of ovarian cancer.[45]

Treatment of abdominal TB follows the standard approach.

(Conditional recommendation, based on moderate evidence)

Surgery is generally advised only in the face of serious complications, such as perforation, bleeding or obstruction.[158]

CENTRAL NERVOUS SYSTEM TB

Central nervous system (CNS) TB includes tuberculous meningitis, tuberculous myelitis and tuberculomas, as well as tuberculous abscesses and cerebritis. In Canada, CNS TB made up 1.4% of all reported cases of TB in Canada in 2010 (Table 3).[14] Meningitis, with or without tuberculoma, occurs in approximately 75% of cases and tuberculoma alone in 25% of patients with CNS TB.[159] Cerebral tuberculomas are thought to be more common in patients with HIV/AIDS and people from low-income countries.[160] CNS involvement is seen in up to 15% to 20% of miliary TB cases, and in up to 50% of these cases it is fatal.[20]

MENINGITIS

TB meningitis should be treated as a medical emergency; time is of the essence in achieving a good outcome, as the condition is frequently associated with devastating consequences: 25% morbidity (i.e. permanent neurologic deficit) and 15% to 40% mortality despite available treatment.[159,161,162] It is believed that the initial lesion is a tubercle in the superficial cortex (subependymal area) or meninges that ruptures into the subarachnoid space (Rich focus). Brain and cranial nerve damage results from the effects of a granulomatous basal exudate (proliferative arachnoiditis). The proliferative arachnoditis may cause both an obstructive hydrocephalus (with subsequent elevation in intracranial pressure) as well as a periarteritis with subsequent thrombosis of blood vessels and brain infarction most commonly in the vessels supplying the basal ganglia and brainstem.[162,163]

The clinical course is characterized by a prodromal headache, malaise, fever and personality changes, followed by meningismus, cranial nerve palsies and confusion, which, if left untreated, can lead to seizures, coma and death within weeks.[161] Outcomes are known to be affected by the following: age, whether hydrocephalus is present at diagnosis, cerebrospinal fluid (CSF) protein levels and, most important, the clinical stage of disease at diagnosis.[164-166] Clinical staging is done at the time of presentation, stage 1 indicating patients who are conscious and rational with no focal neurologic signs, stage 2 patients presenting with lethargy and confusion with focal signs, and stage 3 patients exhibiting stupor, coma and seizures.

Neurologic imaging can suggest the diagnosis. A CT scan or MRI of the brain showing basilar meningeal enhancement, hydrocephalus and infarctions in the supratentorial brain parenchyma and brain stem is highly suggestive of TB meningitis.[167-170]

Lumbar puncture is the usual first diagnostic test to consider in meningitis. At presentation, the CSF measurements are often normal, but subsequent abnormal results include low glucose levels (<45 mg/dL or <2.5 mmol/L [normal 50-80 mg/dL]), elevated protein (100-500 mg/dL or 0.5-5 g/L [normal 15-45 mg/dL]) and a moderate pleocytosis with lymphocyte predominance (cell count 100-500 cells/µL [normal 0-5 white blood cells/µL]).[20,171] The opening pressure is usually elevated.[20,171] Although regularly performed, bacteriologic methods are generally considered inadequate for early diagnosis of TB meningitis because there are too few organisms in the CSF for consistent demonstration by smear, and cultural identification may take several weeks.[164] Serial sampling of CSF for AFB smear and culture may increase the diagnostic yield (up to 87% with daily lumbar puncture for 3 days), and empiric treatment should not be delayed for fear of influencing smear or culture results. The sensitivity of AFB smears may be improved by using the last tube collected, as well as obtaining a large volume sample (10 to 15 mL).[165,166] NAAs are commercially available to identify mycobacteria directly from CSF.

The availability and reliability should be discussed with local laboratories. The major advantage of NAA is a rapid diagnosis, generally within 48 hours, and it is most useful in diagnosing meningeal TB.[21,37,90,172] A positive NAA assay result from the CSF of a patient with a high clinical probability of TB meningitis can be considered a presumptive case, whereas a negative NAA assay in these circumstances cannot be relied upon to exclude the diagnosis.[170] Newer PCR tests amplifying several target gene sites are likely to improve sensitivity in the future.

In meningitis, empiric therapy with standard quadruple therapy should be initiated immediately on suspicion of the diagnosis to prevent complications.

(Strong recommendation, based on moderate evidence)

Isoniazid, rifampin and pyrazinamide all penetrate the CSF well. A meta-analysis has suggested that 6 months of therapy is adequate, although treatment extension to 12 months has been promoted given the severity of disease in tuberculous meningitis and lack of comparative trials.[38,173,174] Given the ability of pyrazinamide to penetrate the CSF well, some physicians promote the use of this medication beyond 2 months; however, specific trials have not confirmed the benefit of this approach to date.[38] Consultation with a TB specialist is recommended in resistant CNS tuberculosis disease given issues of CSF penetration of several second-line agents.[174]

Adjuvant steroid use has been shown to decrease mortality in HIV-negative children and adults with tuberculous meningitis (no evidence of harm with the use of adjuvant steroids in HIV-positive individuals with tuberculous meningitis).

It is therefore recommended that all patients presenting with tuberculous meningitis receive a course of steroids (dose of dexamethasone 0.4 mg/kg IV every 24 hours in adults [2 weeks] and 0.6 mg/kg IV every 24 hours in children [4 weeks], subsequently tapered over a total of 8 weeks).[175-177]

(Strong recommendation, based on strong evidence)

Neurosurgical intervention may be indicated for complications such as hydrocephalus or, less likely, large local collections. [164,175,176]

A recent study has addressed the optimal timing for the initiation of antiretroviral (ARV) therapy in HIV-positive patients with tuberculosis meningitis and has found that early initiation of ARV (within the first 8 weeks of anti-tuberculous treatment) increased morbidity without a mortality benefit.[178] Thus, it is currently recommended that ARV initiation be delayed to 8 weeks in this cohort of patients *(strong recommendation, based on moderate evidence)*. See Chapter 10, Tuberculosis and Human Immunodeficiency Virus.

TUBERCULOMAS

Patients with tuberculoma are usually asymptomatic but may present with headache, seizures (focal or generalized) or focal neurologic signs, depending upon the location of the lesion(s).[20]

Diagnosis of tuberculoma can be suggested by neurologic imaging (CT or MRI) with evidence of ring enhancing lesion(s) with surrounding edema.[167-169] The primary competing diagnosis on CNS imaging is that of cysticercosis. Diagnosis may be obtained with stereotactic biopsy or excisional biopsy (yields provided in Table 2), or an empiric trial of therapy with clinical monitoring can be attempted with radiographic follow-up.[38-41,170-178]

Standard anti-tuberculous therapy for 6 months is recommended, although there are no randomized controlled trials to confirm outcomes in tuberculoma. Adjuvant steroid use in all cases of tuberculoma is not recommended given the lack of randomized controlled trials assessing its effectiveness. Its use can be considered in patients with vasogenic edema and neurologic symptoms, as some case studies have reported decreased neurologic symptoms with the use of adjuvant steroid therapy.[38]

(Conditional recommendation, based on weak evidence)

OCULAR TB

The epidemiology of ocular TB has not been well described in Canada, and there is wide variation reported from around the world. The diagnosis is often problematic given the difficulty in obtaining clinical specimens for mycobacteriologic and histopathologic testing.[179-181] Cases are usually referred to a TB centre by an ophthalmologist for consideration of empiric treatment.

Virtually any part of the eye can be involved. Ocular TB can be characterized by direct infection of external and internal eye structures or an inflammatory hypersensitivity response to mycobacterial antigens, which can lead to retinal vasculitis.[179-181] Direct infection can occur from hematologic dissemination at the time of primary infection or reactivation or, less commonly, direct extension from a site external to the eye.[179-181] Intraocular disease, specifically choroidal TB, is the most common form of ocular tuberculosis.[20,179-181] Choroidal TB can be unilateral or bilateral, and can lead to retinal disease. Patients usually present with decreased visual acuity and often have signs of disseminated TB.

Clinical specimens are easily obtained from external eye structures. Intraocular disease is often a clinical diagnosis, based on ophthalmological findings consistent with TB, evidence of TB infection and response to a clinical trial of anti-tuberculous medications.[179-182] Some studies have suggested that sampling of the anterior chamber fluid for TB PCR may be helpful in confirming the diagnosis.[183]

Standard 6-month TB treatment is suggested for ocular TB.[181]

(Conditional recommendation, based on weak evidence)

However, given the lack of randomized controlled trials there is disagreement in the literature as to the optimal length of treatment in this disease. Some authors recommend discontinuation of therapy if there has been no response after 2 months.[181] Other authors recommend that a minimum of 9 months of therapy is required to achieve cure.[184]

TUBERCULOUS PERICARDITIS

In developed countries the incidence of TB pericarditis has declined alongside the decline in TB incidence, whereas in countries with a high prevalence of HIV and TB coinfection the incidence of TB pericarditis has been steadily increasing.[75]

The pathogenesis of pericardial TB has been attributed to hematogenous spread from initial primary infection or later dissemination of reactivated disease, or contiguous spread from adjacent organs, such as mediastinal lymph nodes. It is often accompanied by tuberculous disease at another site, commonly pulmonary, pleural, mediastinal lymph node and/or peripheral lymph node locations.[20]

The earliest clinical presentation of TB pericarditis is of a serosanguinous exudative effusion that may resolve spontaneously over a few weeks but may progress to cardiac tamponade or pericardial constriction. Common symptoms are nonspecific and are those of the underlying infectious process (fever, night sweats), cardiac compromise (dyspnea, orthopnea) or of disease elsewhere (cough). Physical signs vary depending upon the degree of cardiac compromise.[76,77]

Imaging modalities can include chest radiography, echocardiography, cardiac MRI (helpful in identifying myocardial involvement seen more commonly in HIV-positive individuals) or CT assessment (helpful in identifying mediastinal lymph node involvement).[76,77]

Pericardial fluid assessment typically demonstrates a bloody, exudative effusion that is often predominantly neutrophilic and not lymphocytic. Diagnosis can be made with sampling of pericardial fluid and/or pericardial tissue for AFB smear (4%), culture (25%-75 %) and histopathologic analysis (71%).[76-78] Pericardial fluid ADA and interferon gamma assays have demonstrated reasonable sensitivity and specificity in a recent meta-analysis;[78] however, with the low prevalence of tuberculous pericarditis in Canada these tests are more helpful in ruling out the disease (negative predictive value) than ruling in the disease (positive predictive value).

It is important to remember that pericardial TB is often associated with disease elsewhere, and microbiologic assessment of sputum, pleural effusion, mediastinal lymph node and/or other involved sites can increase the yield of diagnosis significantly. However, given the difficulties in diagnosis and the high morbidity and mortality associated with this condition, empiric treatment may need to be considered (especially in the immunocompromised, as typical histopathology findings may not be present).[78,79]

Six-month anti-tuberculous treatment is recommended and has been shown to reduce the incidence of constrictive pericarditis (10%-20%) and mortality associated with tuberculous pericarditis.[185]

(Strong recommendation, based on moderate evidence)

Adjunctive corticosteroid treatment has been shown in small studies to reduce the mortality and morbidity associated with pericarditis in both HIV-negative and HIV-positive individuals[185,186]

(Strong recommendation, based on moderate evidence)

The recommended adult steroid (prednisone) dosage is 1 mg/kg per day for 4 weeks, tapered slowly over the following 8 weeks. The use of corticosteroids in TB is discussed in Chapter 5, Treatment of Tuberculosis Disease. In patients with recurrent effusions or persistently elevated central venous pressures despite removal of pericardial fluid and use of anti-tuberculous drugs, early pericardiectomy is advised.[185,187]

OTHER TYPES OF NONRESPIRATORY TB

TB can affect any organ or organ system of the body, including the skin, non-nodal glandular tissue (i.e. breast), great vessels and bone marrow.[20,188] It is important to consider TB in the differential diagnosis and submit the appropriate specimens to the laboratory.

TB affecting the skin includes both cutaneous TB (infection of the skin by direct inoculation, contiguous spread from underlying structures or hematogenous spread) and tuberculids (cutaneous hypersensitivity/autoimmune reactions to noncutaneous TB infection).[189] Cutaneous TB disease is not common, as the organism prefers temperatures that are higher than those at the surface of the body. Examples of cutaneous TB are lupus vulgaris, scrofuloderma and tuberculous gumma. Examples of tuberculids are papulonecrotic tuberculid, erythema induratum and erythema nodosum. Erythema nodosum usually implies recent infection and possibly infection that may be more likely to progress to disease. However, it does not necessarily mean underlying active disease.[190]

Diagnosis of cutaneous TB depends on biopsy for histopathology and mycobacterial smear and culture. Diagnosis of tuberculids depends on biopsy specimens demonstrating the typical histopathology of the underlying autoimmune/hypersensitivity reaction and demonstration of TB infection with response to empiric anti-tuberculous therapy.

Standard 6 months of therapy is likely adequate for treatment, and small studies suggest that shorter courses of treatment may be effective[190]

(Conditional recommendation, based on weak evidence)

IMMEDIATELY LIFE-THREATENING FORMS OF TB

Nonrespiratory TB (other than lymph node TB) is more likely to cause a life-threatening complication than is respiratory TB.[14,20] Together, bone and joint, disseminated, CNS, pericardial and adrenal TB account for a relatively small fraction of all reported TB cases, yet they are responsible for a large share of the morbidity and mortality associated with the disease.[14,20] Adrenal insufficiency should be considered in all patients with active or remote TB who are doing poorly, particularly if hypotension, hyponatremia or hyperkalemia is present.[191]

In certain life-threatening forms of nonrespiratory TB, such as CNS, disseminated or pericardial TB, empiric treatment should be instituted with a presumptive diagnosis while confirmation is pending. Successful outcomes of these and other forms of nonrespiratory TB are critically dependent upon the rapidity with which the diagnosis is made and appropriate treatment introduced.[20] Depending upon what drugs remain available for treatment and upon host immune status, multidrug-resistant TB at any site may also be immediately life-threatening.[129]

RECOMMENDED TREATMENT

As a general rule, nonrespiratory TB responds to the same regimens used to treat respiratory TB (see Chapter 5, Treatment of Tuberculosis Disease).[192,193] For example, a 6-month regimen of isoniazid and rifampin supplemented with pyrazinamide for the initial 2 months is as efficacious as a 9-month course of isoniazid and rifampin therapy supplemented for the first 2 months with either pyrazinamide or ethambutol in the treatment of tuberculous lymphadenitis.[194]

The data for the recommendation of a 6-month treatment course for most other forms of nonrespiratory disease is not based on studies as robust as those for pulmonary TB nor is treatment cure as easy to define, thus treatment extension to 9 or 12 months is often considered in patients with complicated conditions.

(Conditional recommendation, based on weak to moderate evidence)

CNS TB and disseminated TB are notable exceptions, in that a longer course of therapy is advised.[193] Unfortunately, in the case of TB meningitis there are no randomized controlled trials to provide guidance as to optimal regimens and length of treatment. As discussed elsewhere, adjunctive therapy with corticosteroids may reduce the inflammatory response and improve outcomes of some forms of nonrespiratory TB, specifically CNS TB and pericardial TB. In contrast to respiratory TB, the management of nonrespiratory TB not uncommonly requires surgical intervention, initially for the purpose of obtaining diagnostic specimens and later in the management of local complications of the disease.

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CHAPTER 8

DRUG-RESISTANT TUBERCULOSIS

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KEY MESSAGES/POINTS

- Globally, the rate of drug-resistant TB is increasing.
- In Canada, two systems are used to track drug-resistant TB: (i) the Canadian TB Reporting System and (ii) the Canadian TB Laboratory Surveillance System.
- The major risk factors for drug-resistant TB in Canada are previous treatment and foreign birth.
- Drug-resistant TB should be suspected in patients who have (i) previously been treated for active TB, (ii) originated from, resided in or travelled to a country where drug-resistant TB is prevalent or (iii) been exposed to a person with infectious drug-resistant TB.
- It is recommended that within programs priority should be given to the prevention, rather than the management, of drug-resistant TB. To prevent resistance it is important to (i) prescribe in proper dosage an appropriate regimen, (ii) ensure that the prescribed regimen is adhered to and that those who abscond from treatment are identified promptly – best achieved by supervising the ingestion of each dose – and (iii) never introduce a single drug to a failing regimen.
- In Canada, it is recommended that all initial isolates of *Mycobacterium tuberculosis* be tested for susceptibility to isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB).
- Further, it is recommended that second-line drug susceptibility tests (DST) should be carried out for all isolates that are RMP-resistant, polydrug-resistant (resistant to two or more first-line drugs other than INH and RMP) and multidrug-resistant (resistant to INH and RMP with or without resistance to other first-line drugs; MDR-TB). Intolerance to these drugs/combinations should also lead to second-line DST.
- For the purpose of these Standards, the third- and fourth-generation fluoroquinolones (FQNs) – levofloxacin and moxifloxacin – are considered interchangeable with INH in the treatment of INH-resistant TB.
- It is recommended that the treatment of MDR-TB be individualized, based upon DST results. Treatment should include a minimum of four drugs to which the initial isolate is susceptible; if at all possible one of these drugs should be an FQN and one an injectable agent (for example, amikacin or capreomycin).
- It is recommended that the initial phase of treatment of MDR-TB be administered for at least 8 months.

- The treatment of MDR-TB is a complex health intervention requiring experience and special expertise. Referral to physicians or centres that offer this experience and expertise is strongly recommended.
- The careful monitoring of patients with drug-resistant TB is important to their safe and successful completion of therapy.
- It is recommended that the treatment of LTBI in close contacts of infectious drug-resistant TB be based upon the DST results of the source case.

INTRODUCTION

People with TB are said to have drug-resistant disease if their strain of *Mycobacterium tuberculosis* is resistant to one or more first-line drugs: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB). The impact of drug resistance on the outcome of TB treatment varies according to which drug, or combination of drugs, is resistant and reflects the different but complementary role each drug plays in the treatment of TB.[1]

Globally, the improper prescription of anti-TB drugs, their proper prescription but unavailability, inadequate supervision or, uncommonly, the malabsorption of these drugs has increased the prevalence of drug-resistant TB. In low- to middle-income countries the resource-driven use of standardized regimens that do not take into account pre-treatment DST results may have inadvertently amplified the problem of drug-resistant TB. In a systematic review and meta-analysis of initial drug resistance and TB treatment outcomes the cumulative incidence of acquired drug resistance with initially pan-sensitive strains was 0.8% (95% confidence interval [CI] 0.5% to 1.0%) compared with 6% (CI 4% to 8%) with initially single drug-resistant strains and 14% (CI 9% to 20%) with initially polydrug-resistant strains.[2]

The fourth global report on *Anti-tuberculosis drug resistance in the world*, produced by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease, describes resistance patterns in 81 countries and 2 special administrative regions of China from 2002 to 2006.[3] The population-weighted mean of resistance to any of INH, RMP, EMB or streptomycin (SM) was 17.0% (95% CI 13.6% to 20.4%) in new cases, 35.0% (CI 24.1% to 45.8%) in previously treated cases and 20% (CI 16.1% to 23.9%) in all TB cases. The global weighted mean of MDR-TB, defined as resistance to at least INH and RMP, the two most important anti-TB drugs, was 2.9% (CI 2.2% to 3.6%) in new cases, 15.3% (CI 9.6% to 21.0%) in previously treated cases and 5.3% (CI 3.9% to 6.7%) in all TB cases. In 2008, an estimated 440,000 cases of MDR-TB emerged globally, India and China accounting for almost 50% of the world's total cases.[4] In the 46 countries that reported continuous surveillance or representative surveys of second-line drug resistance in MDR-TB cases, 5.4% were found to have extensively drug-resistant (XDR) TB, defined as resistance to INH and RMP as well as any fluoroquinolone (FQN) and any one of the second-line injectable agents, amikacin, kanamycin or capreomycin.[3,4]

NATIONAL DRUG-RESISTANT TB TRACKING SYSTEMS

In Canada, two systems are used to track drug-resistant TB.

PHAC CANADIAN TUBERCULOSIS REPORTING SYSTEM (CTBRS)

Provincial and territorial TB control programs participate in the CTBRS national surveillance system by reporting to the Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada (PHAC), all new and re-treatment cases of active TB. Between 2006 and 2010, drug-resistant TB was reported most commonly in people with a past history of TB ("re-treatment cases") and in foreign-born people (see Table 1).[*]

Of 5,807 new active cases of TB, 5.3% had an INH-resistant/RMP-sensitive strain and 0.7% had an MDR strain. Of 427 cases of re-treatment TB, 7.5% had an INH-resistant/RMP-sensitive strain and 2.3% had an MDR-TB strain.[5] Between 2006 and 2010, foreign-born people with TB were 1.9 times more likely to have INH-resistant/RMP-sensitive TB and almost 13 times more likely to have MDR-TB than Canadian-born people. Higher rates of drug resistance among foreign-born people correspond to higher rates of drug resistance in their country or region of birth. Countries in which the majority of the population has access to the DOTS strategy (directly observed treatment, short course; see Chapter 5, Treatment of Tuberculosis Disease) have lower rates of drug resistance.[6] In Alberta the prevalence of MDR-TB was higher among immigrants who arrived in the decade ending in 2011 than in the decades ending in 1991 or 2001 (Figure 1).[7] In Canada, drug-resistant TB cases present earlier after arrival than drug-susceptible TB cases (Figure 2).[8] Immigrants to Canada from the Western Pacific may be at higher risk of MDR-TB due to Beijing/W strains of *M. tuberculosis*.[9] Most TB cases (71.0%) and most MDR-TB cases (84.0%) in Canada were reported in three provinces: BC, Ontario and Quebec.[10]

[*] Before 2008, "re-treatment" cases were referred to as "relapse" cases.

Table 1. Pattern of resistance to INH and RMP in the initial isolate of *M. tuberculosis* complex from TB patients in Canada, by disease type and country of birth, 2006-2010*

		Country of birth							
Resistance pattern	Disease type	Canadian-born		Foreign-born		Unknown		Total	
		N	%	*N*	%	*N*	%	*N*	%
Susceptible to INH and RMP	New active	1,733	84.4	3,600	84.7	89	78.8	5,422	84.5
	Re-treatment	163	7.9	211	5.0	8	7.1	382	6.0
	Unknown	76	3.7	82	1.9	10	8.8	168	2.6
Resistant to INH, susceptible to RMP	New active	66	3.2	268	6.3	3	2.7	337	5.3
	Re-treatment	8	0.4	23	0.5	1	0.9	32	0.5
	Unknown	2	0.1	8	0.2	2	1.8	12	0.2
Resistant to RMP, susceptible to INH	New active	2	0.1	4	0.1	0	0.0	6	0.1
	Re-treatment	1	0.0	2	0.0	0	0.0	3	0.0
	Unknown	1	0.0	0	0.0	0	0.0	1	0.0
Resistant to INH and RMP (MDR-TB)	New active	1	0.0	41	1.0	0	0.0	42	0.7
	Re-treatment	0	0.0	10	0.2	0	0.0	10	0.2
	Unknown	1	0.0	3	0.1	0	0.0	4	0.1
	Total	2,054	100.0	4,252	100.0	113	100.0	6,419	100.0

INH = isoniazid, RMP = rifampin, MDR-TB = multidrug-resistant TB

*Based on the Canadian Tuberculosis Reporting System of TB cases, Public Health Agency of Canada.[5]

Figure 1. Number of foreign-born people with MDR-TB diagnosed in Alberta by year of arrival. The number of cases is represented by the solid line and the trend in MDR-TB case counts by the dashed line.[7]

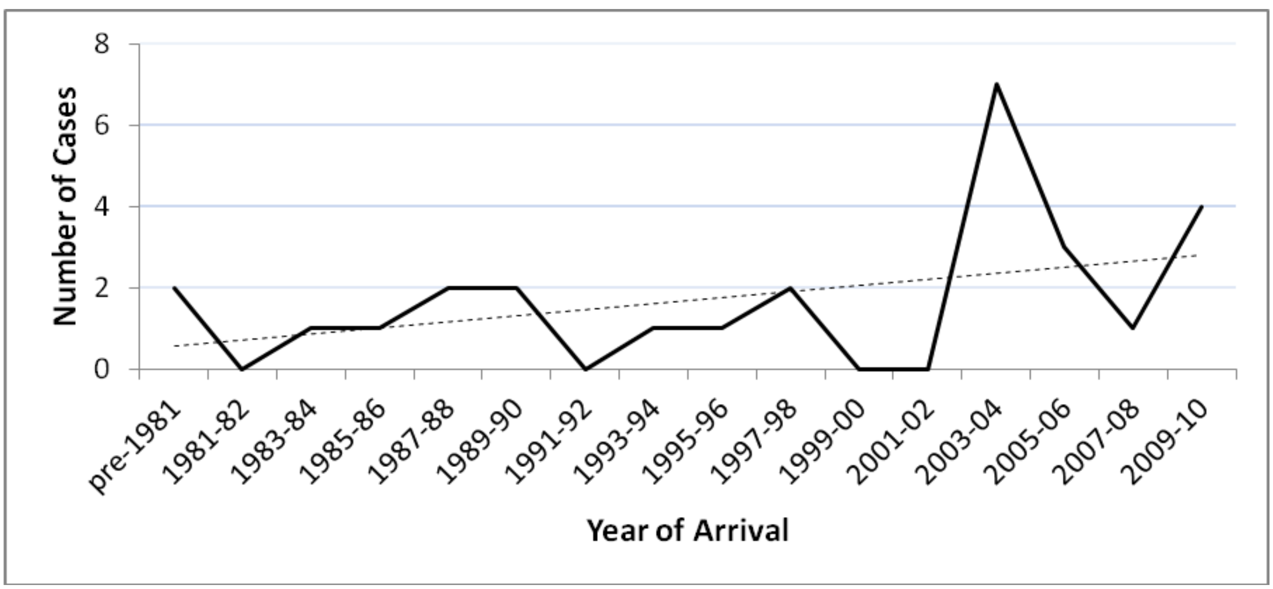
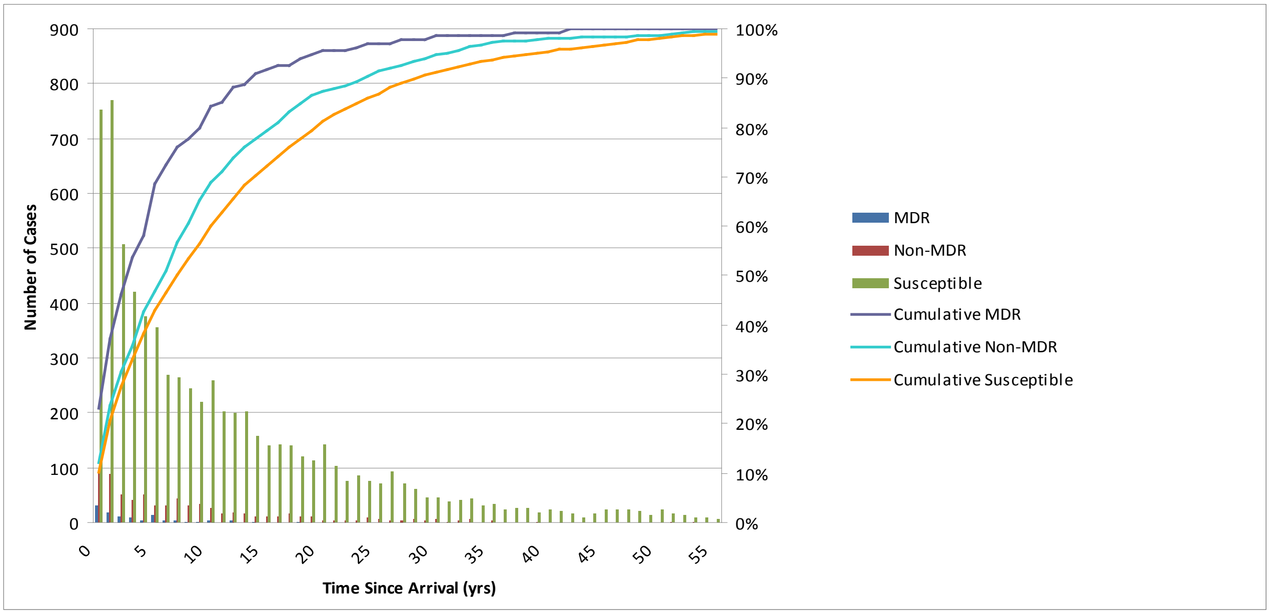


Figure 2. Time from arrival in Canada to diagnosis of foreign-born, culture-positive tuberculosis cases by drug susceptibility pattern of incident case isolate (1997-2008)[8]



Time from arrival to diagnosis was calculated by subtracting year of arrival from year of diagnosis. Year of arrival was known for 6,928 of the 10,589 foreign born cases. Cases with time since arrival between 0 and 55 years displayed.

Bar graph represents the absolute number of cases diagnosed, and line graph represents the cumulative proportion of foreign-born TB cases diagnosed since their time of arrival in Canada.

PHAC CANADIAN TUBERCULOSIS LABORATORY SURVEILLANCE SYSTEM (CTLSS)

This national laboratory-based surveillance system was established in 1998 to collect timely data on TB drug resistance across Canada. Participating laboratories include members of the Canadian Tuberculosis Laboratory Technical Network (covering all provinces and territories). Please see Table 2 for the overall pattern of TB drug resistance in Canada, 2006 to 2010, as reported by this system. For additional reports, see http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php for annual *Tuberculosis Drug Resistance in Canada* reports.[10]

Drug resistance is detected by the performance of *in-vitro* DST on pure cultures of *M. tuberculosis* complex grown from clinical specimens collected from patients (see Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Prompt turnaround times for laboratory results are of paramount importance in rapid diagnosis and appropriate treatment of drug-resistant TB. Recent advances in molecular biology have allowed identification of the genetic loci and biologic mechanisms of resistance to each of the first-line and selected second-line drugs (see next page).

Table 2. Overall pattern of reported TB drug resistance in Canada on initial and follow-up isolates of *M. tuberculosis* complex, 2006-2010*

	Report year											
	2006		2007		2008		2009		2010		2006-2010	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
All isolates	1,389	100	1,267	100	1,356	100	1,331	100	1,276	100	6,619	100
Susceptible isolates	1,263	90.9	1,134	89.5	1,240	91.4	1,204	90.5	1,164	91.2	6,005	90.7
Any first-line drug resistance[†]												
Any resistance to INH	101	7.3	110	8.7	102	7.5	113	8.5	101	7.9	527	8.0
Any resistance to RMP	24	1.7	13	1	19	1.4	21	1.6	18	1.4	95	1.4
Any resistance to EMB	12	0.9	23	1.8	13	1	17	1.3	10	0.8	75	1.1
Any resistance to PZA	16	1.2	27	2.1	22	1.6	18	1.4	25	2	108	1.6
Resistant to ≥1 first line drug	**126**	**9.1**	**133**	**10.5**	**116**	**8.6**	**127**	**9.5**	**112**	**8.8**	**614**	**9.3**
Monoresistant	107	7.7	111	8.8	94	6.9	98	7.4	88	6.9	498	7.5
Polydrug-resistant	3	0.2	11	0.9	7	0.5	11	0.8	6	0.5	38	0.6
MDR	16	1.2	11	0.9	15	1.1	18	1.4	18	1.4	78	1.2

INH = isoniazid, RMP = rifampin, EMB = ethambutol, PZA = pyrazinamide, MDR = multidrug resistant

*Based on the Canadian Tuberculosis Laboratory Surveillance System's drug susceptibility test results for *M. tuberculosis* clinical isolates.[10] These numbers are slightly higher than those in Table 1 as they also include drug-susceptibility test results on selected follow-up cultures.

[†]Some laboratories do not routinely report pyrazinamide or streptomycin resistance.

DRUG RESISTANCE THEORY

Traditionally, drug resistance in TB has been classified into three types.[11]

1. Primary drug resistance

When previously untreated patients are found to have drug-resistant organisms, presumably because they have been infected from an outside source of resistant bacteria. Primary drug resistance is uncommon in Canadian-born people unless they have travelled abroad to a country with a high prevalence of anti-TB drug resistance.

2. Acquired drug resistance

When patients who initially have drug-susceptible TB bacteria later become drug-resistant as a result of inadequate, inappropriate or irregular treatment or, more importantly, because of nonadherence in drug taking. Acquired drug resistance is uncommon in Canadian-born people, perhaps because directly observed therapy (DOT) is frequently used to promote treatment adherence.[12]

3. Initial drug resistance

When drug resistance occurs in patients who deny previous treatment but whose history of prior drug use cannot be verified. In reality it consists of true primary resistance and an unknown amount of undisclosed acquired resistance. It may be best to classify drug resistance in the foreign-born who deny previous drug use as *initial* rather than primary, unless their prior drug use can be verified. The following theory relates to acquired drug resistance.[†]

An understanding of acquired drug resistance theory is key to the prevention of drug-resistant TB. In any large population of *M. tuberculosis* bacteria, there will be several naturally occurring drug-resistant mutants.[13,14] Random mutations that confer resistance to each of the major anti-TB drugs occur at predictable frequencies in *nontreated* populations of TB bacteria (Table 3). A 2 cm diameter TB cavity harbouring 10^8 (100 million) bacteria may contain a few (~100) bacteria resistant to INH, a few (~10) resistant to RMP, a few (~10-100) resistant to EMB, etc. This does not mean that when a sample of this population of bacteria is cultured in the laboratory it will be determined to be resistant to these drugs: for resistance to be reported in the laboratory, at least 1% of the bacterial population needs to be resistant to the drug.[13,15,16] When 1% or more of a bacterial population is resistant to a given drug, clinical success with a regimen that is dependent upon that drug is less likely.[13,15,16]

[†]With respect to the reporting of "disease type" at the time of diagnosis, the terms "new active" and "re-treatment" are used (see Appendix A for definition of terms). Drug resistance among new cases is defined by the WHO as "the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, deny having had any prior anti-TB treatment (for as much as 1 month) and, in countries where adequate documentation is available, for whom there is no evidence of such a history".[3] Drug resistance among previously treated (re-treatment) cases is defined by the WHO as "the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, admit having been treated for tuberculosis for 1 month or more, or in countries where adequate documentation is available in a patient for whom there is evidence of such a history".[3] This category includes patients who have acquired resistance, have been primarily infected with a resistant strain in the past, been treated and subsequently failed or relapsed, as well as patients who have been re-infected.

Table 3. Mutation rates (per bacterium, per generation) and average mutant frequencies (in an unrelated population of bacteria, the proportions of resistant bacilli) for several commonly used drugs[15]

Drug	Mutation rate	Average mutant frequencies
INH (0.2 µg/mL)	1.84×10^{-8}	3.5×10^{-6}
RMP (1.0 µg/mL)	2.2×10^{-10}	1.2×10^{-8}
EMB (5.0 g/mL)	1.0×10^{-7}	3.1×10^{-5}
SM (2.0 µg/mL)	2.9×10^{-8}	3.8×10^{-6}

INH = isoniazid, RMP = rifampin, EMB = ethambutol, SM = streptomycin

The sites of resistance within the mutants are chromosomally located and are not linked. Accordingly, the likelihood of a bacterium *spontaneously* developing resistance to two unrelated drugs is the product of probabilities: for example, for INH and RMP resistance, 1 in 10^8 × 1 in 10^{10} equals 1 in 10^{18}. Because the total number of bacteria in the body, even with far advanced disease, rarely approaches this number (10^{18}), spontaneous evolution of MDR-TB is very rare. As Iseman and Madsen have enunciated so clearly:[17] "This is the salient principle of modern TB chemotherapy. Because naturally occurring two-drug resistance is very uncommon, therapy with two (or more) drugs prevents the emergence of progressive resistance in the following manner: some organisms in the population will be resistant to drug A, and some others will be resistant to drug B, but none will be simultaneously resistant to both drugs. Thus drug B will kill those organisms resistant to drug A, whereas drug A will kill those resistant to drug B. In principle this means a two-drug regimen should be adequate to treat the usual case of *drug-susceptible* TB." Because PZA accelerates bacterial killing in the initial phase and shortens the duration of treatment, and because bacterial loads may occasionally be very large, PZA is usually added to INH and RMP; to prevent acquired resistance to RMP in the event the initial isolate of *M. tuberculosis* (MTB) is resistant to INH, EMB is usually added to INH, RMP and PZA.[1,18] Thus, the standard short-course therapy recommended includes four drugs: INH, RMP, PZA and EMB. If the initial isolate is determined to be fully drug-susceptible, EMB may be discontinued (see Chapter 5, Treatment of Tuberculosis Disease).

If infection (latent TB infection or LTBI) and not disease is present, then it is reasonably safe to assume the bacterial load is small, and treatment need only include a single drug, usually INH.[18]

The emergence of drug resistance is due to the selection of pre-existing resistant mutants in the original bacterial population by "drug pressure." [15,17] For example, if INH alone is prescribed (or is the only first-line drug taken in a multidrug regimen), then it will kill all of the bacteria susceptible to it, including those random mutants resistant to drugs such as RMP and EMB, but it will not kill INH-resistant mutants. These will continue to multiply and will eventually dominate the population because they have a selective advantage in the presence of the drug, and INH will be lost to the armamentarium. The likelihood of this happening is influenced by the duration of such monotherapy: 25% among those receiving INH alone for 2 weeks, 60% for those receiving it for 6 months and 80% for those receiving it for 2 years.[19] If RMP alone is now added to the regimen, then by the same mechanism an MDR strain (i.e. resistant to both INH and RMP) will emerge: RMP will kill all bacteria resistant to INH, but it will not kill those few random mutants in the new population that are resistant to both INH and RMP.[15,17]

This classic theory of drug resistance in TB posits a sequence of events in which the patient effectively receives monotherapy. It does not explain how resistance may emerge solely because of irregularity in drug taking and without monotherapy. Other mechanisms have been proposed to explain resistance under these circumstances.[15,20,21] In essence, they require several cycles of killing (when drugs are taken) and regrowth (when drug taking stops). In each of these cycles there is selection favouring the resistant mutants relative to the susceptible bacterial population. Regrowth back to the size of the original population may occur with the consequent presence of increasing proportions of resistant bacteria at the start of each cycle.

WHEN TO SUSPECT DRUG-RESISTANT TB[22]

The possibility of drug-resistant TB should be considered at the time of selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until DST results become available weeks later can result in unnecessarily inadequate treatment regimens.

In patients who have not yet started their anti-TB drugs the most important predictors of drug-resistant TB are the following:

1. **Previous treatment of TB disease**

   Drug-resistant TB should be suspected if the patient was previously treated for smear-positive or cavitary pulmonary TB; or if the treatment regimen was inadequate or self-administered; or if the patient was nonadherent. Conversely, if the patient is reported to have been lost to follow-up when taking multidrug DOT (i.e. stops all medications at the same time) or has relapsed after completion of a directly observed standardized regimen, then theoretically the likelihood of the isolate being drug-resistant is lower.[23]

   To quote the Francis J. Curry National Tuberculosis Center:[22] “the soliciting of a history of previous TB treatment requires a great deal of patience and attention to detail. In a culturally sensitive and confidential setting one must allow plenty of time, utilize an accurate and unbiased interpreter (if necessary), and be willing to repeat or rephrase a question to obtain the information. One must give the patient encouragement to review accurate information by asking and responding in a nonjudgmental manner. One must ask the patient if he/she has any written information regarding his or her treatment, any old radiographs, etc.” Patients born in Canada may have records of previous treatment at the level of the provincial/territorial TB program. Foreign-born people who have been referred for medical surveillance by Citizenship and Immigration Canada (CIC) because of inactive pulmonary TB, history of TB or another condition that puts them at high risk of active TB may have overseas records of previous treatment that CIC can retrieve (see Chapter 13, Tuberculosis Surveillance and Screening in Selected High-risk Populations).

   If active TB disease is not adequately excluded beforehand, treatment of LTBI, even if only for a month, can result in drug resistance.

2. **Origin from, history of residence in, or frequent or extended (1 month or more) travel to a country/region with high rates of drug resistance**

Although drug-resistant TB is more common in the foreign-born than in other population groups in Canada, transmission of drug-resistant TB from the foreign-born to the Canadian-born is relatively uncommon.[12,24]

3. **Exposure to an individual with infectious drug-resistant TB, including exposure in facilities where drug resistance has occurred, e.g. correctional facilities, homeless shelters or other congregate settings**

While some data suggest that drug-resistant bacteria are less transmissible or less pathogenic once transmitted than drug-susceptible bacteria,[25-34] other data indicate that this may not be so and the transmission risk is offset by longer periods of infectiousness in drug-resistant cases[34,35] or compensatory mutations in drug-resistant bacteria.[36] Clinical evidence of the transmissibility of drug-resistant strains is compelling.[37-40] For practical purposes, i.e. for the ordering of treatment regimens or for contact tracing, drug-resistant bacteria should be considered just as transmissible and just as pathogenic as drug-susceptible bacteria.

4. **Exposure to a person with active TB who has had prior treatment for TB resulting in treatment failure or relapse and whose DST results are not known**

Depending upon the circumstances of the individual case (e.g. likelihood of resistance to more than one first-line drug, severity of disease) an expanded, empiric treatment regimen may be indicated from the outset. Although few countries report drug resistance data disaggregated by HIV status, the two with the most robust data (Latvia and Donetsk Oblast, Ukraine) both showed a significant association between HIV and MDR-TB.[3] This association may have more to do with environmental factors, such as transmission in congregate settings, than biological factors.[41]

A drug-susceptible strain of TB may become drug-resistant, or a monoresistant strain may become polydrug-resistant (see below) during treatment. This is more likely to occur under the following circumstances:

- when the treatment regimen is inadequate to begin with,[15,17]
- when there is intermittent or erratic ingestion of the prescribed anti-TB drugs,[15,17]
- when the patient is malabsorbing one or more of the drugs in the treatment regimen,[15]
- when the patient has cavitary pulmonary TB – cavities contain large numbers of bacteria with correspondingly large numbers of drug-resistant mutants,[42]
- when the patient's disease is sequestered, e.g. TB empyema, a rare condition in which differential penetration of anti-TB drugs has been described.[43]

Rare instances of mixed infection, with selection of a drug-resistant subpopulation during treatment with first-line drugs of a dominant drug-susceptible population, have been reported.[44,45] Also reported have been instances of reinfection with a drug-resistant strain during treatment of disease that is due to a drug-susceptible strain.[46]

Among patients with drug-susceptible pulmonary TB who are treated with standard four-drug therapy, approximately 80% will have negative sputum cultures after 2 months of treatment.[47] Progressive clinical and/or radiographic deterioration or failure of smears or cultures to convert in a timely fashion should lead to suspicion of treatment failure (defined as: [i] sputum smears positive after 5 months or more of treatment or [ii] continued or recurrent positive cultures after 4 or more months of treatment in patients in whom medication ingestion was confirmed) and acquired drug resistance.[47,48] Prior DST results should be reviewed and repeat DST performed. Self-administered treatment, if used, should be abandoned in favour of DOT and, in the event of possible drug malabsorption, serum drug concentrations should be measured.[47] Depending upon the circumstances, consideration should be given to a change or expansion of the treatment regimen. If a decision is made to expand the regimen, then a minimum of two new drugs is recommended – it is inadvisable to add a single drug to a failing regimen. It is advisable for the new drugs to be chosen from those to which the organism is known to be susceptible and/or those that the patient has never received.[22]

MANAGEMENT OF DRUG-RESISTANT TB

For the optimal management of drug-resistant TB, particularly MDR-TB, the following is recommended: the performance of state-of-the-art DST, an uninterrupted supply of first- and second-line anti-TB drugs (see below), the capacity to provide DOT, and access to a physician and team experienced in the management of drug-resistant TB. Steps to ensure that there is an uninterrupted supply of drugs should begin 6 months or more in advance of anticipated need, and drug needs should be estimated as accurately as possible.[49]

The WHO "gold standard" method for *M. tuberculosis* DST for first-line drugs uses an automated liquid culture system and an indirect or direct test.[50] Such phenotypic testing systems are most accurate for INH and RMP and less reliable (the extent to which a test result remains consistent when repeated under identical conditions) and reproducible (the ability of a test to be accurately reproduced or replicated under independent conditions) for PZA, EMB and SM. Liquid culture DST for aminoglycosides, polypeptides and FQNs has been shown to have relatively good reliability and reproducibility.[50] The Clinical and Laboratory Standards Institute, which offers practical operating guidelines that lead to consistent laboratory practices, precision and efficient use of resources, recommends that after having been tested for first-line anti-TB drugs, isolates found to be monoresistant to RMP or to demonstrate resistance to any two of the first-line anti-TB drugs should be tested against a panel of second-line drugs.[51] When FQNs may be added to therapy for cases showing monoresistance to INH (see below), it is also recommended that second-line anti-TB drug testing should be performed.[51] In anticipation of possible INH resistance/intolerance many laboratories are now including routine FQN DST at the time of first-line DST. In Canada in 2011, four laboratories conducted second-line anti-TB drug susceptibility testing: the provincial laboratories in Alberta, Ontario and Quebec, and the National Reference Centre for Mycobacteriology in Manitoba.[10,52]

Among patients with the various patterns of drug resistance, definitive, randomized trials of treatment have not been performed. Recommendations for treatment are based upon less than ideal evidence. With few exceptions the treatment regimens for drug-resistant nonrespiratory TB are the same as those for respiratory TB.[49] Generally, the regimens assume that the pattern of drug resistance has not changed between the time the specimen was collected and the time the phenotypic DST results were reported. Unfortunately, this gap can include several weeks during which the patient is receiving standard or empiric therapy. If the initial isolate of MTB turns out to be polydrug-resistant or MDR, then the standard or empiric regimen may have not only been inadequate in the number and strength of drugs necessary for cure but also have induced resistance to other drugs included in the initial regimen ("amplified" resistance).

There are really only three ways to avoid this scenario: (i) delay treatment altogether until the DST results on the initial isolate are available – rarely an acceptable option, (ii) make certain (within reason) that the empiric regimen is strong enough to cover the possibility that the pre-treatment isolate is highly resistant or (iii) use one of the newer genotypic DST methods that target resistance-conferring mutations and provide an indication, early on, of the existence of resistance to INH and/or RMP (see below).[7]

DIAGNOSTIC CONSIDERATIONS

In Canada, RMP resistance strongly suggests (85% or more of the time) the presence of MDR-TB (see Table 1). Two new WHO-approved molecular tests rapidly detect RMP resistance and by doing so signal the likely presence of MDR-TB: the line probe assays (LPAs) and the Xpert MTB/RIF test.[50] LPAs use a polymerase chain reaction (PCR) hybridization technique to identify members of the MTB complex while simultaneously identifying drug-resistant strains through detection of the most common single nucleotide polymorphisms associated with resistance. The major advantage of LPAs is that they can be performed directly on smear-positive sputum samples, giving rapid (approximately 5 hour) drug susceptibility results without the need for culture. The disadvantages of LPAs are that they are labour intensive and require highly trained personnel, and dedicated laboratory space and equipment. The Xpert MTB/RIF test is a fully automated, closed system that performs both sample preparation and real-time PCR, producing results (detecting MTB complex while simultaneously detecting RMP resistance [targeting the rifampin resistance-determining region of the *rpoB* gene]) in less than 2 hours. The sensitivity and specificity of these two systems for detecting RMP resistance are in the order of 97%-100%.[50,53]

The WHO currently recommends rapid DST of INH or RMP alone over conventional testing or no testing at the time of diagnosis of TB, subject to available resources.[54] The basic assumption is that rapid DST will reduce the delay to the start of appropriate second-line therapy and thus provide benefit to the patient by increasing cure, decreasing mortality, reducing development of additional resistance and reducing the likelihood of failure and relapse. Studies supporting this assumption are just beginning to emerge.[55-57]

With the use of decision analysis modeling,[58] it was found that rapid testing for both INH and RMP at diagnosis rather than later during treatment was the most cost-effective DST strategy available, starting from an MDR-TB prevalence greater than 1% and an INH resistance (other than MDR-TB) greater than 2%, both of which apply to foreign-born TB patients in Canada (Table 1).[8] Origin from, history of residence in or frequent travel to one of the 27 countries[†] with a high MDR-TB burden, especially if residence or travel occurred within recent years, should prompt consideration of rapid testing.[4]

Other patients to consider for rapid testing include those with a history of previous treatment, those who are contacts of MDR-TB cases and those who are HIV coinfected.[4,7] Most Canadian-born TB patients would not be good candidates for rapid testing, given the low positive predictive value of these tests in patient groups in which RMP resistance is rare. It is recommended that use of rapid tests not obviate the need for culture and phenotypic DST. The current status of second-line DST methodology, consensus on reliability and reproducibility, and critical concentrations for different methodologies can be found in a WHO policy document on the rational use of second-line DST.[59] Susceptibility testing to all second-line drugs (cycloserine excepted) is available in Canada.[10,52]

RESISTANCE TO INH WITH OR WITHOUT RESISTANCE TO SM

In Canada, INH resistance is the most common pattern of first-line drug resistance (see Tables 1 and 2). Resistance to INH is usually due to a mutation in either the *katG* or *inhA* gene.[60,61] Less commonly it is due to one or more mutations in other genes, such as the *ahpC* gene.[15]

INH is a prodrug that must be activated by catalase-peroxidase, an enzyme that is regulated by the *katG* gene, in order to be effective against MTB. Mutation of the *katG* gene results in high level resistance to INH (resistance concentration 1.0 µg/mL using solid media [agar proportion method], 0.4 µg/mL using liquid media [indirect proportion method]).[15,62] When the *katG* gene is not mutated, activated INH acts on several *M. tuberculosis* genes, of which those in the *inhA* promoter region are the most important.[62] Mutations in the *inhA* gene or *inhA* promoter region result in low-level resistance to INH (0.2 µg/mL using solid media, 0.1 µg/mL using liquid media). Isolates that have high-level resistance to INH are usually susceptible to ethionamide; isolates that have low-level resistance to INH are usually resistant to ethionamide but susceptible to high dose (15 mg/kg or 900 mg thrice weekly) INH (see below).[62]

In general, on the basis of the research, it is recommended that patients suspected of having INH-resistant TB (with or without SM resistance) should, at a minimum, be started on all four first-line drugs while DST results are pending. An initial four-drug regimen is also advisable whenever the prevailing rate of INH resistance among those in whom there is no history of anti-TB drug use is 4% or more (see Tables 1 and 2).[63]

[†] The 27 countries with a high MDR-TB burden are the WHO member states estimated in 2008 to have at least 4,000 MDR-TB cases arising annually and/or at least 10% of newly registered TB cases with MDR-TB. These countries are Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, DR Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Myanmar, Nigeria, Pakistan, Philippines, Republic of Moldova, Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan and Vietnam.

Recommended regimens for the treatment of INH-resistant TB are listed in Table 4.[64,65] The presence of SM resistance does not affect the efficacy of these regimens. Ideally, each regimen should be regarded as the *minimum* effective therapy, and consideration should be given to administering the regimen as DOT (see Chapter 5).

Direct observation of treatment is especially important in patients with smear-positive pulmonary disease or HIV coinfection. Given that a randomized controlled trial showed moxifloxacin, a fourth-generation FQN, to be equivalent to INH in the initial phase of treatment of smear-positive pulmonary TB, it is assumed that moxifloxacin or, by inference, levofloxacin (a third-generation FQN) would be equally efficacious and therefore could be interchangeable with INH in the treatment of INH-resistant TB.[66]

(Strong recommendation, based on moderate evidence)

Still unresolved is the question of whether an FQN can be used in an intermittent regimen; in theory a thrice weekly regimen of levofloxacin and RMP could be effective as the half-lives of these two drugs tend to be similar. A thrice weekly regimen of moxifloxacin and RMP is not considered advisable, as the half-life of moxifloxacin is longer than that of RMP, resulting in conditions of moxifloxacin monotherapy.[65]

Table 4. Regimens for the treatment of INH-monoresistant TB

Initial phase	Continuation phase
2 months daily (INH) RMP/PZA/EMB*	4-7 months daily or thrice weekly RMP/PZA/EMB[64]
2 months daily (INH) RMP/PZA/EMB	10 months daily or thrice weekly RMP/EMB[22]
2 months daily (INH) FQN/RMP/PZA/EMB†	4-7 months daily or thrice weekly FQN/RMP/EMB[66]

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol, FQN = levofloxacin or moxifloxacin

*If treatment was started with a standard 4-drug regimen, INH (particularly if the resistance is of a high level) can be discontinued once phenotypic resistance is documented.

†If an FQN-containing regimen is used thrice weekly, it should contain levofloxacin and not moxifloxacin. This is because levofloxacin has a shorter half-life than moxifloxacin and is less likely to result in a condition of FQN monotherapy.[65]

ISOLATED RESISTANCE TO RMP

Resistance to RMP is due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase in 95% of cases.[67] Resistance to RMP results in cross-resistance to rifabutin (RBT) in most (~80%) and to rifapentine (RPT) in all (100%) cases. With one exception, i.e. the occurrence of acquired RMP resistance in HIV-infected patients, RMP monoresistance is uncommon. It has been described in AIDS patients taking RBT as prophylaxis against *M. avium* complex and in HIV-coinfected TB patients, in whom the consistent associations are advanced HIV disease (CD4 counts in cases of acquired rifamycin resistance have all been <200 cells × 10^6/L and usually <50 cells × 10^6/L) and the use of an intermittent regimen during the initial phase of treatment.[68-74] In general, for HIV-coinfected TB patients it is recommended that intermittent treatment should be avoided altogether in the initial phase and used selectively in HIV sero-negative patients (see Chapter 5). Treatment options for patients determined to be RMP-monoresistant are given in Table 5.[22,47,75-78]

Table 5. Regimens for the treatment of RMP-monoresistant TB

Initial phase	Continuation phase
2 months daily INH/PZA/EMB/FQN*	10-16 months daily or thrice weekly INH/EMB/FQN[22,47,75]
2 months daily INH/PZA/SM (or other aminoglycoside/polypeptide daily or thrice weekly)	7 months daily or thrice weekly INH/PZA/SM[76]
2 months INH/PZA/EMB daily†	16 months daily or thrice weekly INH/EMB[77,78]

INH = isoniazid, PZA = pyrazinamide, EMB = ethambutol, FQN = levofloxacin or moxifloxacin, SM = streptomycin

*For treatment in patients with extensive cavitary disease or to shorten the duration of treatment (e.g. 12 months), addition of an injectable agent for at least the first 2 months is recommended.

† An injectable agent may strengthen the regimen in patients with extensive disease.

ISOLATED RESISTANCE TO PZA AND EMB

Isolated resistance to PZA or EMB is rare. Isolated PZA resistance occurs genotypically in *M. bovis*.[15] In 2003, PZA monoresistance was reported in isolates of *M. tuberculosis* from Quebec.[79] Patients with these strains had worse clinical outcomes than those with fully susceptible strains.[80] In patients with disease due to PZA-resistant isolates, the total duration of treatment should be 9 months or more. EMB monoresistance will not change the efficacy or duration of treatment with standard regimens.[22,47]

RESISTANCE TO TWO OR MORE FIRST-LINE DRUGS (POLYDRUG-RESISTANT TB) NOT INCLUDING MDR-TB

Polydrug-resistant TB is uncommon in Canada (see Table 2); the range of possible resistance patterns and treatment options are outlined in Table 6.[22,47,49] It is recommended that patients with polydrug-resistant TB be treated with daily DOT in the initial phase and daily or thrice weekly DOT in the continuation phase.

Table 6. Treatment regimens for the management of polydrug-resistant TB[22]

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment	Comments
INH and PZA	RMP, EMB, FQN	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
INH and EMB	RMP, PZA, FQN	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
RMP and EMB	INH, PZA, FQN plus an injectable agent for at least the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
RMP and PZA	INH, EMB, FQN plus an injectable agent for at least the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
INH, EMB, PZA	RMP, FQN plus an oral second-line agent, plus an injectable agent for the first 2-3 months	18 mo	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

INH = isoniazid, PZA = pyrazinamide, RMP = rifampin, EMB = ethambutol, FQN = fluoroquinolone

MDR AND XDR TB

MDR-TB, and especially MDR-TB that is XDR, represents a grave threat to TB prevention and care.[81,82‡] It is recommended that people with MDR or XDR TB be treated with second-line drugs, here listed as the aminoglycosides (streptomycin, amikacin, kanamycin), polypeptides (capreomycin), the FQNs, ethionamide, cycloserine and *para*-aminosalicylic acid, which on balance are weaker, more toxic and more costly than first-line drugs (see Table 7).[22, 47,49,84-87] Furthermore, the duration of MDR or XDR TB treatment is longer, on average 20-24 months. Four MDR-TB case series have been reported in Canada.[7,8,88-90] In all of them, a high proportion of cases were foreign-born (83.3%-95.2%) and undergoing re-treatment (32.9%-67.7%); of those who were HIV tested few were HIV coinfected (0.0%-27.7%). See Table 8. MDR-TB has also been reported in HIV-seronegative Tibetan refugees in Ontario.[91] Longitudinal data from Alberta suggest that MDR-TB cases that report having arrived in Canada in the near past are more likely to have primary drug resistance than those reporting having arrived in the remote past.[7]

[‡] At this time there is no evidence that strains referred to as "totally resistant TB" differ from strains encompassed by XDR TB. Accordingly, for the foreseeable future the term "totally drug-resistant TB" is discouraged.[83]

Table 7. Doses of and common adverse reactions to second-line anti-tuberculosis drugs[22,47,49]

DRUG*	Usual adult daily dosage (pediatric doses)	Peak serum concentration, µg/mL	Recommended regular monitoring	Adverse reactions
Streptomycin	15 mg/kg (20-40 mg/kg daily) (MAX 1 gm)	35-45	Vestibular function, audiometry, creatinine, electrolytes, magnesium and calcium	Auditory, vestibular and renal toxicity. If possible, avoid in pregnancy.
Amikacin Kanamycin Capreomycin	15 mg/kg (15-30 mg/kg daily) (MAX 1 gm)			
Ethionamide	250 mg BID or TID (15-20 mg/kg daily divided BID) (MAX 1 gm)	1-5	Hepatic enzymes, glucose, TSH	GI disturbance, hepatotoxicity, endocrine effects, neurotoxicity. Avoid in pregnancy.
Para-amino salicylic acid	4 g BID or TID (200-300 mg/kg daily in 2-4 divided doses) (MAX 10 gm)	20-60	Hepatic enzymes, electrolytes, TSH	GI disturbance, hepatic dysfunction, hypothyroidism. Avoid if allergic to aspirin.
Cycloserine	250 mg BID or TID (10-15 mg/kg daily divided BID) (MAX 1 gm)	20-35	Mental status, pharmocokinetics of cycloserine	Avoid in patients with epilepsy, mental illness or alcoholism.
Levofloxacin	500-1000 mg OD (< 5 yrs, 15-20 mg/kg daily divided BID) (> 5 yrs, 10 mg/kg OD) (MAX 500 mg)	8-12		GI disturbance, headache, anxiety, tremulousness, prolonged Q-T interval. Avoid in pregnant women or growing children.
Moxifloxacin	400-600 mg OD (10 mg/kg daily OD) (MAX 400 mg)	2.5-4.5		
Rifabutin	300 mg OD		Hepatic enzymes, complete blood count, vision screening	Hepatotoxicity, uveitis thrombocytopenia, neutropenia, drug interactions
Clofazimine	100-300 mg OD	0.5-2.0	Macular pigmentary changes, symptoms	Skin, conjunctiva, cornea, body fluid discoloration, GI intolerance, photosensitivity

BID = twice daily, TID = thrice daily, TSH = thyroid-stimulating hormone, GI = gastrointestinal, OD = once daily

*Kanamycin, capreomycin, ethionamide, *para*-aminosalicylic acid, cycloserine and clofazimine are not available in Canada, except perhaps pursuant to a practitioner's application for treatment of a patient through the Special Access program, available at: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php. Monthly monitoring of body weight is especially important in pediatric cases, with adjustment of doses as children gain weight.[22,85] Pyridoxine may reduce ethionamide and cycloserine neurotoxicity.[86]

Table 8. MDR-TB experience in Canada

Reference	Jurisdiction (time period)	No. of cases	No. (%) foreign-born	No. (%) re-treatment	No. (%) HIV coinfected	Mean no. of first-line drugs to which the isolate was resistant*
88,89	AB & BC (January 1989 to June 1998)	24	20 (83.3)[†]	16 (66.7)	1/17 (5.9)	3.25
90	ON (January 1986 to June 1999)	40	38 (95.0)	26 (65.0)	6/46 (13.0)[‡]	3.20
8	Canada (January 1997 to December 2008)	177	163 (92.1)	55/167 (32.9)	9/38 (23.7)	NA
7[§]	AB (January 1982 to December 2011)	31	27 (87.1)	12 (38.7)	0/22 (0.0)	3.35

AB = Alberta, BC = British Columbia, ON = Ontario

*First-line drugs included isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin.

[†]Two Canadian-born cases were infected with an MDR strain while travelling abroad.

[‡] This study reported only HIV uninfected patients; of all patients over the same time period (*n* = 82), 46 were HIV tested and 6 were positive.

[§]This study included 9 cases from reference #88; there were 31 patients and 32 episodes; one patient (the only MDR-TB case with XDR TB) had a relapse episode.

MAKING A PRESUMPTIVE DIAGNOSIS OF MDR-TB

Prior to the availability of DST results, MDR-TB should be suspected in the following:

- patients who have failed treatment with a standard four-drug regimen;
- patients who were treated for TB in the past and were nonadherent;
- patients who were treated for INH-resistant TB in the past; and
- patients who were close contacts of an infectious MDR-TB case.

In a recent study from California, independent predictors of *acquired* MDR-TB were initial INH resistance, initial RMP resistance, HIV infection and cavitary disease in the absence of DOT throughout therapy.[92] As outlined earlier, the suspicion of drug-resistant TB, and in particular MDR-TB, should precede the introduction of any anti-TB drugs. It should follow meticulous history-taking and the assembly of all available information concerning previous treatment and DST. Patients may recognize drugs as having been taken in the past when they are shown pictures of the drugs or the drugs themselves. Previous treatment with second-line drugs is a strong, consistent risk factor for resistance to these drugs.[93] As informed a prediction as possible should be made about precisely which drugs are likely to be effective in the individual. Great care should be taken to avoid a circumstance whereby an empiric regimen inadequate in the number or effectiveness of drugs allows the emergence of further drug resistance.

Once DST results are available for the current episode, it is recommended that any unnecessary drugs prescribed in an initial surfeit regimen be stopped. Generally, drugs to which there is known *in-vitro* resistance are not recommended. Exceptions to this may be the use of high dose INH in the presence of low-level INH resistance or the use of a fourth-generation FQN in the presence of second-generation FQN (ofloxacin) resistance.[94-98] Previous use of a drug may be associated with reduced clinical response, despite apparent *in-vitro* susceptibility.[19,99]

In a Canadian study, people with MDR-TB were more likely than those with resistant non MDR-TB, and people with resistant non MDR-TB were more likely than those with drug-susceptible TB, to be re-treatment cases.[8] Unless they were infected with a drug-resistant isolate from the outset (primary resistance), it is presumed that some combination of physician error and patient nonadherence to treatment turned fully susceptible organisms, or those with less complex resistance patterns, into MDR-TB.[100] In this regard it is noteworthy that among patients with MDR-TB referred to the National Jewish Medical and Research Center (Denver, Colorado) there were an average of 3.9 physician treatment errors per case.[100] The most common errors were addition of a single drug to a failing regimen, failure to identify pre-existing or acquired resistance, and administration of an initial regimen inadequate in number of drugs or duration of therapy, or both. MDR-TB patients without a history of previous treatment have a better response to treatment than do patients with a history of previous treatment.[101-103]

MDR-TB has been associated with reduced rates of cure and treatment adherence and increased rates of fatality and relapse.[104,105] MDR-TB patients who have XDR TB are yet more difficult to manage, their outcomes yet worse.[106]

TREATMENT REGIMENS FOR PEOPLE WITH A PRESUMPTIVE OR ESTABLISHED DIAGNOSIS OF MDR-TB

The following **recommendations** are based on evidence consisting of multiple observational studies, an individual patient data meta-analysis and expert opinion. *As such, all recommendations below should be considered conditional, based on weak to very weak evidence.* They may change as new and stronger evidence is published. The major sources for the recommendations are the WHO,[54,107] the Francis J. Curry National Tuberculosis Centre,[22] an individual patient data meta-analysis[108] and the Centers for Disease Control and Prevention in Atlanta.[47,109]

- MDR-TB (and de facto XDR TB) should be treated by those with a special interest and expertise in the management of drug-resistant TB.

- Individualized treatment regimens, based upon first- and second-line DST results as opposed to standardized regimens, should be used. If there is reason to question whether resistance to start-up drugs has developed (for example, to PZA or EMB) then repeat DST of these agents should be performed.

- To the extent that it is possible, outpatient (ambulatory) care is encouraged.[54] This recommendation, like the treatment itself and its duration (see below), requires a balance. The aim should be to provide treatment that is optimal in terms of relieving symptoms, reversing infectiousness, preventing further (acquired) resistance, maximizing cure and minimizing mortality while at the same time causing as little inconvenience as possible, e.g. hospitalization, side effects, duration of treatment, surgery. Such a balance serves, among other things, the purpose of promoting adherence. However, it is often the case that a period of hospitalization near the outset of treatment provides an opportunity to achieve rapid control of the infection while securing the patient's future cooperation. Incremental doses of poorly tolerated second-line drugs, such as *para*-aminosalicylic acid, ethionamide and cycloserine, can be introduced under direct observation; peripherally inserted central catheters can be placed for administration of injectable agents; psychosocial issues can be addressed;[110] and the patient and family can be educated. This may have the effect of reducing complications and improving adherence over the long term, justifying the expense of hospitalization.[111]

  Hospitalization is an especially important consideration when the patient is highly infectious (smear-positive) and effective home isolation cannot be provided, when the patient's infection is resistant to many more drugs than just INH and RMP, and when he or she is HIV coinfected. In other patients, and where the necessary program infrastructure, expertise and resources are in place, outpatient care may be possible and has been associated with high cure rates and lower costs.[112] Ideally, patients who require hospitalization should be admitted to specialized centres that meet strict criteria (see Table 9).[113]

- All treatment should be directly observed. DOT for 5 days per week with self-medication on weekends is acceptable if there are no problems with adherence.

- An initial phase of 8 months, followed by a continuation phase of 12-16 months, based upon clinical, radiographic and mycobacteriologic response, and the strength and tolerability of the regimen, is recommended.[54] The minimum total duration of treatment should be 20 months.

- It is suggested that the initial phase should include four or more drugs that are likely to be effective. It is advisable to begin with any first-line agents to which the isolate is susceptible, recognizing that prior use of these drugs in a start-up regimen may, if given for long enough, have induced further resistance and the relative weakness of phenotypic DST for these agents. Then it is recommended that a third- or fourth-generation FQN and an injectable agent be added, on the basis of susceptibilities. This should be followed by the addition of previously unused second-line drugs starting with ethionamide, if there is susceptibility to it, until four to six drugs to which the isolate is susceptible have been prescribed. In adult studies, the inclusion of an FQN is associated with improved outcome.[114] Ideally, the injectable agent should be administered 5-7 days per week (15 mg/kg daily), at least until culture conversion (see below), when thrice weekly dosing (25 mg/kg) is acceptable. The WHO has recently recommended that adults should be given injectable drugs for 8 months because longer durations are associated with better outcomes.[54] This may be appropriate for older children with extensive disease, but for most children 4-6 months of treatment is likely sufficient.[115]

Administration of injectable agents through a central venous line may avoid irritation and persistent pain at the injection site. Whenever drugs such as ethionamide, *para*-aminosalicylic acid, clofazimine or cycloserine are used one may begin with a small dose and increase gradually to the planned dose over a period of several days.[22] The patient may otherwise experience severe drug intolerance and refuse to continue to take the drugs. Therapeutic drug monitoring to place dosages of second-line drugs in the therapeutic range and to minimize toxicity should be performed whenever possible (see Chapter 5).[22, 116] In general, high-end dosing is preferred.[117] The optimum duration and dose and indeed the utility of clofazimine therapy is still debated.[118] Before therapy is initiated adults and children should have their hearing and vision tested as well as their renal and thyroid function. Children old enough to cooperate (usually from about 5 years of age) can be assessed using Ishihara charts and by pure tone audiometry.[119] In designing a treatment regimen for MDR-TB, the potential toxicities (see Table 7), cross-resistances and drug interactions (see Table 10) should be taken into account.[120-122]

- The continuation phase should include three or more drugs likely to be effective.[22,54]

- Antiretroviral therapy is recommended for all patients with HIV and MDR-TB (or other cases requiring second-line anti-TB drugs) irrespective of CD4 cell count, as early as possible (within the first 8 weeks) after initiation of anti-TB treatment.[54]

- In addition to being followed closely for adverse events, patients should be instructed to report immediately any symptoms that suggest drug toxicity.[49]

- Special drug considerations: if an isolate is resistant to RMP, testing for *in-vitro* susceptibility to RBT should be requested. If cross-resistance is not present on phenotypic testing (ideally confirmed on genotypic testing – most RBT-susceptible isolates have RMP *rpoB* mutations at codons 506-508, 511, 512 and 516; most RBT-resistant isolates have RMP *rpoB* mutations at codons 526 and 531) RBT should be added.[123] RBT is as effective as RMP in the treatment of drug-susceptible TB,[124,125] but data on its use for MDR-TB are limited. Although linezolid, an oxazolidinone, is often not listed as a second-line drug, it has been used as such with some success. It has theoretic advantages in that it is rapidly and extensively absorbed after oral dosing, is readily distributed to well-perfused regions of the body and penetrates well into bronchoalveolar tissue. It has activity against *M. tuberculosis in vitro* and inhibits the growth of *M. tuberculosis* in animal models. Linezolid's safety and tolerability are limited by the dose- and duration-dependent occurrence of reversible myelosuppression and peripheral and optic neuropathy.[126-130] In general, a once daily dose of 300 mg is better tolerated than a once daily dose of 600 mg, which in turn is better tolerated than a twice daily dose of 600 mg of linezolid. Observational data suggest that pyridoxine (50-100 mg daily) might mitigate the myelosuppression associated with linezolid.[127]

When extensive resistance to first- and second-line drugs (XDR-TB) has been documented, better outcomes have been reported in those who received more than five drugs.[131] In these patients or in others, such as MDR-TB patients intolerant of second-line drugs, consideration may need to be given to surgery (see below). Several new anti-TB drugs, for example, bedaquiline (TMC207), delamanid (OPC67683), SQ109, PA824, AZD5847 and PNU100480, have entered human trials and may be available for clinical use within the next few years.[79] Results of Phase II trials of bedaquiline and delamanid have been published; outcomes of treatment when these drugs were added to an optimal background regimen were better than with placebo.[132,133] Compassionate use of and expanded access to new drugs are being explored internationally.[134]

It is recommended to make it clear to patients, families and staff from the outset that meticulous adherence to the prescribed regimen is critical to cure. Patients should be counseled to accept minor side effects in order to achieve cure and agree to remain under direct observation with each dose supervised; as well, it is recommended that patients receive in their own language clear and complete instructions before treatment begins, in addition to consistent psychological support during treatment. Traditional roles and responsibilities within families may need to be examined, and social support may need to be provided to secure adherence. Strategies for reducing treatment default in drug-resistant TB have recently been reviewed.[135]

Pregnancy may complicate the management of MDR-TB, and experience with the issues involved is necessary. The teratogenic risks of second-line drugs, the use of holding regimens, the timing of treatment initiation, the risks of vertical and lateral transmission and the role of BCG vaccination in infants have recently been reviewed.[22,49,136,137]

Table 9. Canadian Thoracic Society recommended criteria for specialized centres for the management of MDR-TB patients

- Adequate infection control environment: negative pressure rooms, adequate number of air exchanges/hour, no recirculation of air and patient access to an enclosed outdoor space.
- Expertise.
- Adequate infrastructure to deal with the needs of these patients: psychosocial support, psychiatric and psychological support,[113] nutritional needs, counseling, recreational opportunities, exercise facilities.
- Culturally sensitive environment. In Canada the majority of patients with MDR-TB are born outside of Canada.
- Reliable laboratory support.
- Reliable drug supply.
- Well-established links with public health.
- Well-structured program and follow-up in an outpatient clinic after discharge from the hospital.

Table 10. Cross-resistance and interactions among anti-TB drugs

Cross-resistance

- Resistance to amikacin induces cross-resistance to kanamycin and vice versa.[120]
- Resistance to SM does not induce cross-resistance with amikacin-kanamycin, or capreomycin.[120]
- Isolates acquiring resistance to capreomycin are usually susceptible to kanamycin and amikacin.
- Isolates acquiring resistance to amikacin and kanamycin may or may not be resistant to capreomycin.
- Resistance to one FQN induces class-effect cross-resistance to all other FQNs, though data suggest that this cross-resistance may not be complete. Some isolates resistant to ofloxacin may be susceptible to moxifloxacin.[22,97,98]
- Most isolates resistant to RMP (approximately 80%) are also resistant to RBT.[120] Resistance to RPT is universal in RMP-resistant isolates.
- Cross-resistance to ethionamide may occur when there is low-level resistance to INH.[22]

Drug interactions

- RMP has many drug interactions (see Chapter 5, Treatment of Active Tuberculosis).
- RBT does not induce catabolic enzymes or alter the pharmacokinetics of other drugs to the extent that RMP does (about 40% of that seen with RMP). Nevertheless, the potential for RBT to affect the metabolism of other drugs needs to be considered.[15] Dosage adjustment may be necessary in patients taking antiretroviral therapy.
- INH can result in increased serum concentrations of phenytoin in people taking both drugs.
- Increased risk of neurotoxicity from cycloserine has been associated with concomitant use of INH,[121] ethionamide[121] and FQNs.[122]
- *Para*-aminosalicylic acid and ethionamide have each been associated with hypothyroidism. The probability of hypothyroidism is increased when both agents are used together.[15]

SURGERY FOR MDR-TB

The option of resecting diseased lung tissue becomes more attractive as the number of drugs to which the patient's isolate is resistant increases and the likelihood of a pharmacologic cure decreases. Unfortunately for many patients the extent of disease and/or the severity of the underlying lung function abnormality preclude a surgical option. At the National Jewish Medical and Research Center patients were selected for surgery on the basis of extensive drug resistance, poor response to medical therapy and disease sufficiently localized to permit resection of the bulk of involved lung with enough remaining functioning lung to predict recovery without respiratory insufficiency.[138,139]

The selection of surgical candidates and the timing of adjunctive surgery should be performed on a case-by-case basis. It is recommended that only those patients whose organisms demonstrate drug resistance patterns that predict a high probability of treatment failure should be considered for resection. The goal of surgery should be to remove as much diseased lung as possible, particularly cavities, while avoiding crippling respiratory impairment.[15] The optimal timing of surgical intervention is after 3 to 4 months of therapy and sputum culture conversion, though the latter may not always be possible.[15] Engaging a surgeon experienced in the performance of lung resection in TB patients is recommended. The anticipated site of the surgical stump should be evaluated bronchoscopically before surgery to establish the absence of endobronchial TB, which, if present, is associated with poor healing and a persistent broncho-pleural fistula.[112,140] Surgical outcomes are generally good.[139,141-144] Anti-TB drug treatment should be continued for 18 to 24 months after surgery.[117,139]

MONITORING OF TREATMENT OF MDR-TB PATIENTS

It is recommended that the monitoring of patients with MDR-TB include a systematic, organized approach, such as that outlined in detail by the Francis J. Curry National Tuberculosis Center.[22] Elements of such monitoring should include drug administration, weight and nutrition, drug absorption and drug interactions, substance abuse and mental health, respiratory and systemic symptoms, symptoms of drug toxicity, blood tests, visual screens, audiology and vestibular testing, bacteriology, therapeutic drug monitoring and radiology. Although the exact role of therapeutic drug monitoring in the management of MDR-TB has not been extensively studied, there are a few situations in which drug concentrations are routinely measured: aminoglycoside concentrations, especially in patients who have known renal dysfunction, cycloserine concentrations to help predict and minimize central nervous system adverse reactions and prevent seizure activity, and EMB concentrations in patient with reduced renal function.[22]

With respect to mycobacteriology, the use of sputum smear and culture results, rather than sputum smear alone, is recommended for the monitoring of patients with MDR-TB during treatment. Hospitalized patients with smear- and/or culture-positive pulmonary disease should have sputum submitted at least weekly and remain in airborne isolation until three consecutive sputum samples are culture-negative after 6 weeks of incubation in broth or 8 weeks in solid media. Otherwise, WHO criteria for culture conversion are recommended: two consecutive negative smears and cultures taken at least 30 days apart. Time to conversion is calculated as the interval between the date of MDR-TB treatment initiation and the date of sputum collection of the first of the two consecutive negative cultures.[49] Even after culture conversion specimens should be submitted at least monthly to document the stability of the mycobacteriologic response. An MDR-TB patient is not considered cured until he or she has completed treatment according to the regimen and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.[49,145] An MDR-TB patient is considered to have failed treatment if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive.[145]

Patients who have completed treatment of MDR-TB or XDR-TB should undergo clinical, radiologic and mycobacteriologic follow-up at 6-monthly intervals for a minimum of 2 years.

MANAGEMENT OF CONTACTS OF MDR-TB

Contacts of patients with MDR-TB should be rapidly identified and evaluated, especially when the index case has smear-positive pulmonary TB or laryngeal TB.[49] In settings with a high HIV prevalence, the incidence of MDR-TB among household contacts has been found to be extremely high, most secondary cases occurring shortly after the diagnosis of the source case.[146] Close contacts of an infectious case, especially those who are under the age of 5 years or are immunocompromised, are especially important to screen. After active TB has been excluded, contacts who have a tuberculin skin test (TST) result of 5 mm or more of induration or TST-negative contacts who are under the age of 5 years or are immunocompromised should be evaluated for therapy of latent TB infection (LTBI) (see also Chapter 6, Treatment of Latent Tuberculosis Infection).

There are no randomized controlled trials that have assessed the effectiveness of treatment of LTBI in people exposed to MDR-TB.[147] In a systematic review of the literature on people treated and not treated for LTBI after exposure to MDRTB there were only two observational studies that met the inclusion criteria.[148] A prospective cohort study found individualized treatment, tailored to DST, was effective in preventing active TB in children,[149] and a retrospective cohort study found INH not to be effective.[150] Since then another observational study has found that individualized treatment was effective.[151]

If the isolate from the source case is susceptible to FQNs then daily, self-administered moxifloxacin or levofloxacin for 9 months is recommended for treatment of LTBI. Thrice weekly directly observed preventive therapy may be considered. In the event of FQN resistance there is no consensus on management, although a two-drug regimen, based upon DST, for 6 to 12 months could be considered. The risks and benefits of such regimens should be discussed with the patient beforehand; when accepted, such regimens should be carefully monitored for adverse effects.[147, 152,153] Whether they are offered tailored LTBI treatment or not, close contacts of infectious MDR-TB cases should be followed clinically for 2 years.[154]

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CHAPTER 9

PEDIATRIC TUBERCULOSIS

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KEY MESSAGES/POINTS

- In Canada, pediatric tuberculosis (TB) is largely a disease of Canadian-born Aboriginal and foreign-born children.
- Active TB in children is a sentinel event that should prompt a search for the source case.
- After infection in children under the age of 5 there is a high risk of progression to severe forms of TB.
- Attempts should be made to collect specimens (gastric aspirates/induced sputa) for culture before therapy.
- Sputum induction is a promising technique for diagnosis of TB disease in young children.
- Culture yield in children is low: TB often is diagnosed by the combination of a positive TST or IGRA, abnormal chest x-ray and a history of contact with a case of infectious TB, in addition to compatible clinical signs or symptoms.
- A negative TST or IGRA does not exclude active TB.
- For treatment of TB disease, daily therapy is preferred over intermittent regimens.
- Twice weekly regimens should no longer be used because each missed dose represents a larger fraction of the total number of recommended treatment doses.
- Ethambutol (EMB) is now routinely used as part of initial empiric therapy of TB disease (pending sensitivities) in infants and children, unless contraindicated or if the source case is known to be fully susceptible.
- Pyrazinamide (PZA) doses are higher than in the previous edition of the *Standards*.
- Targeted testing for latent TB infection (LTBI) is recommended according to risk of infection and progression to disease.
- Patients for whom therapy of LTBI is recommended should be informed of the risk of treatment and its side effects. Clear plans of action should be in place for monitoring toxicity.
- The principal recommended regimen for LTBI is 9 months of INH.

PRELIMINARY NOTE

We are fortunate to have World Health Organization (WHO) guidance documents which address the area of drug doses and initial choices of therapy.[74,88] The documents provide a summary of available evidence that is used throughout this chapter. Unless there are good grounds to differ, the recommendations in this chapter are aligned as much as possible with the WHO document and the American Academy of Pediatrics Red Book: 2012 Report of the Committee on Infectious Diseases (http://aapredbook.aappublications.org/).

INTRODUCTION

Childhood TB is a neglected disease; its true prevalence is significantly underestimated in global statistics.[1] There is a need for improved diagnostic tools, new drugs, easy-to-dose formulations and effective vaccines.[1] Pediatric tuberculosis in Canada is largely a disease of foreign-born children, the children of foreign-born parents and Aboriginal children.[2] The incidence of TB among those <15 years of age in Canada has declined from 6.6 per 100,000 in 1970 to <2 per 100,000 in 2009[3] (see Chapter 1, Epidemiology of Tuberculosis in Canada). Clinical management should take into account the global epidemiology of TB and the possibility of drug resistance in the foreign born.

TB in children differs from that in adults in several ways: (1) diagnosis in young children may be difficult, since signs and symptoms are often nonspecific and disease is often paucibacillary; (2) TB disease in a very young child is often a sentinel event indicating recent transmission; (3) in young children, especially infants, there is a high risk of progression from latent TB infection (LTBI) to active and sometimes severe TB disease.[4-7]

This chapter will cover the most important aspects of pediatric TB. Readers are encouraged to refer to other chapters of the *Standards* for detailed information.

PATHOGENESIS AND DEFINITIONS

Details of the pathogenesis of TB are outlined in Chapter 2, Transmission and Pathogenesis of Tuberculosis. Children inhale *Mycobacterium tuberculosis* from adults or adolescents with infectious pulmonary or laryngeal TB.[8] Rarely, children with cough and multibacillary disease may be infectious.[9,10] Inhaled bacteria are taken up by alveolar macrophages and, if not immediately destroyed, result in a primary infection that consists of a small parenchymal focus that spreads via local lymphatics to regional lymph nodes. Primary infection may be associated with complications, especially in children under 5 years of age.[11] The parenchymal lesion may enlarge and caseate, or nodes may enlarge and compress or erode through a bronchus, causing wheezing, segmental pneumonia or atelectasis.

The primary infection is usually accompanied by an occult, subclinical bacteremia that seeds distant sites, including the apices of the lungs, the lymph nodes and the central nervous system (CNS). This may rapidly lead to severe forms of disease, including miliary and CNS TB, especially in children younger than 5 years of age.[11] In general, the risk of progression to TB disease and of severe forms of TB disease after infection is inversely related to age (Table 1).[11] However, in most cases the primary focus heals, and the bacteria continue to survive in a dormant state that is referred to as latent TB infection (LTBI). Similar to adults, children with LTBI and an immunocompromising condition are at increased risk of TB disease.

Table 1. Average age-specific risk for disease development after untreated primary infection[11]

Age at primary infection	Manifestations of disease	Risk of disease (%)
<12 months	No disease	50
	Pulmonary disease	30-40
	TB meningitis or miliary disease	10-20
12-23 months	No disease	70-80
	Pulmonary disease	10-20
	TB meningitis or miliary disease	2-5
2-4 years	No disease	95
	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
5-10 years	No disease	98
	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
>10 years	No disease	80-90
	Pulmonary disease	10-20
	TB meningitis or miliary disease	<0.5

There is no confirmatory test for LTBI. For practical purposes a child with LTBI is considered to have no symptoms related to the infection, a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA), no clinical evidence of disease and a chest x-ray that is either normal or demonstrates evidence of remote infection, such as a calcified parenchymal nodule and/or a calcified intrathoracic lymph node.[12]

Isolation of *M. tuberculosis* in culture from a clinical specimen confirms TB disease. However, because children may be too young to produce sputum or they have paucibacillary disease, recovery of the organism may be difficult, and confirmation is not always possible. The diagnosis of TB disease is often based on a clinical case definition, which usually relies on the triad of (1) a positive TST or IGRA, (2) either an abnormal chest x-ray and/or physical examination and (3) discovery of a link to a known or suspected case of infectious TB.

Many diagnostic scoring systems have been developed but are not well validated and lack specificity.[13,14] Clinical case definitions of childhood intrathoracic TB were recently proposed by an expert panel:[15] these are intended for use in clinical research to evaluate diagnostic assays and not for individual patient diagnosis or treatment decisions.

The distinction between infection and disease is not always easy and can be somewhat artificial, since infection and primary disease are parts of a continuum.[16,17]

CLINICAL PRESENTATION OF TB DISEASE

In Canada many children with TB disease are asymptomatic at presentation. They are often identified through active case finding as contacts of patients with infectious TB and are found to have abnormal chest x-rays. This is especially true of children under 5 years of age.[7]

Children may also present with symptoms or signs suggestive of disease.[7] In young infants, these may be very nonspecific: hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, lethargy or irritability.[18,19] Older children and adolescents are more likely to experience adult-type disease and often present with the classic triad of fever, night sweats and weight loss. Those with pulmonary disease are also more likely to present with respiratory symptoms (cough, sputum and sometimes hemoptysis).[7] As in adults, their physical findings are often minimal relative to their chest x-ray abnormalities.[20] The latter include lung infiltrates, typically but not always in the upper zone(s), that may be cavitated. TB disease in adolescents in Canada and other high-income countries is often extrapulmonary.[21] Presentation may be protean: TB may mimic inflammatory bowel disease or brain and bone tumours or involve almost any system in the body. Delay in diagnosis in adolescents is common and may reflect a lack of suspicion by clinicians.[22] Failure to send sputa for TB smear and culture from adolescents with a productive cough and epidemiologic risk factors for TB contributes to this delay.

Any extrapulmonary site may be involved, most commonly extrathoracic lymph nodes. Mycobacterial cervical lymphadenitis is commonly due to nontuberculous mycobacteria in the Canadian born but may be due to TB, especially in those with risk factors (see Chapter 11, Nontuberculous Mycobacteria). Miliary/disseminated disease and CNS disease, the most life-threatening forms of TB, are more likely to occur in young children and the immunocompromised.[7,19]

Epidemiologic risk factors and/or a clinical picture compatible with TB should prompt appropriate testing.

DIAGNOSTIC TESTS

TUBERCULIN SKIN TEST AND INTERFERON GAMMA RELEASE ASSAYS

Please see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for details about the TST and IGRAs.

In children, the TST and/or IGRA is an important part of the clinical case definition of TB disease, especially if there is a TST conversion or a new positive TST. However, a negative TST does not exclude TB disease. Furthermore, a positive TST or IGRA does not distinguish between latent TB infection and active disease.

RADIOLOGY

Chest radiography is an important part of the diagnostic workup of pediatric TB. The quality of films is crucial. The results may be difficult to interpret, especially if there is rotation of the chest relative to the x-ray beam, or there has been inadequate inspiration or overpenetration. Ideally, films should be reviewed by a radiologist experienced in reading pediatric chest x-rays.[23,24] A classification system relates radiographic appearances of primary pulmonary TB to complications of (1) the primary focus, (2) the regional lymph nodes or (3) both.[25] Useful resources with clinical examples of pediatric TB radiology are available for further information.[15,26-29]

Frontal and lateral chest radiographs are required to detect hilar and paratracheal lymphadenopathy, the most common features expected in pediatric TB.[26] Parenchymal lesions may be anywhere in primary disease and are typically, but certainly not always, in the upper lobes in adolescents. Cavitation is rare in childhood TB but can be seen in children with either adult-type disease, from a progressive primary (Ghon's complex) focus in very young or immune-compromised children, or a caseating pneumonia secondary to lympho-bronchial disease.[25,30] Radiologic abnormalities in children may, in the short term, worsen on treatment before they improve.[4]

Computed tomography (CT) scans of the chest deliver significant radiation doses; children are more vulnerable to the effects of radiation than adults.[29,31,32] CT may be very helpful, but its use for any case must be weighed against the likely benefits of the information gained. Magnetic resonance and CT may be very helpful in the evaluation of suspected active CNS disease, bone and joint disease, and disease at other sites, such as the intra or extrathoracic lymph nodes, pericardium and peritoneum.[29]

GASTRIC ASPIRATES, INDUCED SPUTUM, AND NUCLEIC ACID AMPLIFICATION TESTS

Mycobacterial confirmation of the diagnosis of pediatric TB should always be sought; this is particularly important when (1) an isolate from a source case is not available or there is a possibility of multiple sources; (2) the source case has drug-resistant TB; (3) the child is immune-compromised; or (4) the child has extrapulmonary TB.[24,33]

Gastric aspiration has traditionally been the diagnostic procedure of choice in young children who are unable to produce sputum.[4,5] Children are often hospitalized for the procedure, but it has also been successfully performed in outpatients.[34-36] Details about gastric aspiration, including a video, are available online[36] and in Table 2. The gastric aspirate material should be pH neutralized as soon as possible after aspiration, as gastric acid may kill *M. tuberculosis.* Unless the laboratory is available to immediately pH neutralize the sample, it should be placed in a sterile container with 100 mg of sodium carbonate[37] or a bicarbonate solution.[36] These containers may be obtained from provincial/territorial public health laboratories or made up by a hospital laboratory. The relevant laboratory should be contacted ahead of time for details regarding collection and transport of specimens. Results of acid-fast bacilli (AFB) smears of gastric aspirates usually are negative, and false-positive smear results caused by the presence of nontuberculous mycobacteria can occur.[33] Although the yield of gastric aspirate cultures in infants has been reported as up to 75%,[38] the overall diagnostic yield for culture is probably less than 50%.[33,35]

Table 2. Gastric aspirates: some tips*†

•	During sleep the mucociliary mechanism of the respiratory tract sweeps mucus, which may contain TB bacteria, into the mouth. The material is swallowed and may be a source of organisms, especially if the stomach has not emptied.
•	Aspirates are obtained after at least 6 hours of sleep and before the stomach has emptied.
•	Patients should not drink or eat anything overnight to prevent the stomach from emptying. They should also avoid exposure to the smell or sight of food, which may encourage gastric emptying. The ideal time is just at the time of waking.
•	Aspirate the stomach contents first. Then instill no more than 50 mL of sterile distilled water – the sort used for infant feeding is suitable. Aspirate back and add the aspirate to the first specimen.
•	The fluid has to be adjusted to neutral pH within 4 hours of collection because acid is detrimental to mycobacteria. If that is not possible, it should be directly placed into a buffered solution (see text for details).

*With thanks to Ann Loeffler, Oregon Health Sciences University

†The complete procedure is very well explained and illustrated in: http://www.currytbcenter.ucsf.edu/catalogue/epub/index.cfm?tableName=GAP

Sputum induction (SI) has been performed in high-burden settings as an outpatient procedure by trained personnel.[39-50] By using timed nasopharyngeal suction following administration of hypertonic saline, the technique has been safely performed in infants as young as 1 month of age. Both ultrasonic and jet nebulizers have been used. Details about the procedure[41,51,52] as well as a video[53] are available. The yield may be as good as or better than that of gastric aspirates, and the advantages over gastric aspirates include a shorter period of fasting, no killing of the organisms by gastric acid and higher acceptability to staff and parents.[54] Attention to safety issues, including management of bronchospasm and appropriate facilities and procedures to prevent nosocomial transmission, should be in place (see Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings). The diagnostic yield from bronchoscopy is no higher than that of gastric aspirates or SI, although it may be useful to detect possible tracheobronchial obstruction or explore alternative diagnoses.[55]

Other specimens can be collected if clinically indicated: bronchial washings, pleural fluid, cerebrospinal fluid, urine, other body fluids or tissue biopsy specimens. Nasopharyngeal aspiration[43,45,50,56-59] and the string test[60-62] have also been used, with variable results.[6,63] Fine-needle aspiration biopsy has been useful in children suspected of TB who present with palpable enlarged cervical nodes.[64,65] However, surgical removal has the advantages of higher yields on culture and better outcomes, as lymph nodes may continue to enlarge and drain despite therapy to which the organism is susceptible.[66] A lumbar puncture should be performed in cases of suspected congenital or neonatal tuberculosis and in infants with disseminated disease.[67,68]

Nucleic acid amplification (NAA) tests are useful in confirming the diagnosis in AFB smear-positive respiratory cases. Their ability to improve the sensitivity of gastric aspirates has been disappointing.[31,69-71] A study using a recently developed cartridge-based NAA test on induced sputum in children admitted for suspected TB detected all smear-positive cases but only a third of the smear-negative culture-positive cases: a second specimen increased the yield to 61%.[46] More data are emerging on the type, number of specimens required and the use of NAA tests for the diagnosis of pediatric TB.[50,72,73] Further details of microbiologic isolation, speciation and drug-resistance testing are provided in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

RECOMMENDED MANAGEMENT OF TB DISEASE

A diagnosis of TB infection or disease in a child should be considered a sentinel event and prompt the search for the source case, most likely an adult or adolescent in close contact with the child. Close caregivers should be evaluated to rule out TB disease. Consideration should be given to placing all close caregivers in airborne isolation until they have been evaluated (see Chapter 15).

The principles and phases (intensive and continuation) of TB treatment are discussed in Chapter 5, Treatment of Tuberculosis Disease. A team approach is very helpful in evaluating and treating children with TB disease. The team may include physicians and clinic nurse practitioners, public health nurses, a social worker and an interpreter. The team should, wherever possible, include or involve a pediatric TB specialist. Treatment is aimed at reducing morbidity and mortality, preventing acquired resistance and providing a lasting cure. Interruption of transmission is also important in adolescent patients with pulmonary disease who attend congregate settings, including schools. Before starting therapy for TB disease a baseline alanine aminotransferase, aspartate transaminase and bilirubin level should be obtained. HIV serology is recommended as standard practice for all children and adolescents being treated for TB disease: TB is an opportunistic infection, and the duration of treatment will be influenced by this result.

The most important element of the treatment of TB is the actual ingestion of the medication by the child, since children may not tolerate the pill burden, and the existing formulations are not particularly child friendly.[4]

INDIVIDUAL DRUGS

The drugs used in the treatment of pediatric TB, their doses and side effects are summarized in Table 3. Despite recent information about TB drug pharmacokinetics in children, more research is still needed in this area.[80] In children who are younger than 12 years or who weigh less than 35 kg, isoniazid (INH) recommended doses are 10-15 mg/kg daily (maximum 300 mg).[74,81] Administration is affected by food: INH is better absorbed on an empty stomach. Fat reduces absorption.[82] Sugars, such as glucose, fructose and sucrose, inactivate INH by condensation. A sorbitol-based suspension avoids this problem but may cause diarrhea.[75] Crushed pills are ideally mixed with water, but few children will accept this, and administration with small amounts of food is often suggested.[4,83-87] If necessary, pills may be crushed in a small amount of a sugar-free, low-fat vehicle such as sugar-free pudding, baby food or yogurt.[83]

For the older child or adolescent who weighs between 35 and 60 kg, the optimal dosing of INH is an area of uncertainty. Recommendations for adults are to use 5 mg/kg of INH (see Chapter 5), whereas recommendations from the American Academy of Pediatrics are to use 10 mg/kg to a maximum of 300 mg.[33] On the other hand, forthcoming WHO recommendations state that at 25 kg, children can adopt adult dosage recommendations and use adult preparations, especially with fixed drug combinations.[88] There are no pharmacokinetic or toxicity data to clearly support either dose. For some patients, this results in a “grey zone” in which the dosing would be very different (e.g. a 40 kg adolescent would receive 300 mg of INH daily when dosed as per AAP recommendations and 200 mg when treated as per the adult guidelines).

Table 3. Drugs used for treatment of tuberculosis in children[33,74,75]

Drugs	Daily dose (range)		Thrice weekly dose† (range)		Available dosage forms	Principal side effects
	By weight (mg/kg)	Max (mg)	By weight (mg/kg)	Max (mg)		
INH	10 (10-15)‡	300	20-30	600-900	10 mg/mL suspension 100 mg tablet 300 mg tablet	– Mild liver transaminase elevation – Hepatitis – Gastritis – Peripheral neuropathy – Hypersensitivity
RMP	15 (10-20)	600	10-20	600	10 mg/mL suspension 150 mg capsule 300 mg capsule	– Orange discoloration of secretions – Vomiting – Hepatitis – Flu-like illness
PZA	35 (30-40)	2000	70 (60-80)	*	500 mg scored tablet	– Hepatotoxicity – Hyperuricemia – Arthralgia
EMB	20 (15-25)	**	40 (30-50)	***	100 mg tablet 400 mg tablet	– Optic neuritis with decreased visual acuity and decreased red-green colour discrimination – Gastrointestinal disturbance
Pyridoxine (used to prevent INH neuropathy: has no anti-TB activity)	1 mg/kg	25			25 mg tablet 50 mg tablet	– Few

†Intermittent doses should be prescribed only when directly observed therapy is available. In general daily therapy is definitely preferred over intermittent regimens.

‡Hepatotoxicity is greater when INH doses are more than 10-15 mg/kg daily. For older children and adolescents, the optimal dosing of INH is an area of uncertainty (see text).

*For PZA: 3000 mg according to the American Thoracic Society (ATS),[75] 2000 mg according to the Red Book[33]

**For EMB: 1600 mg according to the ATS,[75] 2500 mg according to the Red Book[33]

***For EMB: 2400 mg according to the ATS,[75] 2500 mg according to the Red Book[33]

Note: Information on second-line drugs for multidrug-resistant TB (MDR-TB) is available in various recent reviews[76-79] and in Chapter 8, Drug-resistant Tuberculosis.

Pyridoxine (vitamin B6) is indicated for children on meat and milk-deficient diets, breastfed infants, those with nutritional deficiencies, children with symptomatic HIV infection and adolescents who are pregnant or breastfeeding.[33]

Rifampin (RMP) is frequently compounded into suspension by pharmacists. These suspensions are usually stable for at least 1 month, and unpublished experience suggests that they are effective.

Ethambutol (EMB) is now routinely used as part of initial empiric therapy of TB disease (pending sensitivities) in infants and children unless otherwise contraindicated.[33] It can cause retrobulbar neuritis, a side effect that is dose-dependent and more likely to occur with renal impairment. It is manifest as decreased visual acuity or decreased red-green colour discrimination and may be reversible upon discontinuation of the drug. EMB should be used with caution in children who are too young for monitoring, although reviews suggest that its use is safe in children.[89,90] When possible, baseline ophthalmological assessment should be obtained in younger children before starting EMB and be repeated regularly during treatment with the agent.[75,86,91]

Acuity and colour vision should be monitored monthly in a clinic setting using isochromatic plates; this is often possible even in young children. While optic neuritis is very uncommon at an EMB dose of 15 mg/kg daily,[89,92] pharmacokinetic data suggest that drug levels may sometimes be subtherapeutic at this dose.[52,90,93] In accordance with the WHO and the AAP, 20 mg/kg daily should be used.[33,74] However, when EMB is a vital part of therapy, e.g. in drug-resistant TB, doses of 25 mg/kg daily should be used with very close monitoring of vision. Baseline serum creatinine levels should be measured to rule out occult renal impairment before initiation of therapy. EMB should be discontinued once the strain is known to be fully drug susceptible.

On the basis of pharmacokinetic data,[94] pyrazinamide (PZA) doses are higher than in the previous edition of the *Canadian Tuberculosis Standards.* The WHO has noted that there is insufficient high-quality evidence to assess whether these higher doses will lead to more hepatotoxicity.[74,81]

Information on second-line drugs for MDR-TB is available in various recent reviews[76-79] and in Chapter 8.

EMPIRIC TREATMENT

In all suspected cases, especially those for whom no source case isolate is available, specimens should be obtained for culture and drug susceptibility testing prior to starting therapy. If there is a known source case, his/her culture and susceptibility test results may be used to guide therapy provided there is no significant possibility of alternative sources (e.g. from recent foreign travel) (see Diagnosis section, above). Treatment should then begin promptly when clinical and laboratory indices support a presumptive diagnosis of active tuberculosis.[75] While culture and susceptibility results are pending or if empiric treatment is deemed necessary, therapy with INH, rifampin, EMB and PZA, unless contraindicated, should be started.[33,81] If the source case is known to be fully drug susceptible, EMB can be omitted. If there is a strong possibility of drug-resistant disease, expert consultation is strongly advised (see section on Multidrug-resistant TB below).

TREATMENT MODIFICATION AND DURATION

Once the susceptibilities of the source case or the child's isolate are available, treatment should be modified as follows:

- For fully susceptible, intrathoracic TB, INH, rifampin and PZA should be used for the first 2 months followed by 4 months of INH and rifampin. The *minimum* duration of therapy is 6 months in total. However, in patients with cavities on initial chest x-ray or positive sputum cultures after 2 months of treatment, the minimum duration of therapy should be 9 months[74,75] (see also Chapter 5).

- If hilar lymphadenopathy alone is present, treatment as for pulmonary disease should be given (unless the isolate is resistant), although regimens using only INH and rifampin have been recommended.[33,95,96] If rifampin or pyrazinamide are discontinued because of side effects, longer durations of therapy are recommended. Rifampin is a cornerstone of anti-TB therapy and should not be discontinued because of minor side effects.

Please see Chapter 5, Treatment of Tuberculosis Disease, for further details on drug side effects and management in cases of hepatotoxicity.

DAILY VS INTERMITTENT REGIMENS

There are few studies of TB treatment in children. Recent systematic reviews have found poorer cure rates with intermittent regimens and prompted the WHO to recommend daily therapy over intermittent regimens for treating pediatric TB disease, especially where HIV infection is common.[74,97,98] Comparing treatment studies is a challenge, considering the important differences in the epidemiology of childhood TB in industrialized countries when compared with that of low- or middle-income countries[99] and since pediatric TB disease cannot be viewed as a single entity.[11] Although intermittent regimens have been successfully used in Canada and the United States, daily regimens are recommended during treatment wherever possible.

Daily regimens are strongly suggested during the intensive phase. On the basis of expert opinion the Canadian Thoracic Society suggests that when daily treatment in the initial phase is very difficult, some patients with minimal mediastinal/hilar lymphadenopathy TB or peripheral TB lymphadenitis may be treated with thrice weekly therapy (directly observed therapy [DOT]) after the first 2 weeks if they are HIV-uninfected, have a low bacillary load (i.e. have noncavitary, smear-negative disease) and have demonstrated excellent adherence to their DOT in the first 2 weeks.

Intermittent three times weekly regimens (i.e. therapy only given on three days of the week, typically with higher doses) should only be considered in the continuation phase for select HIV-uninfected children with pulmonary TB or peripheral TB lymphadenitis. These intermittent regimens should only be used under strict thrice weekly DOT. Twice weekly regimens should no longer be used because each missed dose represents a larger fraction of the total number of recommended treatment doses.[81] However, in exceptional circumstances, patients with minimal disease who are known to be reliable with DOT may be considered for twice weekly therapy in the continuation phase[33] (see also Chapter 5).

DIRECTLY OBSERVED THERAPY AND ADHERENCE

A decision to initiate treatment of TB disease or latent TB should also imply a decision to monitor, minimize the risks of toxicity, follow closely and ensure that therapy is completed. If clinicians cannot achieve this they should immediately refer the patient to centres or teams that can. All patients should receive counselling about side effects and medication administration, and detection of side effects before the next scheduled appointment; access by parents and patients to clinicians and the health service should be facilitated, particularly if there are language and social barriers. If DOT is used, this involves much more than simple observation of pills taken. Integrating a liaison public health nurse into the treatment team facilitates DOT and monitoring, as well as assuring follow-up for patients. In concordance with AAP guidelines, DOT (not by the parents/guardians alone) for the full duration of therapy is strongly recommended for children and adolescents.[33]

Although therapy is given on all days of the week, daily therapy can be given as five observed doses. If resources for DOT are very limited, under all circumstances DOT should always continue for the following cases: (1) Disease due to suspected or proven drug-resistant strains, (2) HIV coinfection, (3) previous treatment failure of active disease, (4) retreatment disease, (5) suspected nonadherence or previous nonadherence, (6) reasonable doubts about the ability of the parents/guardians to supervise treatment for children, (7) substance abuse in an adolescent and (8) psychopathology.[100,101] For those not receiving daily DOT, regular supervision of therapy may help detect side effects and administration errors (see also Chapter 5).

ADJUNCTIVE THERAPY

Corticosteroids are used as adjunctive therapy when the tuberculous inflammatory response is threatening to cause a life-endangering complication.

Corticosteroids are indicated for children with TB meningitis. In prospective, randomized trials they decreased mortality rates, and they may affect neurologic complications, neurologic sequelae and cognitive dysfunction.[102] Dexamethasone (0.3-0.4 mg/kg daily for the first week and weaning over 6 weeks) or prednisone (60 mg/day for 3 weeks tapered over the next 3 weeks) has been used in children older than 14 years of age.[102,103] For children, the AAP[33] and other experts[104] suggest as adequate 2 mg/kg per day of prednisone (maximum, 60 mg/day) or its equivalent for 4 to 6 weeks followed by tapering. Higher prednisone doses (4 mg/kg with a taper over 4-6 weeks) have been evaluated and considered if increasing intracranial pressure continues.[102] Corticosteroids have also improved survival and reduced the need for pericardiectomy in patients with TB pericarditis (see also Chapter 5).

The use of corticosteroids in pleural TB is not supported by current evidence. On the basis of expert opinion, corticosteroids may have a role in endobronchial disease to relieve obstruction and atelectasis.[33,52] They may also be considered for children with severe miliary disease and in the presence of paradoxical reactions, especially when they involve airway compromise.[33] Corticosteroids should only be used in conjunction with effective antituberculosis therapy and should be tapered slowly over weeks to avoid a rebound reaction. Generally in non-meningitic conditions 2 mg/kg daily of prednisone (maximum 60 mg/day) or its equivalent is used, tapered over 6 to 8 weeks.[33,52]

While several reports suggest that a high proportion of children with TB disease and infection may have low vitamin D levels,[105] vitamin D supplementation does not affect treatment outcomes.[106,107]. Existing recommendations regarding vitamin D supplementation for the population should be followed, and monitoring of serum levels in at-risk populations should be considered.[108,109]

SIDE EFFECTS AND MONITORING DURING TREATMENT

Patients and their parents should be informed of the side effects indicating hepatotoxicity and other drug toxicities and should be asked to recall these at each clinic visit. They should be provided with a clear plan of action, preferably written, including contact telephone numbers, should symptoms arise.

Patients should undergo clinical evaluation at least monthly.[33,75,83] At each visit they should be asked about individual side effects and symptoms of TB disease, and undergo a full clinical examination. Monitoring of weight, especially in infants and young children, is especially important to the adjustment of drug doses, since children may rapidly "grow out of" the recommended dose range. On the basis of probable increases in weight some clinicians recommend prescribing 12 mg/kg of INH for infants younger than 12 months rather than 10 mg/kg. Please see Chapter 5 for the management of common adverse reactions.

For adolescents or older children with adult-type disease, follow-up sputum examinations should be performed in the same way as for adults.[6] Repeat cultures from other clinical specimens are not necessary if the patient is improving clinically but should be strongly considered in MDR cases.[110]

Chest radiography 2 months into treatment is recommended to rule out extension of disease.[33] However, persistent radiographic signs are not an indication to change treatment if there is clinical improvement.[30] At the end of a satisfactory course of treatment there may be residual lymphadenopathy or scarring that can persist for 2-3 years.[6,83] Normal radiography is not necessary to discontinue therapy.[33]

Patients should be followed for at least 1 year after treatment completion to achieve clinical health and stability or continued resolution of radiographic findings.[4] Deteriorations (development or worsening of existing lesions and lymphadenopathy) during therapy may occur even with appropriate therapy for drug-susceptible disease in both HIV-infected and uninfected patients. Many of these reactions are paradoxical, due to immune reconstitution, but are difficult to differentiate from acquired drug resistance or clinical failure.[111] Low weight and high disease burden may be associated with more reactions. Clinically significant occlusion of bronchi by enlarging intrathoracic lymph node masses may occur by this mechanism and often responds well to corticosteroid therapy. Drug resistance should be ruled out or accounted for in the treatment regimen if corticosteroids are used.[111]

TREATMENT OF EXTRAPULMONARY TB

It is recommended that extrapulmonary TB in children be treated with the same regimens as pulmonary disease, with the exception of CNS TB, disseminated/miliary TB, and bone and joint TB, for which the recommended duration of treatment is 9 to 12 months. Please see Chapter 7, Nonrespiratory Tuberculosis, for further details.

TREATMENT OF MDR-TB

Please see Chapter 8, Drug-resistant Tuberculosis. Children and adolescents at risk of drug-resistant TB include (1) those with a history of treatment of TB disease, (2) contacts of a patient with drug-resistant contagious TB disease, (3) those born in or who have resided in countries with high prevalence of drug-resistant TB and (4) infected patients whose source case has positive smear for acid-fast bacilli or cultures after 2 months of appropriate therapy or is not responding to a standard treatment regimen.[33] Details of microbiologic isolation, speciation and drug-resistance testing are provided in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

If drug-resistant TB is isolated, an expert opinion should be obtained from a physician experienced in the management of drug-resistant TB. Recent resources summarize drug doses and side effects for the treatment of drug-resistant disease in children.[76-79]

TB AND HIV

Children with LTBI and HIV infection may have an accelerated progression from infection to disease.[112,113] The TST is often negative in HIV-coinfected children. A search for an infectious adolescent or adult is an important step towards diagnosis.

Usually the clinical features of TB in HIV-infected children are similar to those in children without HIV infection, although the disease usually is more severe and can be difficult to differentiate from illnesses caused by other opportunistic infections.[86,114]

The optimal treatment of pulmonary TB in children and adolescents with HIV infection is unknown. Advice from a TB expert should be sought. Please see Chapter 10, Tuberculosis and Human Immunodeficiency Virus for further details.

RECOMMENDED MANAGEMENT OF LTBI

In general, LTBI should be treated with INH (see Table 3 for doses) for 9 months unless the child has been linked to an INH-resistant source case. Routine liver function testing is not indicated for asymptomatic children who do not have underlying liver disease, do not have disseminated disease and are not taking other hepatotoxic drugs. However, although rare, severe hepatotoxicity requiring transplantation or leading to death has occurred during INH treatment of LTBI in children.[115] Therefore, it is strongly recommended that patients receiving INH therapy be advised by the prescribing physician and other relevant health care providers to stop taking the INH *immediately* if they have symptoms such as anorexia, nausea, vomiting, abdominal discomfort, unexplained fatigue, dark coloured urine, scleral icterus or jaundice, and to contact them as soon as possible for further evaluation. They should be provided with a clear written plan of action, including contact telephone numbers, should symptoms arise. If symptoms occur, evaluation should include a physical examination and investigation of liver transaminase values and bilirubin levels. Patients may appear clinically well despite impending significant liver toxicity.[116]

Children should be evaluated monthly, and parents should be questioned about what side effects to watch for, any side effects that have occurred, any symptoms of active TB, adherence to therapy and results of skin testing of family members and other contacts (see also Chapter 6, Treatment of Latent Tuberculosis Infection). Loeffler has offered many helpful suggestions to improve adherence and completion rates (Table 4).[4] Most health departments do not have the resources for directly observed preventive therapy (DOPT). DOPT should be strongly considered for children infected with drug-resistant strains and where adherence is in doubt. DOPT can also be combined with DOT visits for household contacts of adults with TB disease.

Table 4. Recommendations to improve adherence and completion rates for TB therapy[4]

- Use tablets crushed into semisoft vehicles, such as sugar-free pudding, to avoid stomach upset from the liquid preparation.
- Warn the family that the first couple of weeks of therapy will be challenging.
- See the patients monthly and supply only 1 month of medication at a time.
- Provide written educational material regarding reasons for therapy and symptoms of TB and toxicity.
- Develop a small, dedicated and enthusiastic team of staff of providers, nurses and interpreters.
- Develop systems to encourage adherence, such as having the child put a sticker on the calendar for each dose taken.
- Provide convenient clinic hours and short waiting times.
- Develop a system of following up patients who have missed appointments.
- Praise the family and child for good adherence and clinic attendance.

If the source case is INH resistant or there is epidemiologic reason to suspect that the child is infected with an INH-resistant strain, then RMP is recommended for 4 months (see Table 3 for doses).[117] US guidelines recommend the use of RMP daily for 6 months,[118] but this is based on limited experience in adolescents and young adults aged 15 to 23 years.[119] Children taking anticonvulsants and either INH or RMP should be monitored closely because both of these drugs can affect the metabolism and serum levels of anticonvulsants.[75]

Children judged to be infected with a multidrug-resistant strain of *M. tuberculosis* should be referred to a TB specialist (refer also to Chapter 8, Drug-resistant Tuberculosis).

Rifapentine (RPT) is currently unavailable in Canada, except perhaps pursuant to a practitioner's application for the treatment of a patient under the Special Access Program (SAP) (see: http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php). If RPT is obtained through the SAP, clinicians should be aware that there have been some concerns about hypersensitivity reactions. A once-a-week RPT regimen for LTBI has recently been approved in the United States for patients >12 years of age.[120] Please see Chapter 6 for more details on this and other alternative regimens.

A common question is whether INH, or an alternative regimen, should be given for treatment of LTBI in people who have no known contact with a drug-resistant case but have immigrated to Canada from countries with high rates of drug-resistant TB. It is important to remember that 9 months of INH has the best documented efficacy, and of foreign-born individuals less than 20%, in total, of those whose infection is reactivated in Canada have resistant strains. For these two reasons, 9 months of INH is recommended in these people (please see Chapter 6).

MANAGEMENT OF CONTACTS

The most efficient way to prevent pediatric TB is the prompt evaluation and treatment of children exposed to an infectious adult source case. Missed opportunities to prevent cases of pediatric TB include delayed diagnosis of infectious TB, delayed reporting of a source, failure to identify an exposed child during the contact investigation, failure to achieve adherence of the source case, failure to document sterilization of cultures, failure to start preventive therapy or LTBI treatment in the child and failure to ensure that the child takes the treatment.[117] With each pediatric active TB case, the case management team should determine which of these factors may have played a role in the child becoming infected with TB and take corrective action to prevent future cases.

All exposed children should have a symptom inquiry and TST. Those less than 5 years of age, all close childhood contacts and all symptomatic children should also have a physical examination and chest radiography. Children less than 5 years of age with a negative TST and no evidence of active TB by examination or radiology should be given "window" of preventive therapy to prevent the development of TB. This is because it may take up to 8 weeks after infection for the TST to convert to positive, during which time the infection may progress to disease. For children presumed to have been exposed to a drug-susceptible isolate, INH is recommended. The INH may be discontinued if, after a period of 8 weeks after the last contact, the repeat TST is negative, and the child remains asymptomatic and is immunocompetent and more than 6 months of age (for infants <6 months of age, see section on Perinatal Issues: Recommended Management of the Newborn Infant Exposed to TB).

In the exposed child, if the initial TST is positive (≥5 mm) and there is no clinical or radiographic evidence of disease, then a full course of treatment for LTBI is recommended. When a child with new, active TB is the index case, reverse contact tracing must be undertaken, i.e. a vigorous search should be carried out for the source case. Although most source cases are found among adolescent or adult household contacts of the child, other source cases may be found among adolescent or adult non-household contacts, such as babysitters and other caregivers either in or outside the household. Molecular characterization of *M. tuberculosis* isolates by genotyping can lead to identification of previously unrecognized source cases.[121] If the child is hospitalized it is advisable to screen adolescent or adult visitors for evidence of active TB.[122]

The optimal treatment of children in contact with patients with MDR-TB is uncertain.[33,123] Consultation with a TB specialist is recommended (see Chapter 8 for more details).

TARGETED TESTING FOR LATENT TB INFECTION

Universal screening of school children and infants is not indicated. Resources should be devoted to the task of testing children at high risk of LTBI or progression of LTBI to TB disease.[118] These include (1) contacts of a known case of TB, (2) children with suspected active disease, (3) children with known risk factors for progression of infection to disease (see Chapter 4, Diagnosis of Latent Tuberculosis Infection), (4) children who have travelled or resided for 3 months or longer in an area with a high incidence of TB, especially if the visit involved contact with the local population (see Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations) and (5) children who arrived in Canada from countries with a high TB incidence. In the United States, risk assessment questionnaires have been developed to identify children with risk factors for TB and LTBI who should undergo a TST.[12,118] In Canada, a school-based TB screening program and associated investigation targeting recently immigrated children have been evaluated and found to be effective.[124]

PERINATAL ISSUES: RECOMMENDED MANAGEMENT OF THE NEWBORN INFANT EXPOSED TO TB

Management should proceed according to the following principles:

- Untreated TB presents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. INH, RMP and EMB are considered safe in pregnancy, and PZA is likely safe as well (see Chapter 5).
- Administration of first-line TB drugs is not an indication for termination of pregnancy. If second-line drugs are needed, advice from a TB expert should be sought immediately, as several of these agents are known teratogens.[125]
- HIV-negative women receiving first-line agents, including INH and rifampin, may continue to breastfeed. While some of the drugs enter the breast milk, they are deemed safe. The concentrations of drugs in breast milk are insufficient to protect the newborn. Supplementary pyridoxine should be given to the nursing mother receiving INH and to her child.[67]

Infants born to mothers with suspected/confirmed active TB or LTBI need to be managed according to the categorization of the maternal infection. See Table 5 on the next page.

Evaluation of an infant for congenital TB should include a clinical examination, TST, chest radiography, appropriate cultures, including a lumbar puncture, and abdominal ultrasound. A head ultrasound should also be considered. The TST result is usually negative initially, although it may become positive after 1 to 3 months of treatment. There are very few data on the utility of IGRAs in infants. Cases of infants with negative skin tests and positive IGRA whose mothers had TB have been reported.[67]

Table 5. Recommended management of the newborn infant exposed to TB[33,67]

Situation 1	**Evaluation of mother**	**Evaluation of infant**
Mother or household contact with clinical or radiographic evidence of infectious TB at or close to the time of delivery	• Evaluate for TB disease (See Chapter 3). • HIV testing. • Examine placenta for histology smears and cultures.	• Evaluate for congenital TB (see text).
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Separate mother (or household contact) and child until mother (or household contact) and infant are receiving appropriate care, tolerating medication and mother (or household contact) is noninfectious and clinically improving. • If the mother (or household contact) has possible MDR-TB or has poor adherence to treatment and DOT is not possible, the infant should be separated from the mother (or household contact).	• If congenital TB is diagnosed, start appropriate treatment (see text). • If congenital TB is excluded, INH at a dose of 10-15 mg/kg (see text for duration of INH) is advised.	Women with TB disease who have been treated appropriately for at least 2 weeks and who are not considered infectious can breastfeed.
Situation 2	**Evaluation of mother**	**Evaluation of infant**
Mother treated for TB during pregnancy	• Mother should have follow-up smear examinations to confirm she is no longer infectious. • HIV testing. • Examine placenta for history, smears and cultures.	• Evaluate for congenital TB (see text).
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Provided treatment has been adequate to produce clinical improvement and the mother is no longer infectious, separation is not recommended. • If in doubt, proceed as in Situation 1.	• If congenital TB is diagnosed, start appropriate treatment (see text). • If congenital TB is excluded and mother is confirmed to be not infectious and no other household contacts have TB disease, INH is not necessary. • If in any doubt, proceed as in Situation 1.	Women with TB disease who have been treated appropriately for at least 2 weeks and who are not considered infectious can breastfeed.
Situation 3	**Evaluation of mother**	**Evaluation of infant**
Mother with abnormal chest x-ray but no evidence of active disease	• If the chest x-ray abnormality is considered to be secondary to old, healed TB and the mother has not been previously treated, she should be evaluated, including testing of induced sputum. • HIV testing. • The mother should be treated for LTBI if not previously treated.	• The infant should be evaluated clinically and radiographically at birth. • Consider evaluation for congenital TB (see text). • Consider a repeat TST at 3 and 6 months of age.
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• If the mother is no longer infectious, separation is not recommended. • If in doubt, proceed as in Situation 1.	• If there is uncertainty about the status of the mother, the child should be provided with preventive treatment (see Situation 1).	The mother can breastfeed.
Situation 4	**Evaluation of mother**	**Evaluation of infant**
Mother with LTBI and no abnormality on chest x-ray		• No special investigation for the newborn is recommended.
Separation of mother/infant	**Treatment of infant**	**Breastfeeding**
• Separation of mother and infant is not recommended.	• No treatment is recommended.	The mother can breastfeed.

The duration of INH treatment in newborns exposed to TB remains an area of uncertainty. Because of a question of the unreliability of the TST in very young infants – for which data are poor – some authorities recommend continuing an appropriate prophylactic regimen until the infant is 6 months of age,[4,52,126-128] when the TST can be repeated, while others recommend at least 4 months.[33,67,129;130]

Practically, according to expert opinion, if the exposure is higher risk (e.g. household or smear-positive source case) then 6 months of preventive therapy should be used, but if the source case is less infectious and there is no evidence of conversion in exposed older contacts then preventive therapy could be discontinued at 4 months if the TST is negative. The TST could be repeated at 6 months of age.

If the repeat TST is positive, the infant should be reassessed for TB disease. If TB disease is excluded, preventive therapy should be continued for a total of 9 months.

For other aspects not covered in this chapter, please refer to Chapter 11, Nontuberculous Mycobacteria, Chapter 12, Contact Follow-Up and Outbreak Management in Tuberculosis Control, Chapter 15, Prevention and Control of Tuberculosis Transmission in Healthcare and Other Settings and Chapter 16, Bacille Calmette-Guérin (BCG) Vaccination in Canada.

CONCLUSIONS

TB continues to be an important disease in Canadian children. Canadian health care workers should use available tests (currently the TST) to screen children at high risk of infection, both to protect these children now and to avoid their becoming the next generation of adults with infectious TB.

A team approach is recommended for the treatment of pediatric TB and should take into account the possibility of drug resistance. Ultimately, elimination of pediatric TB in Canada depends on controlling the disease globally. We should all find ways to assist with that international struggle. In doing so, we will also serve the interests of present and future Canadian children.[118]

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CHAPTER 10

TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

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KEY MESSAGES/POINTS

DIAGNOSIS OF HIV

- All patients with newly diagnosed TB who are not already known to be HIV-seropositive should undergo informed HIV serologic testing unless they persistently refuse testing (opt-out screening).
- TB programs should take advantage of contact tracing activities to offer provider-initiated HIV testing to at-risk individuals.

DIAGNOSIS OF LTBI

- Every patient with newly diagnosed HIV infection should be assessed with regard to history of active TB, previous tuberculin skin test (TST) results and known or likely TB exposure, including close contact with an infectious case or exposure to a community with high TB prevalence. A clinical assessment and chest radiography should be performed to look for features of previous or active TB.
- Unless there is a history of active TB or a well-documented previous positive TST or interferon gamma release assay (IGRA), every HIV-infected person should have a TST performed with 5 tuberculin units of purified protein derivative and read at 48-72 hours by a health care worker experienced in reading TSTs.
- Use of an IGRA as an additional test may be considered if the TST is negative, particularly if the patient is thought to have a high likelihood of TB exposure.
- TST induration of $\geq$5 mm should be considered indicative of TB infection in HIV-infected individuals.
- Anergy testing is *not* recommended.
- A TST should be repeated annually in patients at markedly increased risk of ongoing TB exposure, e.g. homeless shelter exposure or return travel to high TB endemic countries.

- In patients with an initial negative TST, repeat TST should be considered after institution of antiretroviral therapy (ART) and immune reconstitution indicated by an increase in the CD4 cell count.
- HIV-infected patients found to be TST- or IGRA-positive or with well-documented previous positive TST should be evaluated for the presence of active TB by clinical assessment, chest radiography and any other investigations suggested by the clinical findings. Even when the chest x-ray is normal, sputum should be obtained for *M. tuberculosis* smear and culture.

ART INITIATION AND LTBI DIAGNOSIS

- TST or IGRA positivity may be considered as factors favouring earlier ART initiation.

TREATMENT OF LTBI

Recommendations for the treatment of LTBI in HIV-infected individuals are similar to those for non HIV-infected patients and are reviewed in detail in Chapter 6. It is important to remember that the risk of disease reactivation from LTBI is substantially higher, and drug interactions need to be considered for those taking ART.

- Except when there is a well-documented history of completed treatment of LTBI or completed treatment of active TB, treatment of LTBI should be strongly recommended for every HIV-infected patient with a TST reaction $\geq$5 mm or positive IGRA test, regardless of age or BCG (Bacille Calmette-Guérin**)** vaccination status, after exclusion of active TB.
- HIV-infected people thought to have had recent close contact with an infectious TB patient should receive treatment for presumed LTBI regardless of the TST result.
- In HIV-infected individuals for whom treatment of LTBI is indicated, the recommended regimen is the same as that recommended for HIV-uninfected patients: daily self-administered isoniazide (INH) for 9 months.
- Continuation of INH beyond 9 months is not recommended in Canada, given the relatively low exposure rates.
- Daily rifampin (RMP) for 4 months is an alternative regimen in cases of INH intolerance in the patient or INH resistance in the exposure source, or in patients for whom the shorter duration is felt to be critical to the likelihood of completion, as long as it is compatible with the patient's antiretroviral regimen.
- Daily RMP plus isoniazid is an alternative (Chapter 6) but is associated with the potential toxicity of isoniazid and the potential drug interactions of RMP.
- The 3-month regimen of *supervised* once weekly rifapentine and weekly isoniazid is a promising alternative but is NOT currently recommended for HIV-infected patients.
- The combination of RMP and pyrazinamide (PZA) is NOT recommended for treatment of LTBI, regardless of HIV serostatus.

- It is recommended that consideration be given to practical measures such as clinic hours, staff attitudes, inducements, social supports, close follow-up and linking with adherence supports that may be in place for ART.
- For HIV-infected patients with predictors of poor adherence, such as unstable housing, active substance abuse or major psychosis, or those who have demonstrated poor adherence, consideration should be given, along with other supports, to providing directly observed twice weekly treatment of LTBI; twice weekly regimens should always be given under direct supervision.
- HIV-infected people who are candidates for preventive therapy but who do not receive it for any reason should have regular clinical follow-up. TB should be considered in the differential diagnosis and mycobacterial cultures of appropriate specimens included in the investigation of any unexplained illness.
- In an HIV-infected pregnant woman for whom treatment of LTBI is indicated, it should be initiated as soon as active disease has been excluded and not delayed until after the delivery.

DIAGNOSIS OF ACTIVE TB

- Health care workers caring for patients with HIV infection should maintain a high index of suspicion for TB, particularly in patients with an increased epidemiologic likelihood of either recent or remote TB exposure, when investigating any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB.
- An HIV-infected patient in whom a respiratory tract specimen is found to contain acid-fast bacilli should generally be managed as a suspected TB case until such time as the organism has been shown *not* to be *M. tuberculosis.*

TREATMENT OF ACTIVE DISEASE

TB treatment

- Treatment of TB in HIV-infected patients should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care.
- Anti-TB therapy should be initiated immediately upon the diagnosis of TB, irrespective of ART considerations.
- A standard rifamycin (RMP or RBT)-containing regimen should be used unless the organism is rifamycin resistant or the patient is intolerant of rifamycins (Chapter 5).
- The TB program should achieve successful completion of treatment using measures outlined in Chapter 5, as determined by the patient's requirements, which may include directly observed therapy.
- A treatment duration of 8 months, including INH and RMP for 8 months and PZA for the first 2 months, is recommended in patients with HIV infection who decline or for other reasons do not take ART.

- As in the preferred regimen for HIV-uninfected patients, the first 2 months (intensive phase) should be administered daily in HIV-infected patients and the continuation phase given daily (if self-administered) or thrice weekly, but not twice weekly (if on DOT) in HIV-infected patients, particularly those with CD4 cell counts $\leq$100 x 10^6/L.
- If cavitation is present on the chest x-ray or if treatment response is delayed (culture positive at 2 months), treatment may need to be prolonged from 6 to 9 months (see Chapter 5).
- In patients for whom PI-based ART is judged most appropriate, dose-adjusted rifabutin should be substituted for RMP in standard treatment regimens. (RMP should be switched to rifabutin 2 weeks before ART is initiated to allow for "washout" of the hepatic enzyme induction.)
- Routine measurement of serum concentrations of antituberculous drugs, particularly rifabutin, is suggested, especially in any patient with chronic diarrhea and advanced HIV disease, in whom a drug interaction is suspected to be lowering anti-TB drug levels or who is demonstrating a suboptimal response to TB therapy.

Antiretroviral treatment

- A diagnosis of TB in an HIV-infected individual constitutes an indication for ART.
- In patients not receiving ART at the time TB treatment is initiated, if the CD4 count is <50 x 10^6/L, ART should be initiated within 2 weeks of starting anti-TB treatment; if the CD4 count is >50, ART should be started within 8 weeks.
- For most patients taking standard RMP-containing TB therapy who are not already receiving ART, an efavirenz-based regimen combined with two nucleoside or nucleotide analogues (avoiding the additive peripheral neuropathy risk of stavudine or didanosine) is recommended unless contraindicated by drug resistance, concern over pregnancy risk or intolerance.
- In patients already receiving effective combination ART at the time of the TB diagnosis, a switch to an efavirenz-based regimen may be considered if there are no contraindications.
- Use of a PI-based regimen requires that RMP be replaced by RBT.
- In exceptional circumstances when neither an efavirenz-based or PI-based regimen can be used, a quadruple nucleoside regimen, nevirapine-based regimen or possibly an integrase inhibitor based regimen can be considered.
- In patients with a suboptimal virologic response to ART in whom an interaction with a TB drug is a possible explanation, after optimizing adherence and ruling out antiviral resistance, monitoring of serum antiretroviral concentrations should be considered.
- A "paradoxical IRIS reaction" following initiation of ART should be suspected in a patient with a low initial CD4 count on the basis of fever and localized findings following ART initiation, after exclusion of other possible causes. Corticosteroid therapy (prednisone 1 mg/kg daily) may be considered if the reaction is severe. Neither antituberculous drugs nor ART should be discontinued for an IRIS reaction.
- Patients with CD4 cell counts less than 200 cells x 10^6/L should receive prophylaxis against pneumocystis pneumonia according to current guidelines.

- Pyridoxine supplementation should be given to HIV-infected TB patients receiving INH.
- Treatment for central nervous system (CNS) and pericardial TB should follow guidelines (Chapter 6) for HIV-uninfected patients. After ART initiation patients with CNS TB should have very close monitoring for potentially serious manifestations of adverse neurologic changes due to IRIS.

BCG

- BCG vaccine should not be given to individuals (of any age) known or suspected to have HIV infection or to children of mothers with HIV infection.

Infection control

- Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and implement the necessary practices to allow early identification and effective isolation of patients with possible infectious TB and to minimize the likelihood of exposure of HIV-infected patients to those with infectious TB.
- TB and HIV control programs and care providers should collaborate closely in the care of individual patients and in prevention activities.

INTRODUCTION

The HIV epidemic has had a dramatic impact on tuberculosis (TB) rates and TB control in both industrialized and low-income countries where both infections are prevalent. HIV is the most powerful known risk factor for the development of active TB disease in individuals infected with *Mycobacterium tuberculosis* (see Table 1 of Chapter 6, Treatment of Latent Tuberculosis Infection). TB increases mortality in patients with HIV, particularly in the absence of antiretroviral therapy (ART); globally, TB is the most common cause of death in HIV-infected individuals.[1] In Canada, HIV/TB coinfection is seen disproportionately in immigrants and refugees from TB- and HIV-endemic countries and in Aboriginal peoples (Chapter 1, Epidemiology of Tuberculosis in Canada).

PATHOPHYSIOLOGY

The predominant immunologic effect of HIV is on cell-mediated immunity, the arm of the immune system most important in mediating an effective response against *M. tuberculosis.* The immune deficiency induced by HIV infection decreases the immunologic containment of latent infection, new infection[2] and reinfection with *M. tuberculosis.* It also alters the delayed-type hypersensitivity reaction involved in the tuberculin skin test (TST) and the clinical and radiologic features of TB, which are partly determined by the host response. Although TB can occur at any stage in the course of HIV infection,[3] the risk increases with advancing immune suppression and decreases in patients receiving effective ART.[4,5] The interaction between the two infections is bidirectional; treatment of *M. tuberculosis* decreases HIV replication.[6]

DIAGNOSIS OF HIV INFECTION IN TB PATIENTS

HIV prevalence is markedly increased among TB patients relative to the Canadian population because of both the overlapping of risk groups and the powerful biologic effect of HIV on *M. tuberculosis* activation. Hence HIV screening of TB patients is justified on epidemiologic grounds. Establishing a diagnosis of HIV benefits the individual patient through earlier initiation of HIV care, including ART, and contributes to the public health benefit of reduced onward transmission risk.

RECOMMENDATIONS FOR DIAGNOSIS OF HIV

- **All patients with newly diagnosed TB who are not already known to be HIV-seropositive should undergo informed HIV serologic testing unless they persistently refuse testing (opt-out screening).**

  (Strong recommendation, based on strong evidence)

- **TB programs should take advantage of contact tracing activities to offer provider-initiated HIV testing to at-risk individuals.**

  (Conditional recommendation, based on weak evidence)

DIAGNOSIS OF TB INFECTION IN HIV-INFECTED INDIVIDUALS

Among the HIV and *M. tuberculosis* coinfected, the annual risk of active TB may be as high as 10 per 100 person years in the absence of ART,[7,8] so that identification and treatment of latent TB infection (LTBI), along with early detection of active TB, provide both clinical and public health benefits.

The sensitivity of the TST decreases with decreased CD4 cell counts. Falsely negative TST results may become positive on retesting after the patient has experienced a degree of immunologic reconstitution due to ART.[9] Interferon gamma release assays (IGRAs) have not been shown to perform better than the TST in HIV-infected individuals.[10]

HIV-infected patients are more likely than HIV-uninfected individuals to have active TB with atypical clinical or radiologic features,[11] hence the need for rigorous efforts to exclude active disease before initiating treatment of LTBI. In patients with absolute CD4 counts of $\leq 50 \times 10^6$/L a blood culture for mycobacteria is useful to exclude *M. avium* complex infection and will identify some patients with disseminated *M. tuberculosis.*

RECOMMENDATIONS FOR DIAGNOSIS OF LTBI

- Every patient with newly diagnosed HIV infection should be assessed with regard to history of active TB, previous TST results and known or likely TB exposure, including close contact with an infectious case or exposure to a community with high TB prevalence. A clinical assessment and chest radiography should be performed to look for features of previous or active TB.

  (Strong recommendation, based on moderate evidence)

- Unless there is a history of active TB or a well-documented previous positive TST or IGRA, every HIV-infected person should have a TST performed with 5 tuberculin units of purified protein derivative and read at 48-72 hours by a health care worker experienced at reading TSTs.

  (Strong recommendation, based on strong evidence)

- Use of an IGRA as an additional test may be considered if the TST is negative, particularly if the patient is thought to have a high likelihood of TB exposure.

  (Conditional recommendation, based on weak evidence)

- TST induration of $\geq$5 mm should be considered indicative of TB infection in HIV-infected individuals.

  (Strong recommendation, based on moderate evidence)

- Anergy testing is *not* recommended.

  (Strong recommendation, based on moderate evidence)

- A TST should be repeated annually in patients at markedly increased risk of ongoing TB exposure, e.g. homeless shelter exposure or return travel to countries highly TB endemic.

  (Conditional recommendation, based on moderate evidence)

- In patients with an initial negative TST, repeat TST should be considered after institution of ART and immune reconstitution as indicated by an increase in the CD4 cell count.

  (Conditional recommendation, based on moderate evidence)

- HIV-infected patients found to be TST or IGRA positive or with a well-documented previous positive TST should be evaluated for the presence of active TB by clinical assessment, chest radiography and any other investigations suggested by the clinical findings. Even when the chest x-ray is normal, sputum should be obtained for *M. tuberculosis* smear and culture.

  (Strong recommendation, based on strong evidence)

PREVENTING THE DEVELOPMENT OF ACTIVE TB: ART AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

ART reduces the incidence of active TB in adults by 65%, with the greatest impact in those with lowest CD4 counts[12–14] and in children,[15] although the incidence remains higher than that of HIV-uninfected individuals even after normal CD4 cell count levels are attained.[13]

Treatment of LTBI in TST-positive HIV-infected adults has significantly reduced the risk of development of active TB by about 32%, but a reduction in mortality has not been clearly shown.[16] Some studies suggest that protection may wane in the years after treatment of LTBI, possibly as a result of reinfection in communities with high rates of transmission,[17,18] which might be less relevant to most Canadian environments, where the risk of re-exposure is expected to be low. Provision of treatment of LTBI in tuberculin-negative or anergic HIV-infected individuals has not been shown to be beneficial in several randomized trials.[16,19]

The benefit of INH treatment of LTBI appears to be additive to that of ART in reducing the incidence of active TB in adults[20] and children.[21]

RECOMMENDATIONS FOR ART INITIATION AND LTBI

- TST or IGRA positivity may be considered as factors favouring earlier ART initiation.
  (Conditional recommendation, based on weak evidence)

Completion rates for a full course of preventive therapy in Canadian programs vary widely.[22] Many HIV-infected candidates for preventive therapy are likely to have one or more characteristics associated with poor adherence, such as substance use or unstable housing. A variety of supports and/or incentives may improve treatment completion rates. Directly observed preventive therapy, usually twice weekly, for example in a methadone clinic or by an outreach worker, has been predicted to be cost-effective or cost-saving under a variety of conditions.[23,24]

A 6-month duration has shown proven efficacy in HIV-infected patients in at least five studies, but experience in HIV-uninfected patients indicates that 9 months is the optimal duration (Chapter 6, Treatment of Latent Tuberculosis Infection).

While twice weekly isoniazid (INH) has not been compared with daily chemoprophylaxis, it has been used in two published studies[17,18] and, on the basis of its efficacy in treatment, is generally thought to be comparable.

Two studies, one using daily and the other twice weekly dosing, of RMP and PZA for 2 months in HIV-infected individuals demonstrated efficacy comparable with that of 6 months of INH.[17,25] Subsequent experience with this regimen in another study, which included HIV-uninfected individuals, has revealed a high rate of serious hepatotoxicity.[26,27] This regimen is no longer recommend in HIV-infected or uninfected people (see also Chapter 6).

A 4-month regimen with daily RMP alone (Chapter 6) has not been studied in HIV-infected individuals. For patients unable to take RMP because of its interaction with protease inhibitors rifabutin is the recommended alternative and appears to have comparable efficacy in the treatment of *active* TB,[28] although it is associated with higher rates of hematologic toxicity and has not been studied as treatment for LTBI.

Of two studies, both in settings with very high TB transmission, which examined the benefit of prolonged treatment for LTBI, one showed benefit of extending isoniazid to 36 months[29] and one did not.[30]

In a study of over 7,000 patients receiving treatment for LTBI, of whom 2.7% in the RPT/INH arm were HIV-infected,[31] a 3-month course of directly observed weekly RPT (not currently available in Canada) and isoniazid was at least equivalent to a standard regimen of 9 months of self-administered daily isoniazid alone, with a lower risk of hepatitis but higher rates of overall adverse effects, including allergic or hypersensitivity reactions. The implications of potential interactions with antiretroviral drugs have not been determined.

RECOMMENDATIONS FOR TREATMENT OF LATENT TB INFECTION

Recommendations for the treatment of LTBI in HIV-infected individuals are similar to those for non HIV-infected patients and are reviewed in detail in Chapter 6. It is important to remember that the risk of disease reactivation from LTBI is substantially higher and drug interactions need to be considered for those taking ART.

- Except when there is a well-documented history of completed treatment of LTBI or completed treatment of active TB, treatment of LTBI should be strongly recommended for every HIV-infected patient with a TST reaction $\geq$5 mm or positive IGRA test, regardless of age or BCG (Bacille Calmette-Guérin) vaccination status, after exclusion of active TB.

  (Strong recommendation, based on strong evidence)

- HIV-infected people thought to have had recent close contact with an infectious TB patient should receive treatment for presumed LTBI regardless of the TST result.

  (Conditional recommendation, based on weak evidence)

- In HIV-infected individuals for whom treatment of LTBI is indicated, the recommended regimen is the same as that recommended for HIV-uninfected patients: daily self-administered INH for 9 months.

  (Strong recommendation, based on moderate evidence)

- Continuation of INH beyond 9 months is not recommended in Canada, given the relatively low exposure rates.

  (Conditional recommendation, based on weak evidence)

- Daily RMP for 4 months is an alternative regimen in cases of INH intolerance in the patient or INH resistance in the exposure source, or in patients for whom the shorter duration is felt to be critical to the likelihood of completion, as long as it is compatible with the patient's antiretroviral regimen.

  (Conditional recommendation, based on moderate evidence)

RECOMMENDATIONS FOR TREATMENT OF LATENT TB INFECTION - *Continued*

- Daily RMP plus isoniazid is an alternative (Chapter 6) but is associated with the potential toxicity of isoniazid and the potential drug interactions of RMP.

  (Conditional recommendation, based on weak evidence)

- The 3-month regimen of *supervised* once weekly rifapentine and weekly isoniazid is a promising alternative but is NOT currently recommended for HIV-infected patients.

  (Strong recommendation, based on moderate evidence)

- The combination of RMP and PZA is NOT recommended for treatment of LTBI, regardless of HIV serostatus.

  (Strong recommendation, based on moderate evidence)

- Consideration should be given to practical measures such as clinic hours, staff attitudes, inducements, social supports, close follow-up and linking with adherence supports that may be in place for ART.

  (Conditional recommendation, based on weak evidence)

- For HIV-infected patients with predictors of poor adherence, such as unstable housing, active substance abuse or major psychosis, or those who have demonstrated poor adherence, consideration should be given, along with other supports, to providing directly observed twice weekly treatment of LTBI; twice weekly regimens should always be given under direct supervision.

  (Conditional recommendation, based on weak evidence)

- HIV-infected people who are candidates for preventive therapy but who do not receive it for any reason should have regular clinical follow-up. TB should be considered in the differential diagnosis and mycobacterial cultures of appropriate specimens included in the investigation of any unexplained illness.

  (Strong recommendation, based on moderate evidence)

- In an HIV-infected pregnant woman for whom treatment of LTBI is indicated, it should be initiated as soon as active disease has been excluded and not delayed until after the delivery.

  (Conditional recommendation, based on weak evidence)

DIAGNOSIS OF ACTIVE TB

The clinical presentation of TB may be altered in the presence of HIV infection, particularly in those with more advanced immunosuppression. Extrapulmonary TB is more common, lymph nodes being the most common site, but pleural and pericardial TB, TB meningitis and TB involving more than one organ have all been found to be more common in HIV-infected than uninfected patients.

The radiologic features of TB may be altered in approximate proportion to the individual's degree of immunosuppression.[32] Upper lobe predominance and cavitation are less common, and intrathoracic adenopathy, pleural effusions, disseminated disease or a normal chest x-ray are more common in the HIV-infected, especially in patients with more advanced immune suppression.

Laboratory diagnosis of TB may also be affected by the presence of HIV infection. The rate of sputum smear positivity tends to be lower in those with pulmonary TB who are coinfected with HIV.[33] Characteristic granulomas may be absent or altered on histologic examination of tissue.[34] *M. tuberculosis* bacteremia, uncommon in the absence of HIV, is much more common in advanced HIV disease, so that blood culture may be a useful diagnostic tool in these patients.[35] Acid-fast staining of lymph node aspirates is more sensitive in HIV-coinfected than HIV-negative patients with TB lymphadenitis.[36] Infection with nontuberculous mycobacteria is relatively common in advanced HIV infection; polymerase chain reaction techniques can rapidly confirm or exclude *M. tuberculosis* in a patient with acid-fast bacilli detected on microscopy or culture; this has important clinical and public health implications.

RECOMMENDATIONS FOR DIAGNOSIS OF ACTIVE TB

- Health care workers caring for patients with HIV infection should maintain a high index of suspicion for TB, particularly in patients with an increased epidemiologic likelihood of either recent or remote TB exposure, when investigating any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB.

  (Strong recommendation, based on moderate evidence)

- An HIV-infected patient in whom a respiratory tract specimen is found to contain acid-fast bacilli should generally be managed as a suspected TB case until such time as the organism has been shown *not* to be *M. tuberculosis.*

  (Conditional recommendation, based on weak evidence)

TREATMENT OF TB

TB recurrence is more common among the HIV-infected.[37] When molecular techniques have been used to distinguish between relapse and reinfection, in communities with high levels of ongoing transmission the rates of relapse with the original strain have been similar, whereas reinfection with a new strain of *M. tuberculosis* is more frequent among the HIV-infected.[38] Mortality is higher among HIV-infected TB patients and correlates with the degree of immune suppression.[39] However, with appropriate anti-tuberculosis therapy and timely initiation of ART, the difference in outcomes attributable to HIV can be greatly decreased.

A number of studies have found decreased serum concentrations of antituberculous agents in patients with HIV infection, thought to be due to decreased absorption.[40,41]

Findings from recent randomized trials[42] and a recent meta-analysis suggest that regimens containing RMP for ≤8 months may be associated with higher rates of treatment failure and, particularly, of relapse in HIV-infected individuals who are not receiving ART;[43] the risk of relapse was lower and the benefit of therapy >6 months in duration less clear among TB patients receiving ART.[44]

Several investigators have found that continuation of INH ("secondary prophylaxis") after completion of standard TB therapy was associated with lower rates of TB recurrence in HIV-infected patients, but this may be attributable to prevention of reinfection in settings of high transmission.[45,46]

Treatment failure with acquired RMP monoresistance has been observed during TB treatment in HIV-infected patients with once weekly INH and rifapentine and in twice weekly RMP-based regimens, associated with low serum INH levels. This phenomenon has been observed particularly among patients with CD4 counts $<100 \times 10^6$/L and with twice weekly administration of TB therapy in the intensive phase.[47-51]

TIMING OF INITIATION OF ART

In the HIV-infected patient with active TB, establishment of effective TB treatment is the first priority. If the two therapies were initiated simultaneously, the problems of overlapping drug adverse effects and pill burden, as well as drug interactions and the immune reconstitution inflammatory syndrome (IRIS), could result in unacceptable obstacles to successful TB treatment initiation. On the other hand, undue delay in the initiation of effective ART results in a significant risk of HIV-related death among patients with advanced immune suppression.

Three recent randomized controlled trials found that early initiation of ART, within 2-4 weeks of TB therapy initiation, reduced the mortality and/or incidence of AIDS-defining illness.[52–54] In two of the three studies, this effect was limited to patients with CD4 counts of $<50 \times 10^6$/L. Deferring the initiation of ART in patients with higher CD4 counts until 8 weeks of therapy reduced the risk of IRIS without increasing the risk of HIV progression or death.

The advantage of early initiation of ART is less clear in cases of TB meningitis,[55] perhaps because of the unique risks of IRIS reactions in the closed space of the cranium.

DRUG INTERACTIONS

Drug interactions between antiretrovirals and antituberculous drugs may be complex and sometimes bidirectional. Experience and recommendations continue to evolve, even with older agents such as efavirenz, but particularly with newer drugs. Current information can be obtained from several regularly updated websites:

- HIV Insite (San Francisco, CA), see http://hivinsite.ucsf.edu/insite?page=ar-00-02
- Liverpool (UK), see http://www.hiv-druginteractions.org/
- Toronto General Hospital, see http://www.hivclinic.ca/main/drugs_interact.html

ANTIRETROVIRAL DRUGS

Antiretroviral drugs, particularly those in the protease inhibitor (PI) class but also the non-nucleoside reverse transcriptase inhibitor (NNRTI) group, demonstrate major and sometimes bidirectional interactions with rifamycin antituberculous agents. Clinically important interactions with antituberculous agents have not been found with any of the nucleoside or nucleotide analogues (zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine or tenofovir). Although clinical experience is limited, integrase inhibitors and CCR5 receptor blockers also interact with RMP.

RIFAMYCINS

Critical to the success of short-course TB treatment, these are the only antituberculous agents found to have clinically significant interactions with antiretroviral drugs. Lesser degrees of interaction are seen with RBT than with RPT, which in turn interacts less than RMP.

Specific interactions with rifamycins

Extensive experience has shown that the NNRTI efavirenz at standard dosing of 600 mg/day remains effective when used with RMP, particularly in populations with relatively low body mass, in spite of variable reduction in efavirenz serum concentrations.[56] An increase in dose to 800 mg in those ≥50 kg was recommended in 2012 by the Food and Drug Administration on the basis of kinetics studies.

No PI dosing regimen has been found to be safe and effective in combination with RMP. Rifabutin can be substituted for RMP in TB treatment to permit the use of PIs[28] but is associated with higher rates of hematologic toxicity.

Rifabutin concentrations are increased to varying degrees by concomitant therapy with different PIs. Rifabutin, *with appropriate dose reduction*, can be used together with most ritonavir “boosted” PIs. Rifabutin concentrations may vary when given with lopinavir/ritonavir, and higher than standard recommended doses of rifabutin may be required to achieve effective serum concentrations.[57,58]

RMP reduces serum concentrations of nevirapine to a greater degree than efavirenz concentrations.[59,60] Reports of virologic suppression by nevirapine-based regimens in combination with RMP are conflicting.[61] Nevirapine taken once a day has been shown to be inferior to efavirenz when administered with RMP.[62] There is no published information on the combination of nevirapine and rifabutin.

Therapy with the combination of four nucleoside/nucleotide reverse transcriptase inhibitors zidovudine, lamivudine, abacavir (coformulated as Trizivir) and tenofovir appears comparable in limited studies to standard ART regimens and is not expected to be associated with significant drug interactions.[63]

Although clinical experience remains limited with the newer integrase inhibitor drug class, such as raltegravir,[64,65] dose adjustments are recommended when used with RMP but not if used with rifabutin. Metabolism of the CCR5 receptor blocker maraviroc is also induced by RMP, and dosage increases of maraviroc are also recommended. The manufacturer currently recommends against concomitant use of etravirine and RMP, but use of RBT may be considered in spite of modest decreases in the levels of both drugs. Recommendations regarding these newer agents are likely to evolve.

Because of the possibility of reduced drug absorption, the potential for complex and difficult-to-predict drug interactions and the serious consequences (treatment failure, drug resistance) of inadequate treatment of either active TB or HIV infection, therapeutic drug monitoring of antituberculous[66] (see Chapter 5, Treatment of Tuberculosis Disease) and antiretroviral drug levels is assuming an increasing role in the management of TB in the HIV-infected, particularly when a non-efavirenz based regimen is used or when the response to therapy is poorer than expected or the therapies selected in an individual patient have been less well studied.[67]

TREATMENT OF DRUG-RESISTANT TB, INCLUDING MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TB WITH HIV COINFECTION

(See Chapter 8, Drug-resistant Tuberculosis)

HIV is not clearly associated with increased risk of multidrug-resistant TB (MDR TB) overall but may be associated with nosocomially transmitted MDR disease outbreaks.[68] The early experience with MDR and subsequently extensively drug-resistant TB (XDR TB) and HIV showed very high mortality.[69] Early diagnosis of drug resistance and initiation of ART appear to contribute to improved outcomes.[70,71] There are few data on interactions between second-line anti-TB drugs and ARVs.[72]

IMMUNE RECONSTITUTION REACTIONS

Immune reconstitution inflammatory syndrome may occur during TB therapy, after ART initiation (paradoxical reactions) or following ART initiation in patients with unrecognized TB ("unmasking").[73] Paradoxical IRIS has been reported with a frequency ranging from 8% to 43%.[74] These reactions may present as fever and clinical and radiologic disease progression at involved sites, e.g. enlarging lymph nodes, worsening pulmonary infiltrates or exacerbation of inflammatory changes at other sites.[75-77] Almost all affected patients have low initial CD4 cell counts, typically below 50-100 x 10^6/L.[75–80] Onset has been described between 2 and 40 days after ART initiation.[77,79] Paradoxical reactions can occur even when ART is initiated more than 2 months after starting TB treatment, but the risk may be higher with early ART initiation. Diagnosis is often difficult and requires exclusion of other possible causes of the observed clinical findings, including treatment failure due to drug resistance[81] or development of a different opportunistic infection. A standardized definition of IRIS has been proposed.[82] Mortality attributed to IRIS appears to be uncommon except in cases with neurologic involvement. If the reaction is severe enough to warrant therapy, corticosteroids such as prednisone at doses in the range of 1 mg/kg of body weight have been shown effective in a randomized trial.[83] In almost all cases, patients can be managed successfully without interruption of ART or TB treatment.

Although less well studied in the HIV-infected, available evidence suggests a benefit of adjunctive corticosteroids in TB meningitis and pericarditis.[84-86]

HIV-infected individuals are at increased risk of neuropathy due to HIV or specific antiretroviral agents and may be more susceptible to INH-associated neuropathy.

RECOMMENDATIONS FOR TREATMENT OF ACTIVE DISEASE

TB treatment

- A treatment duration of 8 months**,** including INH and RMP for 8 months and PZA for the first 2 months, is recommended in patients with HIV infection who decline or for other reasons do not take ART.

  (Conditional recommendation, based on moderate evidence)

- As in the preferred regimen for HIV-uninfected patients, the first 2 months (intensive phase) should be administered daily in HIV-infected patients and the continuation phase given daily (if self-administered) or thrice weekly, but not twice weekly (if on DOT) in HIV-infected patients, particularly those with CD4 cell counts ≤100 x 10^6/L.

  (Strong recommendation, based on moderate evidence)

- If cavitation is present on the chest x-ray or if treatment response is delayed (culture positive at 2 months), treatment may need to be prolonged from 6 to 9 months (see Chapter 5).

- In patients for whom PI-based ART is judged most appropriate, dose-adjusted rifabutin should be substituted for RMP in standard treatment regimens.

  (Strong recommendation, based on strong evidence)

  RMP should be switched to RBT 2 weeks before ART is initiated to allow for "washout" of the hepatic enzyme induction.

- Routine measurement of serum concentrations of antituberculous drugs, particularly RBT, is suggested, especially in any patient with chronic diarrhea and advanced HIV disease, in whom a drug interaction is suspected to be lowering anti-TB drug levels or who is demonstrating a suboptimal response to TB therapy.

  (Conditional recommendation, based on moderate evidence)

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- Routine measurement of serum concentrations of antituberculous drugs, particularly RBT, is suggested, especially in any patient with chronic diarrhea and advanced HIV disease, in whom a drug interaction is suspected to be lowering anti-TB drug levels or who is demonstrating a suboptimal response to TB therapy.

  (Conditional recommendation, based on moderate evidence)

RECOMMENDATIONS FOR TREATMENT OF ACTIVE DISEASE

Antiretroviral treatment

- A diagnosis of TB in an HIV-infected individual constitutes an indication for ART.

  (Strong recommendation, based on moderate evidence)

- In patients not receiving ART at the time TB treatment is initiated, if the CD4 count is <50 x 10^6/L, ART should be initiated within 2 weeks of starting anti-TB treatment; if the CD4 count is >50, ART should be started within 8 weeks.

  (Strong recommendation, based on strong evidence)

- For most patients taking standard RMP-containing TB therapy who are not already receiving ART, an efavirenz-based regimen combined with two nucleoside or nucleotide analogues (avoiding the additive peripheral neuropathy risk of stavudine or didanosine) is recommended unless contraindicated by drug resistance, concern over pregnancy risk or intolerance.

  (Strong recommendation, based on strong evidence)

- In patients already receiving effective combination ART at the time of the TB diagnosis, a switch to an efavirenz-based regimen may be considered if there are no contraindications.

  (Conditional recommendation, based on weak evidence)

- Use of a PI-based regimen requires that RMP be replaced by RBT.

  (Strong recommendation, based on strong evidence)

- In exceptional circumstances when neither an efavirenz-based or PI-based regimen can be used, a quadruple nucleoside regimen, nevirapine-based regimen or possibly an integrase inhibitor based regimen can be considered.

  (Conditional recommendation, based on weak evidence)

- In patients with a suboptimal virologic response to ART in whom an interaction with a TB drug is a possible explanation, after optimizing adherence and ruling out antiviral resistance, monitoring of serum antiretroviral concentrations should be considered.

  (Conditional recommendation, based on weak evidence)

- A “paradoxical IRIS reaction” following initiation of ART should be suspected in a patient with a low initial CD4 count on the basis of fever and localized findings following ART initiation, after exclusion of other possible causes. Corticosteroid therapy (prednisone 1 mg/kg daily) may be considered if the reaction is severe. Neither antituberculous drugs nor ART should be discontinued for an IRIS reaction.

  (Conditional recommendation, based on moderate evidence)

- Patients with CD4 cell counts less than 200 cells x 10^6/L should receive prophylaxis against pneumocystis pneumonia according to current guidelines.

  (Strong recommendation, based on strong evidence)

- Pyridoxine supplementation should be given to HIV-infected TB patients receiving INH.

  (Conditional recommendation, based on weak evidence)

- Treatment for central nervous system (CNS) and pericardial TB should follow guidelines (Chapter 6) for HIV-uninfected patients. After ART initiation patients with CNS TB should have very close monitoring for potentially serious manifestations of adverse neurologic changes due to IRIS.

Table 1. Summary of compatible antituberculous and antiretroviral regimens
(see text and recommendations for consideration of monitoring serum drug concentrations)

	TB regimen	ARV regimen
1st line	2 months daily INH/RMP/PZA/EMB daily for 2 months, followed by *INH*RMP daily or 3x weekly for 4 months **daily or 3x weekly in continuation phase*	Efavirenz 600 mg* and two nucleoside/nucleotide analogues (not stavudine or didanosine) **Consider efavirenz 800 mg if weight >50 kg or suboptimal virologic response*
Alternative	2 months daily INH/PZA/EMB rifabutin 150 mg q 2 days, followed by: 6 months *INH*PZA*EMB RBT 150 mg q 2 days **daily or 3x weekly in continuation phase*	Ritonavir "boosted" protease inhibitor and two nucleoside/nucleotide analogues

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol, RBT = rifabutin

BACILLE CALMETTE-GUÉRIN

BCG vaccination is associated with a substantial risk of disseminated disease,[87] and its efficacy appears to be markedly reduced in HIV-infected infants.[88]

RECOMMENDATION FOR BCG

- BCG vaccine should not be given to individuals (of any age) known or suspected to have HIV infection or to children of mothers with HIV infection.

  (Strong recommendation, based on strong evidence)

CONTROL OF TB TRANSMISSION TO HIV-INFECTED INDIVIDUALS: PROGRAM COORDINATION

Outbreaks of TB, including MDR TB, in HIV-infected patients and health workers have been associated with hospitals and clinics caring for HIV-infected patients[69] and with correctional institutions.

RECOMMENDATIONS FOR INFECTION CONTROL

- Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and implement the necessary practices to allow early identification and effective isolation of patients with possible infectious TB and to minimize the likelihood of exposure of HIV-infected patients to those with infectious TB.

  (Strong recommendation, based on moderate evidence)

- TB and HIV control programs and care providers should collaborate closely in the care of individual patients and in prevention activities.

  (Strong recommendation, based on moderate evidence)

▪ ▪ ▪

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CHAPTER 11

NONTUBERCULOUS MYCOBACTERIA

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KEY MESSAGES/POINTS

- Transmission of nontuberculous mycobacteria (NTM) between people is believed to be extremely rare. As such, NTM disease is not reportable, public health case management is not currently required, and treatment is not mandatory but, rather, determined on a case-by-case basis.
- There are many NTM species. Some species are associated with clinical diseases as well as a spectrum of clinical findings, whereas other species are rarely, if ever, associated with disease.
- Isolation of NTM organisms from nonsterile sites, such as sputum, does not necessarily indicate disease. It is recommended that pulmonary NTM disease only be diagnosed in the presence of suggestive clinical symptoms that are not otherwise explained and suggestive radiographic findings; diagnosis should be supported by isolation of NTM, ideally from multiple specimens.
- Treatment benefit/risk ratio is generally poorer than what is seen with TB. Therefore, even when the NTM are judged likely to be clinically significant, a careful assessment of the therapeutic goal and individual risks and benefits is recommended before initiating treatment.
- It is recommended that limited drug susceptibility testing be used to guide therapy of *M. avium-intracellulare* complex (MAC) (macrolide testing only) and *M. kansasii* (rifampin testing). For rapidly growing mycobacteria and other NTM, drug susceptibility results can be used but should be interpreted with caution, as data correlating *in vitro* susceptibility results with clinical outcomes are lacking.
- Therapy is generally species specific and involves multiple drugs for a prolonged duration.
- Clinical outcomes in lung disease are relatively poor, with high relapse rates requiring recurrent or ongoing drug therapy.
- Clinical outcomes in nonpulmonary disease are relatively good.

Major Shifts in Recommendations: none

INTRODUCTION

Pulmonary nontuberculous mycobacterial disease is considered in the context of tuberculosis (TB) for two main reasons. First, lung disease associated with NTM is often characterized by cough, sputum, hemoptysis, a wasting illness, cavities on lung imaging and acid-fast organisms on sputum smear microscopy. Therefore, it can initially be mistaken for TB. Second, TB clinics are often asked to assess patients with known NTM disease because TB clinicians are experienced at prescribing and monitoring antituberculous drugs, many of which are also used to treat NTM disease. In addition, practitioners are not always aware that the provinces and territories do not require NTM disease to be reported, that case management is not mandated by public health, that treatment is not mandatory (rather, determined on a case-by-case basis) and, with some possible very rare exceptions,[1] that NTM disease is not contagious. This chapter provides some background information on NTM microbiology and epidemiology and is followed by a review and clinical recommendations regarding NTM disease.

Historically, the mycobacteriology laboratory served to isolate and speciate *Mycobacterium tuberculosis* complex organisms. This capacity to isolate known mycobacterial pathogens gradually enabled the laboratory to isolate other mycobacteria, of unknown or lesser pathogenicity.[2] These organisms have traditionally been grouped together by what they are not, and are now most often called NTM, a term used here for all mycobacterial species with the exception of *M. tuberculosis* complex organisms and *M. leprae*. At present, there are over 150 recognized mycobacterial species (http://www.bacterio.net/mycobacterium.html), the majority of which have little clinical relevance. This chapter will focus on the small number of NTM that are well associated with defined clinical syndromes.

The significance of an NTM isolate necessitates more deliberation by the clinician than is the case for *M. tuberculosis*, for which treatment is not optional. Certain NTM, such as *M. gordonae*, are rarely associated with clinical illness. It is generally accepted that when *M. gordonae* is found in a sample, treatment is not recommended.[3] At the other end of the spectrum, *M. kansasii* is usually associated with a *bona fide* clinical syndrome.[4] The severity of otherwise unexplained symptoms and suggestive abnormalities on chest imaging generally guide clinical decisions as to the relevance of the NTM isolate. Some patients lack attributable symptoms and chest imaging abnormalities, and the presence of the NTM might be termed colonization. In other patients, there may be a spectrum of findings ranging from minimal and nonprogressive symptoms to more extensive lung disease with chest imaging abnormalities. However, even in the presence of productive cough and radiographic abnormalities, it can still be difficult to judge whether the NTM is contributing to these findings, for instance when a patient also has chronic obstructive pulmonary disease (COPD) or pre-existing bronchiectasis. Suggested criteria for the diagnosis of pulmonary NTM disease are presented in Table 1. The Canadian Thoracic Society (CTS) recommends that, in the context of even a single NTM isolate from a normally sterile site (blood, pleural fluid, organ biopsy), NTM disease should be very strongly considered.

Table 1. Recommended diagnostic criteria for pulmonary NTM disease[3]

1. Clinical

a) Symptoms – pulmonary (such as cough, sputum production, hemoptysis, chest pain, dyspnea) and/or systemic (such as fatigue, weight loss, fever).

b) Other potential causes of symptoms should be excluded.

c) Progressive symptoms increase the likelihood of NTM disease, so that antimicrobial drug therapy may be necessary.

2. Radiology

a) Chest radiograph – nodular or cavitary opacities, or

b) Chest computed tomography – bronchiectasis with multiple small nodules or lung cavitation, or, in some cases, air space disease (consolidation or ground glass opacification).

3. Microbiology

a) Positive culture results from at least two separate sputum samples or

b) Positive culture result from at least one bronchial wash or lavage,* or

c) Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM.

* Sputum induction should be attempted before bronchoscopy. A single bronchoscopic isolate is acceptable for the diagnosis of pulmonary NTM disease when sputum (spontaneously expectorated or induced) cannot be obtained.

A bronchoscopic isolate should be corroborated with sputum results if both samples are available.

A single bronchoscopic isolate in the presence of repeatedly negative sputum samples should be interpreted cautiously.

A key reason to make the clinical determination of whether there is NTM colonization or NTM disease is that the former is not likely to benefit from treatment, while the latter may benefit from targeted therapy. Importantly, treatment of NTM disease, where indicated, benefits only the patient, in contrast to *M. tuberculosis*, for which there are also public health benefits of treatment. Furthermore, there is less urgency in deciding whether to treat NTM, as the clinical evolution of NTM is typically slower than that of TB, and the treatment is more complex (longer duration, greater toxicity). Where there is doubt about whether to treat or defer, one should obtain more specimens and consider further investigations before formulating a treatment plan and defining the therapeutic goal(s). Recommendations in this chapter are focused largely on therapy, and are summarized and rated in Table 2.[3] Ratings for the few remaining recommendations can be found in the text box.

Table 2. Recommended treatment of nontuberculous mycobacterial disease[3]*

Organism	Drugs	Duration
M. avium complex (MAC) lung disease (macrolide susceptible)	Daily Clarithromycin 500 mg bid or azithromycin 250 mg Ethambutol (EMB) 15 mg/kg (may use 25 mg/kg for initial 2 months) Rifampin (RMP) (450-600 mg) or rifabutin (RBT) (150-300 mg) ± aminoglycosides (streptomycin [SM] or amikacin) intermittently *(Conditional recommendation, based on moderate evidence)* Thrice weekly[†] (may be considered for nonadvanced, nodular bronchiectatic pulmonary MAC) Clarithromycin 500 mg bid or azithromycin 500 mg EMB 25 mg/kg RMP 600 mg *(Conditional recommendation, based on moderate evidence)* Clofazimine and fluoroquinolones (FQN) may be useful *(Conditional recommendation, based on moderate evidence)*	12 months after culture conversion to negative *(Conditional recommendation, based on moderate evidence)*
MAC lymphadenitis (macrolide susceptible)	If antibacterial therapy is being considered (see text): daily or thrice weekly clarithromycin or azithromycin plus EMB ± RMP *(Conditional recommendation, based on very weak evidence)*	3-9 months *(Conditional recommendation, based on very weak evidence)*
M. xenopi lung disease	Azithromycin or clarithromycin plus RMP plus EMB Consider, in addition, moxifloxacin (or other FQN), isoniazid (INH), streptomycin (SM), amikacin *(Conditional recommendation, based on very weak evidence)*	12 months after culture-negative *(Conditional recommendation, based on very weak evidence)*
M. abscessus complex lung disease	Clarithromycin or azithromycin + amikacin, cefoxitin or imipenem (+/- tigecycline, linezolid, clofazimine) *(Conditional recommendation, based on moderate evidence)*	2-6 months of combination IV and oral therapy *(Conditional recommendation, based on weak evidence)*
M. kansasii lung disease	Daily RMP, EMB, INH Consider clarithromycin or azithromycin, moxifloxacin, sulfamethoxazole and aminoglycosides *(Strong recommendation, based on moderate evidence)*	12 months after culture-negative *(Conditional recommendation, based on weak evidence)*
M. fortuitum lung disease	Based on *in vitro* sensitivity testing: azithromycin or clarithromycin and RMP or EMB (+/- doxycycline, amikacin, imipenem, FQN, sulfonamides, cefoxitin) *(Conditional recommendation, based on very weak evidence)*	12 months after culture-negative for lung disease *(Conditional recommendation, based on very weak evidence)*
M. fortuitum skin/soft tissue	Based on *in vitro* sensitivity testing: azithromycin or clarithromycin and RMP or EMB (+/- doxycycline, amikacin, imipenem, FQN, sulfonamides, cefoxitin) *(Conditional recommendation, based on very weak evidence)*	4 months for skin/soft tissue (6 months for severe disease) *(Conditional recommendation, based on weak evidence)*
M. marinum skin/soft tissue	Clarithromycin, EMB +/- RMP *(Conditional recommendation, based on weak evidence)*	3-6 months (consider longer if deep structures involved) *(Conditional recommendation, based on weak evidence)*
Disseminated MAC in HIV-infected patients Treatment	[‡]Clarithromycin 500 mg orally daily + EMB 15 mg/kg orally daily +/- RBT 300 mg orally daily *(Strong recommendation, based on very strong evidence)*	Lifelong or until control of HIV viremia with rise of CD4 to >100 x 10^6/L for at least 6 months and 12 months after culture-negative *(Strong recommendation, based on strong evidence)*

Table 2. - *Continued*

Organism	Drugs	Duration
Disseminated MAC in HIV-infected patients Prophylaxis Patients with CD4 <50 x 10^6/L	Azithromycin 1200 mg weekly or RBT 300 mg a day or clarithromycin 500 mg bid *(Strong recommendation, based on very strong evidence)*	Lifelong or until control of HIV viremia with rise of CD4 to >100 x 10^6/L for at least 6 months and 12 months after culture-negative *(Strong recommendation, based on strong evidence)*

Suggested regimens for initial therapy of NTM disease should be modified, if needed, depending upon clinical circumstances such as drug intolerance, the presence of macrolide-resistant MAC and a lack of efficacy.

*More detailed recommendations and treatment guidance regarding other NTM species may be found elsewhere.[3]

†Although directly observed therapy (DOT) is recommended for intermittent therapy of TB, this is not so in NTM disease, because there is no public health consideration of contagion. Intermittent therapy for pulmonary NTM has been suggested to reduce toxic effects and sometimes costs of therapy, and has been shown to be effective in many cases.

‡Doses may need to be adjusted according to interactions with concurrent antiretroviral therapy.

LABORATORY METHODS

The typical mycobacteriology laboratory detects NTM using protocols and media that were optimized for the isolation of *M. tuberculosis* from sputum. If there is clinical suspicion of NTM disease, one should contact the laboratory so that it can modify the protocol, depending on what sample is provided and what organism is suspected. Complete details on the laboratory handling of suspected NTM disease (and additional information for this section) can be found in the following three sources:

- http://estore.asm.org/viewItemDetails.asp?ItemID=908;
- http://mcm10.asmpress.org/;
- http://estore.asm.org/viewItemDetails.asp?ItemID=1033.

Once an NTM has been isolated, in theory this is no longer a biosafety threat, as most NTM are harmless to humans and present a negligible risk to laboratory workers. In practice, NTM clinical work is done in the level 3 laboratory for two reasons. First, it is not known that the organism is NTM until after genetic or phenotypic tests have been conducted. Second, sputum is occasionally positive for both *M. tuberculosis* and NTM; thus, the demonstration of NTM does not guarantee the absence of *M. tuberculosis*. After selection of pure colonies from a culture that has been speciated, all other NTM work can be safely done outside of containment.

Characterization of an NTM isolate begins with a formal species designation, which in the molecular era often includes a combination of phentoypic anlaysis (growth rate, morphology, etc.) and molecular testing (specific probes for certain species and/or 16s rRNA sequence analysis). One consequence of the use of this highly discriminative technique is the identification of a “new” species from within a previously familiar species or group (e.g. *M. chimerae* as a variant of the *M. avium-intracellulare* complex [MAC][5]). This may confuse clinicians if there are new names for which the clinical information is limited to case reports or small case series, such that the clinical importance of the new designation is not immediately apparent.

In the case of antibiotic resistance testing it is relatively straightforward to grow organisms in the presence of various antibiotics and measure the minimum inhibitory concentration; however, the utility of these results for guiding therapeutic decisions remains largely unknown. For rapid-growing mycobacteria, antibiotic drug susceptibility (DS) testing is typically done in a manner comparable to the testing of common bacteria in the microbiology laboratory (e.g. *Staphylococcus aureus*). For slow-growing mycobacteria, there are laboratory issues with standardizing results (antibiotics may degrade during the time of testing) and clinical issues with interpreting results (antibiotics that do not appear effective in the laboratory have apparently provided benefit in the clinic). While there are many possible DS tests that could be requested for any given NTM isolate, the only good correlations between laboratory testing and clinical response to treatment are seen for macrolide resistance in MAC and rifampin resistance in *M. kansasii*.

EPIDEMIOLOGY

The NTM that are most closely linked to human disease inhabit moist environments, both natural and engineered.[6] NTM have been recovered from all types of natural waters and soils from many parts of the world.[7,8] There has been a relatively high rate of NTM recovery from household water and plumbing fixture biofilms, but since NTM are common and NTM disease is rare, it is unclear whether environmental exposure in the home differs between people with and without NTM disease.[9,10] Transmission of NTM between patients is extremely rare and probably only occurs when an index patient with a large burden of NTM organisms comes into contact with someone who is particularly susceptible to NTM infection.[1] The mode of transmission, if it occurs at all, is unknown. For this reason, the CTS sees no public health concerns for the vast majority of patients with NTM disease.

It appears that a defect in pulmonary defences is the most common risk factor for pulmonary NTM disease. Structural lung diseases, especially COPD and bronchiectasis, are important risk factors for pulmonary NTM (30% of pulmonary NTM is associated with COPD).[11] However, the majority of patients do not have pre-existing structural lung disease.[3] In one series, approximately 30% of patients with apparently idiopathic MAC lung disease were found to carry at least one mutation for the cystic fibrosis transmembrane conductance regulator (CFTR) gene, without a prior diagnosis of cystic fibrosis (CF).[12] Cryptic abnormalities in pulmonary mucus and its clearance may represent a major risk factor for NTM lung disease. Both pediatric and adult patients with CF commonly have positive sputum cultures for NTM, ranging from 3.7% to 13%.[13-15] Systemic deficits in host defences are believed to be relatively uncommon in pulmonary NTM, and tumour necrosis factor alpha inhibitors have been inconsistently associated with elevated rates of NTM disease.[16,11] Increasing age is an important risk factor for pulmonary NTM: the prevalence of identified pulmonary MAC disease in Ontario was 1/100,000 in people <50 years old and 48/100,000 in people ≥80 years old.[11]

Historically, the epidemiology of NTM disease has not been well understood because of two key challenges. First, unlike TB, the provinces and territories do not require clinicians to report NTM disease to public health authorities, so there has not been any systematic collection of data regarding NTM disease. Second, the determination that someone has NTM disease, as opposed to simply a positive sputum culture, necessitates the integration of clinical, microbiological and radiological information.

Illustrating this, in 2008 in Ontario, the prevalence of pulmonary MAC isolation was 12.6/100,000, whereas the prevalence of disease was estimated to be 6.8/100,000.[11] Similarly, a British Columbia study reported an annual incidence of 6.7/100,000 for pulmonary NTM isolation and 1.6/100,000 for disease.[17] NTM isolation in Canada is more common than *M. tuberculosis* isolation, but there is great regional variability. In recent reports, the ratio of pulmonary NTM to *M. tuberculosis* was 5.3 in Ontario,[11] 2.7 in Alberta (personal communication: G. Tyrrell, University of Alberta, Edmonton, Alberta, 2011) and 1.4 in British Columbia.[17]

Most investigations into temporal trends of pulmonary NTM have observed increases. In Ontario, prevalence rates of MAC lung disease increased from 4.3 to 6.8/100,000 from 2003 to 2008 overall, and from 11.9 to 18.6/100,000 in people $\geq$50 years old.[11] Similar findings have been described in the United States.[18,19] Numerous factors have been postulated to contribute to these increases, including better laboratory detection and real changes in epidemiology. Improved sample collection practices and the use of liquid culture media, which are more sensitive for detection of NTM than conventional solid media in the TB laboratory, do not appear to completely explain the increase.[20] In addition, increases in at-risk populations (aged, immune suppressed, with chronic lung disease) are also not felt to be sufficiently important to explain the changing epidemiology of NTM disease.[11] “Cross-immunity” between *M. tuberculosis* and NTM has been hypothesized to be a contributing factor, since increases in NTM have usually been seen coincident with decreases in TB rates.[21] Finally increases in exposure to water aerosols, possibly through showering, have also been proposed as a potential contributing factor.[21]

Regional variations exist not only in rates of disease but also in the relative frequency of different NTM species causing disease.[22] For example, *M. xenopi* is common in Ontario and parts of Europe but relatively uncommon elsewhere; *M. kansasii* is common in the south and central United States, Asia and Eastern Europe but rare in most of Canada. The epidemiology of NTM infections is highly dependent upon the geographic region, likely reflecting the environmental NTM that are prevalent in patients’ local environments.

CLINICAL SYNDROMES

LUNG DISEASE

Diagnostic considerations

In adults, NTM disease is usually pulmonary; in Ontario between 2000 and 2007, 95% of people with NTM isolates had a pulmonary isolate. MAC represents the most common species group associated with NTM lung disease, followed variably by *M. xenopi* (second in Ontario), the rapid growers of the *M. fortuitum-chelonae-abscessus* complex (second in British Columbia and Alberta) and *M. kansasii*.[22] As detailed in Table 1, at least two sputum isolates are recommended for the diagnosis of pulmonary NTM disease or, when sputum cannot be obtained (spontaneously expectorated or induced), a single bronchoscopic isolate or one biopsy isolate is suggested. In addition to isolating the organism, otherwise unexplained symptoms and chest imaging changes consistent with NTM infection are also recommended for the diagnosis.[3] In the case of *M. kansasii*, a single isolate is commonly considered to be diagnostic in the appropriate context.[3]

There are two traditionally described imaging patterns seen with pulmonary NTM disease, although overlap is common. The most common radiographic type is called “nodular bronchiectatic” based on a pattern of nodules, often “tree-in-bud,” and bronchiectasis, with or without consolidation. This pattern occurs most often in patients without obvious underlying lung disease and has classically been described in a right middle lobe and lingular distribution in middle-aged to older women (Lady Windermere syndrome).[23] Such patients often share a phenotype that includes a tall slender habitus, scoliosis, pectus excavatum and mitral valve prolapse, and 36.5% have been found to have a mutation in at least one CFTR allele (versus 15.6% in controls).[12] The second pattern is one of predominant cavitation, often in the upper lobes in the setting of emphysema or pre-existing bronchiectasis – described as “fibrocavitary.” The natural history and treatment response with nodular bronchiectatic disease appears to differ from fibrocavitary disease, with poorer treatment outcomes in the latter group.[24-26]

Screening for NTM is recommended in CF patients, with sputum (spontaneously expectorated or induced) collection at least yearly and during periods of clinical decline. The laboratory should be informed that the patient has CF, so that tailored protocols for decontamination of CF sputum can be employed. Patients being considered for chronic macrolide therapy should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of providing macrolide monotherapy (see below, Treatment). It is recommended that CF patients with repeated isolation of NTM not receive macrolide monotherapy without the potential risks of its use or its omission being carefully weighed. On the one hand, macrolide monotherapy is associated with the development of macrolide-resistant NTM disease, which is extremely difficult to treat.[27] On the other hand, azithromycin therapy has been shown to have clinically beneficial effects in CF patients.[28] In general, it is recommended that macrolide monotherapy be avoided in CF patients with repeated isolation of NTM who may have clinically significant NTM isolates. These recommendations may also be considered for patients with non-CF bronchiectasis and COPD if chronic macrolide therapy is being considered.

Treatment (see Table 2)[3]

Fulfilling the diagnostic criteria for NTM-associated lung disease does not necessarily imply the need for treatment. Initiating therapy is a decision that should be made carefully, considering individual patient characteristics,[3] risk factors for treatment toxicities and the frustratingly low cure rates that are compounded by substantial recurrence rates after treatment completion.[29] Although there are no data to support this approach, anecdotal experience suggests that clinicians may wish to consider initiating therapy sequentially, adding a drug every 7-14 days, until a tolerable multidrug regimen is achieved. Staggered initiation may facilitate tolerance of a difficult drug regimen and does not appear to increase the risk of drug resistance using the scheme described above. Clinicians may also consider changes between drugs within a class (e.g. azithromycin versus clarithromycin), changes between drug classes, modification of frequency of administration (thrice weekly versus daily) and modifications of doses to achieve a tolerable and effective drug regimen. The initial regimen will usually require modification because of toxic effects[30] or inadequate efficacy, and the duration of therapy required can vary dramatically among patients. Patients undergoing therapy for NTM lung disease should have careful clinical monitoring and regular sputum mycobacterial cultures. The frequency of clinical monitoring may be dictated by the need to make drug and dose changes and the presence of drug toxicities. The frequency of sputum assessment may depend upon whether results will lead to changes in management. In practice, sputum assessment every 1-3 months is often helpful. Consultation with physicians who have expertise in managing NTM lung disease should be considered as needed. Specific medication regimens and details regarding the recommendations are listed in Table 2.

Patients occasionally have a single or small number of incidental lung nodules found to be due to NTM. The diagnosis is usually made when nodules are biopsied or removed for diagnosis, usually to rule out malignancy. Such patients often are asymptomatic, and there are no robust data to direct clinical care in this context. It appears that in most cases medical therapy is not indicated[3] unless there is significant radiographic progression with the development of symptoms. A schedule of radiographic follow-up may often be determined, at least in part, to assess for the possibility of malignancy when there are residual nodules that were not biopsied. Occasionally, in patients with known NTM lung nodule(s) and risk factors for lung cancer, new and growing nodules raise the concern of possible malignancy. In such instances, instead of repeated biopsies of additional nodules, a trial of antimycobacterial drug therapy may occasionally be useful to demonstrate a reduction in the size or number of nodules.

MAC lung disease

The treatment of MAC lung disease involves multiple antibacterial drugs, including, most importantly, a macrolide, either clarithromycin or azithromycin, and companion medications such as EMB, RMP and traditionally second-line agents such as clofazimine and FQN.[3] In noncomparative studies, regimens using macrolides have demonstrated far superior outcomes over those without macrolides.[29] However, there are very few data directly comparing macrolide versus non-macrolide based regimens.

In a large controlled trial comparing clarithromycin and ciprofloxacin (each combined with EMB and RMP), few differences were observed between the two regimens.[31] The study was complex, including patients with MAC, *M. malmoense* and *M. xenopi*, and it also included immunomodulatory therapy with *M. vaccae*. Patients were not treatment naïve (data regarding macrolide resistance were lacking), subgroups by species were small, and among MAC patients most had cavitary disease. Mortality was high (43%-44% overall), and the investigators could not conclude superiority of either regimen.

Other guidelines have recommended the combination of a macrolide, EMB and a rifamycin as daily or thrice weekly therapy, the former recommended for advanced or recurrent disease, including fibrocavitary disease, while the latter may be adequate for mild disease in treatment-naïve patients.[3] The addition of an injectable aminoglycoside (usually amikacin or SM), with appropriate monitoring, should be considered in advanced cases or if the possibility of surgical resection is being entertained.[32] Several additional or alternative antimicrobials may be considered, as noted above. Antimicrobial drug susceptibility testing is helpful for macrolides, as macrolide resistance predicts a poor response to therapy.[33,34] There are limited data regarding the utility of MAC susceptibility testing for other antimicrobial agents, although a correlation has been shown between good clinical outcomes and the number of drugs used to which the isolate is susceptible.[35] Favorable outcomes of macrolide-resistant MAC lung disease have been described in a retrospective study.[27] Treatment included discontinuation of the macrolide and initiation of EMB 25 mg/kg daily, RBT 300-450 mg daily, and either SM or amikacin. The injectable agent was continued for as long as could be tolerated, and surgical resection for cure or debulking was considered in all cases. Sputum culture conversion was achieved in 11 of 14 patients (79%) who received aggressive combined medical and surgical therapy (including injectable drug), compared with 2 of 37 patients (5%) treated less aggressively.[27] On the basis of this information it is recommended that expert consultation should be considered for the treatment of macrolide-resistant MAC lung disease.

Where the defined therapeutic goal is cure, it is recommended that treatment of MAC lung disease should generally continue until sputum cultures have been culture-negative for at least 12 months.[3] In this setting, successful treatment outcomes may be expected in 56%, according to a systematic review.[29] However, many patients, because of advanced disease or difficulty in tolerating complex drug regimens, cannot attain sustained culture-negative sputum and achieve a “cure.” [30] In such situations, tailoring the (often chronic) regimen is recommended to prevent progression of disease and minimize the adverse effects of therapy. Long-term follow-up is recommended, because recurrence rates approximate 40% in studies with follow-up exceeding 3 years, and many patients require ongoing or repeated therapy.[3] Treatment recommendations are summarized in Table 2.

M. kansasii lung disease

M. kansasii is the most pathogenic of the NTM encountered in the lung and is characteristically associated with lung lesions similar to those seen in TB, including upper lobe involvement and cavitation.[4,37] Evidence for specific drug regimens in the treatment of *M. kansasii* is observational. Treatment for 9 months with RMP and EMB was evaluated in a prospective study in Britain and found to be successful in 88% of 155 subjects.[37] In North America, treatment regimens generally include standard doses of INH (despite frequent *in vitro* resistance to low concentrations of INH), with RMP and EMB. Treatment is generally continued for 12 months of negative sputum cultures.[3] RMP susceptibility testing should be sought routinely, as RMP resistance is associated with poorer outcome. In the event of RMP resistance or drug intolerance, additional susceptibility test results may be considered to help guide selection of a three-drug regimen from clarithromycin or azithromycin, moxifloxacin, EMB, sulfamethoxazole or streptomycin.[3] Alternatively, high dose INH (900 mg/day), EMB (25 mg/kg daily), sulfamethoxazole (1.0 g thrice daily) plus streptomycin or amikacin has been used in RMP-resistant *M. kansasii.*[3] Clarithromycin has been used with RMP and EMB in a thrice-weekly treatment regimen.[38] Treatment recommendations are summarized in Table 2.

M. xenopi lung disease

M. xenopi disease may be manifest as cavities, nodules or infiltrates/consolidation on imaging.[39,40] The management of *M. xenopi* lung disease is controversial, and the available evidence is weak. In British and French studies, RMP and EMB appeared to be beneficial,[40,41] but a systematic review (performed before all of the French data were published) could not identify an advantage of any particular drug class.[39] North American guidelines have recommended azithromycin or clarithromycin, plus RMP, and EMB initially, with consideration of additional agents, including moxifloxacin, INH and amikacin or streptomycin.[3] *M. xenopi* lung disease is probably more difficult to treat than MAC lung disease, but it is unclear whether this is the because of differences among species or differences among patients (more patients with *M. xenopi* lung disease have architectural lung damage).[3] Treatment recommendations are summarized in Table 2.

Rapidly growing mycobacterial lung disease

The clinical presentation and diagnosis of lung disease due to rapidly growing mycobacteria are similar to those of other NTM. Speciation of organisms is important to determine treatment and prognosis.[42] Most primary antituberculosis drugs are not active against rapidly growing mycobacteria. *M. fortuitum* is usually susceptible to newer macrolides, FQN, amikacin, doxycycline and sulfonamides.[3] It is recommended that for rapidly growing mycobacteria drug susceptibility results can be used, but interpreted with caution, as there are no published data correlating *in vitro* susceptibility results with clinical outcomes.

M. abscessus lung disease

M. abscessus complex is the most common rapidly growing mycobacteria causing lung disease.[6] Molecular analyses have determined that *M. abscessus* is a complex consisting of three closely related subspecies (*M. abscessus*, *M. massiliense* and *M. bolletii*). One Korean study showed that treatment response rates were much higher in patients with *M. abscessus* subsp. *massiliense* than with *M. abscessus*.[43] *M. abscessus* complex is inherently resistant to RMP, EMB and INH, and therefore treatment is very challenging. Isolates are usually susceptible *in vitro* to parenteral agents (amikacin, imipenem, cefoxitin) and the macrolides.[3] Therapy typically requires 2-6 months of one or two intravenous antibiotics in combination with an oral macrolide. Macrolides were thought to be the only active oral agent, but the presence an inducible macrolide resistance (*erm)* gene likely diminishes their activity *in vivo.*[44] Choices of antibiotics are limited by drug toxicities and logistical difficulties administering the drugs.[3] Two retrospective studies of treatment, one with standardized and the other with individualized (i.e. tailored to drug susceptibility pattern and/or patient tolerability) antibiotic regimens, have shown that patients often respond clinically to therapy, but the degree and duration of response are variable. Microbiologic results were similar in both studies. Overall, outcomes are poor, and even in expert clinical programs approximately 25% of patients' sputum cultures never convert to negative; prolonged response and/or cure is uncommon. Surgical resection of localized disease may offer additional benefit to antibiotic therapy in select patients.[45,46]

M. fortuitum

This is a relatively rare isolate that is uncommonly associated with lung disease. It is most often seen in patients with underlying lung disease or recurrent aspiration and/or gastroesophageal reflux disease. A Korean study (26 patients) suggests that clinical and radiologic findings may not be progressive, even without treatment (median follow-up 12.5 months).[47]

Lymphadenopathy

NTM granulomatous lymphadenopathy is most commonly seen in children aged 6 months to 5 years.[48] A typical presentation is one of a persistent, unilateral cervical lymph node that may be fluctuant with overlying skin inflammation, which may give way to suppuration. In Canada, NTM account for more childhood granulomatous lymphadenopathy than *M. tuberculosis*.[49] However, TB should be considered in children in Canada who are from First Nations or Inuit communities (please refer to Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples) or whose parents were born in a country with a high incidence of TB.

Since TB is less likely than NTM in Canadian children without such risk factors, unless there is a suggestive history of TB contact it may be reasonable to withhold anti-TB treatment until the microbiologic results of surgically excised lymph node tissue are available. The majority of cases are caused by MAC followed variably by other species.[49-51]

Surgical excision has traditionally been considered to be curative without drug treatment in most cases. Recent studies in Canada and the United States both found that the majority of cases are being treated with surgery, usually followed by adjunctive antimycobacterial drugs.[49,52] When lymph node proximity to the facial nerve makes surgery difficult, successful treatment with antimycobacterial drugs (often clarithromycin and EMB) has been described. When antimicrobial drugs are employed, the species of NTM should be considered and drug susceptibility testing be utilized as appropriate. There are inadequate data to unequivocally support the use of antibiotics or surgery in all patients. With “advanced” disease, defined by overlying skin discoloration, a randomized trial of no therapy versus antibiotics alone (clarithromycin and RBT) found that the median time to resolution (40 weeks with no therapy versus 36 weeks with antibiotics) did not differ significantly between groups.[50] These data argue that specific therapy may not be needed in some cases and that perhaps more randomized trials including a "no therapy" control group are required to define the optimal therapeutic approach.

Currently, there are inadequate data to favour any one of 1) resection, 2) antibacterial drugs or 3) simple observation, as each option has been reported to offer good outcomes in various settings. If the diagnosis was made through an excisional biopsy of all involved nodal tissue, observation without antibacterial drug therapy is likely adequate for many cases. If, however, the diagnosis is made through a needle aspirate, one might consider antibacterial therapy with a macrolide and EMB, simple observation or surgery in the appropriate circumstances. However, the available data are inadequate to provide clear guidance in this regard.

Skin and Soft-Tissue Infections (Bone and Joint Extension)

Skin and soft tissue NTM infections usually occur after trauma, surgery or other procedures.[53] Bone and joint infections are usually acquired by direct inoculation from an environmental source or a contiguous infection. Hands and wrists are the most frequently reported sites of NTM tenosynovitis. A long list of NTM have been reported to cause skin and/or soft-tissue infection, but the most common organisms are *M. marinum, M ulcerans, M. fortuitum*, *M. abscessus* and *M. chelonae.*[54] It is recommended that diagnosis be confirmed by culture of the specific pathogen from drainage material or tissue biopsy. Additional laboratory tasks may be required for recovery of fastidious organisms, therefore good communication between clinicians and laboratory staff is important to achieve timely diagnosis.[53] Clinical manifestations and the severity of disease depend on both the organism isolated and the host immune status.

M. marinum prefers 30 ˚C temperatures and consequently causes superficial peripheral ulcerative lesions after mild trauma, such as an abrasion, and exposure to fish or other aquatic animals. Clarithromycin combined with EMB or RMP may be the best therapy for these so-called fish tank or swimming pool granulomas.[3,55] Clarithromycin in combination with doxycycline, minocycline or cotrimoxazole has also been used with success. It is recommended that treatment should continue for at least 2 months after clinical resolution (usually 3-4 months' duration) or longer, depending on the severity of infection. Surgical debridement of the hand may need to be considered for severe and/or nonresponsive cases.[3,55]

M. fortuitum and *M. abscessus* complex are the most frequent cutaneous pathogens.[56] Approximately half of these cutaneous infections follow surgery or trauma, and they may be associated with the presence of a foreign body.[57] There is a strong association between *M. fortuitum* and prosthetic devices such as breast implants or peritoneal dialysis catheters. Patients with *M. chelonae* or *M. abscessus* complex are more likely than *M. fortuitum* patients to be taking immunosuppressive medications.[57] Treatment of cutaneous, rapidly growing mycobacterial infections may require surgical excision/debridement in addition to antibiotic therapy (with at least two drugs to which the organism is susceptible). Surgery is particularly successful for cutaneous infections associated with prosthetic devices.[3] In general, two active agents are recommended, for approximately 4-6 months, depending on severity of disease *(conditional recommendation, based on weak evidence)*.[58]

Disseminated Infection

NTM infections may disseminate in hosts with impaired immunity.[59] Disseminated MAC was common in AIDS patients prior to the introduction of combination antiretroviral therapy in 1994. Since then, the rate of disseminated MAC in AIDS patients has decreased dramatically in the United States,[60] likely as a result of both the reduction in the number of people with advanced immune suppression because of antiretroviral therapy, and the use of MAC prophylaxis.[61,62] See Table 2 for treatment and prophylaxis of HIV-infected individuals with CD4 counts under 50 x 10^6/L.[63]

It is recommended that treatment of HIV-infected patients with disseminated MAC include concomitant anti-MAC and antiretroviral therapy; therefore, a regimen that minimizes drug-drug interactions is advised. Consultation with HIV and NTM experts and pharmacists is recommended. Patients with disseminated MAC are at risk of immune reconstitution syndromes, similar to that seen with TB, once they begin antiretroviral therapy.[64]

Disseminated NTM disease in non-HIV patients is uncommon but has been reported in patients who have had solid organ or bone marrow transplantation, chronic corticosteroid usage with or without other immunosuppressive agents (e.g. rheumatologic or sarcoidosis patients), hematologic malignancy and interferon gamma receptor and interleukin-12 receptor abnormalities.[65] Apart from MAC, a variety of other NTMs can also cause disseminated infection, including *M. fortuitum* complex, *M. abcesssus* complex*, M. kansasii, M. gordonae, M. simiae, M. haemophilum, M. szulgai, M. genovense* and *M. smegmatis*.[3]

CONCLUSION

The provinces and territories do not require NTM disease to be reported to local public health authorities and it is not generally considered contagious. Treatment is not mandatory but, rather, is determined on a case-by-case basis. NTM-related diseases are incompletely understood regarding the source of the infecting organism, natural history and indications, as well as optimal therapy. Diagnosis of NTM lung disease is complex, involving microbiological, clinical and radiological information, and is only one step in the decision to initiate therapy, wherein the relative risks and benefits of treatment versus observation should be considered.

Therapy for lung disease generally comprises multiple drugs for a prolonged duration, is often difficult to tolerate and is associated with suboptimal outcomes. In contrast, extrapulmonary NTM disease may be more easily treated and associated with better outcomes.

The most recent guidelines prepared by the American Thoracic Society and Infectious Diseases Society of America[3] provide extensive and detailed information regarding the management of NTM disease. Consultation with an expert is suggested when treating NTM disease.

SUMMARY OF MISCELLANEOUS RECOMMENDATIONS*

Recommendations regarding patients with cystic fibrosis (and bronchiectasis from other causes):

- Screening for NTM, with sputum (spontaneously expectorated or induced) collection, is advised at least yearly, and during periods of clinical decline.

  (Conditional recommendation, based on very weak evidence)

- Patients being considered for chronic macrolide therapy should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of macrolide monotherapy.

  (Conditional recommendation, based on very weak evidence)

- Patients with repeated isolation of NTM should not receive macrolide monotherapy.

  (Conditional recommendation, based on very weak evidence)

Patients with COPD who are being considered for chronic macrolide therapy:

- These patients should have sputum cultures for NTM before starting therapy and periodically thereafter, to avoid the risk of macrolide monotherapy for unrecognized NTM disease.

  (Conditional recommendation, based on very weak evidence)

- Patients with repeated isolation of NTM should not receive macrolide monotherapy.

  (Conditional recommendation, based on very weak evidence)

Asymptomatic patients:

- Asymptomatic patients with a single or a small number of randomly distributed, incidental lung nodules due to NTM generally should not be treated unless there is significant radiographic progression with the development of symptoms.

  (Conditional recommendation, based on very weak evidence)

*Other recommendations, relating to treatment, are summarized in Table 2.

■ ■ ■

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CHAPTER 12

CONTACT FOLLOW-UP AND OUTBREAK MANAGEMENT IN TUBERCULOSIS CONTROL

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KEY MESSAGES/POINTS

- Only respiratory tuberculosis (TB), with limited exceptions, is infectious; contact follow-up should be carried out for both sputum smear-negative and smear-positive cases. The objective of contact follow-up is to identify and treat any secondary cases, and to identify contacts with latent TB infection (LTBI) in order to offer preventive treatment. Source-case investigation is recommended for children under 5 years old with a diagnosis of active TB disease.
- Interviews with the infectious case to identify contacts should include questions about locations/activities of potential exposure as well as specific named contacts. The discussion of site-based, social network contact investigation as well as the section on contact follow-up in homeless populations has been expanded from the 6th edition of the Standards.
- Prioritization of contact follow-up is recommended by the infectiousness of the source case, extent of exposure and immunologic vulnerability of those exposed. Thus, the most effort is put into contacts who are most at risk of being infected and/or most at risk of developing active TB disease if infected.
- The classic concentric-circle approach to contact follow-up is no longer recommended. Rather, the initial follow-up should include non-household contacts from the outset when case infectiousness and contact vulnerability indicate, rather than waiting.
- Contacts may be grouped as follows:

  High priority
  - household contacts plus close non-household contacts who are immunologically vulnerable, such as children under 5 years.

  Medium priority
  - close non-household contacts with daily or almost daily exposure, including those at school and work.

  Low priority
  - casual contacts with lower amounts of exposure.

- For smear-positive/cavitary/laryngeal TB, it is recommended that the initial contact follow-up include both high- and medium-priority contacts. For smear-negative, non-cavitary pulmonary TB, the initial contact follow-up should be for high-priority contacts only. In both situations, contact investigation is iterative: it should be expanded if the initial follow-up results indicate that transmission has occurred.
- A single evaluation at least 8 weeks after the end of exposure (with tuberculin skin testing [TST] and symptom assessment) is recommended in most non-household contact settings, in order to maximize participation and minimize overdiagnosis of "conversion" related to boosting. Initial plus 8 week post-exposure TST is recommended for household and other high-priority contacts. Two-step TST is not recommended in the setting of a contact investigation.
- TST is no longer recommended as a primary assessment tool in the contact follow-up of elderly residents in long-term care, in whom it is less reliable and for many of whom the risks of treatment of LTBI in old age will outweigh any benefit. The focus for these individuals should be on early detection of secondary cases.

INTRODUCTION

The first priority of TB control programs is always recommended to be the early identification and successful treatment of all TB cases. This is because treatment rapidly reduces the risk of TB transmission to others. The next priority should be evaluation and follow-up of close contacts of active cases in order to identify secondary cases, source cases in some situations and those with recently acquired LTBI, to offer this group treatment.[1-3] Typically, 1%-2% of close contacts are found to have active disease at the time of contact investigation.[4] In addition, about 5% of newly infected contacts will develop active disease within 2 years of exposure.[5-8] TB programs in North America typically find a median of 4 (average 6) close contacts for each TB case.[4,9]

Reporting of active TB is required in all Canadian jurisdictions. In part this is to ensure that contact investigation can be carried out quickly, in an organized, collaborative manner.

With limited exceptions, only TB in the respiratory tract is infectious and requires contact investigation.[10] Patients who present with nonrespiratory disease can also have concomitant respiratory involvement; thus it is important for all TB patients to have chest radiography (and sputum testing if there are any respiratory symptoms or chest x-ray abnormalities) as part of their medical work-up. Patients with miliary TB are often culture-positive on sputum or other airway secretions and occasionally smear-positive.[11] Induced sputum cultures have been found to be positive in up to 50% of cases of pleural TB, even in the absence of pulmonary disease on chest x-ray.[12] Therefore, both miliary and pleural TB should also be considered as potentially contagious.

Factors associated with TB transmission are outlined in Chapter 2, Pathogenesis and Transmission of Tuberculosis. Cases who are sputum smear-positive or have cavitary disease on chest x-ray are significantly more infectious than smear-negative or non-cavitary cases.[2,8,9]Adolescence, adult age, coughing, sneezing and singing also increase the risk of transmission.[1]

Transmission is rarely thought to occur outdoors; however, indoor environments that are poorly ventilated, dark and damp can lead to increased concentration and survival of *Mycobacterium tuberculosis.*[13,14] In infected contacts who are vulnerable because of young age (under 5 years), HIV or other causes of significant immune suppression infection may progress quickly to active disease;[8] early diagnosis often depends on good contact follow-up.

Contact investigation often demands considerable time, expertise and coordination. It is usually best carried out by public health/TB control authorities in collaboration with treating clinicians and other providers. Anxiety, stigma and lack of knowledge about TB among those exposed may be major issues. Provision of clear, credible and consistent information about TB and the contact follow-up plan is important.

DEFINITIONS

Index case: the first case or initial active case from which the process of contact investigation begins.

Source case: the person who was the original source of infection for secondary case(s) or contacts. The source case can be, but is not necessarily, the index case.

Contact: a person identified as having been exposed to an active case of disease. The closeness and duration of exposure usually corresponds with the risk of becoming infected.

OBJECTIVES OF CONTACT INVESTIGATION

Contact investigation has three main objectives. In order of priority these are as follows:

1. Identify and initiate treatment of secondary cases of active TB disease.
2. Identify and treat the source case who infected the index case, if the index case is under 5 years old.
3. Identify contacts with LTBI in order to offer preventive treatment.

PRINCIPLES OF CONTACT INVESTIGATION

PRIORITIZE THE WORK

This is the most important principle. It is advisable to prioritize by the infectiousness of the source case, extent of exposure and immunologic vulnerability of those exposed. Thus, the most effort can be put into contacts who are most at risk of being infected and/or most at risk of developing active TB disease if infected. Contact investigation is iterative: it should be expanded if initial follow-up results indicate that transmission has occurred.

RAPID INITIATION OF CONTACT INVESTIGATION

Rapid evaluation of close contacts allows prompt identification of those who already have active disease and, if active disease has been excluded, allows initiation of treatment of LTBI for newly infected contacts before disease occurs.

As soon as a suspected case of TB has been reported, it is advisable for public health authorities to ensure that all the medical investigations to confirm the diagnosis and determine the degree of infectiousness are under way (chest radiography plus sputum collection as necessary, even for patients with suspected extrapulmonary TB) and that the patient is in airborne infection isolation. Initiation of adequate TB treatment is the most effective way to rapidly decrease infectiousness and the risk to others. If the clinical suspicion of pulmonary TB is sufficiently strong to begin TB treatment pending microbiologic confirmation, then investigation of household contacts should also begin promptly, especially for any children under 5 years old, HIV-infected contacts and others at high risk of disease progression if infected.[10] A positive nucleic acid amplification test result is sufficient grounds to begin contact investigation (see also Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Investigation of contacts beyond the high-priority group (see below) should always await microbiologic confirmation of the diagnosis.

ASSESSMENT OF TRANSMISSION RISK

Infectiousness of the index case

The single greatest factor determining the extent of contact investigation is the degree of infectiousness of the index case. Neither drug-resistant TB nor coinfection with HIV increases the infectiousness of the case; therefore, the recommended approach and prioritization of the contact investigation is the same. However, treatment of LTBI among contacts should be guided by the drug sensitivity pattern of the source case.

Sputum status is the most reliable indicator of infectiousness. The “worst” (i.e. most positive) result is used to evaluate infectiousness.[15] Cases of laryngeal TB are considered four to five times more contagious than smear-positive pulmonary cases, as they are likely to have a large number of bacteria due to extensive concurrent pulmonary disease.[1,16,17]

Cavitary disease on chest x-ray has been repeatedly linked to higher infectiousness, independent of smear status. Chest CT (computed tomography) may detect smaller, early cavitation that is not apparent on the chest x-ray; however, it is not clear whether these individuals are as infectious as those who have cavitation visible on chest x-ray.[10]

Coughing is the least reliable indicator of infectiousness but is generally linked to it, particularly within households. There are several well-documented clusters of TB transmission related to cough-inducing medical procedures and to smoking crack cocaine.[18] Singing and similar activities (e.g. playing wind instruments) are also associated with increased risk of transmission.[19]

In general, children under age 10 with TB are not considered infectious. However, in unusual circumstances, even very small children can transmit TB – for example, if there has been contamination and inadequate cleaning of respiratory equipment.[20] By contrast, adolescents can be very effective transmitters of TB, partly because they can have extensive disease by the time it is diagnosed, and particularly because in high school they can have large numbers of contacts.[21,22] It is recommended that any child presenting with adult-type pulmonary TB (cough, cavitation on chest x-ray, smear-positive sputum) should be considered infectious and contact investigation undertaken.

Source case investigation

When active TB (whether pulmonary or extrapulmonary) is diagnosed in any child under 5 years old, an immediate search for an infectious source case close to the child is recommended.[10] Most often the source case is an adolescent or adult in the household, or other care-giver. Source case investigation is also recommended when a cluster of TST conversions is identified in an institutional setting with no known source case. However, source case investigations usually give very low yield; even for young children a source case is identified in less than half of investigations.[10,23] Source-case investigation is not recommended for adult TB cases, nor for children or adults who are well but have a positive TST result on a routine screening (outside of an institutional cluster of TST conversions, as above).

Nonrespiratory TB is considered noninfectious, so long as concurrent pulmonary disease has been ruled out; no contact follow-up is necessary. Rare exceptions involve aerosolizing medical procedures (e.g. autopsy, high-pressure irrigation of draining TB abscesses). Source-case investigations for nonrespiratory TB are not recommended other than for children under 5 years old, as above.[10]

Likely period of infectiousness

Cases of pulmonary TB are generally considered to become infectious at the time of onset of cough or worsening of a baseline cough. If no cough is reported or if the duration is difficult to determine, the onset of other symptoms attributable to TB may be used to estimate the onset of infectiousness. In practice, however, it is often difficult to know with certainty when symptoms began.

Generally, priority should always be given to contact tracing during the period when the TB patient had respiratory symptoms (e.g. a cough). However, guidelines published by the US Centers for Disease Control and Prevention[10] recommend that the patient with smear-positive or symptomatic disease should be considered to have been infectious for 3 months before onset of respiratory symptoms or the first positive finding consistent with TB, whichever is longer.

Asymptomatic cases with a negative smear and no cavities seen on chest x-ray should be considered infectious 4 weeks before the date that TB was suspected. However, these guidelines are based on expert opinion rather than clear epidemiologic evidence.

For contact follow-up purposes, the period of infectiousness ends when the index case is in effective airborne isolation from others (this may be before or after diagnosis) or is no longer infectious, whichever comes first. Please see Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for a description of when isolation may be discontinued for a suspected or confirmed TB case.

Degree of exposure to the index case

The interview of an infectious TB patient for contact tracing is one of the most important parts of the investigation. It takes considerable skill and is most successful when done by staff with training/experience in public health interview techniques.[24] Trust and rapport are important for full disclosure, and the initial interview can also lay the foundation for long-term adherence to TB treatment. Face-to-face interviewing, in privacy, is ideal. Most TB patients in Canada were born in countries with high TB incidence or in First Nations/Inuit communities (see Chapter 1, Epidemiology of Tuberculosis in Canada), so language and cultural perceptions about TB and health are very important. Interviews are best carried out in the language the patient is most comfortable with. It is recommended that a professional interpreter or an objective third party (not a family member) be used for interpretation if possible, either in person or participating by telephone. Interviewers should always be respectful and sensitive to patient concerns and beliefs about TB, should incorporate education about TB and stress the confidentiality of contact investigations. Note that legislation may permit or require release of information about the case's diagnosis to specific individuals (e.g. to public health authorities) or in specific circumstances. For example, although precautions can be taken to avoid identification of the case in public or to contacts, some information may have to be shared with selected individuals (e.g. a school principal) in order to identify or reach contacts and ensure that they too get the medical follow-up they need.

Ideally, the treating physician and laboratory should report all new or suspect cases of TB to the appropriate public health authority within 48 hours. The first public health communication with a new infectious patient (and/or the health care providers if the patient is hospitalized) should ideally begin within 1 calendar day of the case being notified. The purpose of this brief initial communication is to achieve adequate airborne isolation, provide any urgent support, identify the household contacts and direct any who are ill to immediate TB assessment. Interviewing to determine the full set of contacts should be initiated within 3 working days. Interviewing is usually best extended over two (or more) sessions, a week or more apart, as the patient becomes more familiar with public health staff, and the initial stress and anxiety over the diagnosis are resolving. Proxy or supplemental interviews (ideally with patient permission) with family, close friends, coworkers, etc., may be helpful if patients are unable or unwilling to participate. It is important to include questions about the places where the case spends time regularly, not just names of individual people, and to get contact details whenever possible (name, alias/nickname, phone, address, email, age, nature of interaction).

Interviews to identify contacts should include the following information:

- Any contact with children and their ages
- Any contact with immunosuppressed people (HIV positive, cancer patients, etc.)
- Description of the household/congregate setting; household contacts and their ages (includes anyone who regularly sleeps in the home)
- Close friends and relatives who are seen at least once per week – how often, for how long?
- Work or school location and description of setting (type of work, size of room, ventilation, etc.)
- Transportation to work/school – bus, car-pool, etc.
- Place of worship, clubs, sports teams, recreation programs or hobbies
- Any other places or groups the case has regularly been in or with while infectious
- Any contacts who are ill with potential TB symptoms or who have known TB
- Any major events (e.g. weddings, funerals, parties) the case attended while infectious
- Any recent travel or visitors staying at the home within the previous 2 years – if so obtain details

A site visit to assess the home is strongly recommended, even if the initial interview is carried out in hospital (for feasibility of home isolation, identification of additional household contacts, identification of any social/practical issues relevant to treatment adherence, etc.). Site visits to the school or workplace and other exposure locations are also very helpful to make contact follow-up decisions (environmental characteristics such as size, layout, use of the space and ventilation; interviews with a direct supervisor can help to identify potential contacts). Discretion is important, as a site visit may precipitate unnecessary anxiety and/or lead to a breakdown of confidentiality and repercussions for the case. In this regard, it is advisable to arrange site visits directly with senior personnel, such as a school principal, division manager or occupational health manager and emphasize with them the importance of maintaining confidentiality as much as possible. See Site-based screening below.

There are so many variables in TB transmission that it is very difficult to quantify the amount of exposure that constitutes a significant risk.[25] In theory, there is no amount of exposure to infectious TB that is absolutely without risk; in practice, each case should be evaluated on its specific characteristics. For context, one study of almost 3,000 contacts demonstrated that TST-positive contacts had a mean of 65 hours more exposure than TST-negative contacts.[26] By contrast, in an outbreak investigation among university students exposed to an index case with laryngeal and cavitary pulmonary TB, the risk of infection per hour of exposure was over 1% in many classes; some contacts converted with as little as 3-4 hours of exposure per week.[27] Exposure in cramped, ill-ventilated spaces may lead to transmission in much shorter exposure times, and genetic fingerprinting has occasionally discovered apparent transmission following close but very brief exposure.[28]

Organized and Systematic Contact Investigation: Prioritizing Contacts

An organized, systematic approach will allow the TB program to put the most effort into those contacts at most risk. In the 6th edition of the Standards, the traditional "concentric circle" approach to prioritizing TB contact follow-up emphasized starting with contacts who have the most exposure (e.g. household contacts) and expanding stepwise to those with progressively less exposure whenever there is evidence of transmission, until the level of TB infection reaches background rates. However, this approach does not take into account contacts who may have less extensive exposure but, if infected, are immunologically vulnerable to rapid development of active TB. It can also lead to long delays in appropriate contact follow-up when the index case is already known to be highly infectious. A fundamental difficulty is that transmission can be very difficult to evaluate when the background rate of positive TST results is unknown or is high (for example, people who immigrated to Canada from high-incidence countries). This is often the case in Canada, where the majority of TB cases – and many of their close contacts – are foreign-born; it is also the context in many Aboriginal communities. A strictly concentric circle approach can also be difficult to apply in complex congregate settings.[22,29]

Instead, recommended priorities for initial contact follow-up and criteria for expansion are outlined below. These are guidelines: it is always important to consider the specific circumstances, work from first principles of TB transmission and re-evaluate according to the results of the investigation as they become available.

For TB follow-up purposes, contacts may be categorized as follows:

Household contacts are those who regularly sleep in the same household as the infectious case on an ongoing basis (e.g. three or more times per week). This may include members of an extended family, room-mates, boarders, "couch-surfers," etc. Household members often have the greatest exposure to the TB case.[8,22,26]

Close non-household contacts are those who have regular, extensive contact with the index case and share breathing space daily or almost daily but do not sleep in the same household most of the time. Close non-household contacts may include caregivers, regular sexual partners, close friends or extended family. They also include daycare and primary/secondary school classroom contacts, and coworkers who work in close proximity, particularly in small rooms. The amount of time that high school classmates spend in the same room as the case will depend on the number of shared courses; prioritize those who share the most actual time together. Similarly, in almost all workplaces it is possible (and important) to define the group of colleagues who spend the most time in the same air space as the case. Regular contacts in specialized health care settings such as dialysis units or rehabilitation programs may also qualify. It is not social closeness to the TB case but, rather, the amount of time in a shared airspace that is the critical issue. For example, computer personnel may report working very closely with others in their group but spend little time together in shared air space if the work is largely done electronically.

Casual contacts are those who spend time regularly but less frequently with the infectious case. These may include high school classmates who share fewer courses with the case, classmates in college/university classes, less exposed colleagues at work; members of a club, team, weekly children's play-group or other social/recreational/religious group; extended family members who are seen occasionally; other students on a school bus.

Community contacts are those living in the same community or attending the same school or workplace but in a different classroom or area of the workplace. Individuals who have only transient or occasional exposure are in this group.

The highest priority contacts are those with the most exposure and those with the highest risk of progression to active TB if infected, as follows:

- household contacts, including those exposed as “household members” in congregate settings such as homeless shelters, jails and long-term care facilities (generally, room-mates or cell-mates)
- contacts who are close non-household or casual contacts AND who are at high risk of progression of LTBI to TB disease, e.g. age under 5 years, HIV, dialysis, transplant, silicosis (see Chapter 4, Diagnosis of Latent Tuberculosis Infection, and Chapter 6, Treatment of Latent Tuberculosis Infection)
- contacts exposed (i.e. without an N95 mask) during bronchoscopy, sputum induction, autopsy or other aerosolizing medical procedures (see Chapter 15).

Medium-priority contacts are the close non-household contacts who are not at high risk of rapid progression from LTBI to active TB. Most close non-household contacts fall into the medium-priority group.

Casual contacts are low priority. It is generally recommended that the investigation be expanded to this group only if there is evidence of transmission or the case is considered to be extremely infectious (e.g. laryngeal TB, see Chapter 2, Transmission and Pathogenesis of Tuberculosis). However, the specific circumstances should always be considered. For example, a choir group meeting once per week may pose significantly more risk than a weekly outdoor soccer game; children riding on long daily school bus routes in winter, when windows are usually closed, may have considerable exposure.[30]

It is rare for community contacts to need investigation (e.g. an entire school beyond the exposed classrooms, general customers of grocery stores or fast-food restaurants).[31] Such an extensive investigation should be undertaken only in very unusual circumstances; consultation with experienced public health colleagues is advised.

For respiratory TB cases who are sputum smear-positive, or have cavitary disease, or have laryngeal TB, the initial investigation should include both high priority and medium priority contacts. If there is evidence of transmission (see below) within these two groups, consideration should be given to expanding contact follow up to casual contacts. *For laryngeal TB*, also consider including any casual contacts (social/recreational groups, etc.) from the outset.[10]

For smear negative respiratory TB cases, household members should always be assessed in the initial contact investigation, along with any other high-priority contacts. However, investigation should be expanded to medium-priority contacts (e.g. other close non-household contacts) only if there is evidence of transmission.[10,15]

High-priority contacts should be assessed for both smear-negative and smear-positive cases. Whenever possible, initial assessment (TST and symptom assessment, then medical assessment and chest radiography if the TST result is ≥5 mm or the patient is symptomatic, plus sputum if symptomatic or the chest x-ray is abnormal) of the high-priority contacts should begin within 7 working days of their being identified as contacts and be completed within 1 month. High-priority contacts should ideally have both an initial and a second TST (at least 8 weeks from the last day of exposure) to identify conversion. Participation rates for TB skin testing may be higher if it is done directly by TB program staff, at home or at a TB clinic[10].

Especially among non-household contacts, participation rates often drop significantly between initial and post-8-week screenings as the level of initial concern declines. Thus, in most non-household settings it is most practical to aim for a single round of screening after 8 weeks from the break in contact. In populations in which many people have prior exposure to TB or BCG vaccination (e.g. immigrants from high-incidence countries), this also avoids false TST "conversion" related to boosting. If casual contacts are investigated, only a single TST after 8 weeks from the last day of exposure is recommended.[32]

Expanding Contact Investigation

Transmission is considered to have occurred if a secondary case is identified in any contact, if there are any TST converters, if the prevalence rate of TST ≥10 mm among contacts is significantly higher than expected (for example, 60% among contacts when the expected prevalence rate is 40%, see Table 1) or if a child contact under age 5 years is infected without another probable source. TST results in Canadian-born contacts, particularly children, may be the most useful in assessing transmission. A TST result is considered positive in contacts with a TST result of 5 mm or greater or in converters who have had an increase of 6 mm from a previous TST result of 5-9 mm. A history of BCG vaccination does not alter the interpretation of the TST results (see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for more information). When there is evidence of transmission, the contact investigation should first address any high-priority contacts who have not yet been assessed and investigate moderate-priority contacts if this has not already been done. Consideration should then be given to expanding to casual contacts. Genotyping to compare index and secondary cases should be requested, but further contact tracing should not be delayed while results are pending.

Table 1. Expected range of prevalence of TST results (≥10 mm induration) in various Canadian populations*

Population	Expected range of prevalence of TST ≥10 mm (%)		
	BCG status not specified	BCG vaccinated	Non-BCG vaccinated
Canadian-born non-Aboriginal children†	N/A	N/A	1–3
Canadian-born non-Aboriginal adults	13	65	7
Canadian-born Aboriginal children	5–29	6–25	0–5
Canadian-born Aboriginal adults	14–30	29–50	17–21
Foreign-born children	15–23	N/A	N/A
Foreign-born adults	53–61	73	25
Health care workers	11–46	27–77	5–18
Residents of long-term care facilities (age ≥60)	6–25	71	18
Residents of homeless shelters	45	N/A	N/A
Correctional facility inmates	12–72	90	63
Correctional facility staff	5–33	N/A	N/A
Injection drug users (TST ≥5 mm)	31	N/A	N/A
Injection drug users (TST ≥10 mm)	66	N/A	N/A
People with pre-existing medical conditions (TST ≥5 mm)	14–24	N/A	N/A
People with pre-existing medical conditions (TST ≥10 mm)	18–26	N/A	N/A
Overall community	6–36	N/A	N/A

N/A = Non applicable

*Based on *Compendium of Latent Tuberculosis Infection (LTBI) Prevalence Rates in Canada*, Public Health Agency of Canada, 2012 (for an electronic copy of the full compendium, contact *TB_surveillance@phac-aspc.gc.ca*).

†Although the Aboriginal status was not specified in the study, it was assumed that the vast majority of the reference population belonged to the Canadian-born non-Aboriginal category.

There is often pressure on a public health department or physician to initiate widespread contact investigation – e.g. to an entire school – from the outset. If this is done, however, it is often impossible to interpret the results of a positive TST result (or interferon gamma release assay [IGRA]) in individual patients. Contacts may then be mistakenly identified as recently infected and the investigation expanded yet further. This can also lead to widespread concern about the risk of transmission to community contacts. If expansion of the investigation beyond high- and medium-priority groups is considered, the decision should be based on evaluation of any evidence of transmission in the initial investigation, the probability of finding infected individuals among less exposed contacts and the likelihood that these casual contacts will follow up on screening and LTBI treatment recommendations. Contacts with less exposure have a positive TST prevalence rate that is usually four to eight times less than that among household contacts.[4,8,33,34] Also, contact participation rates in TB screening, follow-up and LTBI treatment tend to be lower in less close contacts, contacts of less infectious cases and in adults compared with children.[35]

ADDITIONAL APPROACHES TO CONTACT TRACING

DNA genotype fingerprinting:

DNA fingerprinting is available to all Canadian TB control programs, on request or routinely, through the public health laboratories. It can be a useful adjunct to epidemiologic investigations to confirm or disprove suspected linkages between cases and to evaluate potential specimen mix-ups.[36,37] It can be particularly helpful in populations in which contact follow-up is challenging and resource intensive, such as the homeless; routine use of fingerprinting for homeless cases may identify linkages not otherwise suspected and guide expanded contact investigation.[38,39] Rapid fingerprinting techniques (spoligotyping, MIRU [Mycobacterium Interspersed Repetitive Units]) are helpful to quickly identify or rule out potential new cases in evolving clusters or outbreaks. Fingerprinting can also be very useful, and reassuring, in the evaluation of potential clusters if the results do *not* show matching outside known household secondary cases.

Location-based contact investigation and social network analysis:

All cases should routinely be asked about the locations where they spend time. Particularly when infectious cases are unable or unwilling to name specific contacts, or when cases are occurring without identifiable exposure risks or sources, identifying locations where the case spent time may be more productive than traditional name-based approaches.[40] Investigations have identified transmission occurring at bars, crack use sites, etc.,[41-43] which can then be targeted for broad location-based screening clinics and TB education/outreach. Epidemiologic links among cases can be enhanced when questions about common locations are included in case interviews.

Social networks analysis examines the social relationships between cases and contacts to identify settings and behaviours that characterize transmission events. Social network analysis has been extensively studied in sexually transmitted infections and more recently in the study of TB outbreaks.[40,43-45] Formal social network analysis, using special computer software, may be particularly helpful in outbreaks (see http://pajek.imfm.si/doku.php?id=pajek).

Site-base screening and congregate settings:

In some settings, it is far more practical and feasible to carry out contact investigation for an entire group (such as a class at school or coworkers in a work setting) than attempt to identify the specific individuals who were most exposed. Practical factors, such as the ability to reliably measure the degree of exposure of different individuals in the setting, the administrative ability to provide efficient testing and TB education, and the ramifications of extending the investigation to a larger group later if it becomes necessary, should be taken into account in deciding on the extent and number of people to be tested. Similarly, in certain settings (e.g. shelters for the homeless) in which contacts may be difficult to identify or to find, it may be helpful to do wider testing from the outset.

School, workplace and other congregate setting investigations are usually best carried out on site. This leads to higher participation rates among contacts, better communication and less anxiety; it is usually the most effective and efficient way of carrying out the investigation and obtaining the necessary information. However, for this type of investigation it is important to be very organized. The following approach is recommended:

- Identify a single individual at the setting who will be responsible for organizational aspects of the contact investigation and act as liaison, usually a school principal, workplace manager or occupational health manager.
- Protect the confidentiality of the index case (Note investigations should be carried out in compliance with relevant legal/legislative requirements, and that provincial/territorial legislation may permit disclosure in specific circumstances). This may not be easy; there may be considerable pressure for details, and in many situations others may be able to guess the identity of the case. Particularly if the identity of the case is widely known or suspected, enlist the help of setting personnel (e.g. the principal or manager) to plan for successful reintegration of the TB case once noninfectious.
- Visit the site beforehand to get a sense of the environment and organize the screening arrangements; get input from the setting's liaison person to ensure that screening is carried out at a time and in a way that offers the best opportunity for contacts to come to the screening.
- Check that adequate staffing will be available for the screening.
- Include key players at the site, such as occupational health services, human resources or other administrative staff, and union health and safety representatives in planning and communication; they may benefit from information about TB ahead of a general information session as others will likely look to them for advice.
- Prepare a communication plan; identify one individual who will be responsible for media and communications to the general public if necessary; alert public health communications staff.
- Offer general information/education sessions about TB and the contact follow-up for all parents/employees/residents before the screening sessions; if the number of contacts is relatively small, a separate session specifically for them may be helpful.
- Identify the referral plan for contacts who are TST positive or symptomatic; treat all contacts referred for medical evaluation consistently, ideally by a limited number of health care providers working in coordination with public health. It can be confusing and alarming for a group of contacts if the work-up and treatment advice are inconsistent from person to person.
- Ensure the results of the medical evaluation are provided promptly to the appropriate public health authority.

Contact investigations carried out in work or school settings may be associated with high levels of anxiety. Good organization, communication and transparency (to the extent possible while protecting case confidentiality) are critical aspects of all site-based or expanded contact investigations. Anxiety and misinformation can be minimized by limiting the delay between contacting the site and conducting testing, ensuring that key people at the setting get the same information at the same time, and by holding general education sessions about TB and the investigation plan. Communication from all personnel involved in the investigation should be clear, credible and consistent, especially with regard to the actual level of risk involved, interpretation of the TST and decisions regarding treatment of LTBI.

A standard approach to the evaluation of contacts for the presence of active disease and evidence of recent infection:

All identified contacts should be interviewed systematically regarding their exposure to the case, presence of symptoms, risk factors for progression to active TB if infected and history of treatment of TB or LTBI. If there are any concerns, rapid evaluation to exclude active TB should be carried out. Once active disease has been excluded, contacts should receive a TST unless there is a history of prior treatment of TB or a documented prior positive TST result. The TST should be carried out and interpreted regardless of BCG vaccination status. A TST of 5 mm or more is considered positive for contacts. See also Chapter 4, Chapter 6 and Chapter 9, Pediatric Tuberculosis.

Note that TB assessment of contacts may involve TST or an IGRA (see Chapter 4, Diagnosis of Latent Tuberculosis Infection).

A two-step TST is not recommended in the setting of a contact investigation:

Skin test conversion can occur as early as 3 weeks after exposure, and it will generally be impossible to differentiate between true TST conversion and a boosted reaction in the setting of a contact investigation (see Chapter 2 and Chapter 4). This is another reason why only those with significant exposure should be considered contacts.

Window treatment of LTBI for those most susceptible:

Contacts who are at very high risk of progression to active disease if infected (children under 5 years; HIV positive or other immunosuppressed individuals) should receive window prophylaxis in the interval between a negative initial TST result and the definitive TST at least 8 weeks after the last day of exposure because of the high risk of progression to active TB if infected. See Chapter 6 and Chapter 9 for additional information.

Evaluation of Contact Investigation:

The results of each contact investigation should be reviewed as they become available, to guide expansion and/or additional follow-up efforts. In addition, program-wide outcomes should be reviewed annually. Along with qualitative assessment of successes and challenges, they are important elements for program evaluation and future planning. Key indicators should include the following:

- initial list of contacts for each infectious TB case, completed within 7 calendar days;
- assessment of close contacts completed and LTBI treatment started, if indicated and not contraindicated or refused, within 28 calendar days;
- proportion of contacts with a diagnosis of LTBI who begin treatment;
- proportion of contacts beginning treatment for LTBI who complete treatment; and
- proportion of contacts completing LTBI treatment who show active TB disease within 2 years after completion.

SUMMARY POINTS

Recommended Steps in Contact Investigation and Follow-Up

1. The treating physician and laboratory should report all new or suspected cases of TB within 48 hours to the appropriate public health authorities.
2. Each new active case should be interviewed by public health authorities to identify household and other close contacts promptly. TB programs should prioritize contacts by the infectiousness of the source case, the extent of the exposure and the risk of progression to active TB if infected.
3. Each contact should be interviewed regarding the circumstances and duration of exposure, presence of symptoms, previous history of tuberculosis, TB exposure and prior TST.
4. Public health authorities and the treating physician should collaborate to ensure that contacts with no previous history of TB or documented positive tests receive a TST and symptom assessment.
5. In the context of contact investigation, a positive TST result is 5 mm or greater on initial or repeat testing, or an increase of at least 6 mm from a previous TST of 5-9 mm. A history of BCG vaccination does not alter the interpretation of the skin test results for contacts. TST should be repeated at least 8 weeks after the last exposure for all high-priority contacts who had an initial negative test. See Chapter 4, Diagnosis of Latent Tuberculosis Infection, for guidance.
6. A medical evaluation to rule out active TB should be performed for all contacts who have symptoms compatible with TB; a positive TST result, whether before exposure or at initial or repeat testing; and (regardless of the results of the initial TST) all children under age 5, as well as contacts who are HIV seropositive or severely immunocompromised, according to the recommendations in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, Chapter 9, Pediatric Tuberculosis, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus. This should include chest radiography, plus sputum collection as indicated.
7. Once active TB has been ruled out, treatment of LTBI should be offered according to the recommendations in Chapter 6, Treatment of Latent Tuberculosis Infection, Chapter 9, Pediatric Tuberculosis, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus.
8. Public health authorities should determine the need to extend the contact investigation on the basis of the contagiousness of the index case, the results of the investigation of high-priority contacts and the nature of the exposure of additional contacts.
9. Extended contact investigations should be carried out in a systematic and organized manner; public health/TB control should coordinate these investigations.

The results of the contact investigation should be evaluated by the TB management program.

CONTACT INVESTIGATIONS IN SPECIAL SETTINGS

HOMELESS AND UNDERHOUSED PEOPLE AND THOSE WITH DRUG ADDICTIONS

Contact tracing for cases who are homeless, heavy users of illicit drugs and other highly marginalized individuals is very challenging and resource intensive. It is easy to become frustrated and overwhelmed. These challenges can be made more manageable and successful by recognizing that such cases are not “business as usual,” keeping priorities clearly in mind, training staff and allocating adequate resources.

Many homeless TB cases may suffer from alcoholism, drug addiction or mental illness, which complicates the management of their TB.[46] They may have poor access to health services and multiple medical comorbidities, resulting in delayed TB diagnosis, worsening of the disease, prolonged periods of infectiousness and thus large numbers of contacts who need to be assessed. High baseline prevalence rates of TST positivity also mean that a large number of contacts will require further assessment and possible treatment of LTBI.[47-51]

Information that is easily collected from other individuals with TB can prove very difficult to gather from homeless individuals. They may not know the names of friends/associates or only a street name, or where to find them; recall may be severely limited by addiction or mental illness and sometimes by mistrust of authorities. Drug users may be very reluctant to implicate those they use drugs with for fear of legal prosecution. It may be most productive to try to identify any particularly close friends by name and otherwise to focus on setting-based follow-up. Cases may be highly mobile, with many locations exposed. Shelters may have bed logs, which can be used to identify room-mates; in large shared rooms, prioritize those who spent the most nights with the case and slept closest. Bear in mind that ventilation patterns, including fans, can affect transmission. Rooming houses (also known as single-room occupancy hotels) are often very cramped and poorly ventilated. Homeless shelters may be closed during the day; ask about meals, drop-in centres providing services for the homeless (day-use shelters), libraries, bars, parks, etc. Shelter staff or social service agency workers may be able to identify daily patterns, or friends, and family of the case. If there are gaps in the available history during the infectious period, it may also be worthwhile to check for recent hospitalizations or detainment in a correctional facility. It will be extremely helpful to involve staffs who are familiar with the local homeless sector in contact follow-up.

Homeless contacts are often difficult to locate, and have significant challenges following through on screening, medical evaluation, and preventive treatment for LTBI.[52] Non-judgmental and supportive TB staff, and judicious use of incentives and enablers may help increase participation rates. Active participation and encouragement from trusted staff at the shelter or day-program (e.g. a drop-in centre or soup kitchen) during screening clinics is especially helpful. Persistence and flexibility are critical. Someone who is not co-operative one day may be willing to participate another time; interventions which can be carried out on-site or in a single session generally have more success than those involving extra visits or travel (e.g. sputum collection on site, portable chest x-ray , IGRA vs TST planting and reading).[53-55] The primary focus should generally be on early detection of secondary cases; LTBI should be assessed and treated only if individuals meet the medical and social criteria for treatment of LTBI.

See also Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for additional discussion on the prevention of TB in homeless shelters.

CORRECTIONAL FACILITIES

Residents of correctional facilities often have a higher prevalence of TB infection and disease; large outbreaks of TB have occurred in prisons in the United States, Russia and elsewhere.[56-58] Older facilities in particular are often overcrowded and poorly ventilated, increasing the risk of spread. Some residents have comorbid medical conditions, such as HIV infection, that increase progression of TB infection to active disease; mental illness and mistrust of authorities can make clinical assessment difficult.

When an infectious case of TB is identified in a correctional facility, contacts can include fellow inmates and employees at the facility, transportation staff, visitors, courthouses, and family or community members exposed before the case was incarcerated. Multiple corrections facilities may be involved, as both provincial and federal inmates are often moved between sites, and both case and contacts may have had multiple incarcerations during the infectious period.[45] However, where inmates are given a TST on admission and/or annually, these results may be available as a baseline for contact follow-up. To assist in the identification of contacts, correctional facilities should track inmate transfers, releases and movement within a facility and within the system.

Levels of anxiety may be very high among corrections staff during a TB investigation and have sometimes resulted in facility closures or work stoppages. Ongoing relationships with local public health/TB control staff can help mitigate this. It is extremely helpful to include senior corrections staff, particularly chiefs/directors of health care, and union health and safety representatives early in planning and communication; if multiple facilities are involved, provincial/territorial or senior federal corrections officials should be included. If suspect cases are identified during contact follow-up, they should be removed from the general ranges/shared cells pending diagnostic confirmation. Suspect and confirmed infectious cases should be kept in airborne isolation rooms if available within correctional facilities or transferred to hospital.

Correctional Service Canada has developed guidelines for TB prevention and control in institutions that house inmates sentenced to 2 years or longer. Contact publichealth@csc-scc.gc.ca to obtain a copy.

HEALTH CARE INSTITUTIONS

Hospital TB contact follow-up benefits from close coordination and collaboration between public health/TB control staff and hospital infection control/occupational health staff. While almost every type of health care institution has been implicated in nosocomial transmission, there is very little by way of published hospital contact follow-up studies to guide thoughtful contact follow-up.[59-61] Unless the contact investigation is conducted in an organized, systematic fashion, with the basic principles of transmission in mind, it may result in hundreds of “contacts” with limited or unknowable exposure and often dismal participation and follow-up completion rates. It is often very useful to measure air exchange rates in specific hospital exposure locations, in order to help prioritize contact follow-up. It is also important to confirm whether there were any unprotected aerosolizing procedures, such as intubation, carried out on the infectious case (i.e. when staff did not use N95 masks). Some types of patients are extremely vulnerable (e.g. transplant patients) and even short exposures may be relevant (see Chapter 6).

Visitors to the case and to room-mates may have significant exposure. Hospital infection control and occupational health departments often take advantage of TB exposures to get staff TST documentation up to date, but within this larger group of staff being tested it is important to distinguish those who have the most actual exposure to the infectious case – particularly if there are conversions detected. Pooling the results of contact follow-up within and outside of the hospital can help to focus the investigation and determine the need, if any, for expansion. Notification of contacts may come from the hospital and/or public health authority, and testing can be done by the hospital, public health authority or personal physicians, but the plan should be agreed on by all parties to avoid confusion and gaps.

Individuals who are immunosuppressed are at much higher risk of TB disease after infection with TB; thus, TB exposures in specialty services or clinics may pose an especially high risk. For example, among dialysis patients in British Columbia, the annual rate of TB was 25 times higher than among age-matched population controls.[62] Nosocomial transmission of TB to people with HIV is well documented in both inpatient and outpatient settings.[63,64] See Chapter 4, Diagnosis of Latent Tuberculosis Infection, Chapter 6, Treatment of Latent Tuberculosis Infection, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus, for additional information on assessment and management of these contacts. See also Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings.

LONG-TERM CARE

Many of the same issues for hospitals apply to TB exposures in long-term care facilities. For residents who are contacts of an infectious case of TB, the most critical follow-up is assessment for active disease through careful symptom evaluation, chest radiography and sputum testing. Diagnosis of active TB in the elderly can be difficult, and expert clinical consultation may be necessary. Gastric washings may be easier to obtain than spontaneous or induced sputum in demented or very elderly residents. TST is not recommended as a primary contact assessment tool for residents over 65 years.[65] Interpretation of TST results in the elderly is often complicated by both immune suppression and the potential for boosting related to remote TB exposure or BCG.[66-69] As well, for many elderly contacts the risks of LTBI treatment outweigh the potential benefits. However, contacts among staff and visitors ≤65 years old should receive a TST. In the absence of secondary cases, their results are likely to be a more reliable indicator of transmission in the facility.

REMOTE COMMUNITIES

Contact investigation in a remote community may be especially challenging. Access to diagnostic tests, staffing, TB expertise and resources may be difficult. In remote First Nations or Inuit communities there may also be significant language and cultural barriers to successful contact tracing. Nowhere are organization, education, communication and a collaborative, nonjudgmental approach more important. The provincial/territorial TB program, the local public health/TB control program, Health Canada’s First Nations and Inuit Health Branch if it is involved in the delivery or funding of health services in the community, local health care providers and the community should work closely together to identify secondary cases and contacts quickly, and then to see that they are properly managed over the duration of medical investigation and treatment.

A mobile or portable radiography unit may need to be brought to the community; liberal use of sputum screening may also be useful in coordination with the public health laboratory. Otherwise, a special effort should be made to facilitate the timely transport of people with suspected TB to a larger medical centre for investigation. Directly observed preventive therapy is a treatment option for newly infected contacts in First Nations and Inuit communities.[70] See also Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples.

CONTACTS DURING AIR TRAVEL AND OTHER PUBLIC TRANSPORT

The World Health Organization (WHO) publishes guidelines[71] outlining the procedures for notifying certain contacts of people with infectious TB who have travelled on an international flight with a total duration of ≥8 hours within the previous 3 months. The 8 hour duration is based on epidemiologic studies reviewed in the WHO guidelines. In Canada, reports of people with TB who report a history of air travel while infectious should be made to the Public Health Agency of Canada (PHAC) through the provincial/territorial TB program (even if the flight occurred more than 3 months ago, as passenger records are usually still available). The reporting form and detailed guidelines can be found at http://www.phac-aspc.gc.ca/tbpc-latb/reports-eng.php. The report to PHAC should be made as soon as possible (even if culture and antibiotic sensitivity results are still pending), as this speeds up the process of risk assessment and securing the necessary passenger information from the airline. However, a systematic review of 12 studies suggests that the value of actively screening airplane passengers is limited.[72]

The few published reports of contact tracing after exposure to TB on buses and trains indicate that transmission is sometimes possible on repeated daily exposure, such as on school buses or on long-distance trips.[73] Such events appear to be rare, involving highly infectious cases and specific environmental circumstances (e.g. daily travel on a crowded long-duration school bus route in winter). There is no evidence to support contact tracing related to local public transportation, particularly given the logistic hurdles and considerable inefficiency of contact tracing in these circumstances.[73]

POSSIBLE CONTACT WITH INFECTIOUS TB CASES DURING RESIDENCE OR TRAVEL IN A COUNTRY WITH HIGH TB INCIDENCE

Please refer to Chapter 13, Tuberculosis Surveillance and Screening in Selected High-Risk Populations.

MANAGEMENT OF A TB OUTBREAK

TB outbreaks generally last for several years; response and control are major undertakings.[74-76] In addition, outbreaks are more likely to occur in already challenging settings, such as homeless, impoverished, or other marginalized populations, isolated Inuit or First Nations communities, etc.[44, 54]

DEFINITION

The definition of an outbreak of any disease is the occurrence of more cases in a given population than expected in a given time. Spatial or temporal associations may suggest ongoing transmission and an outbreak. TB outbreaks may be identified only retrospectively, after cases have been found to be linked epidemiologically or by genetic analysis. Any such clustering within the last 2 years should suggest a possible outbreak and prompt further investigation.

The following working definition of outbreak for planning investigations is based on that proposed by the U.S. Centers for Disease Control and Prevention:[22]

- During and because of a contact investigation, two or more of the identified contacts are diagnosed as secondary cases of active TB; or
- Any two or more cases occurring within 1 year of each other are discovered to be linked, but the linkage is recognized outside of a contact investigation. For example, two patients who received a diagnosis of TB independently, outside of a contact investigation, are found to work in the same office, yet they were not previously identified as contacts of each other. A more extreme example is when a second generation of transmission has already occurred at the time an index case is diagnosed – i.e. secondary cases have already generated their own secondary cases. The linkage between cases should be confirmed by genotyping results if cultures are available.

This definition emphasizes the pace of secondary cases occurring and the ability of the TB program to keep up with multiple contact investigations. In practice, the ability of the local TB program to manage a growing cluster of TB cases and the concurrent contact investigations in a timely way, within its usual operations, is also a key factor in determining whether or not to consider the situation an outbreak for response purposes. Most situations that have been recognized as TB outbreaks involve chains of many more than two secondary cases, or one previously unrecognized link to a secondary case, and extend over several years. The above definition is an operational one intended to help identify and contain rapidly evolving clusters. Note that a slower cluster of linked cases that spans several years may still require heightened TB program response for an identifiable population group yet not be an “outbreak” by the above definition.

GOALS

The goals of the investigation and management of an outbreak of TB are as follows:

- To promptly identify the source case or cases, so that the risk of ongoing transmission of infection is rapidly reduced by isolation and initiation of appropriate treatment;
- To rapidly identify new cases of active TB within the at-risk population, and initiate airborne isolation and treatment;
- To identify people with recently acquired LTBI, so that preventive therapy can be given before active disease develops.

MANAGING AN OUTBREAK

Organization and resources

Given the scale and duration of most TB outbreaks, it is important that there be adequate staffing and resources for investigation and management from the onset of the response efforts. Assistance from outside the TB program may be necessary. Advice from experienced colleagues who have managed TB outbreaks elsewhere can be invaluable.

The following components are recommended in any TB outbreak response:

- an identified outbreak manager, appointed for the duration, with overall responsibility for management and coordination of the outbreak response;
- public health/TB control staff to register and case-manage patients with TB, define infectiousness, coordinate the investigation and provide consultation and communication with those in the field;
- sufficient field staff to carry out the contact investigation and follow-up; for outbreaks dispersed across remote communities, mobile specialized teams may be an effective strategy to support local staff;
- information technology (IT)/database and epidemiologic support;
- consistent, coordinated clinical and diagnostic supports with expertise in TB;
    - prompt, local access to chest radiography of adequate quality
    - identified medical consultants with expertise in TB to review chest radiology, evaluate patients for TB, hospitalize if necessary, and manage suspected cases and contacts in a consistent manner, without delay; for remote communities telemedicine links (including review of digital radiology) can be extremely effective
    - hospital facilities that can offer airborne isolation rooms, diagnostic examinations and treatment without delay
    - links to public health laboratories for specialized supports (arrangements to handle larger numbers of specimens, fingerprinting, etc.)
    - rapid and safe transportation of specimens and, if necessary, patients
- sufficient case-management and DOT staff to provide supervision of the complete course of drug treatment for all active cases – at least 1 year’s additional staffing after the outbreak is over may be required;

- communications personnel to provide regular updates to the media and community on the status of the investigation;
- staff and resources to carry out the evaluation.

Roles and responsibilities

It is crucial, from the onset of the investigation, that the roles of all those involved in the investigation and management are clearly defined. Establishing an outbreak coordinating group, including the key individuals from public health/TB control, clinical expert care, hospitals, laboratory, the affected community and communications, can be very helpful. Collaboration and regular feedback among all levels of health care are important. There should be clear agreement to be followed in the investigation and the management of suspected cases and contacts, and written protocols.

Communication with health care providers

Local health care providers, particularly those who are most likely to first see new cases of TB in the outbreak population (emergency room, primary care in the outbreak neighbourhood, etc.) are key partners. Presentation at medical rounds, written notification about the outbreak and other ongoing communication will help to raise the index of clinical suspicion for TB, provide up-to-date information about TB diagnosis and management, and help decrease barriers to care, including early hospitalization for suspected infectious cases when necessary.

Staff training

Given the scale of TB outbreaks and response, many staff involved may not be experienced in TB work; including training and education/clinical rounds at all the organizations involved in the response plan can be helpful.

Prompt isolation and treatment of cases of active disease

An outbreak should markedly raise the index of clinical suspicion for TB when anyone in the affected community presents with compatible symptoms, particularly for respiratory (i.e. infectious) TB. All suspected infectious cases should be promptly isolated – in hospital if necessary – and investigated to confirm the diagnosis and the degree of infectiousness. Suspect cases should not return to congregate settings until infectious TB has been ruled out.

Case-finding, identification of source case, and contact investigation

In outbreaks among homeless and other marginalized populations, outreach street nursing, primary care clinics on site at shelters or other homeless services, and other low-threshold types of care are often critical for early diagnosis.[44,52,75,76] Shelter staff may be the first to identify an ill resident; training about TB and infection control precautions, basic symptom screening on admission, and mechanisms to rapidly isolate and refer suspect TB cases for medical evaluation should be implemented.

If not apparent, the source case or cases should be identified through aggressive investigation of all symptomatic individuals in the at-risk community. Once the initial investigation is under way, a review of the history of TB in the community is important. Review of “old cases” by provincial/territorial and local public health/TB programs may identify previously inadequately treated cases. In some circumstances it may be helpful to locate and reassess previously identified high-risk contacts who were lost to follow-up or did not take or complete treatment for LTBI.

In small communities or in closed settings it may be more efficient to screen the entire community or those in the facility at baseline, especially as it may be difficult to determine the exact level of contact in a small, close-knit community. In some settings, especially if members are very mobile, offering on-site active case-finding (sputum and/or chest radiography as well as symptom screening) on an ongoing basis over an extended period of time may be the only way to ensure that most contacts are identified and screened.[53-55,75-77] Many remote communities have members who travel back and forth frequently to other communities; tracking these individuals is particularly difficult, yet they can be a conduit to spread the outbreak to additional communities. Coordination and shared follow-up arrangements with TB programs in these other communities may be very helpful in the assessment and management of mobile contacts and cases.

In populations in which treatment of LTBI is not realistic as a major outbreak control strategy, the primary emphasis should be on early detection and treatment-to-cure of active cases, rather than extensive efforts to do skin testing. Examples include elderly residents (over 65 years) in long-term care facilities and some homeless populations (e.g. older alcoholics). See also Chapter 15.

A heightened index of clinical suspicion and perhaps case finding efforts should be maintained for several years after the outbreak subsides, as there is usually a pool of recently infected people remaining in the community. It may be possible to follow infected contacts who refuse or are not eligible for treatment of LTBI in order to detect early TB disease (e.g. periodic clinical assessment for 2 years after exposure).

Data management and epidemiologic support

Contact investigation and management in a TB outbreak is very data-heavy. Tracking hundreds of contacts, often through multiple sites and assessments, demands a good database and IT support. Rapid, thoughtful evaluation of the aggregate results as they become available requires a dedicated epidemiologist.

Identify fundamental causes

TB outbreaks mainly take place in settings where rapid transmission is possible – inadequate housing (overcrowding, inadequate ventilation) and prolonged infectiousness often related to limited health care access. A high prevalence of vulnerability factors among contacts accelerates the development of secondary cases: the presence of many young children, diabetes and other causes of immunosuppression, smoking, malnutrition, etc. In facility-based outbreaks (homeless shelters, hospitals, jails) a systematic assessment of conditions and practices, including ventilation, may identify areas for intervention (see also Chapter 15). Individual cases can be treated and cured, but it is very difficult to contain outbreaks or reduce endemically high rates of TB without addressing the fundamental causes. These aspects, too, should be recognized, and when possible addressed in the outbreak response.

Community outreach and education

TB outbreaks can be anxiety-provoking and stigmatizing. Often they take place in a context of limited or inaccurate information about TB and sometimes quite negative cultural/historical associations. All these can prolong the situation through delayed diagnosis if individuals either do not recognize the significance of their symptoms or are afraid to receive a diagnosis of TB. It is crucial to provide information about TB and the outbreak response to the affected community or setting as early as possible in the investigation of the outbreak, with regular updates for them and for the general local population. The information should be in a style and format that is accessible and takes into account the cultural and practical setting of those affected. Standard materials may need to be adapted, ideally with input from community members. Peer outreach may be very useful, particularly for hard-to-reach individuals. This will help reduce the level of anxiety and will likely lead to greater cooperation and adherence to recommendations.

Evaluate the process and outcome of the outbreak investigation

Ongoing evaluation and a formal evaluation at the end of the outbreak, including both the process and outcome of the outbreak investigation, are crucial. DNA genotyping of isolates may be useful in identifying the presence of an outbreak, mapping its extent and evaluating the results of the outbreak investigation and control. Identification of key contributing factors, often social determinants of health, may point to future non-TB-specific interventions.

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CHAPTER 13

TUBERCULOSIS SURVEILLANCE AND SCREENING IN SELECTED HIGH-RISK POPULATIONS

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KEY MESSAGES/POINTS

- Screening for and treatment of latent tuberculosis infection (LTBI) should only be undertaken if the local TB control program already effectively manages active TB cases and their contacts.
- The selection of people for targeted LTBI screening and treatment is based on their risk of prior TB exposure and their risk of reactivation, balanced against the likelihood of safe completion of treatment, including the risk of hepatotoxicity, which increases with age.
- Groups discussed in this chapter that may warrant targeted screening are the foreign-born, people with non-HIV immune suppression and other medical or behavioural risk factors for TB, and long-term visitors to countries with higher TB incidence.
- Other groups that may be considered for targeted LTBI screening are discussed in other chapters and include TB contacts, people with HIV infection, Canadian-born Aboriginal Peoples, children, and employees and users of health care and correctional facilities.
- Most foreign-born groups undergo a mandatory medical examination prior to arrival in Canada, which includes chest radiography to detect active TB. Those found to have active TB must be treated prior to arrival to ensure that they are no longer infectious. Citizenship and Immigration Canada (CIC) requires that individuals with previously treated TB and those with abnormal chest radiographs but without active TB detected in this program undergo TB surveillance after arrival.
- Only a small proportion of all cases of active TB diagnosed in the foreign-born after arrival in Canada are detected during the immigration post-landing surveillance program. This underscores the need for additional screening programs for subgroups of the foreign-born at increased risk of TB reactivation.
- To improve uptake of LTBI screening and treatment in the foreign-born population, investment in TB education programs for patients and providers should be considered together with delivery of care in a culturally sensitive manner with good access to interpreters.

- To improve the likelihood of safe completion of LTBI treatment in vulnerable groups, such as injection drug users and the homeless, it is suggested that patients be assessed to determine coexisting viral hepatitis in order to decrease the possibility of hepatotoxic effects of LTBI treatment. Those at highest risk of reactivation should be considered for special measures to enhance adherence, such as directly observed LTBI treatment and/or incentives and enablers.

INTRODUCTION

The last three decades have seen marked shifts in the epidemiology of TB in Canada. Active disease is increasingly concentrated in specific population subgroups, notably the foreign-born, Aboriginal Peoples and people with medical, social and/or behavioural risk factors, such as HIV infection, homelessness and injection drug use (see Chapter 1, Epidemiology of Tuberculosis in Canada).

While it is recommended that the first priorities in TB control remain the timely detection and treatment of active TB followed by suitable management of contacts at risk, the concentration of TB in specific groups makes it relevant to consider targeted screening. Targeted screening interventions systematically seek to diagnose and treat active TB or LTBI among those at increased risk of infection and/or progression to active disease. In this chapter, the focus is on TB surveillance and screening of immigrants and refugees; people with non-HIV immune suppression and other medical, social or behavioural risk factors for TB; and long-term visitors to higher-incidence countries. Screening and management of active TB and LTBI among TB contacts, people with HIV infection, Aboriginal Peoples, children, and employees and users of health care and correctional facilities are discussed in other chapters.

SURVEILLANCE

Surveillance refers to an ongoing process of (a) systematic collection of pertinent, high-quality data; (b) orderly consolidation and evaluation of these data; and (c) prompt dissemination of the results to those who need to know, particularly those who are in a position to take action.[1]

Generally, the objectives of a surveillance program are to guide health interventions, estimate trends, identify groups at high risk, monitor changes in patterns of transmission, evaluate prevention strategies and suggest hypotheses for further research.

It is important for providers and public health authorities to understand the distribution of TB in Canadian communities and to detect transmission. Moreover, suitable documentation of the outcomes of screening interventions (e.g. contact investigation, chest radiography for immigrants) allows for quality control assessment and informed decision-making about future policies and their potential targets.

In the context of immigration, the term “medical surveillance” refers to the process whereby immigrants and refugees with inactive TB or previous TB treatment detected in the pre-arrival TB screening program are required by CIC to report to local public health authorities for examination and follow-up.

SCREENING – DEFINITIONS, TOOLS AND GOALS

Screening refers to a process that attempts to discover conditions suitable for early preventive or curative intervention. These conditions may not be sufficiently symptomatic to induce patients to seek medical help on their own. Screening may be justified by the prevalence and/or potential severity of the target condition, when its detection permits intervention that improves outcomes.[2] In the case of active TB, the goal is to reduce unfavourable outcomes and interrupt transmission by instituting prompt and effective treatment. The goal of targeted screening for LTBI is to reduce the likelihood of subsequent progression to active disease among people at increased risk by appropriate initiation, supervision and successful completion of treatment.

Symptom screens and chest radiography are the primary screening tools when the focus is the identification of prevalent, undiagnosed active cases of infectious pulmonary TB (so as to treat and render them noninfectious). Subsequent microbiologic confirmation with sputum smear and culture or other suitable specimens is always recommended (See Chapter 6, Treatment of Latent Tuberculosis Infection).

When the focus of screening is the detection of LTBI, either the tuberculin skin test (TST) or the interferon gamma release assays (IGRAs) may be used. Conditions under which either test is preferred and their interpretation are reviewed in Chapter 4, Diagnosis of Latent Tuberculosis Infection. Positive screening tests for LTBI should be followed by chest radiography to address the possibility of subclinical active TB. Chest radiography also identifies abnormalities that are associated with increased reactivation risk.

- **The highest priority in TB control programs is to detect and treat active TB cases and to investigate their contacts.**
- **Screening and treatment for LTBI should only be undertaken if the TB control program effectively manages active TB cases and their contacts.**
- **Screening for LTBI is only appropriate when available infrastructure and resources allow the monitoring and support needed to achieve safe and complete treatment.**[3]

  (Strong recommendations, based on moderate to strong evidence)

TARGETING GROUPS FOR SCREENING

The choice of which groups should be targeted for LTBI screening and treatment should be based on a number of factors, and the assessment is usually performed in various settings by different professionals, such as public health, occupational health, primary care or subspecialty physicians. The most important factors to take into consideration when selecting people as suitable candidates for LTBI screening and treatment are their risk of prior TB exposure (Table 1) and of reactivation, balanced against the risk of hepatotoxicity (see Chapter 6, Treatment of Latent Tuberculosis Infection). The likelihood that individuals will safely complete treatment as prescribed should also be taken into account. Hence, the benefit of screening programs for LTBI will be greatest in those with a higher probability of infection and/or significant risk factors for reactivation, coupled with a low risk of toxicity and a high probability of treatment completion. LTBI treatment may be particularly beneficial in certain subgroups, such as young children and those with severe immunosuppression, for whom there is increased risk of progression to active disease and also a greater risk of severe forms of the disease, such as miliary TB or TB meningitis (see Chapter 6).

Table 1. Groups with increased risk of TB exposure and latent TB infection[4]

Groups at risk	Prevalence of positive TST	Setting or group usually responsible for screening
Close contacts of an active case of pulmonary TB	Variable, higher than source population	Public health, primary care
Immigrants from countries with high TB incidence		Public health, primary care
Children	15%-23%	
Adult (lived >20 years in country with high TB incidence)	53%-61%	
Injection drug user		Primary care, treatment facilities
(TST ≥10 mm)	66%	
(TST ≥5 mm)	31%	
Homeless	18%-51%	Primary care, shelters, public health
Aboriginal communities*		Public health, primary care
Adults	14%-30%	
Children	5%-29%	
Health care workers*	11%-46%	Occupational health, public health
Residents of long-term care facilities*	6%-25%	Primary care, facility director of care, public health
Residents of correctional facilities*	12%-72%	Inmate health services, public health
Travellers to countries with high TB incidence	Variable	Travel medicine, primary care
Reference		
Canadian-born non-Aboriginal children	1-3%	Targeted screening not recommended
Canadian-born non-Aboriginal adults, not BCG vaccinated	7%	
Canadian-born non-Aboriginal adults, BCG vaccinated	65%	
Canadian-born non-Aboriginal adults, BCG vaccination nonspecified	13%	

*BCG status not specified

SCREENING IMMIGRANTS FOR TUBERCULOSIS INFECTION AND DISEASE

OVERVIEW OF IMMIGRATION TO CANADA

Over the course of the last four decades, international migration has increased at an unprecedented rate, the total number of international migrants estimated to be 200 million people.[3] Canada is a leading destination for migrants and receives on average ~250,000 immigrants and refugees annually, who account for almost 20% of the population (2006 Census[5,6]). Over the past 40 years, there has been a major demographic shift in the source countries of new migrants. Before the 1960s, most individuals immigrating to Canada originated from European countries. Since the 1970s, however, most immigrants (>70%) have originated from countries with intermediate or high TB incidence rates in Asia, Africa and Latin America.[5,6]

The two main administrative classifications of migrants arriving in Canada are 1) permanent residents who come to Canada to resettle and 2) temporary residents who are visiting, studying or working in Canada but who maintain their own nationality. Permanent and temporary residents are further classified into several subgroups (see Table 2). In addition, Canada receives more than 35 million international visitors per year.[8] Most groups apply for permission to come to Canada while still living in their countries of origin, an important exception is refugee claimants who apply for status after arrival in Canada.[6]

Table 2. Classification of international migration to Canada (2010)[7]

Immigration category	Annual number of migrants*
Permanent residents	
Economic class (business and economic migrants)	187,000
Family class (family reunification)	60,000
Humanitarian class (refugees resettled from abroad or selected in Canada from refugee claimant population)	25,000
Others	9,000
Total	**281,000**
Temporary residents	
Migrant workers	182,000
International students	96,000
Refugee claimants (those arriving in Canada and claiming to be a refugee)	23,000
Others	81,000
Total	**382,000**
Other migrants	
Irregular migrants (no official migration status)†	~200,000
Visitors	~35,000,000

*Numbers rounded to nearest 1,000. Data from Citizenship and Immigration Canada Facts and Figures 2010.[6]

†Includes those who have entered Canada as visitors or temporary residents and remained to live or work without official status. It also includes those who may have entered the country illegally and did not register with authorities or apply for residence.

EPIDEMIOLOGY AND PREDICTORS OF TB AMONG THE FOREIGN-BORN IN CANADA

Canada is a low-incidence country and had an overall TB disease rate of 4.6 per 100,000 population in 2010.[9] The majority of the 1,577 reported cases (66%) occurred in the foreign-born population, which has an overall 13-fold greater incidence of TB than the non-Aboriginal Canadian-born population (13.3 vs. 1.0 cases/100,000 population), although rates are as high as 500 times greater in certain subgroups of immigrants.[9,10] The strongest predictors of active TB development in immigrant populations are the global region of origin, immigration category (refugees at 2-fold increased risk compared with other immigrants), the presence of underlying medical comorbidities, the time since arrival in Canada and recent travel to countries with a high TB incidence[10-17] (also see Chapter 1, Epidemiology of Tuberculosis in Canada). Refugees and foreign-born children from high-incidence countries are particularly important subgroups to consider for targeted screening, for the reasons listed below.

Refugee populations have consistently been reported to have an approximately 2-fold increased risk of active TB compared with the immigrant population, at least within the first year after arrival.[18-21] This may be due to a higher prevalence of LTBI in the refugee population and crowded conditions that increase the likelihood of recent exposure to TB.[22]

Foreign-born children less than 11 years of age from high-incidence countries do not undergo pre-arrival radiographic screening for TB (see http://www.cic.gc.ca/english/department/partner/pp/pdf/IMEI_Tuberculosis.pdf).[23] For this and several other reasons children may particularly benefit from LTBI screening and treatment. In children less than 5 years of age there is higher likelihood of severe or rapidly progressive disease, such as miliary TB or TB meningitis.[24,25] Furthermore, TB in young children is more often paucibacillary or extrapulmonary and therefore more difficult to diagnose.[24,25] Finally, children with LTBI have many years of life in which active TB may develop and a relatively low risk of hepatotoxicity (see Chapter 9, Pediatric Tuberculosis).

IMMIGRATION TB SCREENING REQUIREMENTS FOR THE FOREIGN-BORN

Pre-entry tuberculosis screening

CIC requires all individuals applying for permanent residency and certain individuals applying for temporary residency to undergo an immigration medical examination (IME) before arrival, which includes a chest radiograph for applicants ≥11 years of age (see Table 3) (see http://www.cic.gc.ca/english/resources/manuals/op/index.asp).[26] The objective of this program is to detect prevalent active TB in migrants prior to arrival in Canada so as to ensure that they are treated and are no longer infectious on arrival. This screening program does not aim to detect or treat LTBI. Once the IME has been completed it is valid for a period of 12 months.[27] Most visitors do not require this examination. CIC's determination of which temporary residents or visitors require an IME is based on their place of origin (a 3-year average incidence rate of all cases of TB of ≥30/100,000 population), the duration of the visit (longer than 6 months) and occupation (workers in close contact with others). For most migrants the IME is performed before departure from the country of origin by a designated medical professional, and the cost is borne by the applicant. The exceptions to this are convention refugees for whom the examination is provided free and refugee claimants, who claim refugee status after arrival in Canada and undergo an IME shortly after arrival.

Note: In 2009 the World Health Organization changed its method of reporting the global burden of TB and began reporting annual incidence of ALL TB cases per 100,000 rather than annual incidence of smear-positive TB. To reflect this change, the definition of high TB incidence countries/territories has changed from 15 per 100,000 smear-positive TB cases to 30 per 100,000 for all forms of active TB cases (3-year average).[11] The 3-year moving average is used to adjust for unstable rates in some jurisdictions. Furthermore, estimated rates adjusted for under-reporting of cases are used for some countries, rather than the country's reported incidence rate. To view current international incidence rates, see http://www.publichealth.gc.ca/tuberculosis.

Chest x-rays are examined for evidence of active or inactive TB disease by a local radiologist. CIC, in consultation with Canadian TB specialists, grades chest x-rays according to an 18-factor ascending scale of findings characteristic of active TB disease or inactive TB infection.[27] Individuals with certain abnormalities on their chest x-ray must submit three consecutive sputum samples for smear and culture. Those unable to submit sputum will be required to repeat the chest radiography 6 months after the initial one to establish stability. Those found to have active TB must complete a course of treatment consistent with Canadian standards. Before being given permission to enter Canada by CIC, they must submit proof of successful treatment completion, three negative sputum smears and cultures, and stable and/or improving chest x-rays taken over a minimum period of 3 months. In 2011 active TB was identified during 0.09% of 500,992 immigration medical assessments (Dr. Sylvain Bertrand, Citizenship and Immigration Canada, personal communication).

Applicants identified as having inactive pulmonary TB are permitted to enter Canada but are placed under medical surveillance and referred to provincial/territorial public health authorities to report for post-landing surveillance (see below) within 30 days of arrival.

Inactive pulmonary TB is defined as follows:

a) a history of treated active TB and/or

b) an abnormal chest x-ray suggestive of TB and
   i) two chest x-rays taken at an interval of 3 months apart with stable appearance and three negative sputum smears and cultures or
   ii) two chest x-rays taken at an interval of 6 months apart with stable appearance.

Table 3. Citizenship and Immigration Canada requirements for an immigration medical examination[24]

Entrants to Canada	Criteria
Foreign nationals applying for permanent residency (immigrants and refugees selected abroad)	Mandatory for all.
Foreign nationals claiming refugee status in Canada	Mandatory for all.
Foreign nationals applying for temporary residency (including students, workers and visitors)	Those who will stay in Canada for more than 6 months and who have spent 6 or more consecutive months in a country/territory with high TB incidence, as designated by the Public Health Agency of Canada, during the 1 year immediately preceding the date of seeking entry (application) to Canada.
Foreign nationals applying for temporary residency and seeking to work in certain occupations	Mandatory for all who are seeking to work in an occupation in which the protection of public health is essential regardless of length of stay and country of origin AND for agricultural workers from a country/ territory with high TB incidence, as designated by the Public Health Agency of Canada. The occupational list is available at http://www.cic.gc.ca/english/information/medical/medexams-temp.asp#occupational
Seriously ill foreign nationals	May be requested to undergo an immigration medical examination if an Immigration Canada or Canada Border Services Agency officer has reasonable grounds to believe that the person is medically inadmissible to Canada, regardless of anticipated length of stay in Canada and country of origin.

Post-landing surveillance

CIC's Medical Surveillance Program is designed to refer applicants found in the course of their IME to have previously treated TB or inactive pulmonary TB to the Canadian provincial or territorial public health authorities as soon as possible upon their arrival in Canada. Approximately 2% of those who undergo pre-arrival chest radiographic TB screening are targeted for medical surveillance (Dr. Sylvain Bertrand, Citizenship and Immigration Canada, personal communication). Immigrants requiring medical surveillance receive a Medical Surveillance Undertaking Form (IMM 0535B) and an information handout with instructions on how to contact provincial/ territorial public health authorities upon arrival in Canada. They must report to, or be contacted by, a public health authority within 30 days of entry. For complex inactive pulmonary TB cases, evaluation and follow-up should begin within 7 days (see http://www.cic.gc.ca/english/resources/manuals/bulletins/2011/ob340.asp).

This is a passive surveillance system, and the implementation varies among the different provinces and territories, some having a centralized process and others having a decentralized system. Provincial/territorial public health authorities report to the CIC Medical Surveillance Program as to whether the immigrant has been compliant with the requirement for medical surveillance. Compliance is defined as keeping the first appointment with the clinician or being assessed by a specialist designated by public health. Compliance with surveillance varies by province/territory, averaging ~70% (Dr. Sylvain Bertrand, CIC, personal communication). Participation in the Medical Surveillance Program is a formal "condition of landing."

While there is currently no enforcement of participation, CIC will not process any further immigration applications from an immigrant under the Medical Surveillance Program (e.g. to extend a visa or apply to become a citizen) until they have met the program requirement.

Immigrants are responsible for their own health care funding until eligible for provincial/territorial health care insurance, which in some jurisdictions may not be until 90 days after arrival. For those under medical surveillance, this may mean a delay of examination, radiography, other necessary procedures and treatment for LTBI for at least 3 months. Temporary health care for refugees and refugee claimants may be covered by the Interim Federal Health Program, a health care coverage program managed by CIC. This will provide coverage for the IME when done in Canada, screening for and treatment of active TB, if detected, as well as screening for and treatment of LTBI in all groups eligible for the Public Health and Public Safety package. Information on the Interim Federal Health Program is available at http://www.cic.gc.ca /english/refugees/outside/summary-ifhp.asp.

Timely compliance with the requirement for medical surveillance has been shown to improve in the following circumstances:[28]

- Advising the immigrant of the need for medical surveillance before travel to Canada or at the port of arrival;
- Providing documents requesting medical surveillance in the language of the immigrant (if not fluent in English or French);
- Provincial/territorial health insurance coverage for medical surveillance immediately upon arrival in Canada with no waiting period;
- Pre-screening of individuals by public health staff prior to clinician assessment in order to identify those with symptoms and signs of active TB or those at high risk of rapid progression of LTBI to active disease;
- Centralized clinics for assessment, when feasible, allowing staff to become more experienced and efficient;
- Extended clinic hours; and
- Readily available and culturally sensitive interpretation services.

During the initial assessment of these individuals, active TB should be ruled out with special attention to symptoms or signs of active TB. If these are present chest radiography and sputum smears and cultures should be performed as deemed appropriate.[29] For those found not to have active TB, testing for LTBI (TST or IGRA), unless previously known to be positive, should be performed and those identified as having LTBI should be considered for treatment as outlined in Chapter 6, Treatment of Latent Tuberculosis Infection. Those who have completed an adequate and well-documented course of LTBI treatment can be discharged. The need for and duration of follow-up for those not completing LTBI treatment is unclear. In general, such people should be advised of the potential risk of reactivation and told to return for evaluation if symptoms arise (see also Chapter 6). People who are discharged from follow-up should be advised to seek medical attention promptly if symptoms develop that are suggestive of TB and to tell their health care provider about their history of medical surveillance for TB as a result of their IME.[29]

Post-arrival domestic LTBI screening

There are no routine post-arrival domestic LTBI screening programs for immigrants in Canada. There are, however, published primary care guidelines and several screening programs managed by different organizations, for example, school-based screening, immigrant and refugee clinics, services for migrant workers and targeted screening of certain high-risk migrants.[10,30-45] Undocumented migrants are difficult to access and remain a challenge, as they are not systematically screened in any of the existing programs.

EFFECTIVENESS OF TB SCREENING PROGRAMS FOR IMMIGRANTS

Active and inactive TB

Recent estimates of the yield of active TB and inactive TB found in pre-immigration chest radiography screening in migrants to Canada was found to be 0.05% and ~2% respectively.[46] In a recent systematic review and meta-analysis 1.3% of migrants assessed in the post-landing surveillance program in Canada were found to have active TB.[47] Only 67% of those targeted for this surveillance actually completed the screening process, thus highlighting the importance of improving the functioning of these programs.[47] Furthermore, only 2%-15% of all cases of active TB in the foreign-born population in Canada and the United States are detected during required immigration screening programs (post-landing surveillance, refugee claimants or people applying to change immigration status).[48-51] The majority of TB in the foreign-born occurs outside of pre-immigration screening as a result of reactivation of LTBI. Although TB rates among the foreign-born are highest in the first 5 years after arrival (see Chapter 1, Epidemiology of Tuberculosis in Canada), the risk of TB is higher than that of the non-Aboriginal Canadian-born population throughout their lifetime.[13,45,52] The Canadian Thoracic Society believes this highlights the importance of additional screening programs to control TB in the immigrant population.

Latent TB infection

Detecting (for example, with TSTs or IGRAs) and treating LTBI in the immigrant population after arrival is an attractive alternative to chest radiography screening programs. Unfortunately, LTBI screening programs for immigrants perform poorly. In a systematic review and meta-analysis of studies of LTBI screening and treatment in immigrants after arrival in low TB incidence countries (Canada, United States, Spain, Italy and Australia), only 32% of TST-positive immigrants completed LTBI treatment.[53] This suboptimal performance was due to losses and dropouts at all steps of the process: 69.0% completed screening, and 77.0% of those with a diagnosis of LTBI were offered treatment; of these, 83.0% started treatment, of whom 71.0% completed treatment.[53] Similarly, LTBI screening and treatment in the post-landing surveillance program in Canada and the United States resulted in only 26% of people with a positive TST completing LTBI treatment.[47]

Challenges and barriers to the uptake of LTBI screening and treatment in immigrants

Implementing widespread, comprehensive LTBI screening and treatment programs in migrants is challenging for many reasons, the most important of which is the extremely large pool of migrants at risk who are not easily accessible through present health care programs. The potential pool of migrants at risk of reactivation of LTBI to active disease is enormous, given that there are ~6 million migrants living in Canada, ~200,000 new permanent residents and 1.2 million visitors arriving from countries with high TB incidence each year, of whom ~50% have LTBI.[4,7,8] In addition there are 350,000-400,000 new temporary residents, including foreign workers, foreign students, refugee claimants and those in humanitarian groups, arriving each year in Canada.[6] A recent US study highlights the importance of the potential large pool of unscreened people with LTBI at risk of TB reactivation: only 41% of cases of active TB diagnosed within 1 year of arrival occurred in those who had been screened in the pre-landing screening program. The majority of cases occurred in unscreened people, i.e. temporary workers and exchange students (37%), business travellers and tourists (16%) and non-immigrant visitors from Canada and Mexico (7%).[54] In Canada some temporary workers are screened, but most of these other groups are not (Table 3).

Exposure in countries with high TB incidence may also be an important risk factor in immigrants who have been living in Canada for more than 2 years and return home for prolonged periods. Several studies have estimated that 20%-50% of active TB cases in the foreign-born population are due to recent return travel to their countries of origin.[15-17] Accessing this population is a challenge, as only a minority (20%-30%) seek pre-travel advice, and there are no programs to routinely re-evaluate returning travelers.[55-57] Furthermore, people at increased risk of LTBI reactivation who have medical and/or behavioural risk factors are not easily identified, current diagnostic tools do not permit identification of those at higher risk, and the length of LTBI treatment regimens deters completion (see Chapter 4, Diagnosis of Latent Tuberculosis Infection).

Finally, LTBI screening programs for immigrants and refugees encounter many barriers at the level of the patient, provider and infrastructure/institution. Patient-level barriers include the stigma of TB and its association with HIV, linguistic barriers and difficulties coming to appointments because of inconvenient clinic locations or limited clinic hours.[42,58-60] Provider barriers to offering screening to migrants are related to inadequate knowledge of which migrants should be screened or how they should be followed up.[61-63] Poor adherence to treatment for LTBI is associated with barriers similar to those for LTBI screening. They include linguistic barriers, cultural taboos and stigmatization, low education level, perceived low risk of progression from LTBI to active disease, belief that positive results from TSTs are due to BCG (Bacille Calmette-Guérin), reluctance to undergo venipuncture, and economic factors (costs of travel, lack of insurance, delays in obtaining insurance, missed days at work).[58-60,64-66] Until these issues can be addressed, LTBI screening and treatment in Canada after arrival should be focused on migrants at increased risk of active TB.

Strategies to optimize LTBI screening and treatment in the foreign-born

Control of TB in low-incidence settings will need novel strategies to more effectively access all foreign-born groups at risk of LTBI. Improving cultural and linguistic infrastructure may increase the uptake of screening and treatment in the immigrant population.[42,67-69] Several studies show that having a cultural case manager or that matching migrants to a health care provider with similar language or cultural background increased the probability of LTBI treatment completion.[42,64,67] Educating health care providers in identifying migrants at risk is also an important strategy. In a study in which primary care providers were educated about how and whom to screen for TB, the proportion of patients screened for LTBI increased, and the proportion identified with active TB also increased.[61]

Some of the barriers to delivering LTBI treatment may be best addressed by providing it in an integrated primary care setting where a trusting relationship has been established and where several health issues are being managed at the same time. Clinics with longer hours after the usual work day may help people who have difficulties getting time off work to come to clinic visits. Similarly, engaging migrants will require effort on several levels, including care that is tailored to their linguistic and cultural backgrounds, and better pre-travel counselling in the primary care setting.[55-57] Engaging immigrant community resource agencies may be effective.[70] In addition to programmatic improvements, the development of new diagnostic tests that can identify the 10% of people with LTBI whose disease will ultimately reactivate, and shorter LTBI treatment courses would be ideal. Given the magnitude of human migration, the long-term solution will ultimately depend on investment in global TB control to decrease the TB morbidity and exposure in source countries.[71]

SCREENING OF PEOPLE WITH MEDICAL OR BEHAVIOURAL RISKS FOR TB INFECTION AND DISEASE

MEDICAL RISK FACTORS THAT INCREASE TB REACTIVATION

There are several medical conditions and therapies that increase the risk of TB reactivation (see Chapter 6, Treatment of Latent Tuberculosis Infection). Subgroups with an increased prevalence of LTBI (Table 1) who also have medical conditions that increase the risk of LTBI reactivation should be targeted for screening and treatment.[52] Diabetes is a particularly important medical risk factor, as it is more common in certain immigrant groups and the Aboriginal population, and is associated with a 2-3.6 fold increased risk of active TB development.[72] Diabetes affects more than 2 million Canadians and has an overall prevalence of 6%, increasing with age up to a prevalence of 20% in the 75-79 age group.[73] Immigrants from South Asia have a 3-4 fold higher risk of having diabetes as compared with the Canadian-born population, and immigrants from Latin America, the Caribbean and sub-Saharan Africa have about a 2 fold increased risk.[74,75] End-stage renal disease is another important medical risk factor, as it is a common complication of diabetes. Patients receiving hemodialysis are at substantially elevated risk of active TB, with cited relative risks ranging from 10-25 times the background incidence.[76]

There are no systematic evaluations of screening for and treatment of LTBI among people with medical risk factors for active TB, other than HIV. A recent cost-effectiveness analysis suggested that, at a group level, screening and treatment of individuals with these conditions would have little public health impact and would confer limited gains in quality-adjusted survival.[77] This analysis, however, was based on relative risks of reactivation of 2 or less for most of these conditions.

RECOMMENDATIONS FOR LTBI SCREENING IN THE FOREIGN- BORN AND THOSE WITH UNDERLYING MEDICAL CONDITIONS

For the following recommendations, see Table 1 for a list of those with an increased prevalence of TST positivity and Table 1 in Chapter 6, Treatment of Latent Tuberculosis Infection, for the conditions that increase the risk of TB reactivation. The recommendations are summarized in Table 4.

- **Routine screening of people with a low prevalence of LTBI and medical risk factors with a low relative risk for LTBI reactivation (i.e. a relative risk of <2.0 compared with a healthy individual without known risk factors for reactivation) is not recommended.**

  (Conditional recommendation, based on moderate evidence)

- **Foreign-born children up to age 20 should be offered LTBI screening and treatment as soon as possible after arrival.**

  (Conditional recommendation, based on moderate evidence)

- **Refugees from countries with high TB incidence should be offered LTBI screening and treatment up until age 50 years, because refugee status is associated with a slightly increased risk of TB reactivation.**

  (Conditional recommendation, based on weak evidence)

- **Population groups with increased prevalence of LTBI (such as the foreign-born from countries with high TB incidence) and with conditions presenting a slightly increased risk of reactivation (i.e. refugee status) should be offered LTBI screening and treatment up until age 50 years.**

  (Conditional recommendation, based on weak evidence)

- **Population groups with increased prevalence of LTBI and with conditions that pose a moderate risk of reactivation (i.e. diabetes) should be offered LTBI screening and treatment up until age 65 years.**

  (Conditional recommendation, based on weak evidence)

- **Everyone with conditions associated with a high risk of LTBI reactivation should be considered for screening (see Table 4).**

  (Conditional recommendation, based on moderate evidence)

- **Providing LTBI screening and care to the immigrant population in a culturally sensitive manner with good access to interpreters should be considered.**

  (Conditional recommendation, based on weak evidence)

Table 4. Recommendations of the Canadian Thoracic Society for groups for targeted LTBI screening

Group at risk	Group to be screened	Age limit for screening
1. Close contacts of an active case of pulmonary TB	As soon as possible after diagnosis of the index case (see chapter 12)	Any age
2. Immigrants from countries with high TB incidence	Fibronodular changes on chest x-ray (usually in the context of Post-Landing Surveillance)	Any age
	All children and adolescents as soon as possible after arrival	Up to age 20 years
	Refugees	20-50 years
	Immigrants and refugees with underlying medical comorbidities with the following risk of TB reactivation:*	
	High risk Moderate risk Slightly increased risk	Any age Up to 65 years Up to 50 years
3. Medical comorbidities*	All individuals regardless of prior TB exposure should be considered for screening if they have certain medical comorbidities that increase risk of TB reactivation (see Table 1 in Chapter 6 for categorization of risk)	
	High risk Moderate risk Slightly increased risk	Any age Up to 65 years Up to age 50 years
4. Injection drug user OR the homeless	In the presence of underlying medical comorbidities with the following risk of TB reactivation*	
	High risk[†] Moderate risk Slightly increased risk	Any age Up to 65 years Up to 50 years
5. Travellers to countries with high TB incidence‡	≥1 month of travel with very high risk contact, particularly direct patient contact in a hospital or indoor setting, but possibly including work in prisons, homeless shelters, refugee camps or inner city slums.	Up to 50 years if single post-travel TST
	≥3 months of travel to TB incidence country >400/100,000 population**	Any age if documented TST conversion
	≥6 months of travel to TB incidence country 200-399/100,000 population	
	≥12 months of travel to TB incidence country 100-199/100,000 population	
HIV positive	See Chapter 10	
Aboriginal Peoples	See Chapter 14	
Health care workers	See Chapter 15	
Residents of long-term care facilities	See Chapter 15	
Residents of correctional facilities	See Chapter 15	

For categories 1-3, *conditional recommendation, based on moderate to weak evidence.*

For category 4, 5, *conditional recommendation, based on weak evidence.*

*Risk of reactivation for different medical comorbidities is outlined in Table 1 of Chapter 6, Treatment of Latent Tuberculosis Infection.

[†]For those at **high risk**, strongly consider measures to enhance adherence, such as directly observed LTBI treatment with financial incentives. For all others only consider LTBI screening and treatment provided treatment completion and adequate follow-up for hepatotoxicity can be achieved.

[‡]For those >50 years and at higher risk of prior TB exposure, i.e. foreign-born, current or previous IDU, Aboriginal people, health care workers or those with pre-existing liver disease, consider doing a pre- and post-travel TST to detect recent conversion. In this case, performance of two-step TST pre-travel would enhance the accuracy of testing after travel to detect true conversions from recent infection. For all other travellers, perform a single TST 2 months after return from travel.[78]

**TB incidence expressed as all TB cases/100,000 (see http://www.phac-aspc.gc.ca/tbpc-latb/itir-eng.php for international TB rates).

HOMELESS PEOPLE

The incidence rate of active TB in homeless populations is markedly higher than in their non-homeless counterparts. Despite the challenges in accurately quantifying the number of homeless people, one study estimated the incidence rate of active TB in Toronto's homeless population to be 71 cases per 100,000.[79] Homeless people are also frequently envisioned as Canadian-born individuals; however, recent studies have identified a growing proportion of foreign-born homeless people with active TB.[80] Given the elevated risk of TB drug resistance in many foreign-born populations, this study highlights the risk of drug-resistant disease emerging and propagating within urban shelter systems; hence, adequate infection control measures, including environmental controls in these institutions are recommended (see also Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings).

The prevalence of LTBI in homeless populations is also markedly elevated relative to non-homeless populations and has been reported as ranging between 18% and 51%.[81] Many homeless people are at increased risk of active TB not only because of repeated TB exposures but also because of the high frequency of medical comorbidities that can compromise their immunity.[82] Among homeless people with active TB, the frequency of HIV coinfection has been reported to range from 5% to 60%.[80,83-85] While LTBI therapy offers the potential to significantly reduce the risk of active TB in homeless people, it is complicated by challenges with adherence to therapy and adverse drug reactions. LTBI treatment completion rates in homeless populations have been reported to be as low as 19%. However, the use of incentives and enablers, and directly observed (preventive) therapy have been used effectively to increase the likelihood of successful treatment completion up to 44%.[86]

Alcohol and/or substance abuse can complicate the treatment of LTBI, not only by affecting adherence to therapy but also by increasing the risk of adverse drug reactions. Concurrent alcohol abuse during LTBI therapy, particularly with isoniazid, markedly increases the risk of hepatotoxicity (up to 4 fold with daily alcohol intake).[87] While LTBI treatment with rifampin is much shorter in duration than isoniazid and is associated with a lower risk of hepatotoxicity,[88] it is important that health care providers carefully assess and exclude active TB before considering its use. This is because the development of rifampin resistance (if individuals are inadvertently treated for LTBI with rifampin when they have subclinical, undetected active TB) would have very serious short-term clinical implications for patients, and could have lasting public health repercussions to those accessing or providing services within the shelter system.[89] Given the potential risk of hepatotoxity due to high rates of associated alcohol use and low rates of treatment completion, efforts to offer LTBI screening and treatment should be reserved for those with a moderate or high risk of TB reactivation.

- **The homeless should be offered LTBI screening and treatment up to age 65 if they have an underlying medical condition that confers moderate risk of reactivation or at any age if there is a medical condition that confers a high risk of reactivation.**

  (Conditional recommendation, based on weak evidence)

- **Homeless people with medical conditions associated with a high risk of reactivation should be considered for special measures to enhance adherence, such as directly observed LTBI treatment and/or incentives and enablers.**

  (Conditional recommendation, based on weak evidence)

INJECTION DRUG USERS

Injection drug use is associated with a heightened prevalence of LTBI[90-92] and with blood-borne pathogens. In particular, chronic hepatitis C infection has been identified with high frequency in studies of injection drug users (IDUs), prevalence rates exceeding 60%.[93,94] Chronic infection with hepatitis B is also frequent among IDUs,[84] and although concurrent infection with hepatitis B, C and/or HIV is less common, these viral infections in combination can accelerate the course of liver disease and consequently present heightened risks of hepatotoxicity to those receiving LTBI treatment. Despite the increased risk of drug toxicity, many studies have shown that LTBI treatment can be safely administered to IDUs provided that their liver function tests and clinical status are carefully and regularly monitored.[95-97] While asymptomatic, low-grade elevations in liver function tests are not uncommon in individuals with viral hepatitis, a significant proportion of these people are still able to safely complete LTBI therapy. People with LTBI who have experienced complications with isoniazid or have a high baseline risk of hepatotoxicity could be considered for treatment with rifampin once the presence of active TB has been carefully excluded.

The benefits of LTBI therapy can be substantial, particularly for IDUs with HIV infection or other forms of immunosuppression. However, treatment adherence among currently active IDUs may be suboptimal and consequently can decrease the overall effectiveness of treatment. A systematic review of LTBI therapy among IDUs in Canada and the United States revealed that treatment completion rates ranged between 39% and 70%.[98] As with other vulnerable populations, incentives and enablers and/or directly observed therapy for LTBI can increase the likelihood of successful treatment completion.[98] Two US-based studies modeling the health and economic effects of programs dedicated to LTBI treatment in IDUs have shown that such programs can be cost-effective.[99,100] Given the potential risk of hepatotoxity due to a high rate of associated alcohol use and/or coinfection with viral hepatitis, and low rate of treatment completion, efforts to identify and offer LTBI screening and treatment should be reserved for those with a moderate or high risk of TB reactivation.

- **Current or past intravenous drug users should be offered LTBI screening and treatment up to age 65 if they have an underlying medical condition associated with moderate risk of reactivation, and should be offered screening at any age if they have a medical condition associated with a high risk of reactivation.**

  (Conditional recommendation, based on weak evidence)

- **Those at highest risk of reactivation should be considered for special measures to enhance adherence, such as directly observed LTBI treatment and/or incentives and enablers.**

  (Conditional recommendation, based on weak evidence)

TRAVELLERS

Travellers to countries with higher TB incidence are at risk of acquiring infection during travel. The risk increases with longer duration of travel and higher TB incidence in the destination country, and is also affected by the type of travel and the work done (if any) in these countries. Long-term travellers to countries with higher TB incidence have a similar risk of acquiring infection during their visit as the local population.[101] Risk is particularly elevated for travellers who work in health care.[101] Similarly, immigrants who return to their home countries to visit friends and relatives are at risk of exposure to TB infection and development of disease. Two U.K. studies in immigrants from the Indian subcontinent estimated that ~20% of cases of TB in the U.K. were due to recent travel to their countries of origin.[16,17] More recently, 56% of TB cases in the Moroccan immigrant population in the Netherlands were associated with recent travel to Morocco.[15]

The Committee to Advise on Tropical Medicine and Travel (CATMAT) has published guidelines on risk assessment and prevention of TB in travellers, including screening for and treatment of LTBI in travellers who make prolonged or high-risk trips.[78] These are summarized in Table 4 but have been modified to reflect the change in the definition of a high TB incidence country, from 15/100,000 smear-positive cases to 30/100,000 population of ALL TB cases. See http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-5/index-eng.php for additional information. For most travellers judged to require screening for LTBI, a single post-trip TST or IGRA (see Chapter 4) should be sufficient.[102] For individuals who are expected to undergo serial or repeated testing (e.g. health care workers), a pre-travel two-step TST is recommended (and IGRA is NOT recommended, see Chapter 4). Pre-travel testing is also recommended for people in whom the distinction between conversion and longstanding infection is particularly important, e.g. those at increased risk of treatment toxicity because of older age, alcohol consumption or liver disease.

(*Conditional recommendation, based on weak evidence)*

CONCLUSIONS AND RECOMMENDATIONS

The selection of people as suitable candidates for targeted LTBI screening and treatment is based on consideration of their risk of prior TB exposure and of reactivation, balanced against their risk of hepatotoxic effects and the likelihood of safe completion of treatment. To improve uptake of LTBI screening in immigrants, investment in TB education programs for patients and providers and in infrastructure is suggested, as well as programs that can be offered in a culturally sensitive manner with good access to interpreters. In the homeless population and injection drug users, patients with LTBI should be assessed for hepatitis comorbidities that may increase hepatotoxicity; incentives, enablers and directly observed therapy should be considered to achieve LTBI treatment completion for those who have immunosuppressive illness or are HIV positive. For a summary of specific recommendations for each group see Table 4.

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CHAPTER 14

TUBERCULOSIS PREVENTION AND CARE IN FIRST NATIONS, INUIT AND MÉTIS PEOPLES

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KEY MESSAGES/POINTS

- In Canada, the incidence rate of TB is higher among Aboriginal people than the foreign-born and Canadian-born non-Aboriginals, but the greatest burden of disease, as measured by the number of cases, occurs in the foreign-born.
- Status Indians in Manitoba and Saskatchewan and the Inuit in Nunavut have the highest incidence rates among Aboriginals in Canada.
- In the 1980s, after decades of decline, the incidence of TB among the Inuit began to level off. However, beginning in the late 1990s and continuing until 2010, rates increased, resulting in Canada's own "U-shaped curve of concern".
- Determinants of TB infection and disease in the Aboriginal people of Canada differ with respect to comorbidities, genetic factors, transmission factors and the social determinants of health when compared to the rest of Canada.
- Social determinants of health, including lack of food security, housing, health care access, education and income are seen with higher frequency in Aboriginal groups in Canada.
- Programmatic issues in TB prevention in Aboriginal groups in Canada that can be strengthened include strong TB partnerships with communities, increased community awareness, improving adherence to TB medications and underscoring the importance of effective contact investigation.
- According to the most recent statistics released in 2012, the current rate of TB among the Canadian-born Aboriginal population is 26.4 per 100,000. Across Canada rates of new active and retreatment TB cases for the Aboriginal population were as follows: North American Indian 22.2 per 100,000 (188 cases), Inuit 198.6 per 100,000 (116 cases) and Métis 7.5 per 100,000 (26 cases).
- In 2005, FNIHB set a long-term goal to reduce TB incidence to 3.6 per 100,000 among on-reserve First Nations and Inuit regions in Canada by 2015. Results to date suggest that this goal will not be met.

- To meet these goals and achieve a substantial reduction in rates of TB among Canadian-born Aboriginal peoples it seems likely that intensified and coordinated efforts using novel approaches will be necessary.

THE ABORIGINAL POPULATION OF CANADA

The *Constitution Act* of 1982 recognizes three major groups of Aboriginal people in Canada: First Nations (North American Indian), Métis and Inuit (see Appendix A, Glossary). Estimates from the 2006 Canadian census (data from the 2011 Census were not available at the time of publication) for the Aboriginal population were as follows: 1,172,790 people identified their ethnic origin as Aboriginal, 698,025 of these as First Nations/North American Indian, 389,780 as Métis and 50,480 as Inuit.[1] Of the total First Nations (FN) population, 564,870 people (81%) are registered according to the terms of the *Indian Act* of 1876 as Status Indians.[2] As of December 2011, these individuals are associated with over 600 bands, and 53% of registered FN individuals live on one of more than 1,000 reserves. The First Nations population resides primarily in Ontario and the western provinces.[3] The Inuit span four regions that constitute Inuit Nunangat (Inuit Homeland): Inuvialiut (Northwest Territories), Nunavut, Nunavik (Northern Québec) and Nunatsiavut (Labrador). The Métis are distinct from First Nations, Inuit and non-Aboriginal people and are of mixed Aboriginal and European ancestry. Little is said about the Métis in this chapter because routine surveillance data on Métis status are not systematically collected, and census-based population estimates of Métis are dependent upon self-identification.

Unique challenges exist in the prevention and control of tuberculosis (TB) in First Nations and Inuit populations. These include the wide dispersal of populations over large and remote geographic areas, jurisdictional issues in health care delivery, the imperative to deliver culturally appropriate care, and the prevalence of socioeconomic and biologic risk factors for TB, including poverty, malnutrition, poor housing, diabetes and renal disease.

HISTORICAL AND CULTURAL ASPECTS OF TB IN FIRST NATIONS AND INUIT POPULATIONS

North and South American human remains dating from the time of pre-European contact show anatomic and radiological evidence of mycobacterial disease, and *Mycobacterium tuberculosis* complex has been identified.[4] However, epidemic TB in Canadian FN and Inuit populations occurred after European contact in the 19th and 20th centuries. Recent work suggests that *M. tuberculosis* was dispersed across Canada by the fur trade.[5] This dispersal appears to have been associated with small populations of *M. tuberculosis* infected individuals existing at a relatively stable level until ecologic, political and economic factors led to expansion in the late 19th and early 20th centuries.

Social and environmental risk factors for the epidemic spread of TB in these populations included the movement of individuals to reserves, hamlets and residential schools. In addition to crowded living conditions, which favoured transmission of infection, malnutrition both on and off reserve fostered progression of infection to disease.[6-10] The story of the TB epidemic in FN and Inuit populations speaks of transgenerational loss and suffering.[6-10] Families and communities were disrupted as children, parents and grandchildren were sent to sanatoria throughout southern Canada for long periods of time, sometimes never to return. Survival was often accompanied by a legacy of emotional, psychological and physical “scars.” Those who work in prevention and care in the 21st century must be aware of the existence of a “collective memory” of the suffering associated with the TB epidemic in these populations.

EPIDEMIOLOGY OF TB IN ABORIGINAL POPULATIONS

The epidemiology of TB in Aboriginal populations in Canada is described in Chapter 1, Epidemiology of Tuberculosis in Canada. The following points deserve emphasis:

- In Canada, the incidence rate of TB is higher among Aboriginal people than the foreign-born and Canadian-born non-Aboriginals, but the greatest burden of disease, as measured by the number of cases, occurs in the foreign-born.[11]
- While the incidence rate of TB in FN and Inuit populations as a whole is higher than in Canadian-born non-Aboriginal populations, there are wide variations in rates among regions and communities.[11,12]
- Status Indians in Manitoba and Saskatchewan and the Inuit in Nunavut have the highest incidence rates among Aboriginals in Canada.
- TB incidence rates have remained stagnant in the FN population over the past decade.
- In the 1980s, after decades of decline, the incidence of TB among the Inuit began to level off. However, beginning in the late 1990s and continuing until 2010, rates increased, resulting in Canada’s own “U-shaped curve of concern.” [13]
- TB is proportionately more common among the very young in Canadian-born Aboriginal populations than in Canadian-born non-Aboriginals, in whom a greater proportion of cases is seen in older age groups.[11]
- In western Canada, significantly greater clustering of TB cases has been noted in Canadian-born Aboriginal groups than in non-Aboriginal groups.[14]
- Estimates of the prevalence of latent tuberculosis infection (LTBI) in Canadian-born Aboriginal people vary widely (0% to 50%) because of the heterogeneous nature of the study groups. See Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for further details.
- In some areas of Canada, the incidence of TB among FN persons living off-reserve, either in communities adjacent to reserves or in the core area of cities (which may function as “urban reserves”), is equal to the incidence among those living on-reserve.[15]

RESPONSIBILITY FOR TB PREVENTION AND CONTROL IN FIRST NATIONS AND INUIT POPULATIONS

(From Health Canada's Strategy Against Tuberculosis for First Nations On-Reserve[16])

Provinces and territories have the legislated authority for TB prevention and control within their jurisdictions. In the territories, ultimate responsibility for TB prevention and care for the entire population rests solely with the territorial governments. In contrast, within the provinces, TB prevention and care for FN and Inuit is a shared responsibility that varies by region according to each region's level of collaboration with Health Canada's First Nations and Inuit Health Branch (FNIHB) regional offices, provincial governments and FN or Inuit organizations/communities. These collaborations are influenced by the respective provincial public health legislation. For the Inuit communities within the geographic boundaries of provinces, such as in Nunavik in Northern Québec and Nunatsiavut in Labrador, the provinces are responsible for TB prevention and control. In Nunavik, Québec provides all TB services. In Nunatsiavut, the provincial government of Newfoundland and Labrador offers some services, and FNIHB provides funding to the Nunatsiavut Government to complement the provincial services provided.

DETERMINANTS OF TB INFECTION AND DISEASE IN ABORIGINAL POPULATIONS

Determinants of infection and disease are associated with the agent (*M. tuberculosis)*, the host (affected person) and the environment (social, economic, cultural and political). These factors may affect the risk of infection, disease or both. Determinants may be causally linked (risk factor) with infection and/or disease, or linked through an association (risk marker) that is not necessarily causal. Behaviours such as alcohol and drug abuse may be considered host determinants, but they also relate to the environment as it applies to health.

AGENT

In Manitoba, central nervous system TB is associated with Aboriginal ethnicity and a particular strain, identified by restriction fragment-length polymorphism, which is prevalent in Aboriginal communities in that province.[17] Cytokine assays and studies of *in vivo* mouse models suggest that this strain is hypervirulent compared with other clinical isolates.[18,19] In Alberta there is no evidence that the Beijing/W family of strains, imported from the Western Pacific, is associated with greater transmission, clustering or penetration into the Aboriginal population of the province.[20]

HOST

Comorbidities

The following are recognized risk factors for the development of active TB disease in relation to the Canadian Aboriginal population (details regarding the risk factors mentioned below, including the risk of active TB development associated with each, are described in Chapter 6, Treatment of Latent Tuberculosis Infection).

- **HIV infection** is increasing in incidence and prevalence in Aboriginal populations[21] and is the strongest known risk factor for the development of disease in those with remotely or recently acquired TB infection. HIV status was reported to the Public Health Agency of Canada for 17% of Aboriginal Canadian cases in 1997, rising to 68% by 2010. The proportion of TB cases that have been HIV tested and reported has been increasing almost certainly as a result of two very explicit national advisories, the introduction of highly active antiretroviral therapy and the demonstrated feasibility of using an "opt-out" approach to HIV testing in TB patients.[22] In Alberta, where universal HIV testing of TB patients has been in place since 2003, HIV/TB coinfection was significantly greater in middle-aged (35-64 years) than young adult (15-34 years) patients and in Aboriginal and sub-Saharan African than Canadian-born non-Aboriginal people and immigrants to Canada from other regions combined.[23] On the prairies, two HIV exposure categories appear to predominate among Aboriginal peoples: injection drug use and heterosexual sex.[24] The connection between HIV, ulcerogenic sexually transmitted infection and TB has all the features of a syndemic, the latter defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease.[25]

- **Diabetes mellitus** – the age-adjusted prevalence of diabetes (predominantly type 2) in First Nations populations is 3.3 times higher among males and 5.3 times higher among females than in the Canadian population as a whole.[26] An increasing prevalence of diabetes has been noted among the Inuit.[27] Overall rates of diabetes were higher in the Aboriginal population in Alberta, although increases in the incidence and prevalence appear to be lower, than in the general population.[28]

- **End-stage renal disease** – the age-standardized incidence of chronic renal failure among Aboriginal people is 2.5 to 4.0 times higher than the national rate, primarily because of diabetes mellitus and glomerulonephritis.[29]

- **Undernutrition** – occurs in subpopulations of Aboriginal populations.[30-32]

- **Tobacco use** – the Canadian Aboriginal population has a higher prevalence rate of recreational tobacco use than the rest of the Canadian population. According to FNIHB of Health Canada, 59% of on-reserve FN and 58% of Inuit smoke.[33] In 2006, 31% of Métis adults smoked daily, and 67% of Inuit >15 years smoked daily, as compared with the Canadian average of 15% for the same year.[34]

- **Alcohol and drug abuse** – Aboriginal youth have high rates of binge drinking and marijuana use.[35-39] Alcohol and drug abuse occur in both Aboriginal and non-Aboriginal populations. In the Aboriginal population, in particular, substance abuse must be understood within a socioeconomic, political and historical context in order to avoid stigmatization.

GENETIC FACTORS

- Linkage between susceptibility to symptomatic TB disease and chromosome 2q35 loci near the NRAMP1 (natural resistance associated macrophage protein 1) gene was demonstrated in a large Alberta Aboriginal family undergoing an epidemic of tuberculosis.[40]Studies of Dene and Cree First Nations have shown a higher frequency of single nucleotide polymorphisms, affecting cytokine and vitamin D receptor expression, which are associated with increased risk of TB disease.[41,42] A recent study also suggests that Mycobacterium-induced toll-like receptor signaling and resulting downstream cytokine responses may be differentially regulated in the Dene compared with Caucasians.[43]

ENVIRONMENT

Social determinants of health, TB and Aboriginal peoples

The World Health Organization (WHO) defines social determinants of health as the conditions in which people are born, grow, live, work and age (http://www.who.int/social_determinants/en/). Socioeconomic inequalities, high levels of population mobility and population growth give rise to unequal distribution of social determinants of TB.[44] These factors are seen with higher frequency in the Aboriginal groups in Canada. Some of the key social determinants of health related to TB include 1) food insecurity and malnutrition, 2) poor housing and environmental conditions and 3) financial, geographic and cultural barriers to health care access.

Food security

- Food security, as defined by the WHO, occurs when "all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life." [45]
- Inuit in Nunavut experience a high prevalence of food-insecure households.[46] Compounding the problem of inadequate access to foods is the significantly higher cost of food in remote parts of Canada, where many Canadian-born Aboriginal people reside.[47]
- Canadian-born Aboriginal people continue to experience a nutritional transition that has occurred over the years from traditional foods obtained from the land that they inhabit to market foods imported from elsewhere. Significant loss of important nutrient intake due to the shift to market foods has increased the risk of diet-sensitive chronic diseases.[48,49]
- Food insecurity and decreased traditional food intake[49] may lead to specific nutritional deficiencies that can also increase the risk of TB, such as vitamin D deficiency.[50] Vitamin D deficiency, which is prevalent in First Nations and Inuit populations,[51,52] has been associated with increased risk of TB disease.[53,54] A recent study among the Dene showed that vitamin D supplementation enhanced innate immune macrophage responses to *M. tuberculosis* lipoprotein in Caucasian but not in Dene participants.[43]

One recent randomized clinical trial conducted in patients from across the United Kingdom with smear-positive TB did not show a significant difference in the time to sputum culture conversion among all comers who received vitamin D supplementation versus placebo; however, a significant difference was noted in the time to sputum conversion in people with the tt genotype of the *TaqI* vitamin D receptor polymorphism.[55] In a systematic review of all trials using nutritional supplements for patients being treated for active TB, routinely supplementing at or above recommended levels of micronutrients, including vitamin D, in active TB did not result in any significant clinical benefits.[56,57]

- Smoking, alcohol and drug abuse is sometimes associated with poor nutrition, which can also increase the risk of malnutrition as a consequence of deficiency of key micronutrients.

Housing

Aboriginal communities are at high risk of living in houses that are overcrowded and in disrepair.[58] Higher TB incidence was shown to be associated with a higher average housing density among First Nations.[59] Furthermore, another study showed an association between the number of people living in a house and self-reported TB in First Nations.[60] In communities with new cases of infectious TB disease, an increased number of individuals will be exposed if there is overcrowding and cramped living conditions, along with poor ventilation in some cases, leading to propagation of infection and disease.

Health care access

- Geography – the incidence of TB is higher in Canadian Aboriginal communities that are considered isolated, as defined by access to airplane, road, telephone and radio service.[61] Isolated communities maybe faced with delays in the transportation of patients and diagnostic specimens because of logistical challenges such as inclement weather.
- Staff – understaffing,[62] high staff turnover rates and limited knowledge of TB by some casual and temporary health care staff are common in many remote communities. Acute health care needs often claim the attention of overworked staff in preference to public health programs, including TB control.
- Diagnostic services, including but not limited to smear microscopy and radiologic equipment, may be limited in isolated communities.
- Cultural barriers – lack of Aboriginal health care staff results in lack of traditional knowledge integration. Language barriers often exist between health care staff and community members, limiting access to care.[63]

Education/income

- A strong socioeconomic gradient is present with an increased risk of TB for people living in poverty and/or social deprivation within countries and within communities.[63]
- Poverty increases the risk of being exposed to all of the aforementioned TB risk factors; that is, people who experience poverty have a higher likelihood of being exposed to food insecurity, poor housing conditions and limited health care access.

- For example, First Nations individuals with an annual income <$10,000 are less likely than others to use health services.[64]

Furthermore, poverty increases the risk of being exposed to many of the biological risk factors such as smoking, alcohol, drug use and malnutrition.[63]

Transmission Factors

Broadly speaking there are only two ways to eliminate TB: to interrupt transmission altogether and to prevent active TB disease in those with latent TB infection. On the prairies and in the territories, where the incidence of TB in Status Indians is particularly high, three independent lines of evidence point to the importance of ongoing transmission – a high index of transmission, determined by calculating the average number of culture-positive pulmonary cases generated by a single source case,[12] high rates of disease in children[65] and a high proportion of clustered *M. tuberculosis* isolates.[66,67] Preliminary data from the Determinants of TB Transmission Project[68] (a mixed-method study of TB transmission on the prairies) found that 90% of the Canadian born “potential transmitters” (adult culture-positive pulmonary cases) were of Aboriginal origin.[69]

PROGRAMMATIC ISSUES IN TB PREVENTION AND CARE IN ABORIGINAL POPULATIONS

In many provinces, FN populations are highly mobile in terms of travel between reserves and from reserve to urban areas.[35] This presents challenges to contact investigation and case management, requiring communication and coordination between health jurisdictions. Partnership and collaboration with the community is important for TB prevention and care. Health care workers must be sensitive to the historical and current concerns of their patients. Information sharing and control over health resources are frequent areas of concern for Aboriginal people in the context of the implementation of TB control (and other health care) programs.[70] Lack of knowledge about TB is strongly associated with negative attitudes about, and a worse experience of, the disease.[71] A proactive TB health education program that makes use of lay community resources, such as individuals who have recovered from TB, their family members, elders and community health workers, is required in order to achieve a successful prevention and control program in Aboriginal communities. In 2012, Health Canada produced a renewed TB strategy for First Nations On-Reserve,[72] which aims to improve program delivery and performance measurement while establishing standardized, culturally appropriate TB prevention and care services, including community-based initiatives.

ADHERENCE TO TB MEDICATIONS IN ABORIGINAL POPULATIONS

Adherence or nonadherence to treatment of latent and active TB is not consistently associated with age, sex or race.[73] Adherence is a task-specific behaviour, not a personality trait.[74] The terms “adherence” and “nonadherence” may only be used when the patient and provider have agreed to a care plan. Establishing this initial agreement is a critical and often overlooked step.

Various criteria that trigger closer supervision of patients with active TB disease have been suggested in the literature, on the basis of missed appointments or home visits, pill counts in the case of self-administered therapy, urine isoniazid testing or concern voiced by the health worker.[73] Barriers to adherence derive from a complex interaction between the health system, and personal and social factors. Suggested interventions[75] to remove barriers to adherence at the health system level are as follows:

- Enhanced programs of directly observed therapy and directly observed preventive therapy that bring care closer to the patient (e.g. to the home), use incentives (e.g. food) and enablers (e.g. vouchers), assist the patient to deal with competing life priorities (e.g. work, school), are holistic and provide efficient care (e.g. through development of reminder and follow-up mechanisms, simplification of protocols, reduction of referral times and rigorous tracking of migrating patients).
- Provision of “permeable” care that does not require negotiation on the part of those who lack power, voice and material means. Permeable health services are emotionally/culturally “accessible”; they work at making patients feel valued and respected, and the focus of care.
- Aboriginal community health workers, preferably from the local community/area, function as educators, advocates and cultural brokers, ensuring that staff are knowledgeable and well trained to understand and address patient needs, and are given support (e.g. protected workload).

Interventions[75] shown to be effective at the personal and social levels include the following:

- Incorporate indigenous beliefs about causation and cure into the program, including traditional healing practices, as guided by patient wishes. Ensure that the key language concepts that are used are developed in partnership with Aboriginal people.
- Use creative multimedia methods to bring life to the educational process.
- Effective education conveys cognitive messages but also affective messages of empathy, openness, concern and respect. The messenger is the message.
- TB therapy will not be successful if it competes with addictions. Use harm-reduction methods.
- Use techniques from other health models (e.g. identify sponsors/mentors). Engage family and community groups for patient support. Utilize verbal or written “contracts” if appropriate.

Cases of nonadherence to TB care frequently highlight potential conflicts between personal and collective rights. In the context of Canadian indigenous communities, an open discussion of these issues is encouraged in order to determine solutions that are culturally and legally sensitive and appropriate.[75]

THE IMPORTANCE OF EFFECTIVE CONTACT INVESTIGATION IN ABORIGINAL COMMUNITIES

Successful contact investigation is extremely important in Aboriginal communities, not only because of the burden of active TB disease but also the remote location of many communities, limited access to health care and chronic under-housing, all of which can facilitate transmission.[76] General contact investigation guidelines[4-6] (see also Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control) may be of limited use as they are not specific to the unique social structure and environment of Aboriginal communities.[77-79] There are other inherent challenges to conducting effective contact investigation in some settings, including language and cultural barriers, as well as the social stigma associated with TB. Inadequate contact investigation leads to missed opportunities to identify secondary active cases and ensure that infected contacts are identified and treated.[80]

Because of the limitations of routine contact investigation and the negative consequences of inadequate contact investigation, new approaches are under investigation and, in some cases, in use to establish effective TB control in those people and communities at greatest risk. A recent publication detailed some of these newer methodologies, including social network analysis (SNA), geographic information systems (GIS) and genomics, in the context of TB contact investigation in low-prevalence countries.[81] How these approaches could be implemented in Aboriginal communities requires investigation. SNA methods, alone and in combination with conventional and molecular epidemiology, have been used to examine TB clusters and outbreaks both retrospectively and prospectively in both Aboriginal and non-Aboriginal settings.[82-85] Network methods have also clearly documented that locations are key to contact investigation. With respect to Aboriginal TB control, network analysis has helped an understanding of outbreak boundaries, locations of transmission and the risk of TB in contacts in remote communities in Manitoba.[85] GIS techniques are used to visualize data involving distance and location.[86]. These techniques have been used to examine the distribution of TB cases, risk factors for acquiring disease and the relationship of TB to the surrounding environment.[87-89] In a recent outbreak investigation involving TB in Aboriginal people, genomic (bacterial genetics) data from the clustered *M. tuberculosis* organisms were used to identify transmission events and confirm multiple simultaneous outbreaks within the community.[89] This investigation integrated clinical data, SNA and genomics to better characterize an outbreak that had significantly affected community members. It also confirmed that social factors played a larger role in the outbreak than organism virulence.

According to the most recent statistics released in 2012,[90] the current rate of TB among the Canadian-born Aboriginal population is 26.4 per 100,000. Across Canada rates of new active and retreatment TB cases for the Aboriginal population were as follows: North American Indian 22.2 per 100,000 (188 cases), Inuit 198.6 per 100,000 (116 cases) and Métis 7.5 per 100,000 (26 cases). In 2005, FNIHB set a long-term goal to reduce TB incidence to 3.6 per 100,000 among on-reserve First Nations and Inuit regions in Canada by 2015.[16] Results to date suggest that this goal will not be met (see Chapter 1, Epidemiology of Tuberculosis in Canada). To meet these goals and achieve a substantial reduction in rates of TB among Canadian-born Aboriginal peoples it seems likely that intensified and coordinated efforts using novel approaches will be necessary.

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CHAPTER 15

PREVENTION AND CONTROL OF TUBERCULOSIS TRANSMISSION IN HEALTH CARE AND OTHER SETTINGS

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KEY MESSAGES/POINTS

- The scope of this chapter includes hospitals; other health care settings; and residential and community care settings.
- Health care organizations and individual health care workers (HCWs) have a shared responsibility to apply effective tuberculosis infection prevention and control measures.
- The risk of health care associated transmission of *M. tuberculosis* varies with the type of setting, HCW occupational group, patient care activity, patient/resident/client population and the effectiveness of tuberculosis (TB) infection prevention and control measures.
- The most important contributors to health care associated transmission of *M. tuberculosis* are patients with unrecognized, respiratory TB disease. Hence, the most important element of any TB management program is rapid diagnosis, isolation and start of effective therapy for these patients.
- Remote and isolated health care settings in which at-risk populations are cared for should have access to resources to facilitate implementation of essential administrative, environmental and personal protective controls.

MAJOR RECOMMENDATIONS

- All health care settings should have a TB management or infection prevention and control program supported at the highest administrative level. This involves a hierarchical approach to infection prevention and control measures categorized as administrative, environmental and personal protection controls.

- Airborne precautions should be initiated immediately for everyone with suspected or confirmed respiratory TB disease admitted to a hospital. The criteria for discontinuation of airborne precautions include the following: establishment of an alternative diagnosis, clinical improvement, adherence to effective therapy, sputum smear and/or culture conversion, and drug-susceptibility tests that indicate fully sensitive organisms or low clinical suspicion of drug resistance.
- U.S. National Institute for Occupational Safety and Health (NIOSH)-certified respirators (N95 or higher filter class) should be used by HCWs providing care for or transporting patients with suspected or confirmed respiratory TB disease.
- Masks should be used by patients/people with suspected or confirmed respiratory TB disease when outside an airborne infection isolation room.
- Baseline tuberculin skin testing (TST) is recommended for all HCWs in health care and community care settings. Recommendations for periodic and serial (repeated) TST for HCWs vary with the setting. Interferon gamma release assays are not recommended for serial testing.

INTRODUCTION AND GENERAL PRINCIPLES

While the incidence of tuberculosis (TB) in Canada is generally low, exposure to people with unsuspected active respiratory TB disease followed by transmission of *M. tuberculosis* does occur in health care settings.[1,2] A survey of TB control services in all Canadian provinces and territories in 2008 reported a total number of 1,562 cases of active TB disease and 11,935 people treated for latent TB infection (LTBI).[3] Approximately 50% of people with active TB disease in this survey were admitted to hospital for an average of 21 days. Although the overall number of people admitted to Canadian health care facilities with active TB disease is low, both health care and community settings (e.g. homeless shelters and drop-in centres) serving at-risk populations continue to pose a hazard for the transmission of *M. tuberculosis*.[4-6] Populations at risk of active TB disease include people with a history of active TB disease; staff and residents of homeless shelters; urban poor; staff and inmates of correctional facilities, including previously incarcerated people; injection drug users; people born in Canada prior to 1966; Aboriginal Canadians; people infected with human immunodeficiency virus (HIV); those born or previously residing in countries with a high TB incidence (in Asia, Eastern Europe, Africa and Latin America); and HCWs serving these at-risk groups.[7-10]

Literature reviews show that the incidence of LTBI among HCWs increases with certain occupational risk factors, including number of years working in health care settings where patients with active respiratory TB are cared for, providing direct care to those with respiratory TB disease, working in emergency departments or medical wards, providing services for patients infected with HIV, and participating in aerosol-generating medical procedures (e.g. sputum induction and bronchoscopy) on individuals with TB.[5,11,12]

In hospitals, clinics, community care centres and correctional facilities, where people congregate and share indoor air (in the same room or via the building ventilation system), the risk of *M. tuberculosis* transmission can be increased if ventilation and other infection prevention and control measures are inadequate. In addition, exposure to people with active, undiagnosed and untreated respiratory TB disease has resulted in high rates of positive TST results in HCWs.[1,2,5,13] Reported TB outbreaks within health care facilities are often due to failure to implement appropriate TB infection prevention and control measures.[4] These observations have heightened concerns and resulted in the formulation of recommendations for the prevention of health care associated transmission of *M. tuberculosis* to HCWs, patients and visitors.[7,14,15] A review of the literature suggests that implementation of a full hierarchy of infection prevention and control measures in many hospitals, as recommended in published guidelines, has led to successful reduction in *M. tuberculosis* transmission[5] and is therefore considered integral to preventing transmission in hospitals, other health care settings, and residential and community care facilities.

This chapter reviews factors that determine or affect transmission of *M. tuberculosis* within hospitals, other health care settings, and residential and community care settings while focusing on measures to prevent transmission. The term HCWs refers to individuals in health care settings who provide health care or support services, such as physicians, nurses, nurse practitioners, paramedics, emergency first responders, respiratory therapists, unregulated health care providers, clinical instructors, students, volunteers, and housekeeping, dietary and maintenance staff.[16]

Recommendations are based, as much as possible, on published evidence to date. However, the evidence applicable to infection prevention and control of *M. tuberculosis* that is based on randomized controlled trials, generally considered the strongest level of evidence, is limited. This type of study design is generally not feasible or practical when analyzing risk factors or situations involving natural exposure (e.g. TB outbreaks). As a result, the majority of the available evidence comes from observational studies, such as cohort or case-control studies, and from qualitative analyses of outbreaks. This chapter cites the evidence base from these primary studies, as well as from several published literature reviews[5,9,17] and from a systematic review that includes recommendations from the US Centers for Disease Control and Prevention (CDC).[7] Recommendations are itemized in boxes, tables or algorithms with the strength of the recommendation and the quality of its evidence indicated (see Preface for explanation of rating). Where detailed information is beyond the scope of this chapter or further references are of interest, refer to the relevant chapter(s) in this book.

DETERMINANTS OF TRANSMISSION OF *MYCOBACTERIUM TUBERCULOSIS*

Aerosolization of infectious *M. tuberculosis* bacteria occurs when individuals with respiratory TB disease cough, sneeze, sing, play wind instruments or speak. Cough-inducing procedures (e.g. bronchoscopy, sputum induction) as well as some laboratory and autopsy procedures can also cause aerosolization of mycobacteria. Once infectious *M. tuberculosis* bacteria are aerosolized, they are carried throughout a room or building by air currents and can be inhaled by another individual, with the possibility of resulting in TB infection. Although the risk of transmitting *M. tuberculosis* is highly variable, the presence of certain factors (see Table 1) predicts an increased transmission risk. In general, the more of these factors present, the greater the risk of *M. tuberculosis* transmission. For further discussion on determinants of *M. tuberculosis* transmission, see Chapter 2, Transmission and Pathogenesis of Tuberculosis.

Table 1. Factors associated with increased risk of transmission of *M. tuberculosis*

Patient factors	Diagnostic/laboratory risk factors	Treatment factors	Environmental factors
Respiratory (pulmonary or laryngeal) disease* Number of patients with respiratory TB disease* Respiratory secretions that are acid-fast bacteria (AFB) smear positive Presence of cough HIV infection* Atypical manifestations of disease	Cough-inducing procedures, e.g. sputum induction, bronchoscopy or administration of aerosolized therapies Delayed diagnosis* Autopsy and preparation of pathology specimens Improper handling of laboratory specimens containing *M. tuberculosis*	Incorrect, ineffective or no therapy* Delayed treatment	Inadequate ventilation to remove airborne infectious *M. tuberculosis** Inadequate TB infection prevention and control measures for containment of *M. tuberculosis* Duration of exposure and proximity to infectious patient* Overcrowding* Absence of sunlight High humidity

*These factors are discussed below.

RESPIRATORY (PULMONARY OR LARYNGEAL) TB DISEASE

People with laryngeal TB disease show the highest infectivity of all forms of TB. While most people with nonrespiratory TB alone are not infectious, it is important to exclude concomitant respiratory involvement, which occurs in a significant proportion of those with nonrespiratory TB.[18] Pleural TB disease in the absence of concomitant respiratory involvement is not considered infectious, see Chapter 2, Transmission and Pathogenesis of Tuberculosis.

NUMBER OF PATIENTS WITH RESPIRATORY TB DISEASE

It is generally understood that the number of hospitalized patients with respiratory TB disease, particularly before diagnosis and treatment, is an important determinant of institutional transmission risk. Results from one study involving 17 acute-care hospitals in Canada showed that with effective implementation of infection prevention and control measures the number of patients might not be the best indicator of transmission risk. In this study, institutional risk of *M. tuberculosis* transmission was found to be better correlated with delayed diagnosis and treatment.[19] Thus, prompt diagnosis followed by early isolation and appropriate treatment has a mitigating effect on this risk factor.[5]

HIV INFECTION

There is no clear evidence that people infected with *M. tuberculosis* are more infectious if they are coinfected with HIV. However, there will often be rapid development of active TB disease,[20] and HIV-related TB disease will often have atypical clinical manifestations, leading to delayed diagnosis. The increased risk of *M. tuberculosis* transmission by this population is related to the potential for delayed isolation if the index of suspicion for respiratory TB disease is low. See also Chapter 10, Tuberculosis and Human Immunodeficiency Virus.

DELAYED DIAGNOSIS

See "Identification of patients with active respiratory TB within hospitals" in this chapter.

INCORRECT, INEFFECTIVE OR NO THERAPY

The administration of incorrect or ineffective therapy or no therapy at all contributes to the risk of transmission. See Chapter 5, Treatment of Tuberculosis Disease.

INADEQUATE VENTILATION

The exchange of indoor air with outdoor air reduces the risk of infection by diluting the concentration of viable airborne *M. tuberculosis* bacteria present.[1] Theoretically, the risk of transmission should decrease exponentially with increasing fresh-air ventilation.

DURATION OF EXPOSURE AND PROXIMITY TO INFECTIOUS PATIENT

The risk of TB infection varies with duration of exposure, form of tuberculous disease and type of patient care activity. In one study, an hour of exposure during bronchoscopy on a patient with unrecognized smear-positive disease resulted in a 25% risk of infection,[12] and in another study exposure to a patient with laryngeal TB resulted in a 1.7% risk of infection per hour.[21] Even when the relative risk of infection is low, repeated exposure can lead to a higher cumulative risk. For example, if a HCW is exposed for 1 hour each week, the cumulative risk can approach 100% after 10 years of repeated exposure.

OVERCROWDING

Overcrowding contributes to transmission in settings like homeless shelters and correctional facilities. The relative importance of select factors (such as overcrowding, duration of exposure and proximity to infectious people in a confined space) to *M. tuberculosis* transmission has not been quantitatively described in the literature, but some reports suggests that their impact is highly variable.[22]

RISK CLASSIFICATION

HEALTH CARE SETTINGS

The risk of health care associated transmission of *M. tuberculosis* to HCWs, patients (or residents) and visitors varies with the type of setting, occupational group, effectiveness of TB infection prevention and control measures, and patient/resident population.[7] A review of the community profile of TB disease, as well as the risk category of the health care facility and unit, can be used to conduct facility and/or unit risk assessments. This provides a framework for institutions to predict whether their workers are at increased risk of TB exposure so that the necessary infection prevention and control strategies can be implemented.

An approach to classifying risk of *M. tuberculosis* transmission in health care settings is described in Table 2. The risk categories presented have been modified from previous classifications[4,23] and are based upon review of the available literature.[7] While the number of people with respiratory TB disease in a facility during a year is considered a key determinant of transmission risk, the likelihood of exposure to any one patient or resident can vary considerably among facilities. To account for this, the classification below is based on the number of active patient or resident beds and number of cases of respiratory TB disease diagnosed in the facility in a typical year.

Table 2. Risk classification for health care settings

Risk category	Facility size	Number of active TB cases present annually
Low	Hospitals: ≥200 beds	<6
	Hospitals: <200 beds	<3
	Long-term care institutions including homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre	<3
Not considered low	Hospitals: ≥200 beds	≥6
	Hospitals: <200 beds	≥3
	Long-term care institutions (as listed above)	≥3
	Infirmaries in correctional facilities*****	≥3

*Correctional facilities that have never reported active TB cases can be considered low risk.

HCW ACTIVITIES

Patient care activities performed by HCWs are associated with varying degrees of exposure risk and subsequent infection with *M. tuberculosis* (see Table 3). This risk increases with the duration of exposure and higher amounts of airborne mycobacteria. As a result, it is recommended that HCWs perform a risk assessment prior to interactions with people suspected of or confirmed as having active TB disease.[16] This risk assessment involves evaluating the likelihood of exposure to *M. tuberculosis* for a specific patient care activity, with a specific patient, in a specific environment and under particular conditions. This is referred to as a point-of-care risk assessment and is described in a recent publication from the Public Health Agency of Canada (PHAC).[16] The assessment informs HCWs' decisions regarding the appropriate infection prevention and control measures needed to minimize the risk of exposure for themselves, other HCWs, patients and visitors.

Table 3. Risk categories for activities performed by health care workers

High-risk activities	Intermediate-risk activities	Low-risk activities
Cough-inducing procedures (such as sputum induction) Autopsy Morbid anatomy and pathology examination Bronchoscopy Mycobacteriology laboratory procedures, especially handling cultures of *M. tuberculosis*	Work requiring regular direct patient contact on units (such as emergency departments) where patients with respiratory TB disease may be present[*] Work in pediatric units where patients with TB may be admitted[†] Cleaning of rooms of patients with respiratory TB disease	Work requiring minimal patient contact (such as clerical, reception and administration) Work on units where patients with respiratory TB disease are unlikely to be present[‡]

[*] This includes work done by all HCWs in these units.

[†] Pediatric patients with respiratory TB disease should be considered infectious until infectiousness is ruled out by radiography and negative acid-fast bacteria sputum smears in patient, parents or caregivers. See "Isolation considerations for pediatric patients" in this chapter and Chapter 9, Pediatric Tuberculosis.

[‡] Classification of such units as low risk may be inaccurate if the population they are serving has a high incidence of TB (e.g. patients born or previously residing in countries with a high TB incidence or other at-risk populations). Some of the longest delays in diagnosis may occur in such settings.

LABORATORY PERSONNEL HANDLING *M. TUBERCULOSIS*

There are risks associated with handling *M. tuberculosis* in the laboratory that are not typically present in health care settings. Compared with the general population, laboratory HCWs have been found to have a greater risk of acquiring LTBI.[7] Although this risk stems mainly from aerosol formation during specimen or isolate manipulation, other mechanisms of transmission have been described in this setting. At the time of publication of these Standards, PHAC's Laboratory of Biosafety and Biosecurity was in the process of preparing a biosafety guideline, *Mycobacterium tuberculosis* Complex (MTBC) Biosafety Directive. See Appendix D for details on laboratory standards. Recommendations on safe laboratory procedures, training programs, infection control plans, respiratory protection, TST screening for personnel and safe transportation of samples are also available from other sources.[7,24,25]

PREVENTION AND CONTROL OF TRANSMISSION OF *M. TUBERCULOSIS*

Current recommendations for the prevention of health care associated transmission of *M. tuberculosis* involve a hierarchical approach to infection prevention and control measures, including the following:

- **Administrative controls** – institutional policies or measures that aim to reduce the time between the arrival of people with respiratory TB disease at a health care facility, diagnosis of their condition and placement in an airborne infection isolation room (AIIR). The purpose of these policies is to provide overarching protection for all HCWs, patients and visitors in a facility. Administrative control measures include occupational health programs incorporating skin testing of HCWs for LTBI after exposure and at regular intervals, access to treatment of LTBI, exclusion of HCWs with respiratory TB disease, facility and unit risk assessments, as well as a HCW education program. Details on performing a risk assessment and on HCW education can be found elsewhere.[7,16]
- **Environmental (engineering) controls** – environmental measures to reduce the likelihood of exposure of HCWs, other patients and visitors to viable airborne *M. tuberculosis*. These include mechanical ventilation systems (to supply clean air) in patient care areas, use of ultraviolet germicidal irradiation (UVGI) and high-efficiency particulate air (HEPA) filters.
- **Personal protection controls** – measures directed to individual HCWs either to prevent infection (such as use of respirators) or to prevent disease if infected (such as detection and treatment of LTBI).

Each control measure is further explained below.

ADMINISTRATIVE CONTROLS WITHIN HOSPITALS

RECOMMENDATIONS

(Conditional recommendations, based on very weak evidence)

All hospitals, regardless of risk category, should have a TB Management Program (or TB Infection Prevention and Control Program) supported at the highest administrative level with components detailed below. This program may be facilitated through existing infection prevention and control programs with administrative responsibility clearly delineated.

Other health care settings may refer to the hospital TB Management Program to identify procedures that are applicable to the setting.

TUBERCULOSIS MANAGEMENT PROGRAM

The goal of a TB management program is to prevent *M. tuberculosis* transmission to HCWs, patients and visitors.

RISK ASSESSMENT

The first step of an effective TB management program in a hospital or other health care setting should be to perform an organizational risk assessment in order to decrease the risk of patient and HCW exposure to and acquisition of *M. tuberculosis*. The exposure risk for HCWs engaged in different activities should be evaluated during this assessment. For further information on an organizational risk assessment, see a recent PHAC publication.[16]

In hospitals of all risk categories, the following features should be in place as components of the TB management program:

- Policies and procedures should clearly delineate administrative responsibility for developing, implementing, reviewing and evaluating various program components. The evaluation should include quality control and audits for all components of administrative, environmental and personal protection controls. Personnel with responsibility for the program within the facility should be designated.
- Policies and procedures should be in place for rapid identification, isolation and treatment of patients; reduction of health care associated transmission through environmental controls; and protection of staff through appropriate use of personal protective equipment, education and TST.
- An annual review of the indices of health care associated transmission should be done. This includes (i) TST conversion rates among HCWs; (ii) the total number of people with respiratory TB disease admitted annually; (iii) the number of occupational exposure episodes (i.e. admitted individuals with respiratory TB disease who were not placed under airborne precautions while receiving care); and (iv) the number of previously admitted patients whose TB was diagnosed only at autopsy.
- An annual summary of the clinical, epidemiologic and microbiologic features of patients whose TB is diagnosed within the hospital should be made available to HCWs caring for these patients. This will increase awareness of which patients in the population served are at risk of respiratory TB disease and the clinical manifestations.
- Additional considerations (such as higher index of suspicion or increased vigilance to prevent transmission before diagnosis) are recommended when caring for immunocompromised patients, whose infection may carry a higher risk of progression from LTBI to active TB disease. This includes patients in oncology, HIV and haemodialysis units or clinics.

In hospitals that are not considered low risk (Table 2), the following additional items should be in place as components of the TB Management Program:

- The hospital Infection Prevention and Control Committee (or other appropriate existing committee) should be given responsibility for the TB management program. Committee members should include people with day-to-day responsibility for infection prevention and control. There should also be representation from senior administration; occupational health and safety; laboratory, nursing and medicine; and other health disciplines or groups as needed (e.g. respiratory technology, public health, central supply, housekeeping, laundry, pharmacy, physical plant and maintenance).

In low-risk hospitals (Table 2), the following additional items should be in place as components of the TB management program:

- The TB management program may consist of screening protocols for diagnosis in patients with symptoms of respiratory TB disease and pre-arrangement to transfer all such patients to another centre where appropriate environmental measures are available.
- In hospitals with a transfer-out policy, there should be at least one separate, well-ventilated area[26] or a single room with the door closed, away from high-risk patients,[16] where patients can be maintained until they are transferred.
- Hospital administrators in collaboration with appropriate jurisdictional authorities should coordinate the planning of adequate numbers of hospitals with resources to receive such patients with minimum delay.

EDUCATION OF HCWS

A very important component of any TB management program is education of HCWs on how to protect themselves from exposure to *M. tuberculosis*. HCWs should be educated about TB infection prevention and control measures at the time of hiring and periodically thereafter. Education for HCWs should be relevant to their duties. For health care professionals, this should include awareness of epidemiologic and medical risk factors for TB, signs and symptoms of active TB disease (respiratory and nonrespiratory) and mechanisms of transmission. All HCWs, including orderlies, housekeeping and maintenance staff, should be educated to respect signage and to understand the importance of administrative, environmental and personal protection controls in the prevention of transmission.

IDENTIFICATION OF PATIENTS WITH RESPIRATORY TB DISEASE WITHIN HOSPITALS

Delayed diagnosis occurs in almost half of all hospitalized patients in whom respiratory TB disease is subsequently detected. This often results in significant exposure for HCWs and other patients. One study found that for each unrecognized case of respiratory TB disease, an average of 24 HCWs were exposed.[27] Certain locations within the hospital, such as emergency departments, are a frequent point of first contact with the health care system for people with undiagnosed respiratory TB disease.[28,29] This was observed in a Canadian study: from 1994 to 1998, 47% of 250 people with TB made a total of 258 visits to emergency departments during the 6 months before their diagnosis.[28]

RECOMMENDATIONS

(Conditional recommendations, based on strong evidence)

- **A cough of 2-3 weeks' duration with or without weight loss and fever in a person belonging to one of the at-risk groups below should prompt a thorough investigation to determine whether active respiratory TB is the cause:[7,10]**
  - People with a history of active TB;
  - Staff and residents of homeless shelters;
  - The urban poor;
  - Staff and inmates of correctional facilities and previously incarcerated people
  - Injection drug users;
  - Aboriginal Canadians residing in communities with high TB rates;
  - People infected with HIV;
  - People born in Canada and other low TB incidence countries prior to 1966;
  - People born or previously residing in countries with a high TB incidence in Asia, Eastern Europe, Africa and Latin America;
  - People with high risk factors listed in Chapter 6, Table 1;
  - HCWs serving at-risk groups.

To consider someone a suspect for active respiratory TB disease (for investigation and/or initiation of airborne precautions), cough of 2 weeks duration is a more sensitive criterion, but cough of 3 weeks duration will be more specific. Selection of 2 or 3 weeks as the criterion depends on the local experience and epidemiology of TB.

The TB incidence rate in Canada prior to 1966 was similar to that in a high TB incidence country (see Chapter 1, Epidemiology of Tuberculosis in Canada) thus the inclusion of this birth cohort as an at-risk group.

Concomitant respiratory TB disease should be ruled out in cases of nonrespiratory TB. See Chapter 2, Transmission and Pathogenesis of Tuberculosis, and Chapter 7, Nonrespiratory Tuberculosis.

Prompt diagnosis of active respiratory TB can be a major challenge if the clinical features of TB are atypical, such as negative AFB sputum smears, non-cavitary lesions on chest radiograph and the absence of cough and sputum production.[19] Atypical features of respiratory TB disease are more frequently observed in the elderly and people who are immunocompromised because of medical conditions (renal failure, HIV) or therapy (steroids, anti-tumour necrosis factor). See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

AIRBORNE PRECAUTIONS FOR PATIENTS WITH SUSPECTED OR CONFIRMED RESPIRATORY TB DISEASE

RECOMMENDATIONS
(Strong recommendations, based on strong evidence)

- Airborne precautions should be initiated as soon as possible for all those with suspected or confirmed respiratory TB disease who are admitted to a hospital.
- Patients (including children of any age) who show signs and symptoms of TB, or whose respiratory secretions, e.g. sputum or bronchial alveolar lavage, have yielded AFB, or who have a chest radiograph indicative of active TB should be immediately isolated in an AIIR. See Figure 1.

RECOMMENDATIONS
(Conditional recommendations, based on very weak evidence)

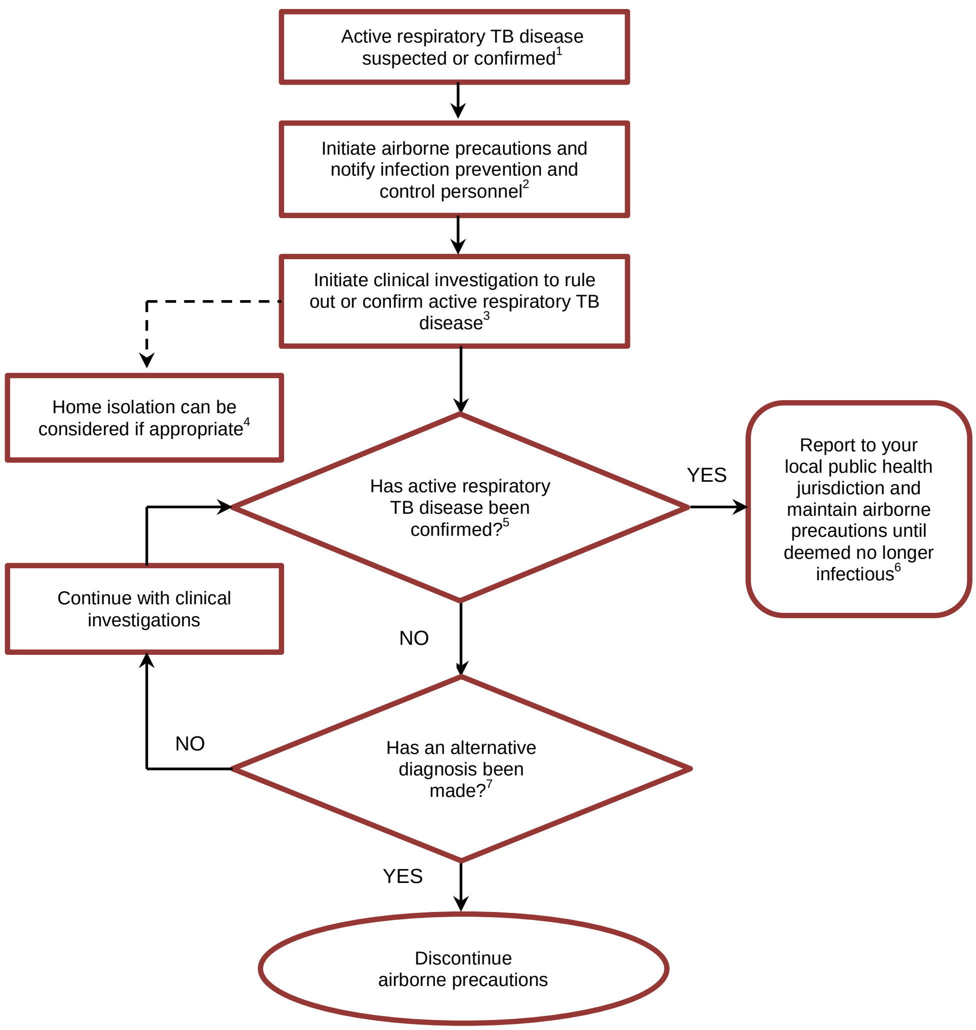
- Once airborne precautions have been initiated, the patient should remain in the AIIR until isolation is discontinued by designated medical personnel. Patients kept under airborne precautions can leave an AIIR for medical reasons.
- A patient may be allowed to leave an AIIR but only if it can be ensured that he or she adheres to airborne precautions; these include the proper wearing of a mask.
- See Figure 1 for detailed recommendations.

In the absence of an AIIR, the patient should be placed into a single room (with the door closed and a portable air filtration unit used if available) until transfer to a facility where an AIIR is available. Airborne precautions also include the use of respirators by HCWs caring for patients with suspected or confirmed active TB disease.

ISOLATION CONSIDERATIONS FOR PEDIATRIC PATIENTS

If isolation in the hospital is necessary for young children (under 5) with suspected or confirmed respiratory TB disease, it should be noted that they likely acquired their disease from adult family contacts, who may pose a risk to HCWs and other patients while visiting. Thus, for these patients, considerations for infection prevention and control in the hospital should include potentially infectious family members.[30,31] Visitors (limited to immediate adult family or guardians) should be screened by symptoms and radiography for active TB disease and should wear a mask during visits (when not in the AIIR) until active TB disease is ruled out. See Chapter 9, Pediatric Tuberculosis, for information on TB infection and disease in children.

Figure 1. Recommended steps for isolation for suspected or confirmed active respiratory TB disease in hospital*



*Includes infirmaries in correctional facilities

Figure 1. Legend

[1]It is recommended that patients suspected of having active respiratory TB disease be isolated immediately rather than wait for confirmation of disease prior to initiating airborne precautions.

Airborne precautions are recommended during procedures that may generate aerosols from wound drainage in non-respiratory active TB disease.

See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

[2]Airborne precautions include (in addition to routine practices):

- placement in an AIIR;
- respirator use by healthcare workers and if deemed necessary, by visitors also;
- mask use by patient when out of AIIR;
- restriction of patient to AIIR except for medically essential procedures;
- education of patient, families and visitors on the precautions.

Visitors should be restricted to immediate family or guardians. Visiting family or guardians of pediatric patients should be screened for active respiratory TB disease. Visits by children under age five and immunocompromised persons should be discouraged.

[3]Cough inducing procedures (e.g., sputum specimen collection, sputum induction) should be performed in an AIIR.
See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, for details of clinical investigations.

[4]See Figure 2 Legend for conditions for home isolation.

[5]The examination of smears of respiratory specimens for acid-fast bacteria is widely used as a presumptive rapid test, however mycobacterial culture provides a definitive diagnosis of active TB disease.

[6]Airborne precautions may be discontinued when the patient has clinical evidence of improvement, three consecutive negative sputum smears for acid-fast bacteria and there is evidence of adherence to at least two weeks of effective therapy. Multi-drug resistant TB cases and those with mono-resistance to rifampin (RMP) should have three consecutive negative sputum cultures after six weeks of incubation prior to discontinuing airborne precautions.

[7]Airborne precautions can be discontinued if another diagnosis is made (e.g., cancer, non-tuberculous pneumonia) and concomitant active respiratory TB disease is considered unlikely.

AIIR: airborne infection isolation room

TRANSPORT OF PATIENTS WITH SUSPECTED OR CONFIRMED RESPIRATORY TB DISEASE

RECOMMENDATIONS
(Conditional recommendations, based on very weak evidence)

- Prior to transport, HCWs involved in patient transport, transport personnel and the receiving health care facility should be advised of the infectious state of the patient.
- Patients should be escorted by a HCW during transport/transfer of patients from one facility to another or within a facility.
- Patients with respiratory TB disease should wear a mask, and HCWs involved in transport should wear a respirator (see “Respirators and masks”).
- If transport between facilities is required, patients should not use public transport.
- Patients should be transported in well-ventilated vehicles (i.e. with the windows open when possible).
- Where air transport is required (e.g. from remote settings), transport personnel should refer to their organization's policies on medical transport of patients with airborne infections.

PREVENTING PATIENT-TO-PATIENT TRANSMISSION OF *M. TUBERCULOSIS* WITHIN HOSPITALS

Measures should be taken to reduce the risk of *M. tuberculosis* transmission to people within the hospital, including patients, HCWs, other staff, volunteers and visitors. Until placement in an AIIR, a patient with suspected or confirmed active respiratory TB should wear a mask as a source control measure to prevent viable *M. tuberculosis* from being disseminated (see "Respirators and masks"). Source control measures, patient placement in a single room and limiting of patient movement all contribute to reducing the risk of patient-to-patient transmission.[16] When availability of single rooms is limited, priorities for placement of patients should be determined by risk assessment. Patients with suspected or confirmed respiratory TB disease have priority and should not share rooms with each other, since their strains and levels of infectivity may be different.[16]

A review of HCWs' LTBI screening records for conversions as well as patient surveillance data and medical records for cases of respiratory TB disease can help to identify whether patient-to-patient transmission occurred before initiation of airborne precautions. This possibility should be considered under the following circumstances:[7]

- A high proportion of people with respiratory TB disease were admitted to or examined in the same setting during the year preceding onset of their disease.
- Isolates from multiple patients in the same health care facility have identical anti-mycobacterial susceptibility and molecular genotypes.
- An increase occurred in the number of people with drug-resistant respiratory TB disease compared with the previous year (applicable if the transmission was from a drug-resistant patient).

See Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for further information.

DISCONTINUATION OF AIRBORNE PRECAUTIONS

Institutional policies should designate people with the authority (e.g. the infection prevention and control personnel) to discontinue airborne precautions as well as manage both breaches of and adherence to airborne precautions.

RECOMMENDATIONS
(Strong recommendations, based on moderate evidence)

Suspect TB cases

- **Airborne precautions may be discontinued if three successive samples of sputum (spontaneous or induced) are negative on smear unless TB is still strongly suspected and no other diagnosis has been made.[24,32,33]**

Note: Where feasible, three sputum specimens (either spontaneous or induced) can be collected on the same day, a minimum of 1 hour apart with at least one of them taken in the early morning. As previously done, the evidence used to inform sputum collection recommendations for discontinuation of airborne precautions originates from available studies related to diagnosis of respiratory TB disease. See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance for the current evidence base.

A single negative AFB smear from bronchial alveolar lavage does NOT definitively exclude respiratory TB disease; three induced sputa provide superior yield for the diagnosis and therefore are preferred to a single bronchoscopy. See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, for further explanation and references.

Confirmed TB cases

Although the degree and duration of infectiousness of patients after initiation of effective therapy remains unclear, it is known that effective therapy (i.e. therapy with two or more drugs to which the TB organisms are susceptible) will rapidly reduce cough and the number of viable bacteria in the sputum.

Note: Drug susceptibility test results are usually available within 4 weeks in a smear-negative, culture-positive case and 3 weeks in a smear-positive case; this confirms the effectiveness of therapy to date. See Appendix D on Tuberculosis and Mycobacteriology Laboratory Standards: Services and Policies.

RECOMMENDATIONS

(Strong recommendations, based on moderate evidence)

Confirmed TB cases

- **Patients with smear-negative, culture-positive drug-susceptible respiratory TB**:

  These patients should be kept under airborne precautions until there is clinical evidence of improvement and a minimum of 2 weeks of effective therapy has been completed. Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB is not suspected and there is no contraindication for home isolation (see Figure 2).

- **Patients with smear-positive, culture-positive drug-susceptible respiratory TB:**

  These patients should be kept under airborne precautions until there is clinical evidence of improvement, evidence of adherence to at least 2 weeks of effective multidrug therapy based on the known antibiotic sensitivity of the patient's organism, and three consecutive negative AFB sputum smears.[34] Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB is not suspected and there is no contraindication for home isolation (Figure 2).

Note: Specimens can be collected within 1 hour of each other on the same day, with at least one of them taken in the early morning. As previously done, the evidence used to inform sputum collection recommendations for discontinuation of airborne precautions originates from available studies related to diagnosis of respiratory TB disease. See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance for the current evidence base. In patients who are no longer able to spontaneously produce a sputum specimen, sputum induction is useful and appropriate. More invasive testing, such as bronchoscopy, is not recommended for monitoring response to therapy.

Although smear-positive patients are still potentially infectious, their household contacts have already been heavily exposed and are often receiving therapy for LTBI when discharge from hospital is being considered. Thus, the risk of further transmission to these contacts should be balanced by the social, mental and physical health benefits of the patient's return home.

RECOMMENDATIONS
(Strong recommendations, based on moderate evidence)

Confirmed TB cases

- **Patients with persistent smear-positive sputa:** Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB is not suspected and there is no contraindication for home isolation (Figure 2). If sputum specimens continue to be culture-positive after 4 months of anti-tuberculosis treatment or if culture results become positive after a period of negative results, drug susceptibility tests should be repeated and a TB expert consulted.[7]

- **Patients known to have active multidrug-resistant TB or mono-resistance to RMP**: These patients should be kept under airborne precautions for the duration of their hospital stay or until three consecutive sputum cultures (not smears) are negative after 6 weeks of incubation. See also Chapter 8, Drug-resistant Tuberculosis.

Figure 2. Recommended steps for isolation for suspected or confirmed active respiratory TB disease in the home

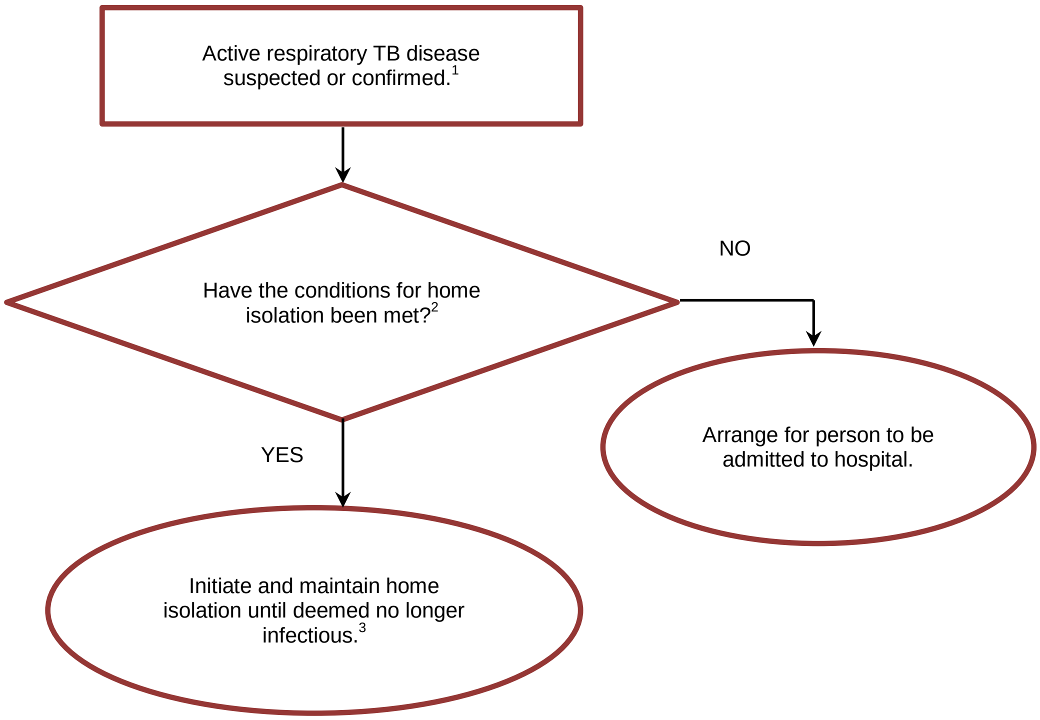


Figure 2. Legend

[1]See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

The person being assessed for active respiratory TB disease should wear a mask. HCWs should wear a respirator when sharing a common airspace with the person.

[2]Conditions for home isolation:

- Supervised therapy, if indicated, has been arranged;
- The person does not share a common airspace with non-household members (e.g., rooming house) and the household air is not being recirculated to other housing units (e.g., apartment complex);
- All household members have been previously exposed to the person. If any household members are TST negative, they should be informed and understand the potential risks;
- No children under the age of 5 or persons with immunocompromising conditions are present in the home (an exception would be if they are receiving prophylaxis or treatment for active TB disease or latent TB infection);
- No visitors should be allowed in the home except for HCWs;
- The person is counselled on and is willing and able to comply with limitations to their movement outside of the home (e.g., does not go to work, school or any other public indoor environment);
- The person should not be allowed to use any form of public transportation (if absolutely necessary, a taxi can be used to attend essential healthcare appointments provided the person is wearing a mask);
- The person should be allowed to ambulate outdoors since the risk of transmission is negligible provided they are not in very close contact with susceptible individuals for prolonged periods of time.

[3]Home isolation may be discontinued when the patient has clinical evidence of improvement, three consecutive negative sputum smears for acid-fast bacteria and there is evidence of adherence to at least 2 weeks of effective therapy. Multi-drug resistant TB cases and those with mono-resistance to RMP should have three consecutive negative sputum cultures after 6 weeks of incubation prior to discontinuing home isolation.

HCWs: health care workers

ENVIRONMENTAL (ENGINEERING) CONTROLS WITHIN HOSPITALS

VENTILATION GUIDELINES

Ventilation recommendations for AIIRs and select areas in hospitals are of critical importance because of their impact on reducing the risk for health care associated transmission of *M. tuberculosis*. Increasing air changes per hour (ACH) from 1 ACH to 6 ACH will result in four to five times more rapid clearing of infectious microorganisms from the air within a room. However, further increases above 6 ACH will have progressively less effect, and increases above 12 ACH may provide minimal additional benefit.[29,35] In general, as air exchange rates are increased, there are increased costs for building and maintaining the ventilation system.

A number of recognized organizations have made recommendations regarding ventilation levels to reduce the risk of health care associated transmission of airborne pathogens, including *M. tuberculosis* and varicella-zoster viruses.[7,36,37] These organizations have published different ventilation standards for AIIRs and other patient care areas within hospitals (see Table 4). Differences among these recommendations are not based on consideration of different evidence but, rather, on the risk-benefit assessment of each organization. See Table 4 for current ventilation recommendations by different organizations.

General hospital areas

It is important to ensure that there is adequate ventilation in general (i.e. non-isolation) areas such as inpatient rooms and examination or treatment rooms. This is because people with unsuspected respiratory TB disease may be placed in them, posing a risk of transmission to other patients and HCWs.[1] Recent literature on room ventilation rates has not provided definitive evidence for the ideal number of ACH to prevent transmission of TB in non-isolation rooms within hospitals.[38]

Airborne infection isolation rooms (all hospitals except low risk with transfer-out policy)

Measures to ensure that adequate ventilation is in place are outlined below and are also discussed in more detail in other guidelines.[7,16]

RECOMMENDATIONS

(Strong recommendations, based on moderate evidence)

- With the exception of rooms in which operative procedures are done, the direction of air flow should be inward from the hall into the room (negative pressure), and then the air should be exhausted outdoors. If an anteroom is used, the air from both the anteroom and patient room should be exhausted outdoors.[16] To achieve this, the ventilation system should be designed to function such that the anteroom and/or the AIIR are at lower pressure relative to the hallway outside. An anteroom is not essential if the pressure differential is adequate. See the CDC's recent recommendations on pressure differentials.[7]
- Windows and doors should be kept closed at all times, including during and after aerosol-generating procedures (long enough for air clearance in the room). Opening the window may cause reversal of the direction of air flow, depending upon the prevailing wind direction and outdoor temperature.
- Air should be exhausted to the outdoors through a dedicated exhaust system, ideally exiting from the roof of the building. It is important that the exhausted air does not re-enter the building or an adjacent occupied building. If the air will be recirculated, or if the exhausted air could re-enter the building, it should be passed through a HEPA filter before being exhausted.[7] Within existing facilities, use of HEPA filtration units that recirculate air back into the room and/or ultraviolet germicidal irradiation (which has bactericidal activity against *M. tuberculosis*) may be adjunctive methods to remove or reduce viable airborne *M. tuberculosis*; these are discussed later in this chapter.
- The rate of air changes and direction of air flow should be verified at least every 6 months when the room is not being used as an AIIR. When the AIIR is in use, the direction of air flow should be verified daily using electronic pressure monitors, and should be recorded. Where electronic monitors are unavailable, such as in older buildings, in resource-constrained settings or in temporary isolation settings, smoke tubes placed at all four corners of the door can be used.[16]
- The number of AIIRs required in hospitals not considered low risk should be based on the number of patients admitted each year with suspected respiratory TB disease. In organizations with very few admissions for TB, the number of AIIRs should be decided by the organizational authorities according to an analysis of AIIR utilization in the previous 2 or 3 years. The Canadian Thoracic Society suggests one or two more AIIRs than what was needed in the past at peak times. Appropriate resources should be made available to hospitals that will have such rooms and therefore receive patients with respiratory TB disease.

Sputum induction and administration of aerosolized pentamidine (all hospitals)

RECOMMENDATIONS
(Strong recommendations, based on moderate evidence)

- The smaller the room where these procedures are performed the easier and more practical it is to achieve required ventilation levels. Ideally, specially constructed "booths" (which are commercially available) should be used.
- Doors and windows should remain closed during and after the procedure, long enough for air clearance in the room (see Table 5).
- The air should be exhausted through a dedicated exhaust system or HEPA filtered.

Bronchoscopy and autopsy (all hospitals)

Areas where these procedures are performed tend to be much larger, making it difficult to achieve consistently high levels of ventilation with an inward direction of air flow. The increased risk of transmission associated with these activities warrants the significant expenditures required to achieve higher ventilation requirements.

RECOMMENDATIONS
(Strong recommendations, based on moderate evidence)

- Doors and windows should remain closed during and after the procedure, long enough for air clearance in the room (see Table 5).
- The air should be exhausted through a dedicated exhaust system or HEPA filtered.

Table 4. Ventilation recommendations for selected areas in health care facilities

Area	Number of mechanical air changes per hour Recommending agency				Direction of air movement (all agencies)*
	CTS (2013)	*CSA (2010)*	CDC (2005)	ASHRAE (2008) in FGI (2010)	
Autopsy suite	12	20	12	12	Inward
Bronchoscopy room Sputum induction/pentamidine aerosol	6–12†	20	12	12	Inward
Emergency department (waiting rooms) Trauma	2‡	12 15	12–15	12 15	Inward
Radiology waiting rooms	2‡	9	12–15	12	Inward
Operating room or surgical room	15	20	15	20	Outward
Airborne infection isolation rooms§					Inward
- Existing buildings	6	‖	6	¶	
- New buildings	9	12	12	12	
General patient care/non-isolation rooms	2‡	6	**	4††	N/A

CTS = Canadian Thoracic Society; CSA = Canadian Standards Association;[36] CDC = US Centers for Disease Control and Prevention;[7] ASHRAE = American Society of Heating Refrigeration and Air-conditioning Engineers;[37] FGI = Facilities Guidelines Institute.[37]

*****Direction of airflow from hallway or corridor relative to space; inward means from hallway **into** room. The US CDC provides further detail on direction of airflow specific to some inpatient settings, such as emergency departments and surgical suites/operating rooms.[7]

†Six ACH for existing room and 12 ACH for new constructions.

‡Note that the CTS recommendations for these areas were developed following a systematic review of the available evidence on ventilation rates for preventing transmission of *M. tuberculosis*. The scope of the review included general hospital areas, emergency departments, as well as trauma and radiology waiting rooms.

§Air-cleaning devices may be used to increase the equivalent ACH.

‖Portable or fixed HEPA filtration units may be used as a temporary measure to help older facilities achieve the minimum required number of air exchanges per hour, but the facilities should be considered for upgrade. See CSA document for details.[36]

¶Portions of a structure can be renovated if facility operation and patient safety in the renovated areas are not jeopardized by existing features of sections retained without complete corrective actions. See ASHRAE document for details.[37]

******Not stated, no recommendation made specific to these areas.

††Recommendation is for patient corridor

Note that the CTS ventilation recommendations in Table 4 should be considered a minimum, as the CSA recommends higher ventilation rates for all areas. The CTS recommendations were developed on the basis of a systematic review of currently available published evidence. Specific ACH rates are not recommended here; rather, Table 4 provides health care organizations with current recommendations provided by various organizations. In deciding which recommendations to implement, hospital administrators may need to take into account factors such as resources, facility design and available scientific evidence. The current paucity of evidence for adequate ACH rates to prevent transmission of *M. tuberculosis* and gaps in existing literature indicate that further research is needed in this area.

Entering rooms after generation of infectious aerosols has ended or patient with respiratory TB disease has been discharged

Health care workers often ask when it is safe to enter a room previously occupied by a patient with respiratory TB disease without needing to wear a respirator or when a procedure room can be used for another patient after generation of infectious aerosols has ceased. As shown in Table 5, this is dependent upon the level of ventilation in the room (expressed as ACH), if room sizes are relatively similar.

Table 5. Time needed (by number of air changes per hour) to remove airborne microorganisms after generation of infectious droplet nuclei has ceased*

Air changes per hour	Minutes required for removal of airborne microorganisms	
	99% removal	99.9% removal
2	138	207
4	69	104
6	46	69
12	23	35
15	18	28
20	14	21
50	6	8

*This table was adapted from the CDC recommendations.[7]

The values apply to a room in which the generation of aerosols has ceased, and ongoing mixing of the air in the room is assumed. Consideration should also be given to keeping the relative humidity of the air in the hospital at ≤60%. This range has been cited to minimize environmental contamination and provide acceptable indoor air quality.[7]

Cleaning of rooms

If a room previously occupied by a patient with respiratory TB disease has been ventilated for the appropriate amount of time (see Table 5), the routine hospital cleaning procedures used in non-isolation rooms may be used for terminal cleaning of AIIRs.[7,16] If a room is still in use during cleaning, housekeeping personnel should wear a respirator (see “Respirators and masks” below).

Ultraviolet Germicidal Irradiation

There is good evidence that short wave ultraviolet germicidal irradiation (UVGI) has excellent bactericidal activity against *M. tuberculosis* and can reduce infectious droplet concentrations by an amount equivalent to ventilation with 20 ACH, depending upon the room volume and type of lights used.[39] Upper-room UVGI is considered a supplement or adjunct to ventilation.[40] Use of UVGI has been controversial because of potential skin cancer and eye damage. However, the risk of skin cancer with new, commercially available UVGI units is essentially eliminated. Possible eye complications can be avoided by proper installation of these units above head height, as well as a schedule of regular inspection and maintenance.

A detailed review of the use of UVGI was published in 2010.[41] This technology is being used with increasing frequency in settings such as homeless shelters to reduce airborne infectious microorganisms without the cost of renovating the heating, ventilation and air conditioning (HVAC) system.

For further information on the safe and effective use of UVGI, including proper installation above head height and maintenance, refer to the recent CDC guidance document for using upper-room UVGI to control spread of *M. tuberculosis* in health care settings.[40] Use of UVGI may be considered in bronchoscopy and sputum induction rooms, emergency departments, autopsy areas and HIV clinics if ventilation is inadequate and cannot be upgraded. It can also be used where exposure is unpredictable, such as emergency departments in hospitals that are not considered low risk (see Table 2).

High-efficiency Particulate Air (HEPA) Filtration

HEPA filtration can be used to filter the exhaust from airborne infection isolation rooms, bronchoscopy suites or rooms where sputum induction is performed. Small HEPA units, either fixed or portable, may also be used to filter recirculated air in a room without the need for an increase in the amount of outdoor air supplied. HEPA filters require careful monitoring and regular change, as clogged filters will result in decreased efficacy. People performing maintenance and replacing filters on any ventilation system that is probably contaminated with *M. tuberculosis* should wear a respirator[7] (see "Respirators and masks"). For further information on HEPA filtration and details on safety issues when handling spent filters, see the CDC guidelines.[7]

With both UVGI and HEPA filtration environmental controls, regular maintenance (including procedures for installation, removal and disposal) and corresponding documentation are necessary.

PERSONAL PROTECTION CONTROLS WITHIN HOSPITALS

Personal protection controls are the final level in the hierarchy of control measures for preventing health care associated transmission of *M. tuberculosis*.

RESPIRATORY PROTECTION PROGRAM

Respiratory protection is one element of personal protection control measures. All hospitals should have a respiratory protection program in place. An essential component of the program involves selecting appropriate NIOSH-certified respirators for HCWs, as discussed below. For cost-efficiency purposes, it is also important to provide respirator models with inherently good fit characteristics, as these have been shown to fit more than 90% of workers.[42,43]

The health care organization should ensure that appropriate respirators are available as needed for use by HCWs, other staff and visitors, contractors, etc., and that masks, as needed for use by patients with respiratory TB disease, are available. Another essential component of a hospital respiratory protection program is education of HCWs regarding the occupational risk of TB and the role of respiratory protection in reducing that risk.

Respirators and Masks

Respiratory protection of HCWs involves the use of a respirator with a filter class equivalent to or higher than an N95, to prevent inhalation of aerosols containing infectious microorganisms. The most widely used respirators by HCWs in North America are the NIOSH-certified half-facepiece disposable respirators with an N95 filter class, commonly referred to as N95 respirators.[15,16] These respirators are certified to filter 95% of particles of diameter 0.3 microns (µm) or larger with less than a 10% leak, thus protecting wearers against airborne infectious microorganisms such as *M. tuberculosis*.[7,44]

A mask (either surgical or procedure) is used as a physical barrier. Masks are worn by HCWs to protect their skin and mucous membranes (nose and mouth) from droplets from an infected patient (or source). Masks are not designed for respiratory protection of HCWs as they are less than 50% effective in filtering small droplet nuclei (1–5 microns) containing *M. tuberculosis*.[45]

Masks worn by patients with respiratory disease serve as a source control measure to trap the droplets that these patients expel. There is concern that because masks are loose-fitting they may allow the escape of airborne droplets (particularly during coughing); tight-fitting respirators, on the other hand, may be uncomfortable for patients (particularly those with limited respiratory reserve).

It is recommended that in all hospitals, including those with a transfer-out policy for cases of active TB disease, N95 respirators should be available for HCWs whenever a patient is suspected of or confirmed to have respiratory TB disease. This is particularly important because most low-risk hospitals will not have AIIRs in which to house patients while awaiting transfer.

Fit Testing

Fit testing is used to determine whether a particular size and model of respirator fits a given person by assessing leakage around the face-respirator seal. Each time HCWs put on a respirator, a user seal check (according to manufacturer's instructions) is required to determine whether the respirator is properly sealed to the face. When TB patients are housed in AIIRs, the contribution of respirators in preventing TB transmission to HCWs appears to be minimal.[46] Hence, despite published literature on fit testing[47-49] there is insufficient evidence showing that a fit testing program results in reduced risk of health care associated transmission of *M. tuberculosis*. Nevertheless, most Canadian jurisdictions require fit testing for HCWs to determine their ability to obtain a satisfactory seal during respirator use.[50] HCWs are referred to jurisdictional requirements regarding the processes and frequency of fit testing. In the absence of requirements, consult provincial/territorial public health authorities.

RESPIRATOR RECOMMENDATIONS FOR HCWS
(Strong recommendations, based on strong evidence)

- NIOSH-certified respirators (N95 or higher filter class) should be used by HCWs providing care to patients with suspected or confirmed respiratory TB disease.
- NIOSH-certified respirators (N95 or higher filter class) should be used by HCWs involved in the transport of patients suspected of or confirmed as having respiratory TB disease, e.g. paramedics.
- Refer to jurisdictional requirements for fit testing of respirators.

MASK RECOMMENDATIONS FOR PATIENTS
(Strong recommendations, based on strong evidence)

- Masks should be used by patients with suspected or confirmed respiratory TB disease when leaving their AIIRs.
- Masks should be used by patients with suspected or confirmed respiratory TB disease during transfer to a different location.

SCREENING FOR LTBI AS PART OF INFECTION PREVENTION AND CONTROL IN HOSPITALS

Baseline TST (all HCWs in all health care facilities)

The importance of conducting proper baseline TST for all potentially exposed HCWs in all health care settings cannot be overemphasized. At the time of employment, many HCWs may already be TST positive because of prior exposure, particularly HCWs born or previously residing in countries with high TB incidence who may have been exposed and infected before moving to Canada. In addition, older Canadian-born HCWs in some provinces/territories may have received bacille Calmette-Guérin (BCG) vaccination, which can interfere with TST results. Prior exposure to *M. tuberculosis*, nontuberculous mycobacterial infection or BCG vaccination can result in a boosting phenomenon that is misdiagnosed as a TST conversion. The occurrence of boosting phenomena has been documented in 3% to 10% of Canadian HCWs.[13,51] Therefore, a two-step TST is recommended (see Chapter 4, Diagnosis of Latent Tuberculosis Infection). PHAC has developed a compendium of the expected prevalence of TST positivity in various Canadian populations; see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for a summary table from the compendium.

Periodic TST (specific clinical personnel in hospitals not considered low risk or those performing high-risk activities in all health care settings)

Recommendations for serial screening of specific HCWs for LTBI are given in the box below. Periodic TSTs should not be performed on previously TST-positive HCWs as there is no value in doing so; rather, they should be referred for medical evaluation by a physician experienced in TST interpretation and treatment of LTBI, and should also be educated on the signs and symptoms of active TB disease (see Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Information on performing a TST, the definition of skin test conversion and management of the TST-positive worker can be found in Chapter 4, Diagnosis of Latent Tuberculosis Infection.

Post-exposure TST (all hospitals)

Any HCW who has unprotected exposure (termed an exposure episode) to a patient eventually confirmed to have respiratory TB disease should be considered at risk of having been infected. This includes situations in which a patient with undiagnosed respiratory TB disease was not in an AIIR or was cared for by a HCW who was not wearing a respirator. Exposure could also occur when such patients are not treated for a sufficient amount of time or with an effective regimen before isolation is discontinued.

RECOMMENDATIONS FOR SCREENING HCWS FOR LTBI
(Strong recommendations, based on moderate evidence)

- Baseline two-step TST for all HCWs upon starting work. An exception applies where documented results of a prior two-step TST exist, in which case a single-step TST should be given and prior TST results transcribed into the HCW's health record.
- Annual TST for HCWs (with negative baseline TSTs) involved in intermediate-risk activities in health care settings not considered low risk and those involved in high-risk activities in all health care settings (see Tables 2 and 3).

Note: After 2 or more years of annual screening, if the annual risk of infection (based on TST conversion rate in those screened) is shown to be less than 0.5%, consideration could be given to reducing the frequency of screening to every other year or to developing criteria that restrict annual screening to fewer workers who are at higher risk, and not testing the remaining workers except after exposure.

RECOMMENDATIONS FOR SCREENING HCWS FOR LTBI
(Strong recommendations, based on moderate evidence)

Post-exposure:

- Single TST 8 weeks after exposure for TST-negative HCWs exposed to people with respiratory TB disease without adequate protection.
- For previously TST-positive HCWs exposed to people with respiratory TB disease without adequate protection:
  - Refer for medical evaluation and educate on signs and symptoms of active TB disease. See Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.
  - For HCWs with a history of BCG vaccination, see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for information on the use of interferon gamma release assays.

Protocols for TST can be found in Chapter 4, Diagnosis of Latent Tuberculosis Infection.

Interferon gamma release assay (IGRA)

The use of IGRA for serial (repeated) testing of HCWs is not recommended because serial testing studies have shown high rates of conversions and reversions, unrelated to exposure or treatment. There is no consensus on the appropriate cut-offs for deciding on IGRA conversions and reversions, and data show substantial variability in IGRA results around the cut-off used for LTBI diagnosis. Thus, TST is the preferred test for serial testing for new LTBI (see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for details).

IGRAs may be useful for confirming a positive TST in low-risk HCWs who are found positive on baseline TST as part of their pre-employment screening.

BCG vaccination

The efficacy of BCG vaccination against *M. tuberculosis* has varied from zero to more than 80% in randomized controlled trials.[52] As a result, it is not recommended that HCWs be routinely vaccinated with BCG. See Chapter 16, Bacille Calmette-Guérin (BCG) Vaccination in Canada, for details about the vaccine. The issue more relevant to most health care settings in Canada is how to interpret a positive TST or IGRA when there is a history of BCG vaccination in adulthood (see Chapter 4, Diagnosis of Latent Tuberculosis Infection, for information on this). An on-line TST/IGRA interpreter is available at http://www.tstin3d.com/index.html. A summary of the provincial and territorial usage of BCG over time is available from PHAC at http://www.publichealth.gc.ca/tuberculosis, and a BCG world atlas is available at www.bcgatlas.org.

Adherence to TB Infection Prevention and Control Measures

Low adherence to TB infection prevention and control measures by HCWs and to treatment of LTBI by both HCWs and patients will impede TB prevention efforts. Pre-employment screening for active TB disease is not sufficient to prevent *M. tuberculosis* transmission incidents involving HCWs in health care settings. Periodic HCW screening, recommended as above, and a high index of suspicion coupled with early assessment of HCWs with symptoms suggestive of TB are needed. Employers have reported greater success in encouraging HCWs to participate in screening programs when they are performed in conjunction with some other required activity (e.g. orientation, WHMIS [Workplace Hazardous Materials Information System] training, employee updates, vaccination days).[14] Administrative controls such as HCW training and education, in addition to a convenient schedule and location for screening, can increase adherence to TB infection prevention and control measures.[7,53]

INFECTION PREVENTION AND CONTROL OF *M. TUBERCULOSIS* IN SPECIFIC UNITS AND POPULATIONS WITHIN HOSPITALS

SPECIFIC UNITS

All patients exhibiting signs and symptoms of TB in a hospital setting should be assessed to rule out active TB disease. In certain units, special consideration is required to prevent the transmission of TB to HCWs, other patients and visitors. A unit that treats or cares for at-risk patients (e.g. chemotherapy, HIV and dialysis units) should have a plan in place for how it will manage a patient with respiratory TB disease so that the patient's treatment is not interrupted and other people are not exposed.

RECOMMENDATIONS FOR SCREENING HCWS FOR LTBI
(Strong recommendations, based on strong evidence)

- **Intensive care unit (ICU):** Every patient with suspected or confirmed respiratory TB disease who requires care in an ICU should be placed in an appropriately ventilated AIIR within the ICU. If this is not available, arrangements should be made to transfer the patient to a facility with an AIIR within the ICU as quickly as possible. For patients requiring intubation and mechanical ventilation, an appropriate bacterial filter should be placed on the endotracheal tube to prevent contamination of the ventilator and the ambient air.[16] When endotracheal suctioning is performed a closed suction apparatus should be used.
- **Emergency department:** A high index of suspicion for TB is required when assessing patients presenting with signs and symptoms of respiratory TB disease. Such patients should be immediately transferred to an AIIR. If such a room does not exist within the emergency department but exists elsewhere in the hospital, patients should be promptly transferred to this room until respiratory TB disease has been excluded (see "Transport of patients with suspected or confirmed active respiratory TB").
- **Surgery:** Surgery should either be postponed (if feasible) until the TB patient is no longer considered infectious or scheduled to allow adequate ventilation of the room after surgery (see Table 5). Surgery is sometimes required in patients with multidrug-resistant or extensively drug resistant TB, or to drain tuberculous abscesses. Because of the presence of infectious mycobacteria (and anaesthesia gases), the air supplied to the operating room should be exhausted to the outside and not exit the room to other patient care areas. HCWs should wear appropriate respirators (see "Respirators and masks"). Post-operative recovery of the patient with suspected or confirmed respiratory TB disease should take place in the operating room or in an AIIR.

Special Populations

There are certain individuals whose immunocompromising conditions or immunosuppressive therapy places them at higher risk of progression from LTBI to active TB disease.[7,54] They include HIV-infected individuals, transplant patients, people undergoing anti-tumour necrosis factor therapy and those undergoing dialysis or treatment for renal disease. A high incidence of LTBI and anergy has been reported among patients with chronic renal failure requiring dialysis.[55,56] The risk of active TB disease in this population appears to be high in the first 6 to 12 months after dialysis is initiated.[56] Providing care for patients in a specialized clinic or in other settings might require special considerations, a higher index of suspicion for respiratory TB disease or increased vigilance to prevent transmission before diagnosis. See Chapters 10 and 13 for further information. The CDC provides guidance on infection prevention and control considerations for dialysis units.[7]

PREVENTION OF TRANSMISSION OF *M. TUBERCULOSIS* WITHIN OTHER HEALTH CARE SETTINGS

Although the principles of TB infection prevention and control are the same across the continuum of health care, there is variation in the risk associated with different settings, and thus modification of the control measures applied is required. The availability of control measures needs to be considered when recommending interventions to prevent transmission of TB in non-hospital health care settings.

LONG-TERM CARE FACILITIES

Long-term care (LTC) facilities include homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre. Residents of LTC facilities are considered to be at the same risk as other populations in the community, with the exception of those belonging to at-risk groups (see "Identification of patients with active respiratory TB within hospitals").

Due to the decreasing utility of TST to diagnose LTBI after age 65 and the increasing risk of adverse effects from LTBI treatment in this age group, screening with a posterior-anterior and lateral chest x-ray for active TB is preferred upon admission for those over 65 years old. See Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for further discussion and references. A baseline 2-step TST is still recommended upon admission for those 65 years old and under who also belong to an identified at-risk group. Detailed screening recommendations for both HCWs and residents in LTC facilities are provided in Table 6.

AMBULATORY CARE/OUTPATIENT CLINICS

Ambulatory care settings include locations where health services are provided to patients who are not admitted to inpatient hospital units. This includes, but is not limited to, outpatient diagnostic and treatment facilities (e.g. diagnostic imaging, phlebotomy sites, pulmonary function laboratories, TB treatment facilities), community health centres or clinics, physician offices and offices of allied health professionals (e.g. physiotherapists).[7,16] If the patient mix includes members of at-risk populations, a high index of suspicion should be maintained for the presence of respiratory TB disease. See "Identification of patients with active respiratory TB within hospitals" for a description of this population.

RECOMMENDATIONS

(Conditional recommendations, based on weak evidence)

If possible, visits by people with suspected or confirmed respiratory TB disease should be postponed until no longer infectious.

- If a visit cannot be postponed, it should be scheduled at the end of the day to minimize exposure to others, and, when possible, staff should be alerted of these visits to allow for prompt use of precautions.[16]
- The patient should be provided with a mask before arrival or immediately upon reception to be worn until an AIIR becomes available. If unavailable, the patient should be temporarily assessed or treated in a single room with the door closed, away from vulnerable patients, and transferred as soon as medically feasible to a facility with AIIRs if admission is required.[16]
- HCWs caring for people with suspected or confirmed respiratory TB disease in outpatient clinics should wear a respirator (see "Respirators and masks").
- See Table 6 for further infection prevention and control recommendations for this setting.

PARAMEDICS AND OTHER EMERGENCY MEDICAL SERVICES

Exposure to airborne infectious agents remains a substantial hazard for emergency medical services (EMS) providers. Such exposure can occur during resuscitation or routine transportation of patients.

RECOMMENDATIONS

(Strong recommendation, based on strong evidence)

EMS providers should wear appropriate respirators when attending to people with suspected or confirmed respiratory TB disease. See "Transport of patients with suspected or confirmed active respiratory TB."

REMOTE AND ISOLATED HEALTH CARE SETTINGS

In remote and isolated communities there are many challenges to TB infection prevention and control. Resource limitations may result in difficulties with access to adequate diagnostic facilities for bacteriologic examinations and chest radiography. In some remote and isolated First Nations and Inuit communities, the average TB incidence rates are high but vary considerably among communities.[57] See Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples.

Respiratory TB disease should be ruled out for anyone presenting with unexplained cough for more than 2 weeks with or without fever, unexplained weight loss, hemoptysis, loss of appetite and night sweats. This requires a chest radiograph and analysis of three sputum smears for AFB. The most important measure for infection prevention and control is a high index of suspicion in members of at-risk populations (see "Identification of patients with active respiratory TB within hospitals") with rapid use of diagnostic procedures (including sputum examinations and chest radiography) and early initiation of therapy. If chest radiography is difficult to organize because patients must fly out of the community, then sending sputum samples for AFB smear and TB culture may be a more rapid way to make a diagnosis.

RECOMMENDATIONS
(Strong recommendations, based on moderate evidence)

- In high-prevalence areas where primary care nurses may be required to collect sputum samples for examination for AFB, they should wear a respirator and separate themselves from the area where the person is providing the sputum specimen.
- Health care facilities that care for at-risk populations should have access to resources that will facilitate implementation of essential administrative, environmental and personal protective controls.
- See Table 6 for further infection prevention and control recommendations for this setting.

Where resources remain limited because of lack of the infrastructure needed to implement necessary infection prevention and control measures, strategies used in low-resource countries could be implemented:[58]

- Schedule visits from people with suspected or confirmed respiratory TB disease at the end of the day or after regular hours.
- If patients needing medical attention cannot be transferred to a facility with an AIIR, cohort smear- positive TB patients, provided they are receiving treatment and there is no suspicion of drug resistance (or the prevalence of drug-resistance is known to be very low).[26]
- Establish effective out-patient services with community-based treatment programs (in homes) to complete treatment started in the hospital, especially where AIIRs are unavailable.[58]
- When outdoor temperature permits, use natural ventilation to assist in reducing the risk of transmission of airborne pathogens. The World Health Organization has produced evidence-based guidelines on natural ventilation with minimal hourly ventilation rates.[59]

HOME CARE SETTINGS

Home care is delivered to patients who reside in their home or a community care residence. *M. tuberculosis* transmission to HCWs who work in home-based health care settings has been documented with recommendations developed to prevent transmission.[7] The room in the home where the patient spends considerable amounts of time should be well ventilated.[16]

RECOMMENDATIONS
(Conditional recommendations, based on very weak evidence)

- Home care agencies in consultation with public health authorities should develop a system for screening at-risk clients for signs of respiratory TB disease before and during visits, thus facilitating earlier diagnosis and use of appropriate infection prevention and control measures.
- HCWs caring for clients with respiratory TB disease at home should wear a respirator (see "Respirators and masks").
- HCWs should not perform cough-inducing or aerosol-generating medical procedures on clients with suspected or confirmed infectious TB disease, because recommended infection prevention and control measures will probably not be in place in the home.[7]
- See Table 6 for further infection prevention and control recommendations for this setting.
- See Figure 2 on home isolation and Chapter 5, Treatment of Tuberculosis Disease.

PREVENTION OF TRANSMISSION OF *M. TUBERCULOSIS* WITHIN RESIDENTIAL AND COMMUNITY CARE SETTINGS

While guidance is available on preventing *M. tuberculosis* transmission in health care settings, less has been written about prevention in community care settings, even though the incidence of LTBI and active TB disease in these settings exceeds that in the general population who are not receiving care.[60]

ADULT DAY CARE CENTRES

For the purposes of these guidelines, adult day care facilities include basic or specialized day care centres for adults or other special adult populations requiring care. Adult day care services often include group programs designed to meet the social and health needs of functionally and/or cognitively impaired adults. Examples of clients include individuals with Alzheimer's disease, developmental disabilities, traumatic brain injury, mental illness, vision and hearing impairments.[37] See Table 6 for screening recommendations for clients and employees.

These recommendations apply only to clients who expect to use these services for 4 or more hours per week or for 150 or more hours per year.

HOMELESS SHELTERS AND DROP-IN CENTRES

Recent extended outbreaks of *M. tuberculosis* in homeless and under-housed individuals in Canada and the United States highlight the risk of ongoing transmission within this population.[61,62] Overcrowding increases transmission risk, as does failure to recognize signs and symptoms of respiratory TB disease and inability to take immediate steps to prevent transmission. An upsurge in foreign-born homeless people in Canada could present an increased risk of drug-resistant strains being introduced into the homeless shelter system.[6] Employees and regular volunteers of shelters are at increased risk of becoming infected with TB because of frequent exposure to undiagnosed cases, compounded by inadequate ventilation. Screening for LTBI among the homeless can be labour intensive and complicated, and adherence to therapy for LTBI is often low in this population. Active case finding can also be challenging, as a large proportion of homeless people may have chronic cough and other symptoms that can imitate those of TB. Furthermore, following up on contacts of active cases can be extremely difficult.

Primary prevention of TB through improved environmental controls is perhaps the most important control strategy. This includes cleaning, repair and upgrading of air filter units as well as adding in-duct and upper-air UVGI, which will help reduce the risk of TB transmission.[63] Opening windows to improve fresh air ventilation can also result in a dramatic decrease in *M. tuberculosis* transmission, especially in shelters with inadequate ventilation.[64] However, this is not feasible for most of the year in Canada because of cold temperatures. Guidelines to assist shelter operators and staff in reducing the risk of *M. tuberculosis* transmission in homeless shelters have been published.[64,65]

RECOMMENDATIONS

(Conditional recommendations, based on very weak evidence)

- With support from local public health authorities, homeless shelters should develop and implement a TB management program that provides education to staff, volunteers and clients.
- See Table 6 for further infection prevention and control recommendations for this setting.

ADDICTION TREATMENT CENTRES

A high prevalence of positive TST concurrent with increasing duration of injection drug use has been documented in this population. In addition, drug users have also been shown to have an increased risk of progression from LTBI to active TB disease.[10] The benefit of TST screening for this high-risk population in terms of follow-up medical evaluation and adherence to therapy has been low.[10] Incentives have been shown to be a consistent and effective strategy for increasing participation in TB screening as well as educational activities for this population.[10,66] See Table 6 for further recommendations for this setting.

In populations known to have poor rates of return for TST reading (e.g. homeless individuals and intravenous drug users), use of IGRAs can help achieve a higher rate of test completion and follow-up, although completion of LTBI treatment may still be challenging.

PREVENTION OF TRANSMISSION OF *M. TUBERCULOSIS* WITHIN CORRECTIONAL FACILITIES

The following is based in part on the Correctional Service Canada (CSC) guidelines for TB prevention and control in institutions in which inmates are sentenced to 2 years or longer.[67] At the time of publication of this Standard, the CSC guidelines were under revision. An additional resource is the guideline published by the CDC on the prevention and control of TB in US correctional and detention facilities.[68] It should be noted that the recommendations below were developed mainly for federal facilities, as TB prevention and control activities and capacity vary across Canada for provincial/territorial correctional facilities. The latter facilities generally have more inmates, most of whom have shorter stays than inmates in federal facilities. The shorter duration of incarceration in provincial/territorial facilities, make it more difficult to implement recommendations developed for federal facilities.

The risk of TB transmission is higher in correctional facilities as a result of several factors:

1. The prevalence of LTBI among correctional facility inmates is higher than in the average Canadian population.
2. The risk of reactivation of LTBI to active TB disease is increased because of the higher prevalence of HIV infection, other comorbidities, previous or current cigarette smoking, and alcohol and injection drug abuse in this population.
3. Diagnosis may be delayed because of poor use of medical services.
4. Ventilation is often inadequate because of recirculation of air and a lack of open windows. This is more common in older prisons that were built to achieve security, not airborne infection control.
5. The density of inmates may be high (crowding).
6. Transfer of inmates within and between facilities may be frequent.

TB CONTROL PROGRAM FOR CORRECTIONAL FACILITIES

It is recommended that the first step of a TB management program in a correctional facility should be to perform an institutional risk assessment in order to decrease the risk of inmate and staff exposure to and acquisition of *M. tuberculosis*. This risk assessment is based on the baseline TB status of inmates and staff and an annual review of active respiratory TB cases diagnosed among inmates (and, if any, among staff). This involves inquiries into the medical and TB history as well as risk factors and symptoms.

Past TB-related history should be collected, if necessary, by accessing a comprehensive electronic medical database. The history should be reviewed carefully, including results of previous TSTs and any chest radiography, as should prior treatment of LTBI or active TB disease. Incomplete treatment should prompt a thorough evaluation of the possibility of active TB disease by means of chest radiography, medical evaluation and sputum analysis for AFB smears and cultures. Active case finding by symptom check is recommended for inmates on admission (baseline) and annually thereafter. At all other times a high index of suspicion should be maintained in order to minimize delays in the diagnosis of active respiratory TB. Suspicion should be particularly high if the inmate has a prior history of TB, even if treatment was judged to have been adequate, since actual adherence to treatment may have been suboptimal, leading to increased risk of relapse.

AIIRs exist across Canada in CSC facilities with at least one per geographic/administrative region. The direction of air flow should be into the room, and the air should then be exhausted outdoors. This should be verified when the room is occupied. For treatment of LTBI in inmates and staff, see Chapter 6, Treatment of Latent Tuberculosis Infection.

RECOMMENDATIONS

(Strong recommendations, based on strong evidence)

- Inmates who are suspected of having respiratory TB disease should be placed immediately in an AIIR until TB is ruled out or they have received sufficient treatment and are deemed no longer infectious (see Figure 1).
- Inmates and staff who are exposed to people with respiratory TB disease should be investigated in close collaboration with local public health authorities using the principles outlined in Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control.
- See Table 6 for further infection prevention and control recommendations for this setting.
- If an inmate is discharged while still being treated for active TB disease, follow-up should be arranged directly with local public health authorities, so that supervised treatment is not interrupted, even for a day.

Table 6. Summary of recommendations for TB infection prevention and control measures in non-hospital settings

For the purposes of this table, "people with infectious TB" refers to people with suspected or confirmed respiratory TB disease unless otherwise indicated.

Facility/setting	Administrative controls	Environmental controls[*]	Personal respiratory protection controls	Screening and surveillance[†]
Long-term care (homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre)	Facility risk assessment by retrospective review of all TB cases in preceding 5 years and all available TST results for staff and volunteers. This should inform the decision to routinely screen residents. Educate staff about TB symptoms, risk factors and infection prevention and control measures.[‡] People with infectious TB should be transported as soon as possible to an appropriate medical facility and should not return to the setting until they are no longer infectious.	CTS: 2 ACH CSA: 4 ACH CDC: NR FGI/ASHRAE: 2-6 ACH	Respirators for HCWs in contact with people with infectious TB.[§] Mask for people with infectious TB if not in airborne infection isolation room (AIIR) and during transport.	**Employees/volunteers[‖]:** Baseline screening upon hire or placement using two-step TST.[¶] Annual TST unless conversion rate is shown to be ≤0.5%.[**] **Residents/clients:** Baseline posterior-anterior and lateral chest radiography on admission for people >65 years old from identified populations. [††] Baseline two-step TST upon admission for identified population ≤65 years old[¶] Annual TST not necessary. Facility risk assessment/local epidemiology should inform decision. [‡‡]
Ambulatory care and outpatient clinics See Table 4 for ACH recommendations for AIIR	Signage at entry requesting use of surgical mask by people with respiratory symptoms that suggest infection. High index of suspicion if signs and symptoms of active TB disease. Schedule visit by people with infectious TB for end of day.	CTS: 2 ACH CSA: 6–9 ACH CDC: NR FGI/ASHRAE: 6 ACH	Respirators for HCW in contact with people with infectious TB.[§] Mask for people with infectious TB if not in AIIR or during transport.	**Employees/volunteers[‖]:** Baseline screening upon hire or placement using two-step TST. [¶] Annual TST not necessary. **Patients**: See Chapter 13, Tuberculosis Surveillance and Screening in High-risk Populations, for information on which individuals should be screened.
Clinic or nursing station etc. in remote and isolated settings or communities See Table 4 for ACH recommendations for AIIR	Schedule visits for people with infectious TB at the end of the day or after hours. Educate staff on TB symptoms, risk factors and infection control measures. Community-based treatment program (see Figure 2 on home isolation). Patient with infectious TB who cannot be medically managed at home should be transferred to an appropriate hospital as soon as possible.	CTS: 2 ACH and/or UVGI to supplement CSA: 6–9 ACH CDC: NR FGI/ASHRAE: 6 ACH Natural ventilation where no mechanical ventilation exists and weather permits.	Respirators for HCWs in contact with people with infectious TB.[§] Mask for people with infectious TB if outside the home.	**Employees/volunteers[‖]:** Baseline screening upon hire or placement using two-step TST.[¶] Annual TST if previously negative and people with infectious TB are being seen in the facility. Otherwise, annual TST is not necessary.[**] **Patients**: See Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, regarding which individuals should be screened upon admission.
Home care	Educate staff on TB symptoms, risk factors and infection prevention and control measures. See Figure 2 for home isolation recommendations.	ACH: NA People with infectious TB should not share common airspace with non-household members. Use of natural ventilation when weather permits.	Respirators for HCWs in contact with people with infectious TB.[§] Mask for people with infectious TB if leaving home for necessary appointment.	**Employees/volunteers[‖]:** Baseline screening upon hire or placement using two-step TST.[¶] Annual TST if employee's results were previously negative and agency provides care for people with infectious TB. Otherwise, annual TST is not necessary.[**] **Clients**: NA

Table 6. *Continued*

Facility/setting	Administrative controls	Environmental controls[*]	Personal respiratory protection controls	Screening and surveillance[†]
Adult day care centres	See recommendations for long-term care (LTC) above.	NR	See LTC above.	See recommendations for LTC above.
Homeless shelters **Drop-in centres** **Addiction treatment centres**	TB management program. Educate staff on TB symptoms, risk factors and infection prevention and control measures. Head-to-foot bed arrangement. Incentives and enablers may be considered to encourage resident screening for LTBI. People with infectious TB should be immediately placed in a separate room, transported to an appropriate health care facility and returned only when they are no longer infectious.	CTS: 6 or 0.708 m^3/min/person.[§§] CSA: NR CDC: 25 cubic feet of outside air/minute/person FGI/ASHRAE: NR Maintenance and upgrade of HVAC filter units as required. UVGI[‖‖] Use of natural ventilation where no mechanical ventilation exists and weather permits.	Respirators for HCWs performing medical assessment of people with infectious TB prior to transfer for medical care.[§] Mask for people with infectious TB pending and during transport to a health care facility.	**Employees/volunteers[‖]:** Baseline screening upon hire or placement using two-step TST.[¶] Annual TST if negative.[**] **Clients**: See Chapter 13, Tuberculosis Surveillance and Screening in High-risk Populations, for information on which individuals should be screened. In outbreaks consider outbreak case finding.
Correctional facilities	Airborne precautions (see Figure 1 legend) for people with infectious TB until deemed no longer infectious. Supervised therapy for people with infectious TB. Educate inmates on importance of completing therapy and on precautions. High index of suspicion for active respiratory TB. If possible, separate housing of symptomatic new inmates until screened for respiratory TB disease. Health teaching for people with respiratory TB disease to increase isolation and treatment adherence.	General inmates areas: CTS: 2 ACH CSA: NR CDC: 6-12 ACH FGI/ASHRAE: NR AIIR : See Table 4 for ACH recommenda-tions for non-isolation rooms and AIIR in the infirmary. HEPA filtration.[¶¶] UVGI[¶¶]	Respirators for HCWs and prison staff in contact with people with infectious TB.[§] Mask for people with infectious TB if not in AIIR or during transport.	**Employees/volunteers:** Baseline screening upon hire or placement using two-step TST.[¶] Baseline assessment for signs, symptoms and risk factors for TB. Annual TST if negative.[**] Annual assessment for signs and symptoms of active TB disease. **Inmates**: If >1 year stay, baseline screening at admission using two-step TST.[¶] Returning inmates receive a single-step TST. Annual TST thereafter (if TST negative) and assessment of risk factors for active TB disease.[**] Annual assessment of signs and symptoms for inmates with positive TST or history of TB, and medical examination for inmates with symptoms of active TB disease. If <1 year stay, assess for symptoms and signs of TB, past history of TB and known immunosuppression at admission. If any of these is present, chest radiography and medical evaluation should be done.

Table 6. *Legend*

AIIR = airborne infection isolation room; ACH = air changes per hour; NA = not applicable; NR = no recommendation for ACH.

*Recommendations for ACH are from the Canadian Thoracic Society (CTS),[15] Canadian Standards Association (CSA),[36] US Centers for Disease Control and Prevention (CDC),[7,68,69] and Facilities Guidelines Institute/American Society of Heating Refrigeration and Air-conditioning Engineers (FGI/ASHRAE).[37] Consult the reference document for complete ACH recommendations prior to implementing.

†If an exposure episode occurs in any of the settings in this table, post-exposure screening should be conducted. See Chapter 4, Diagnosis of Latent Tuberculosis Infection, and Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for information on post-exposure TST protocol and contact investigation respectively. It is recommended that the investigation be done in close collaboration with the local public health/TB control authorities.

‡Various facility operators can contact their regional public health office for resources that can be used to educate staff on control measures for TB. Some educative materials can be found at http://www.currytbcenter.ucsf.edu/abouttb/index.cfm.

§Respirators should be NIOSH-certified and filter at least 95% of particles of diameter 0.3 micron or larger with less than a 10% leak (e.g. N95 respirators).

||A regular volunteer may be defined as one who expects to work 150 or more hours during the coming year, meaning approximately a half day per week. Volunteers expecting to work less than 150 hours during the coming year should be tested if they are known to belong to an at-risk population group listed in the section "Identification of patients with active respiratory TB within hospitals" in this chapter. If volunteers have a history of active TB, or a history of a chest x-ray suggesting possible past TB, or have symptoms consistent with active TB (fever, cough for more than 2 weeks with or without fever, unexplained weight loss, hemoptysis, loss of appetite and night sweats), they should be referred for full medical evaluation rather than simply a TST.

¶A one-step TST may be given to people who meet the following criteria: (1) documented results of a prior two-step TST with a result of <10 mm at any time in the past, (2) documented, single negative TST result within the past 12 months or (3) two or more documented negative TST results at any time, the most recent one being less than 12 months ago. If prior results exist, these should be transcribed into the person's health record. Staff with a positive TST at baseline screening do not need to be re-tested but should be assessed by a physician knowledgeable in the treatment of LTBI. Such staff should also be instructed to promptly report any symptoms suggesting TB disease, such as cough of more than 2 weeks' duration with or without fever, night sweats or weight loss.

**See Chapter 4, Diagnosis of Latent Tuberculosis Infection, for TST protocol. If a HCW or staff member has an exposure episode following which he/she is tested as a contact of a person with confirmed active respiratory TB and found negative, the HCW or staff's next annual test should be 12 months after the negative result. All TST conversions should be reported to the local public health authority, as this may be indicative of TB transmission within a facility. HCW or staff with a positive TST on annual screening should be assessed by a physician knowledgeable in the treatment of LTBI. They should also be instructed to promptly report any symptoms suggesting TB disease (as per jurisdictional requirements), such as cough of more than 2 weeks' duration with or without fever, night sweats or weight loss.

††Applies to people known to belong to an at-risk population group listed in the section ″Identification of patients with active respiratory TB within hospitals″ in this chapter.

‡‡The decision to routinely screen (annually or otherwise) should be based on past incidence of active TB in the resident population served by the institution. For example, were there any active TB cases within the past 10 years?

§§Natural ventilation recommended for areas frequented by clients, use whichever is higher.

||||Shelters that cannot afford upgrades to their HVAC systems to provide recommended air exchange rates should consider appropriately placed UVGI systems, as these can achieve equivalent air exchanges at a fraction of the cost.[64]

¶¶Adjunctive use of HEPA filtration units and UVGI can be considered in AIIRs, especially in older correctional facilities where it is not practical or feasible to achieve the recommended levels of natural ventilation.

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CHAPTER 16

BACILLE CALMETTE-GUÉRIN (BCG) VACCINATION IN CANADA

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KEY MESSAGES/POINTS

- BCG vaccination has historically been provided in several provinces/territories of Canada.
- With declining rates of TB in many settings and concern about the risk-benefit ratio associated with a live, attenuated vaccine, BCG is currently only recommended in certain high-incidence communities in Canada.
- BCG is currently recommended in Canada for infants in high-incidence settings and also may be administered to travellers returning for extended stays to a high TB incidence country where BCG is routinely given.

MAJOR SHIFTS IN RECOMMENDATIONS

- BCG is not recommended for adults, such as health care workers, before travel to high-incidence settings.

RECOMMENDATIONS

- BCG vaccination is recommended in high-incidence communities for infants in whom there is no evidence of HIV infection or immunodeficiency. If vaccination is delayed beyond 6 months of age, a TST (tuberculin skin test) should be done and documented as negative before vaccination. For infants aged between 2 months and 6 months, an individual assessment of the risks and benefits of tuberculin skin testing prior to BCG vaccination is indicated.
- For infants born in Canada who will be moving to and staying for extended periods of time in a country with high TB incidence and where BCG vaccination is still standard practice, vaccination is recommended soon after arrival in the high-incidence country.

INTRODUCTION

Bacille Calmette-Guérin (BCG) is the collective term applied to a family of live, attenuated vaccines derived from the passage of *Mycobacterium bovis* by Calmette and Guérin (hence the name Bacille Calmette-Guérin). The original strain was developed at the Pasteur Institute in Paris between 1908 and 1921. Subsequent strains have undergone further development through repeated subculturing in many laboratories around the world. These strains are now known to differ in terms of their genome and a number of biologically intriguing phenotypes, such as those with the ability to make virulence lipids and produce antigens.[1,2] While there are clear data showing that this variability translates into strains with different immunogenicity in humans[3] it remains unknown whether different BCG strains offer comparable or divergent protection against TB in humans. Three parent strains of the BCG collective – Danish, Tokyo and Pasteur – now account for more than 90% of the TB vaccines used. The Pasteur strain of BCG serves as the reference strain of the vaccine, and its complete genome sequence has been determined.[4] BCG is the only vaccine currently in use against tuberculosis (TB).

According to the World Health Organization (WHO), 161 member states have BCG on their vaccination schedule, such that in 2002 the global BCG coverage of infants less than 1 year of age was 81%.[5] A global registry of BCG usage, the BCG World Atlas (www.bcgatlas.org), was recently launched to provide detailed information on current and past BCG policies and practices in a searchable, on-line format.[6] In Canada there has been a longstanding interest in BCG.[7] Beginning in 1926 in Quebec[8] and 1933 in Saskatchewan,[9] the National Research Council sponsored controlled trials of the safety and efficacy of BCG. Thereafter, BCG vaccination, either universal or selective, was promoted throughout Canada. Gradually, as anti-TB drugs became available and incidence rates fell, BCG was discontinued in most populations. In recent years its use has been limited to the First Nations and Inuit populations, in which it has been part of a TB elimination strategy.[10] However, in the wake of reports of disseminated BCG in children born with congenital immunodeficiencies[11-13] and questions about its indication,[14,15] BCG is also being phased out in this group.

EFFICACY

The efficacy of BCG has been debated for many years, despite the fact that over 3 billion doses of the vaccine have been administered. The prevailing opinion, based upon epidemiologic and autopsy data, has been that BCG does not prevent the establishment of infection in an exposed subject.[16,17] However, data from interferon-γ release assays have challenged that opinion, suggesting that BCG, while not preventing the establishment of infection in everyone, may prevent it in some.[18] If infection does occur it is widely accepted that BCG increases the resistance to uncontrolled multiplication and dissemination of *M. tuberculosis* from the primary focus of infection to other parts of the lung and body. BCG will not prevent the development of active TB in individuals who are already infected with *M. tuberculosis*.

The results of trials aimed at assessing the ability of BCG to prevent TB disease have been variable: protection has ranged from 0% to 80%. The reasons for this variability remain unclear, but there is some evidence that the more scientifically rigorous trials demonstrated higher efficacy rates, approaching 80%. The efficacy of BCG in adults is uncertain but is thought to be lower than that in children. There is good evidence that repeat BCG vaccination does not confer additional protection over a single dose. In addition to clinical trial data, there have been a number of case-controlled studies of BCG. A meta-analysis involving 10 case-controlled studies of BCG efficacy[19] provided a summary estimate of protection from BCG vaccination of 50%. Meta-analysis has also shown high rates of protection against meningeal and miliary TB in the vaccinated, as high as 85% in one clinical trial.[20]. More recently, there was a natural experiment of BCG discontinuation in Kazakhstan because of programmatic issues. In that setting, compared with infants not vaccinated, cohorts of infants vaccinated with different strains of BCG showed 50%-90% less culture-confirmed TB and 70%-90% less TB meningitis.[21]

The duration of the protective effect of BCG is disputed. A meta-analysis that examined protection over time demonstrated a decrease in efficacy of 5% to 14% in seven randomized controlled trials and an increase of 18% in three others.[22] A 55-year follow-up analysis of a study conducted in the 1930s found that BCG protective efficacy can persist for 50 to 60 years, indicating that a single dose might have a long-lasting effect.[23] In the recent study from Kazakhstan, the difference in TB rates between the non-vaccinated cohort and the vaccinated infants was largely confined to those aged 2 or less.

Unlike the high efficacy shown by vaccines against many viral infections, BCG vaccine does not provide a high degree of protection against TB. As a result, disease should still be considered in any vaccinee with a suggestive clinical presentation of TB, regardless of vaccination history.

ADMINISTRATION

BCG is available as a culture of live bacilli and is given intradermally. The manufacturer's instructions regarding administration should be carefully followed. The vaccine is supplied in a multidose vial, which is reconstituted using aseptic technique with a supplied diluent of sterile phosphate-buffered saline. The reconstituted product requires protection from heat and direct sunlight, and should be stored according to the manufacturer's instructions at 2 °C to 8 °C, and used within 8 hours. The dose in neonates is 0.05 mL, half the usual dose of 0.1 mL. The higher dose is recommended in children greater than 12 months of age. It is administered in a 1.0 mL syringe with a 26-gauge needle, the bevel facing upwards. BCG invokes the development of delayed-type hypersensitivity with a maximum response observed by 12 weeks, when the TST is usually positive. However, neither the presence nor the size of the TST response predicts protection: persistent skin test positivity is not correlated with continued protection.[24] Interpretation of the TST results of BCG-vaccinated individuals is problematic, but this issue is largely resolved with the introduction of interferon-γ release assays, which test for antigens that are not present in BCG. Details on evaluation for latent TB infection (LTBI) in the BCG-vaccinated individual are provided elsewhere (see Chapter 4, Diagnosis of Latent Tuberculosis Infection). Although for most children a scar develops after BCG vaccination, recent studies show that not all children with a record of receipt of BCG have a scar. In a series involving internationally adopted children, 27% of children with a record of BCG vaccination did not have a scar.[25]

Freeze-dried preparations of BCG for intravesical use in the treatment of primary and relapse carcinoma-in-situ of the urinary bladder are formulated at a much higher strength and must not be used for TB vaccination purposes.

RECOMMENDED USAGE

A summary of the provincial and territorial usage of BCG over time is provided by the Public Health Agency of Canada (http://www.publichealth.gc.ca/tuberulosis). In more recent years, BCG use in Canada has been limited to Inuit and on-reserve First Nations children born to mothers who tested negative for HIV prenatally. However, recommendations concerning the continued use of BCG in this and other Canadian populations have recently been revised. Currently, the National Advisory Committee on Immunization (NACI) does not recommend BCG vaccination for all Canadians. However, it allows that, in some settings, consideration of local TB epidemiology and access to diagnostic services may lead to the decision to offer BCG vaccination.[26,27]

- Vaccination in infants in First Nations and Inuit communities or groups of people with an average annual rate of smear-positive pulmonary TB greater than 15/100,000 population, or an annual rate of culture-positive pulmonary TB greater than 30/100,000 during the previous 3 years, or an annual risk of TB infection (ARI) greater than 0.1%, or if early identification and treatment of LTBI are not available. HIV testing in the mother of the child should be negative, and there should be no evidence or known risk factors for immunodeficiency in the child being vaccinated. Typically, BCG is given at birth, but if vaccination is delayed after birth a TST test is recommended in those over 6 months of age to ensure that the vaccine is only given to TST-negative infants. For infants aged between 2 months and 6 months, an individual assessment of the risks and benefits of tuberculin skin testing before BCG vaccination is indicated.

  (Strong recommendation, based on moderate evidence)

The annual risk of TB infection quoted, greater than 0.1%, is the ARI below which the International Union Against Tuberculosis and Lung Disease (IUATLD) recommends that selective discontinuation of BCG vaccination programs be considered.[11] If BCG vaccination is currently offered to all infants in a community that does not meet one of the criteria described, the vaccination program should be discontinued as soon as a program of early detection and treatment of LTBI can be implemented (see Chapter 9, Pediatric Tuberculosis).

- Vaccination of travellers planning extended stays in areas of high TB incidence, particularly when a program of serial TST and appropriate chemotherapy is not possible or where the prevalence of drug resistance, especially multidrug-resistant TB, is high. This recommendation largely pertains to infants born in Canada who will be moving to and staying for extended periods of time in a country with high TB incidence and where BCG vaccination is still standard practice.

  (Strong recommendation, based on moderate evidence)

In this situation, it is often more practical to recommend vaccination soon after arrival in the high-incidence country. For adults, such as health care workers, planning temporary travel to high-incidence countries, previous editions of these guidelines suggested that BCG vaccination should be considered. In the absence of evidence for the efficacy of BCG in such a situation, this is no longer recommended. Infection can be monitored using serial skin testing.

BCG vaccination of First Nations infants has now been discontinued in the Atlantic provinces, in Quebec and British Columbia. In Alberta, the rationale for continued use of the BCG has been challenged,[14] and a process of systematic withdrawal has begun. Elsewhere, on the prairies and in the territories, the benefits of BCG vaccination in preventing severe forms of TB in infants and young children may still outweigh any risks.

A consent form should be signed before vaccination. If BCG is discontinued in a community it should be replaced with a program of enhanced surveillance to ensure that TB disease and LTBI are detected early, particularly in high-risk communities. Delivery of enhanced surveillance and compliance with program recommendations may be challenging in some communities.

BOOSTER DOSES AND REVACCINATION

Revaccination with BCG is not recommended as there is no evidence that it confers additional protection. Because there is no correlation between skin test reactivity and protection, the TST is not recommended as a method to evaluate immunogenicity.[28]

ADMINISTRATION WITH OTHER VACCINES

The co-administration of BCG with other vaccines is not typically a problem in Canada, because when BCG is indicated it is given at birth. Infrequently, BCG is being given but other vaccines might also be scheduled, in which case the following is recommended. BCG vaccine may be administered concomitantly with inactivated vaccines (such as diphtheria/pertussis/tetanus /polio) and other live parenteral vaccines (such as measles/mumps/rubella) at different injection sites using separate syringes and needles. It may also be given with live intranasal influenza vaccine. If not given concomitantly, a minimum interval of 4 weeks is recommended between administration of two live parenteral vaccines (such as BCG and measles/mumps/rubella) to reduce or eliminate interference from the vaccine given first with the vaccine given later. Live *oral* vaccines, like rotavirus vaccine, may be given concomitantly with, or at any time before or after, live parenteral vaccines, such as BCG vaccine.

ADVERSE REACTIONS

Adverse events following BCG vaccination are reportable only in some provinces/territories, and thus their frequency may be underestimated. In order to provide accurate surveillance, the Public Health Agency of Canada (PHAC) collects case reports on adverse events following immunization from provincial and territorial health departments, health care professionals and the pharmaceutical industry. After intradermal injection of BCG an indurated papule forms within 2-3 weeks. A pustule or superficial ulcer develops by 6-8 weeks and heals within 3 months, leaving a 4-8 mm scar at the vaccination site in the majority of vaccinees. Regional adenopathy in the absence of erythema or vesicle formation should be considered an expected reaction to the vaccine.[29]

LOCAL REACTIONS

The majority of local reactions occurs within 5 months of vaccination and consists of prolonged skin ulceration, suppurative adenitis and localized abscess. *M. bovis* BCG can be cultured from approximately 5% of lymph nodes.[29] A European study found the mean risk of adenitis to be 0.387/100,000 in infants (i.e. children less than 1 year of age) and 0.25/100,000 in vaccinees aged 1 to 20.[30] Factors contributing to regional adenitis include the type of vaccine strain, the total number of viable and nonviable bacilli in the vaccine preparation and the dose of BCG given. The age of the person vaccinated is also important. Reducing the dose for newborns to 0.025 mL of vaccine further reduces the number of adverse reactions.[31] Treatment of suppurative adenitis is controversial. The WHO has suggested surgical drainage with direct installation of an anti-TB drug for adherent or fistulated glands, but no data exist to support this recommendation.[32] It appears that systemic treatment with anti-TB drugs is ineffective.[33]

SYSTEMIC REACTIONS

Osteitis is a rare complication of BCG vaccination developing within 4 to 144 months of vaccination. It appears to be associated with the administration of BCG in the gluteal region or thigh, and it has been reported most commonly from Scandinavian countries with a particular strain of BCG (BCG Swedish, also known as BCG Gothenberg). Less common reactions include fever, conjunctivitis, iritis and erythema multiforme. The most serious complication of BCG vaccination is disseminated BCG. It usually occurs within 6 months of vaccination, although long latent periods have been reported,[34] and it is usually fatal. In a study conducted by the IUATLD, disseminated BCG occurred in 3/1,000,000 recipients.[30] In studies conducted in Canada a different rate of occurrence of disseminated BCG is being reported.[11-13] Between 1993 and 2002, 21 BCG vaccine-related adverse events were reported, 15 of which were designated as serious, i.e. the patient died or was in hospital for longer than 3 days. There were six cases of disseminated BCG in immunocompromised infants, five in First Nations and Inuit children, all of whom subsequently died. There were also two cases of osteomyelitis, five abscesses and two cases of adenitis. All six disseminated cases were deemed very likely or certainly associated with the vaccination. An additional fatal case of disseminated BCG was identified in 2003.[13] Although the range estimates for adenitis and osteomyelitis appear to be consistent with global rates, the rate of disseminated BCG among First Nations children was much greater than the highest global rates.[35]

This high rate suggests that immunodeficiency states might be more common in First Nations and Inuit children, a possibility that is now being explored through Health Canada's First Nations and Inuit Health Branch and the Canadian Paediatric Surveillance Program, a collaborative initiative of the Canadian Paediatric Society and PHAC. As a consequence of these concerns related to disseminated BCG, NACI has revised its recommended usage of BCG.

CONTRAINDICATIONS TO BCG VACCINATION

BCG vaccination is contraindicated in people with immune deficiency diseases, including congenital immunodeficiency, HIV infection, altered immune status due to malignant disease, and impaired immune function secondary to treatment with corticosteroids, chemotherapeutic agents or radiation. Maternal HTLV-1 (human T-cell lymphotrophic virus type 1) infection and possible neonatal HTLV-1 infection are not a contraindication to BCG, as neonatal HTLV-1 infection does not result in significant immune suppression in the child. Extensive skin disease or burns are also contraindications. BCG is contraindicated for individuals with a positive TST result, although vaccination of tuberculin reactors has frequently occurred without incident. Before a newborn is vaccinated with BCG the mother should be known to be HIV negative, and there should be no family history of immunodeficiency. The vaccine should not be administered to individuals receiving drugs with anti-TB activity, since these agents have activity against the vaccine strain.

OTHER USES OF BCG VACCINE

Intravesical BCG is used for the treatment of transitional-cell bladder cancer, the most common form of bladder cancer. BCG immunotherapy has been associated with systemic side effects, including pneumonitis and miliary spread of the organism, which can be fatal.[36] Miliary spread occurs in patients who are otherwise deemed to be immunocompetent and responds to conventional anti-TB therapy, with the caveat that the organism is always resistant to pyrazinamide (PZA).

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APPENDIX A

GLOSSARY

Aboriginal Peoples
Descendants of the original inhabitants of North America. The *Constitution Act* of 1982 recognizes three major groups of Aboriginal people in Canada: Indians (Status and non-Status North American Indians), **Métis** and **Inuit**.

Absconded
See **Default**

Acid-fast bacteria (bacilli)
Microorganisms that are distinguished by their retention of specific stains even after being rinsed with an acid solution. The majority of acid-fast bacteria (AFB) in patient specimens are mycobacteria, including species other than *Mycobacterium tuberculosis* complex. The relative concentration of AFB per unit area on a slide (the **smear** grade) is associated with infectiousness. A positive culture is required for laboratory confirmation of *M. tuberculosis* complex.

Active tuberculosis (disease)
Active clinical disease that is usually symptomatic and for which microbiologic tests are usually positive and radiologic tests usually abnormal.

Adherence
Patient's and health care provider's ability to follow disease management recommendations appropriately; used interchangeably with **compliance**.

Aerosol
Small droplets that are exhaled or coughed up. In a patient with **pulmonary tuberculosis** these may contain *Mycobacterium tuberculosis* bacteria that are suspended in the air and lead to the spread of infection.

Air changes per hour (ACH)
The number of air changes per hour in a room, one air change being a volume of air equal to that of the room (height times width times length).

Airborne infection isolation
The conditions into which a patient with suspected or proven **active tuberculosis** may be placed for purposes of preventing transmission to other people (formerly termed airborne **respiratory isolation**).

Airborne infection isolation room (AIIR)
Formerly, negative pressure isolation room. An AIIR is a single-occupancy patient care room used to isolate people with a suspected or confirmed airborne infectious disease. Environmental factors are controlled in an AIIR to minimize the transmission of infectious agents that are usually transmitted from person to person by droplet nuclei associated with coughing or aerosolization of contaminated fluids. An AIIR should provide negative pressure in the room (so that no air flows out of the room into adjacent areas) and should direct exhaust of air from the room to the outside of the building or recirculate the air through a HEPA filter before returning it to circulation.

Anergy — A condition in which there is diminished ability to exhibit delayed T-cell hypersensitivity reaction to antigens because of altered immune function. When referring to an inability to react to a skin test, the correct term is "cutaneous anergy". Anergy skin testing is no longer recommended in the context of interpret-tation of a **tuberculin skin test** result.

BACTEC — A previous broth-based laboratory culture technique for *M tuberculosis* using radiometric methods (the technology is now discontinued).

Bacille Calmette-Guérin (BCG) — A live attenuated vaccine derived from *Mycobacterium bovis*.

Booster phenomenon — Increase in **tuberculin skin test** (TST) response after an initially negative test when the test is repeated at any time from 1 week to 1 year later, in the absence of exposure or other evidence of new TB infection.

Break of contact (see also Contact) — Moment when exposure to a person with active **infectious** tuberculosis ends. This can be when the active case is placed in airborne infection isolation or when he or she is deemed no longer **infectious** after a period of treatment.

Cavitary disease — Evidence on chest x-ray or pathology tests of lung destruction resulting in cavities or cystic areas that communicate with a bronchus. Cavities generally harbour large numbers of bacteria and, as a result, patients with cavitary disease tend to be highly **infectious**.

Chemoprophylaxis — See **treatment of latent tuberculosis infection.**

Cluster — Two or more isolates with a shared identical genotype ("fingerprint") detected using a method such as mycobacteria interspersed repetitive unit (MIRU) testing, insertion sequence *6110* (IS*6110*) based **restriction fragment length poly-morphism (RFLP)** testing or spoligotyping.

Completion (active tuberculosis) — See **Treatment completion.**

Compliance — See **adherence.**

Contact: — A person identified as having been exposed to *Mycobacterium tuberculosis* by sharing space with an **infectious** case of tuberculosis. The proximity and duration of contact usually corresponds with the risk of becoming infected.

Conversion (tuberculin conversion) — An increase in the size of a **tuberculin skin test** (TST) reaction on repeated testing that reflects new TB infection. Tuberculin conversion is defined as **induration** of 10 mm or greater when an earlier test resulted in a reaction of less than 5 mm. If the earlier result was between 5 and 9 mm, there are two criteria:

1. An increase of 6 mm or more—this is a more sensitive criterion, which is suggested for those who are immune compromised with increased risk of disease or for an **outbreak**;

2. An increase of 10 mm or more—this is a less sensitive but more specific criterion. In general, the larger the increase, the more likely that it is due to true conversion.

Culture-positive disease	The isolation of *Mycobacterium tuberculosis* complex (excluding BCG strain) from clinical specimens (sputum, body secretions or tissue).
Cure (active non MDR/XDR-TB)	Culture-negative at the **completion** of treatment.
Cure (active MDR/XDR-TB)	At least five negative cultures in the final 12 months of treatment. With strong clinical evidence of cure, a patient may be considered cured with one positive culture of these five as long as the last three consecutive cultures, taken at least 30 days apart, are all negative.
Defaulter	A patient who stops tuberculosis treatment, for 2 months or more, before **completion** of 80% of doses (see also **Return after Default).**
Delayed-type hypersensitivity (DTH)	Cell-mediated inflammatory reaction to an antigen that is recognized by the immune system, typically because of previous exposure to the same or similar antigens. DTH responses are usually maximal 48-72 hours after exposure to the antigen.
Designated area/country/territory	As per the *Immigration and Refugee Protection Act* Regulations 30(2)(e), "Every foreign national who has undergone a medical examination as required under paragraph 16(2)(*b*) of the Act must submit to a new medical examination before entering Canada if, after being authorized to enter and remain in Canada, they have resided or stayed for a total period in excess of six months in an area that the Minister determines, after consultation with the Minister of Health, has a higher incidence of serious communicable disease than Canada." To make such a determination, the designation of an area/country/territory is based primarily on World Health Organization estimated TB incidence rates and information on other serious communicable diseases. For a list of such designated areas/countries/territories, see Citizenship and Immigration Canada: (http://www.cic.gc.ca/english/information/medical/dcl.asp).
Directly observed preventive therapy (DOPT)	The process whereby a health care worker or pill dispenser watches the patient swallow each dose of medication for **latent tuberculosis infection**, to enhance **treatment completion** rates. DOPT is also known as directly observed prophylaxis (DOP).
Directly observed therapy (DOT)	The process whereby a health care worker or pill dispenser watches the patient swallow each dose of medication as part of the treatment of active disease, to enhance **treatment completion** rates.
Disseminated tuberculosis	Active TB disease that affects three or more sites, or positive blood culture(s) for *M. tuberculosis*. See also **miliary TB.**
DNA probe	A molecular diagnostic technique whereby the organism grown on culture can be rapidly speciated within a matter of hours.
Droplet nuclei	Airborne particles resulting from a potentially infectious (microorganism-bearing) droplet from which most of the liquid has evaporated, allowing the particle to remain suspended in the air.
Drug resistance	In-vitro determination that growth of a strain of *Mycobacterium tuberculosis* is not inhibited by standard concentrations of an anti-TB drug.

Elimination	The elimination of tuberculosis as a global public health problem, meaning an incidence of tuberculosis disease of less than 1 per million population (see http://www.stoptb.org/global/plan/).
Enabler	A practical item given to a patient to facilitate **adherence** to treatment, clinic appointments or other aspects of treatment.
Extensively drug resistant tuberculosis (XDR-TB)	Tuberculosis due to bacteria resistant to at least isoniazid and rifampin and any fluoroquinolone, and at least one of three injectable **second-line drugs** (capreomycin, kanamycin and amikacin).
Extrapulmonary tuberculosis	Site of TB that is outside the lungs and respiratory tract. This includes tuberculous pleurisy and TB of the intrathoracic lymph nodes, mediastinum, nasopharynx, nose (septum) or sinus (any nasal) and all nonrespiratory sites. Note that this term is often used interchangeably with non-respiratory TB, but the definitions are slightly different.
Failure (active tuberculosis)	See **Treatment failure.**
First-line anti-tuberculosis drug	First-line antibiotics for the treatment of **active tuberculosis disease.** These are isoniazid, rifampin, ethambutol and pyrazinamide, and are considered the most effective and best tolerated. Streptomycin is no longer considered a first-line drug in Canada.
First Nations People	Indian people in Canada, both “Status” and “non-Status”. **Status Indians** are registered with the federal government as Indians, according to the terms of the *Indian Act.*
Fit testing	The use of a qualitative or quantitative method to evaluate the fit of a specific manufacturer, model and size of respirator on an individual.
Health care-associated infection	Infections that are transmitted within a health care setting during the provision of health care (previously referred to as nosocomial infection).
High-efficiency particulate air (HEPA) filter	A filter that is certified to remove >99.97% of particles 0.3 μm in size, including *M. tuberculosis*-containing droplet nuclei; the filter can be either portable or stationary.
High tuberculosis incidence countries/territories	The **TB** incidence rate (all forms, 3-year average) as estimated by the World Health Organization of 30 per 100,000 or higher. The 3-year average is used to adjust for unstable rates in some jurisdictions. Estimated rates are used for some countries rather than the country's reported incidence rate to adjust for under-reporting of cases and to be more indicative of the current risk of being infected by residence or prolonged travel in the country/territory. To view current international incidence rates, see http://www.publichealth.gc.ca/tuberculosis.
Immunocompromising condition	A condition in which at least part of the immune system is functioning at less than normal capacity.

Inactive pulmonary tuberculosis	Abnormal chest x-ray with findings considered typical of previous TB infection or disease, plus at least three sputum cultures negative for tuberculosis or the chest x-ray abnormalities stable for at least 6 months.
Incentive	A gift given to patients to encourage or acknowledge their **adherence** to treatment.
Incidence	The number of new occurrences of a given disease during a specified period of time.
Index case	The first or initial active case from which the process of **contact** investigation begins.
Induration	The soft tissue swelling that is measured when determining the **tuberculin skin test** response to **purified protein derivative (PPD) tuberculin**. It is to be distinguished from erythema or redness, which should not be measured.
Infectious	The condition whereby the patient can transmit infection to others by virtue of the production of **aerosols** containing TB bacteria. Patients with **smear**-positive, **cavitary** and laryngeal disease are usually the most infectious.
Interferon gamma release assay (IGRA)	In-vitro T-cell based assays that measure interferon-γ (IFN-γ) production and that have been developed as alternatives to **tuberculin skin testing** (TST) for the diagnosis of latent TB infection. At the present time, two different types of IGRAs are registered for use in Canada. These are the Quantiferon®-TB Gold In-Tube (Cellistis Limited, Carnegie, Victoria, Australia) and the T-SPOT.*TB*® (Oxford Immunotec, Oxford, UK) assays.
Intermittent therapy	Therapy administered three times a week. This therapy must always be administered in a fully supervised, directly observed fashion and is usually reserved for the period after the initial intensive daily portion of therapy.
Intradermal	The method of injecting either **PPD** skin test antigen using the Mantoux technique or vaccinating with **BCG vaccine**.
Inuit	Original inhabitants of northern Canada who are distinct from other Aboriginal groups in heritage, language and culture. The Inuit live primarily in Nunatsiavut (Labrador), Nunavik (northern Quebec), Nunavut and the Inuvialuit Settlement Region in the Northwest Territories.
Latent tuberculosis infection (LTBI)	The presence of latent or dormant infection with *Mycobacterium tuberculosis*. Patients with LTBI have no evidence of clinically active disease, meaning that they have no symptoms, no evidence of radiographic changes that suggest active disease and negative microbiologic tests; they are non-infectious.
MDR TB	See **multidrug-resistant tuberculosis.**
MGIT	Mycobacteria growth indicator tube; a nonradiometric broth-based culture system. Detection of growth is due to the development of measurable fluorescence as a result of oxygen consumption.
Mantoux technique	The recommended method of administering the **tuberculin skin test** – the **intradermal** injection of 5 tuberculin units of **PPD** into the forearm.

Métis — People of mixed Aboriginal and European ancestry who identify themselves as Métis and are distinct from **First Nations people**, **Inuit** or non-Aboriginal people.

Miliary tuberculosis — Disseminated active TB with abnormal chest X-ray showing diffuse micro-nodules (see also **disseminated TB**).

Multidrug-resistant tuberculosis (MDR-TB) — Tuberculosis due to bacteria resistant to isoniazid and rifampin with or without resistance to other anti-tuberculosis drugs.

***Mycobacterium tuberculosis* complex** — *M. tuberculosis* (including subspecies *M. canetti*)*, M. bovis, M. bovis* BCG*, M. africanum, M. caprae, M. microti* and *M. pinnipedii*. All of these species except *M. bovis* BCG are included in the Canadian case definition of tuberculosis.

Natural ventilation — Use of natural forces to introduce and distribute outdoor air into a building, to replace the indoor air. These natural forces can be wind pressures or pressure differences generated by temperature differences between indoor and outdoor air.

New active case of tuberculosis disease — No documented evidence or history of previously **active tuberculosis.**

Non-nominal reporting — A reporting system in which no names or other identifying information are provided to public health officials when tuberculosis data are reported.

Non-respiratory TB — Refers to all other disease sites not part of respiratory TB. The definition overlaps with, but is slightly different from that of extra-pulmonary TB.

Nontuberculous mycobacteria (NTM) — All mycobacterial species except those that cause tuberculosis (*Mycobacterium tuberculosis* [including subspecies *M. canetti*], *M. bovis, M. africanum, M. caprae, M. microti and M. pinnipedii*) and those that cause leprosy (*M. leprae*). These are also known as MOTT (mycobacteria other than tuberculosis).

Nucleic acid amplification tests (NAAT) — A process whereby genetic material is amplified and then subsequently evaluated for the presence of DNA material; useful to identify specific mycobacterial species.

Organizational risk assessment — The activity whereby a health care organization identifies the following:

a. a hazard;
b. the likelihood and consequence of exposure to the hazard;
c. the likely means of exposure to the hazard;
d. and the likelihood of exposure in all work areas in a facility/ office/practice setting;

and then

e. evaluates the available administrative, environmental and personal protection controls needed to minimize the risk of the hazard.

Outbreak	The following working definition of an outbreak for planning investigations is based on that proposed by the U.S. Centers for Disease Control and Prevention: • During a contact investigation, in two or more of the identified contacts a diagnosis is made of active TB; or • Any two or more cases occurring within 1 year or less of each other are discovered to be linked, but the linkage is recognized outside of a contact investigation. For example, two patients who received a diagnosis of TB independently, outside of a contact investigation, are found to work in the same office, yet they were not previously identified as contacts of each other. The linkage between cases should be confirmed by genotyping results if cultures are available.**PPD**: See **Purified protein derivative (PPD) tuberculin**.
Pediatric tuberculosis	Active TB in a child or adolescent.
Polymerase chain reaction (PCR)	Method of **nucleic acid amplification** that is patented with license held by Roche.
Post-primary tuberculosis	older term – see **reactivation tuberculosis.**
Prevalence	The number of people that are alive and have the disease during a specified period of time.
Preventive therapy	See **treatment of latent tuberculosis infection**.
Primary respiratory tuberculosis	This includes pulmonary (lung parenchyma) tuberculosis, as well as tuberculosis of the intrathoracic lymph nodes, larynx, trachea, bronchus or nasopharyngeal sinuses due to infection within the preceding 24 months (ICD-9 codes 010, 010.0, 010.8, 010.9; ICD-10 codes A15.7 and 16.7). This diagnosis excludes tuberculous pleurisy in primary progressive tuberculosis (see below).
Primary tuberculosis	This includes **primary respiratory tuberculosis** and **tuberculous pleurisy in primary progressive tuberculosis** (ICD-9 codes 010-010.9; ICD-10 codes A15.7 and 16.7).
Pulmonary tuberculosis	In Canada, pulmonary tuberculosis includes tuberculosis of the lungs and conducting airways, and includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia and tuberculous pneumothorax. (ICD-9 codes 011-011.9, 012.2, 012.3; ICD-10 codes A15.0-A15.3, A15.5, A15.9, A16.0-A16.2, A16.4, A16.9).
Purified protein derivative (PPD) tuberculin	A preparation of purified protein derived from culture filtrate of *Mycobacterium tuberculosis*. The **tuberculin skin test** uses 0.1 mL or 5 tuberculin units of PPD standardized to a common lot.
Reactivation tuberculosis	The development of active disease after a period of **latent tuberculosis infection**. In Canada, the term "reactivation" tuberculosis was previously used to refer to a **recurrence**.
Recurrence	Patient previously successfully treated (**cure** or completed) for active TB disease in whom **active tuberculosis** develops a second time, but without proof that this is the same organism.

Registry — The systematic collection of data pertaining to all active cases of tuberculosis in a given jurisdiction, to allow for effective case management and the collection of epidemiologic information.

Reinfection — Individual who was previously infected with *Mycobacterium tuberculosis* and is exposed and infected a second time. This can be proven only if the individual had active disease once, then disease develops a second time and the organism has a different "DNA fingerprint" from the original organism. Such cases are to be reported as a **re-treatment case**.

Relapsed — Patient with tuberculosis disease that was treated successfully (**cure** or completed), but it recurred. In the strictest sense the isolate should be the same (i.e. confirmed to have the same "DNA fingerprint" as the original organism), but relapse is commonly used interchangeably with **recurrence**. Such cases are to be reported as a **re-treatment case**.

Respiratory isolation — See **airborne infection isolation**.

Respiratory tuberculosis — This consists of **pulmonary tuberculosis**, tuberculous pleurisy (non-primary) and tuberculosis of intrathoracic lymph nodes, mediastinum, nasopharynx, nose (septum) and sinus (any nasal) (ICD-9 codes 010-012; ICD-10 codes A15-16).

Restriction fragment length polymorphism (RFLP) — A technique whereby the genetic "fingerprint" of individual organisms can be compared with that of other organisms. When isolates share an identical RFLP pattern it suggests an epidemiologic link, either recent or in the remote past, between the individuals from whom the organisms were isolated. This is the most specific of three commonly used methods for "genetic fingerprinting" of *M. tuberculosis.*

Re-treatment case of tuberculosis

1. a) Documented evidence or adequate history of previously active TB that was declared **cured** or treatment completed by current standards, and

   b) At least a 6-month interval since the last day of previous treatment[§] and

   c) Diagnosis of a subsequent episode of TB that meets the active TB case definition.

OR

2. a) Documented evidence or adequate history of previously active TB that cannot be declared **cured** or treatment completed by current standards, and
   b) Inactive[**] disease for 6 months or longer after the last day of previous treatment* and
   c) Diagnosis of a subsequent episode of TB that meets the active TB case definition.

Return after default — A patient who has current evidence of active TB disease and had received treatment before, but this was interrupted for 2 or more consecutive months.

[§] If less than 6 months have passed since the last day of previous treatment and the case was not previously reported in Canada, report as a re-treatment case. If less than 6 months have passed since the last day of previous treatment and the case was previously reported in Canada, do not report as a re-treatment case. Submit an additional form, "Treatment Outcome of New Active or Re-treatment Tuberculosis Case" at the end of treatment, see Appendix B.

[**] Inactivity for a **respiratory tuberculosis** case is defined as three negative tuberculosis **smears** and cultures plus a 3-month duration of stability in serial chest radiographs or a 6-month duration of stability in serial chest radiographs without laboratory testing. Inactivity for a nonrespiratory tuberculosis case is to be documented bacteriologically, radiologically and/or clinically as appropriate to the site of disease.

Second-line anti-tuberculosis drug

Anti-tuberculosis drugs reserved for use as alternative treatment to the **first-line** drugs. Second-line drugs consist of :

(1) aminoglycosides, such as amikacin, kanamycin and streptomycin;

(2) cyclic polypeptides, such as capreomycin, (3) analogs of d-alanine, such as cycloserine;

(4) fluoroquinolones, such as levofloxacin, moxifloxacin and ofloxacin;

(5) rifamycins other than rifampin, such as rifabutin or rifapentine;

(6) salicylic acid-antifolates, such as para-aminosalicylate (PAS);

(7) thioamides, such as ethionamide and protionamide; and

(8) phenazine derivatives, such as clofazimine.

Smear

A laboratory technique for preparing a specimen so that bacteria can be visualized microscopically.

Source case

The person who was the original source of infection for secondary case(s) or **contacts**. The source case can be, but is not necessarily, the **index case**.

Source control measures

Methods to contain infectious agents from an infectious source. These can include separate entrances, partitions, triage/early recognition, airborne infection isolation rooms, diagnosis and treatment, respiratory hygiene (including masks, tissues, hand hygiene products and designated hand washing sinks), process controls for aerosol-generating medical procedures, and spatial separation.

Sputum-smear positive

Cases of **pulmonary tuberculosis** with positive smear results obtained from either spontaneously expectorated sputum, induced sputum, tracheal or bronchial washings/aspiration, or gastric wash.

Status Indian

A person who is registered with the federal government as an Indian, according to the terms of the *Indian Act*. Status Indians are also known as Registered Indians.

Transferred out

A patient who moved to a different jurisdiction and for whom the treatment outcome is not known.

Treatment completion (active tuberculosis)

Treatment completed without **culture** at the end of treatment and therefore the case does not meet the criteria for **cure** or for **treatment failure**.

Treatment failure (active non-MDR/XDR-TB)

Positive sputum cultures after 4 or more months of treatment or two positive sputum cultures in different months during the last 3 months of treatment, even if the final culture is negative and no further treatment is planned.

Treatment failure (active MDR/XDR-TB)

Two or more of five cultures recorded in the final 12 months are positive, or any one of the final three cultures is positive, or a clinical decision has been made to terminate treatment early because of poor response or adverse events.

Treatment of latent tuberculosis infection (LTBI)

The provision of therapy to individuals with LTBI to prevent progression to active disease; formerly termed **preventive therapy** or chemoprophylaxis.

Triage

In the context of TB infection control, a system for early identification of people suspected to have active TB, and prompt action to reduce the risk of transmission from them.

Tuberculin skin test (TST)	Skin test to identify whether a person has **delayed-type hypersensitivity** reaction to tuberculin antigens.
Tuberculosis case	A reportable case of disease in Canada caused by *Mycobacterium tuberculosis* complex (i.e. *M. tuberculosis* [including subspecies *M. canetti*], *M. bovis* [excluding BCG strain], *M. africanum*, *M. caprae*, *M. microti* or *M. pinnipedii*).
Tuberculous pleurisy in primary progressive tuberculosis	This disease state is characterized by pleuritis and pleural effusion due to recent (within the preceding 24 months) infection with *Mycobacterium tuberculosis* complex (ICD-9 code 010.1; ICD-10 codes 15.7 and 16.7). The diagnosis excludes non-primary tuberculous pleurisy due to infection more than 24 months prior to diagnosis (ICD-9 code 012.0 and ICD-10 codes A15.6 and 16.5). If another site of tuberculosis disease, such as CNS (central nervous system) or disseminated/miliary disease, is believed to have been involved as a consequence of recent infection (within the preceding 24 months), it ought to be referred to and reported as tuberculosis of the meninges or miliary tuberculosis.
XDR TB	See **extensively drug resistant tuberculosis.**

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APPENDIX B

CANADIAN TUBERCULOSIS SURVEILLANCE SYSTEMS

THE CANADIAN TUBERCULOSIS REPORTING SYSTEM (CTBRS)

Provincial and territorial tuberculosis control programs participate in the CTBRS national surveillance system by reporting to the Centre for Communicable Diseases and Infection Control (CCDIC), Public Health Agency of Canada (PHAC), all new and re-treatment cases of active tuberculosis that meet the Canadian case definition (given below). (NOTE: Prior to 2008 in Canada, re-treatment cases were reported as relapsed cases.)

CONFIRMED CASE

- **Laboratory-confirmed case**
  Cases with *Mycobacterium tuberculosis* complex demonstrated on culture, specifically *M. tuberculosis, M. africanum, M. canetti, M. caprae, M. microti, M. pinnipedii* or *M. bovis* (excluding *M. bovis* Bacillus Calmette Guérin [BCG] strain).

- **Clinically confirmed case**
  In the absence of culture proof, cases clinically compatible with active tuberculosis that have, for example:
  i. chest x-ray changes compatible with active tuberculosis;
  ii. active nonrespiratory tuberculosis (meningeal, bone, kidney, peripheral lymph nodes, etc.);
  iii. pathologic or post-mortem evidence of active tuberculosis;
  iv. favourable response to therapeutic trial of antituberculosis drugs.

NEW AND RE-TREATMENT CASES OF TUBERCULOSIS

- **New case**
  No documented evidence or adequate history of previously active tuberculosis.

- **Re-treatment case**

  1.
     i) documented evidence or adequate history of previously active TB that was declared cured or treatment completed by current standards, and
     ii) at least a 6-month interval since the last day of previous treatment* and diagnosis of a subsequent episode of TB that meets the active TB case definition.

  OR

  2.
     i) documented evidence or adequate history of previously active TB that cannot be declared cured or treatment completed by current standards; and
     ii) inactive† disease for 6 months or longer after the last day of previous treatment;* and
     iii) diagnosis of a subsequent episode of TB that meets the active TB case definition.

REPORTING OF CASES TO THE CTBRS

Whether treatment was started or not, report all cases of tuberculosis diagnosed in Canada in the following groups: Canadian citizens, permanent residents, refugees, refugee claimants and protected people.

For temporary residents (visitors, students and people granted work permits) and those foreign nationals who are in Canada illegally, report only those cases for **which treatment was started** in Canada. The province/territory in which the treatment is started should report the case.

DATA SUBMISSION

Data are submitted either on paper forms mailed or couriered to CCDIC, or in an electronic dataset submitted via protected email to CCDIC. Regardless of the format, the submitted data comprise the items contained in two reporting forms (see below), the *Active Tuberculosis Case Report Form - New and Re-treatment Cases* and the *Treatment Outcome of a New Active or Re-treatment Tuberculosis Case.* The *Canadian Tuberculosis Reporting System Form Completion Guidelines* were developed to assist in the completion of the reporting forms. Current versions of the reporting forms and completion guidelines are available at http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php.

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* If less than 6 months have passed since the last day of previous treatment and the case was not previously reported in Canada, report as a re-treatment case. If less than 6 months have passed since the last day of previous treatment and the case was previously reported in Canada, do not report as a re-treatment case. Submit an additional form, *Treatment Outcome of New Active or Re-treatment Tuberculosis Case*, at the end of treatment.

† Inactivity for a respiratory tuberculosis case is defined as three negative tuberculosis smears and cultures with a 3-month duration of stability in serial chest radiographs or a 6-month duration of stability in serial chest radiographs in the absence of laboratory testing. Inactivity for a nonrespiratory tuberculosis case is to be documented bacteriologically, radiologically and/or clinically as appropriate to the site of disease.

From the data collected by the CTBRS, PHAC publishes an annual report on the epidemiology of tuberculosis called *Tuberculosis in Canada,* first published in 1995, after the transfer of responsibility for this national surveillance system from Statistics Canada to PHAC. Data are reported to reflect disease trends federally and provincially/territorially and include breakdowns by demographic characteristics (including age, sex and origin), laboratory and clinical findings, treatment details, HIV status and other risk factors or markers of disease, and the final outcome of treatment. National data are available in published form back to 1924 and in electronic case-level format back to 1970.

THE CANADIAN TUBERCULOSIS LABORATORY SURVEILLANCE SYSTEM (CTLSS)

This national laboratory-based surveillance system was established in 1998 to collect timely data on TB drug resistance across Canada. Participating laboratories include members of the Canadian Tuberculosis Laboratory Technical Network (covering all provinces and territories). These laboratories report data annually on drug susceptibility test results for all TB isolates to the CCDIC, PHAC. Data are reported in both paper and electronic format and comprise the information found on the *M. tuberculosis Complex Antimicrobial Susceptibility Reporting Form*.

PHAC publishes an annual report using data collected by the CTLSS called *Tuberculosis Drug Resistance in Canada*. This report includes federal, provincial and territorial results on TB drug resistance patterns, including multidrug- and extensively drug-resistant strains.

For paper copies of the documents, please contact:

Surveillance and Epidemiology Division
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada
100 Eglantine Drive, AL 0603B
Ottawa, ON K1A 0K9

TB_surveillance@phac-aspc.gc.ca

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APPENDIX C

TUBERCULOSIS TRAINING AND EDUCATION RESOURCES

Tuberculosis (TB) education and training are fundamentally important to TB prevention and control. The aim of this appendix is to provide useful information for health care providers, organizations and individuals on some of the many excellent TB education and training resources that are available within Canada and internationally. Where gaps in resources are identified, it is hoped that the existing collaborative partnerships will continue to work together to develop and disseminate new resources to fill those gaps.

TB education and training materials are available for several target audiences and in a variety of formats: text-based, Web-based, video, podcasts and CD/DVD. There are also a number of TB courses, workshops and TB-related conferences that may be attended in person or through videoconferencing.

Health care providers, community agencies, people infected with TB and the general public have unique needs with regard to TB education and/or training. Needs range from basic information on TB to complex issues related to TB diagnosis, treatment, management and control.

The following resource list provides a variety of resources to address these needs. While it is provided as a public service, it is the responsibility of users to evaluate the resources they access from these sources prior to use. Additional education and training resources may be found through provincial/territorial/regional/local public health TB prevention and control programs.

TB RESOURCES FOR HEALTH CARE PROVIDERS, PATIENTS AND THE GENERAL PUBLIC

CANADIAN SOURCES

- Canadian Lung Association
  http://www.lung.ca (lung diseases/infectious diseases)
  Lung Health Framework
  http://www.lunghealthframework.ca

- Canadian Thoracic Society
  http://www.respiratoryguidelines.ca/ (Canadian Tuberculosis Standards, 7th edition)
  http://www.lung.ca/cts-sct/home-accueil_e.php

- Health Canada - First Nations and Inuit Health Branch
  http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/fnihb-dgspni/fact-fiche-eng.php (general)
  http://www.health.gc.ca/tuberculosis (tuberculosis)

- *Health Canada's Strategy Against Tuberculosis for First Nations On-Reserve*
  http://www.hc-sc.gc.ca/fniah-spnia/pubs/diseases-maladies/_tuberculos/tuberculos-strateg/index-eng.php

- Public Health Agency of Canada
  http://www.phac-aspc.gc.ca (general)
  http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php (tuberculosis prevention and control)

  For health care provider education and training resources on TB prevention and control see General Resources/Education and Training, available at: http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php.

- The Online TST/IGRA Interpreter
  An interactive website created by McGill University and the Research Institute of the McGill University Health Centre, which provides estimates of positive predictive value, likelihood of developing active TB, and risk of drug induced hepato-toxicity if treated with INH. Available at: http://www.tstin3d.com/en/calc.html.

- BCG World Atlas

  An interactive website created by McGill University and the Research Institute of the McGill University Health Centre, which provides a database of detailed information on current and past global BCG vaccination policies and practices for over 180 countries, available at: http://bcgatlas.org/

- Canadian International Development Agency (CIDA) – tuberculosis
  CIDA has contributed substantially to global TB control, including funding of numerous TB programs in developing countries. This site provides information and links to international programs, such as the World Health Organization (CIDA's main partner) housed Stop TB Partnership, and is available at:
  http://www.acdi-cida.gc.ca/acdi-cida/acdi-cida.nsf/eng/FRA-32394626-J6K

- TAIMA TB
  The Website provides resources and training material developed for a public health campaign being implemented in Nunavut to enhance the existing preventive efforts in the fight against tuberculosis, and is available at:
  http://www.tunngavik.com/taimatb

- Stop TB Canada
  http://www.stoptb.ca

- *Teaching Tuberculosis: A Resource Guide for Aboriginal and Non-Aboriginal Youth*
  Available at: http://tbper.ualberta.ca/en/publications/tb-education.aspx

U.S. SOURCES

Note: U.S. recommendations may differ from those found in the Canadian Tuberculosis Standards because of different TB epidemiology, public health practices and clinical practices in the United States.

- American Thoracic Society
  http://www.thoracic.org

- The Centers for Disease Control and Prevention, Division of Tuberculosis Elimination (DTBE),*Core Curriculum on Tuberculosis: What the Clinician Should Know*(5th ed), available at: http://www.cdc.gov/tb/education/corecurr/default.htm

  This document is intended for use as a self-study guide or reference manual for clinicians and other public health professionals caring for people with or at high risk of TB disease or infection. The *Core Curriculum* also includes a slide set designed to be useful in developing educational programs.

- Tuberculosis Education and Training Network
  http://www.cdc.gov/tb/education/tbetn/default.htm

- TB Education and Training Resource Guide
  http://www.cdcnpin.org

  This guide was developed as a cooperative effort between the Centers for Disease Control and Prevention and the National Prevention Information Network

- Find TB Resources
  http://www.findtbresources.org
  This site is a searchable database of education resources and tools.

- U.S. Regional Training and Medical Consultation Centers
  http://www.cdc.gov/tb/education/rtmc/default.htm

  While each centre serves a geographic part of the United States, they all list various resources on their Websites that may be useful for TB prevention and control activities outside that country.

- Country guides
  These are country-specific TB resources and training guides for working with foreign-born individuals. They include the background of the country, epidemiology, common misperceptions, beliefs, attitudes and stigmatizing practices related to TB and HIV/AIDS. These resources, information on general practices and translated educational materials are available at: http://sntc.medicine.ufl.edu/About.aspx

TUBERCULIN SKIN TEST (TST) RESOURCES

- Online TST/IGRA (interferon gamma release assay) interpreter is available at: http://www.tstin3d.com/index.html
- The U.S. Centers for Disease Control and Prevention podcast entitled “Mantoux Tuberculin Skin Test” provides a clear, detailed demonstration of the steps involved in administering and reading the test. It can be downloaded free of charge and is available at: http://www2c.cdc.gov/podcasts/player.asp?f=3739# (English only).
- Find TB Resources
  http://www.findtbresources.org

  Education resources and tools specific to TB skin testing are available. One example is mannequin "practice arms" for performing practice injections and/or reading TST reactions.
- Bruce-Grey Health Unit, “TB Skin Test - Mantoux Method”, available on YouTube at: http://www.youtube.com/watch?v=bR86G-itrTQ

OTHER ORGANIZATIONS THAT PROVIDE INFORMATION/RESOURCES ABOUT TB

- Stop TB Partnership/World Health Organization (WHO)
  http://www.stoptb.org
  An international partnership of over 1,000 partners aligned to address and defeat TB. It operates through a secretariat hosted by the World Health Organization.
- World Health Organization
  http://www.who.int/topics/tuberculosis/en
- International Union Against TB and Lung Disease (IUATLD)
  http://www.theunion.org/

  A global initiative to promote social and political action to stop the spread of TB worldwide
- TB Alliance
  http://www.tballiance.org

  This organization is a not-for-profit partnership that leads the search for new TB cures and catalyzes global efforts for new TB drugs.

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APPENDIX D

TUBERCULOSIS AND MYCOBACTERIOLOGY LABORATORY STANDARDS: SERVICES AND POLICIES

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INTRODUCTION

The diagnosis of tuberculosis (TB) is a collaborative effort involving physicians and other health care providers, the public health department and mycobacteriology and clinical laboratories. Before offering mycobacteriology services, each laboratory should assess the level of services required and the capacity and capability for the provision of these services.[1,2] A complete questionnaire for the assessment of a laboratory's capacity for handling *Mycobacterium tuberculosis* complex (MTBC) organisms can be found in the publication *MycobacteriumTuberculosis: Assessing Your Laboratory,* 2009 edition*,* produced by the Association of Public Health Laboratories.[1,2] This appendix addresses some specific standards for the Canadian mycobacteriology laboratory.

LABORATORY REQUIREMENTS

BIOSAFETY REQUIREMENTS

Compared with the general population, laboratory personnel have a 3- to 9-fold greater risk of acquiring latent TB infection.[3,4] Laboratories that handle human pathogens and microbial toxins in Canada must comply with the *Human Pathogens and Toxins Act* (http://lois-laws.justice.gc.ca /eng/acts/H-5.67/index.html) and the corresponding operational and physical biosafety requirements outlined in the Government of Canada's *Canadian Biosafety Standards and Guidelines* (CBSGs) (http://canadianbiosafetystandards.collaboration.gc.ca/cbsg-nldcb/index-eng.php?page=0). The pathogens found within the MTBC are examples of Risk Group 3 pathogens, for which biosafety Containment Level (CL) 3 is required for research and other higher risk activities, but for which certain diagnostic activities can be conducted safely at CL2 with additional practices, as specified in the new MTBC Biosafety Directive. This Directive is a comprehensive overview of the activities and MTBC sample types that can be handled with derogated containment requirements (CL2 with additional physical containment and operational practices). The *MTBC Biosafety Directive* is to be used in conjunction with the Public Health Agency of Canada's CBSG.

REPORTING CRITERIA AND TURNAROUND TIMES

The following are suggested for each laboratory reporting system:

- Established turnaround times and reporting parameters for each testing methodology (Table 1) should be readily available in the laboratory standard operating procedures.
- Reports should be date stamped and signed by the reporting technician.
- Reported information should be disseminated by secure telephone, facsimile or e-mail within 24 hours of test completion and the original hard copy mailed within the following 24 hours.
- Whenever possible, reported results should not be transcribed, in order to avoid transcription errors. Original reports should be forwarded to the appropriate personnel.
- Anticipated delays should be communicated to the client by a preliminary report.
- Reports on non-standardized testing (such as antimicrobials not recommended by the Clinical Laboratory Standards Institute [CLSI] for susceptibility testing) should indicate these limitations.
- Turnaround times should be monitored periodically (monthly) to check compliance and evaluated annually.

Table 1. Summary of standard turnaround times (refer to individual section for more information)[2]

Procedure	Turnaround time to completion/report
Specimen collection and arrival at the laboratory	24 hours
Acid-fast bacteria (AFB) smear microscopy	24 hours from specimen receipt
Nucleic acid amplification testing (NAAT) for MTBC detection	24 hours from smear result or 24 hours from receipt of specimen
Bacteriological diagnosis – culture	Up to 6 weeks for broth cultures and 8 weeks for solid media cultures from specimen receipt
Identification of mycobacterial species	Maximum 21 days from specimen receipt
Primary phenotypic susceptibility testing	15 to 30 days from receipt of specimen in a primary laboratory[5] 7-15 days from a positive culture in reference laboratories
Reporting of all test results (electronically)	24 hours from test completion
Reporting of all test results (mailed hard copy)	48 hours from test completion

QUALITY ASSURANCE AND PROFICIENCY TESTING

All laboratories should be accredited by a recognized national/international accrediting organization and should participate in internal and external quality assurance/quality control activities in conjunction with a reference laboratory. These programs will assess the reproducibility and the inter-laboratory variability of the methods used and adherence to standardized testing procedures.

All laboratories should have a document control system in operation that will detect and correct significant clerical or analytic errors that could affect patient management.[6,7]

LABORATORY SERVICES

RECEIVING AND TRANSPORTING SPECIMENS

Most specimens submitted for mycobacterial culture originate from the respiratory tract, but tissue, sterile body fluids, urine and gastric aspirates are also commonly submitted (Table 2) (see Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). If a laboratory does not have processing facilities, specimens should be referred to a laboratory that does. This should be done within 24 hours of specimen collection to avoid overgrowth by other microorganisms or deterioration of the sample. Specimens should be kept refrigerated at 4 °C (except blood culture and cerebrospinal fluid specimens) if not transported immediately.

All types of clinical specimens are potentially contagious and therefore should be handled with the same procedures. However, cultures of MTBC are much more hazardous than clinical specimens or cultures of nontuberculous mycobacteria (NTM) and require specific procedures for packaging and shipment. Laboratories are required to adhere to the *Transportation of Dangerous Goods Act* Canada) and the *International Air Transport Association's Dangerous Goods Regulations* (for transport by air) when submitting clinical specimens or cultures to another facility. The accepting facility is required to accept and process the incoming specimens according to the relevant acts and regulations. The most current information, legislation and regulations are available from the Pathogens Regulation Directorate: http://www.phac-aspc.gc.ca/lab-bio/about-apropos-eng.php.

Table 2. Ideal specimens for submission to the mycobacteriology laboratory[8,9]

Specimen type	Ideal specimen submissions	Unacceptable specimens
Abscess contents, other aspirated fluid	As much as possible in sterile plastic container.	Dry swab Swabs in anerobic transport medium.
Blood (for culture)* *See section 3.6 for interferon gamma release assays	• 7 mL SPSSPS (yellow top) or • 7 mL heparin (green top) blood collection tube or • 10 mL isolator tube or • 5 mL inoculated directly into Myco/F Lytic medium.	Blood collected in EDTA, which greatly inhibits mycobacterial growth even in trace amounts; coagulated blood; serum or plasma.
Body fluids (pleural, pericardial, peritoneal, etc.)	As much as possible (10–15 mL minimum) in sterile container.	
Bronchoalveolar lavage or bronchial washing	≥5 mL in sterile container.	
CSF	≥2 mL in sterile container.	<0.5 mL
Gastric lavage fluid	5-10 mL in gastric lavage container. Collect in the morning soon after patient awakens in order to obtain sputum swallowed during sleep.	Specimen in which the acidity has not been neutralized.
Sputum (spontaneous or induced)	5-10 mL in sterile, wax-free, disposable container. Do not pool specimens. Where feasible, three sputum specimens (either spontaneous or induced) can be collected on the same day, a minimum of 1 hour apart.	24-hour pooled specimens; saliva.
Tissue biopsy sample	1 g of tissue, if possible, in sterile container without fixative or preservative. Normal saline is acceptable.	Specimen submitted in formalin. Inappropriate because of inability to culture and degradation of DNA for molecular tests.
Urine	Catheter or midstream urine as much as possible (minimum 40 mL) of first morning specimen. For suprapubic tap, as much specimen as possible with needle removed and Luer Lock cap in place. Aspirate can be sent in sterile container.	24-hour pooled specimens; urine from catheter bag; specimens of <40 mL unless larger volume is not obtainable. Urine specimens should only be tested if renal or urinary tract TB is suspected and should not used as a routine screen.

SPS = Specimen Preparation System, EDTA = ethylene diamine tetraacetic acid, CSF = cerebrospinal fluid

DETECTING AND IDENTIFYING MYCOBACTERIUM SPECIES

Mycobacteriology laboratories should have the capability to detect MTBC and NTM using rapid molecular methods. Table 3 illustrates the types of specimens and samples encountered by the mycobacteriology laboratory and the suggested method for detection and identification of AFB in those specimens as well as the resulting cultures.

Table 3. Recommended methods for detection and identification of AFB from clinical samples and cultures[2,9,10,11]

Mycobacterium species	Clinical sample/culture	Detection/identification method
Mycobacterium tuberculosis	Sputum	• AFB staining and smear microscopy • culture • NAAT (commercial or in-house)
Mycobacterium tuberculosis	Tissue (fresh or paraffin embedded) or fluids	• AFB staining and microscopy • NAAT • Culture (if possible; not performed for formalin-fixed or paraffin-embedded specimens)
Mycobacterium tuberculosis	Culture	• Commercial DNA probes/NAAT • gene sequencing (e.g. 16s rRNA, *gyr*B) • line-probe assays
Nontuberculous mycobacteria	Sputum	• AFB staining and smear microscopy • culture • NAAT
Nontuberculous mycobacteria	Culture	• Commercial DNA probes (*M. avium* complex, *M. gordonae, M kansasii*) or commercial NAAT kits • Gene sequencing (e.g. 16s rRNA , *hsp*65 gene , *rpo*B gene) • line-probe assays

NAAT = nucleic acid amplification tests

DIGESTION, DECONTAMINATION AND CONCENTRATION OF SPECIMENS

Digestion, decontamination and concentration of a clinical specimen are commonly performed using the established N-Acetyl-L-Cysteine–sodium hydroxide (NALC-NaOH) procedure.[11] All specimen concentrates should undergo acid-fast smear microscopy and be inoculated to both liquid and solid media.

ACID-FAST SMEAR AND MICROSCOPY

The early and rapid diagnosis of TB still relies on the traditional AFB smear. For rapid results some laboratories perform a "direct smear" from the specimen, without digestion, decontamination and concentration steps. Direct smears are discouraged because of the inherent lack of sensitivity. If direct smears are performed, the result should always be considered as a preliminary step before transfer of the specimen to a reference laboratory where a concentrated (more sensitive) smear can be performed for confirmation. Overall, smears have a reported sensitivity of 20%-80%, depending on many factors including the type of specimen, stain used and the experience of the technologist.[12-15] A minimum of 5,000 to 10,000 bacteria/mL are needed in a sputum sample to obtain a positive result from concentrated smear, as compared with culture, which can detect a bacillary load as low as 10 bacteria/mL.[12]

The following guidelines should be observed:[1,2,10,16,17]

- Slides should be individually stained to prevent cross-contamination.
- Control slides that contain known acid-fast and non-acid fast organisms should be run with each batch of smears prepared.
- All primary specimen smears should be stained and reviewed using the fluorochrome method. Laboratories should confirm new AFB positive smears by a second reader. Smears that are questionable should be repeated or can be stained using a carbol-fuschin method for review.
- Fluorochrome stain performance should be confirmed with each new lot of reagents by reviewing AFB positive and AFB negative control slides prior to reading patient smears.
- For purposes of quality control, 10% of negative slides should be examined by a second qualified person.
- Smears should be reported following an established grading system
(see Chapter 3 Diagnosis of Active Tuberculosis and Drug Resistance).
- Laboratory technologists should read a minimum of 15 smears/week for proficiency.[2]
- Laboratories should participate in an approved proficiency program that includes acid-fast smears.[2]

The American Thoracic Society, U.S. Centers for Disease Control and Prevention (CDC) and the Canadian Thoracic Society recommend that laboratories not performing a minimum of 15 AFB smears/week should refer specimens to another laboratory or reference laboratory.[1,7]

MOLECULAR DETECTION OF MYCOBACTERIA DIRECTLY FROM CLINICAL SAMPLES

Nucleic acid amplification (NAA) tests, which amplify target sequences of DNA or RNA from the MTBC, have several important advantages over smear microscopy and culture.[18,19] They are rapid, have excellent specificity and provide results within 2 to 24 hours. Additionally, they are more sensitive than AFB smears, although less sensitive than TB cultures. They are currently recommended for use only on airway secretion specimens, excluding pleural fluid, although upon special request they can be used on other specimens (e.g. CSF). At least one respiratory sample should be tested with a Health Canada approved or validated in-house NAAT in all new, smear-positive cases. In addition, NAA testing may be performed in smear-negative patients upon request by the physician or the TB control program. NAAT results should not be used for monitoring TB treatment response (see Chapter 3 on Diagnosis of Active Tuberculosis and Drug Resistance) or for infection control purposes (e.g. removal of patient from isolation).

There are many commercially available options that provide rapid, molecular tests for the identification of MTBC in clinical samples (see Medical Devices Active License Listing online query website at http://webprod5.hc-sc.gc.ca/el-le/prepare-search-recherche-mdel-lepim.do?lang=eng).

Health Canada has approved assays from Roche (COBAS® Taqman® MTB; real-time polymerase chain reaction [RT-PCR]), Becton Dickson (BD ProbeTec®, strand displacement amplification), Gen-Probe (Amplified Mycobacterium tuberculosis Direct [AMTD], transcription mediated amplification), Hain Lifescience (GenoType® Mycobacteria Direct, PCR) and Cepheid (Xpert MTB/RIF®, automated, cartridge-based nested PCR). The COBAS® Taqman® MTB, AMTD, and Xpert MTB/RIF tests are approved for direct testing on sputum specimens. The Xpert MTB/RIF (Cepheid, Sunnyvale, CA) system was recently approved by Health Canada, and recommendations for the use of this new assay are provided in Chapter 3. None of the NAA tests can be used to the exclusion of culture and phenotypic drug susceptibility testing (DST), which are required for confirmation of all direct molecular detection testing.[9,20]

False-positive and false-negative rates should be monitored, as the rates can be very high without careful attention to proper technique by highly trained and closely supervised laboratory staff.

In some cases, results may be "indeterminate" because of inhibitors in the specimen or a very low bacterial load. Appropriate controls should be included when applicable to rule out inhibition by the specimen. Special care should be taken to avoid cross-contamination of NAA specimens because of the sensitive nature of these tests. Laboratories should ensure that there is a clean environment and should follow proper molecular testing hygiene in the preparation of solutions used in NAA tests. There should be a physical separation of the laboratory areas used to prepare solutions, to add DNA template and to conduct post-amplification detection.

“In-house” PCR methods targeting the IS*6110* element in the genome of MTBC[21] are less costly than commercially available methods but are less reproducible, are non-standardized and require advanced technical skill. Such methods can be used for detection of MTBC in specimens not recommended for testing with a commercial kit, such as formalin-fixed tissue blocks. The analytical limitations (i.e. limits of sensitivity and processing) of such tests should be reported with the results. Before using an in-house or a “home-brew” molecular assay, laboratories should consult the Clinical and Laboratory Standards Institute (CLSI) guideline, *Molecular Diagnostic Methods for Infectious Disease*[21] for guidance on the validation and implementation of a new molecular diagnostic test. Validation of any new or adapted test methods should be completed to evaluate the performance characteristics and technical competence of the test. All test methods should be verified as being appropriate and adequate before being undertaken.[22]

The design of validation studies should include the following:[21]

- comparison of the new method with a “gold-standard” test;
- evaluation of both inter- and intra-laboratory reproducibility;
- number of samples/isolates determined by a mathematical model or according to validation guidelines where they exist;
- testing of reference strains and isolates exhibiting a range of known, characterized values;
- performance characteristics to be evaluated and the statistical analysis to be used.

Results from NAA testing should be reported as soon as they are available and within 24 hours of a smear- positive result or receipt of the specimen. At a minimum the report should include information on the organism tested, the target of the NAA test and an interpretation of the results. The CLSI MM3-A2 guideline can be consulted for further information.

MYCOBACTERIAL CULTURE

Culture remains the gold standard for a positive laboratory diagnosis of TB.[1,2,20] As outlined in the section on digestion, decontamination and concentration (section 3.2.1), at least one solid and one liquid medium should be inoculated from each clinical specimen for culturing of AFB. Cultures should be kept an average of 6-8 weeks for observation of growth. Positive cultures should be retained for at least 1 year should additional testing be required.[2,10]

It is important to remember that occasionally cultures can be falsely positive for MTBC, primarily because of cross-contamination within the laboratory, although specimen contamination and "mix-up" by the submitter has been documented.[22,23] A report of a single positive culture from a patient with a low clinical suspicion for TB, particularly if the culture has taken much longer than the average time (8-12 days) to become positive, should be reviewed and investigated as a potential false-positive. Laboratories should have an established process in place to investigate possible incidents of cross-contamination or other false-positive cases.

IDENTIFICATION OF MYCOBACTERIAL SPECIES FROM CULTURE

Mycobacterial identification based on biochemical and/or physical characteristics is labour-intensive and slow, and may not adequately identify the organism.[24,25] DNA sequence analysis, such as 16S rDNA gene sequencing, provides rapid, accurate and highly reproducible data and can be used in the absence of organism propagation. Rapid, accurate species identification is a necessity for public health and clinical reasons.[21]

Mycobacteriology laboratories should have the capability to differentiate *M. tuberculosis* from *M. bovis* and *M. bovis* BCG in view of the intrinsic resistance of the latter two organisms to pyrazinamide (PZA), and for public health reporting and investigation. Laboratories not differentiating MTBC organisms should refer to a reference laboratory. Current molecular approaches available for MTBC differentiation include analysis of polymorphisms of the *gyrB* gene,[24] identification of regions-of-difference[25,26] and spoligotyping, and commercial assays.[27-29]

Similar criteria used for identification of the MTB complex should be used for the NTM species. For CL2 and CL3 laboratories that can perform identification tests of the MTBC and other NTM, identification of the *M. avium* complex, *M. kansasii* and *M. gordonae* can be accomplished by the use of commercial DNA probe assays; other mycobacteria can be identified by molecular sequencing targets, such as the 16S rDNA, *rpoB,* the ITS region and *hsp*65 genes.[30-32]

Accurate sequence analysis requires that both the positive and negative strand of DNA be sequenced and analyzed for single nucleotide polymorphisms. For quality control of sequence data, consistent use of a reference sequence should be included in the test procedure. Culture identification should be completed before other testing, such as susceptibility testing, is carried out to ensure that the most appropriate testing method is used and that tests are interpreted accurately.

- **The time frame for culture identification of *M. tuberculosis* complex is dependent on the growth rate of the organism. Culture identification should make use of rapid, state-of-the art technologies such as molecular-based techniques. In the absence of such resources, culture specimens should be sent to a reference laboratory for identification.**[33]

SUSCEPTIBILITY TESTING FOR ANTITUBERCULOUS DRUGS

Agar proportion is still considered the gold standard for MTBC antibiotic DST.[1,5] However, because of the labour-intensive nature and lengthy incubation time for the assay, the more rapid liquid media detection methods using continuous monitoring systems are now recommended.[5,10] The most current CLSI guideline[5] should be consulted for testing parameters.

- Laboratories should perform DST of first-line antibiotics or ensure that this is available for all MTBC cases. First-line antibiotics are:
  - isoniazid (INH);
  - rifampin (RMP);
  - ethambutol (EMB); and
  - pyrazinamide (PZA).
- Second-line DST should be limited to accredited reference laboratories. In laboratories where such DST is not available, culture specimens should be referred to a reference laboratory for testing if resistance to one or more of the first-line antibiotics is detected.
- Second-line DST should be set up when resistance to first-line antituberculous drugs is detected, regardless of whether the first-line DST is repeated.
- Second-line antituberculous drugs for which there are standards[5,34] for DST in Canada include the following:
  - injectable agents (streptomycin, amikacin, kanamycin, capreomycin);
  - fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin);
  - rifabutin;
  - ethionamide;
  - *p*-aminosalicylic acid;[5,10]
  - linezolid.
- Laboratories should test at least one drug from each class;[6] in particular, at least one fluoroquinolone should be tested, and the selection of which fluoroquinolone to test is based on consultation with the physicians who manage most of the patients with drug-resistant TB. Note that streptomycin, ciprofloxacin and ofloxacin are *no longer* recommended for use in the treatment of TB in Canada.[5]
- Although cycloserine is a viable treatment option, the **CLSI does not recommend testing of cycloserine.**[5]

MOLECULAR DETECTION OF ANTITUBERCULOUS DRUG RESISTANCE

The molecular detection of antituberculous drug resistance in MTB has become an important tool in the rapid identification of multidrug-resistant TB. These molecular methods can decrease the time it takes to detect resistance using phenotypic methods and can guide therapy. Molecular detection of MTB and determinants of drug resistance is considered presumptive, and the use of these tests does not eliminate the need for conventional culture and DST. Culture and DST are required to confirm initial results and also detect resistance to drugs other than RMP and INH (see Chapter 3).

These methods should be validated just as any other method would be and used only in conjunction with phenotypic susceptibility testing. The methods include in-house PCR and sequence- based assays, approved commercial line-probe and real-time PCR-based assays.

DNA sequencing is the only technology option to identify both known and novel insertions, deletions or mutations and remains the gold standard for molecular work.[7] Table 4 lists the genes that should be sequenced in order to identify the most commonly encountered molecular determinants of resistance.

Reporting of molecular gene sequence data for antibiotic resistance should include the genetic region tested, nucleotide and amino acid mutation, and the limitations of the testing.[30] **In the absence of a mutation, a statement should be included in the report explaining that the lack of a mutation does not exclude the possibility of phenotypic resistance.**[5,35,36]

Table 4. Genes to be sequenced for the molecular detection of first-line antibiotic resistance[35]

Antibiotic	Gene(s) to sequence for detection of resistance
INH	*inh*A *kat*G
RMP	*rpo*B
EMB	*emb*B
PZA	*pnc*A

GENOTYPING OF M. TUBERCULOSIS

The gold standard for genotyping of *M. tuberculosis* remains IS*6110* restriction fragment-length polymorphism (RFLP) analysis.[37,38] In the majority of cases, the technique has the highest discriminatory power, although this power is limited in cases in which fewer than six copies of the IS*6110* insertion element are present in the genome.

There are many factors that make this method less than ideal:[37,38]

- The technique requires large amounts of DNA and therefore requires weeks of culture growth.
- Strict adherence to the standardized protocol is required for accurate comparisons to be made both between and within laboratories.
- Interpretation of banding patterns is subject to observer bias.

The currently accepted international standard for PCR-based genotyping of MTBC is mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) genotyping.[37,39] This methodology requires very small amounts of DNA and provides a numerical output for ease of comparison.[39] The Public Health Agency of Canada, the Public Health Ontario Laboratories, the US CDC and many European countries have implemented the MIRU-VNTR method as the first-line genotyping test, in conjunction with spoligotyping.[40] Reporting of MIRU-VNTR results should include the order of the loci as they are presented, as this order is not standardized among laboratories. It is essential to be able to re-order the loci for accurate comparison.

MIRU-VNTR genotyping requires a high level of technical expertise and has higher accuracy when capillary-electrophoresis is used, which can be costly. Laboratories should establish technical competency and proficiency with MIRU-VNTR genotyping before embarking on in-house testing. In laboratories where technical expertise is lacking, or where through-put is low and expertise is hard to maintain, specimens should be referred to a reference laboratory for testing. Alternatively, commercially standardized kits are available, which rely on specialized capillary electrophoresis equipment, but they are costly and still require a high level of aptitude with the technique.[40] A proposal for standardization of optimized MIRU-VNTR typing of *M. tuberculosis* has been published.[37,39]

Spoligotyping,[27] another commonly used PCR-based genotyping method, lacks the individual discriminatory power of the MIRU-VNTR, but in conjunction with MIRU-VNTR genotyping it can provide reasonable discriminatory power approaching that of RFLP.[39]

INTERFERON GAMMA RELEASE ASSAYS (IGRA)

IGRA are tests that have been developed for identifying latent TB infection (LTBI). They detect cell-mediated immune responses to specific antigens found in MTBC that are absent from *M. bovis* and *M. bovis* BCG, and most nontuberculous mycobacteria. Detection of a response to these antigens indicates infection with MTB. There are two assays currently approved for use in Canada, the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) (Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.*TB* (T-SPOT) (Oxford Immunotec, Abingdon, UK).

IGRA use whole blood samples and may be performed by any licensed laboratory in Canada. They do not require specialized TB and mycobacteriology laboratory expertise or a CL3 laboratory facility. The assays do, however, require specific technical expertise in specimen collection and transportation, and performing the assay. These skills are available within most laboratories that perform serum, plasma and whole-blood assays for various biological and other markers, but the two IGRAs require specific technical training.

Laboratories should also ensure that specimen collection and transportation, two critical components of the assay performance, can be provided appropriately. As well, standardization of pre-analytical procedures is required, such as tube shaking, time interval between blood draw and incubation, and exact duration of incubation. If portable incubators are used, it is important to make sure that such incubators can accurately stabilize the temperature at 37 °C. Laboratories should avoid manual entry of results, utilizing laboratory information systems where possible to achieve optimal data entry and decrease the risk of data-entry errors. Test kits should be transported and stored in optimum conditions to prevent exposure to excessive heat. Strict quality assurance is necessary to detect unusual patterns in results (such as a spike in the number of indeterminate results due to low mitogen response or high negative control responses), and it is important to run both positive and negative controls with each assay.[41-47]

ASSAY PERFORMANCE, QUALITY ASSURANCE AND RESULTS INTERPRETATION – KEY TECHNICAL INFORMATION

*NOTE: for technical accuracy, the use of the word "must" indicates a requirement that must be followed when obtaining specimens and performing the assays. Please refer to the product inserts (referenced below or as supplied by the kit manufacturers) for specific details.

QFT-GIT[41,42]

Specimen collection

- QFT-GIT has special collection tubes consisting of the Nil Control (grey cap), TB Antigen (red cap) and Mitogen Control (purple cap). Tubes must be kept at room temperature (17-25 °C).
- The TB antigens are dried onto the inner wall of the tubes, so the tube contents, after blood draw, *must be mixed thoroughly.*
- Ensure that a volume of 1 mL is collected into each tube (to the black mark on the tube).
- Tubes must be shaken immediately after blood is collected approximately 10 times, such that the entire inner surface of each tube is coated with blood. Thorough mixing dissolves the heparin in the tubes, preventing clotting, and re-solubilizes the stimulating antigens. Do not shake over-vigorously as gel disruption in the tubes could lead to aberrant results.

Specimen transportation, incubation and processing (pre-analytical)

- According to the product insert, blood tubes must be incubated at 37 °C within 16 hours of collection. However, studies show that immediate incubation is optimal, as this reduces indeterminate results. Thus, incubation within 4 hours would be optimal where feasible.[43,44]
- Before incubation, tubes must be maintained at ambient temperature (22 °C ±5 °C). Do not refrigerate or freeze blood samples.
- If tubes are not incubated immediately after collection, they must be re-mixed by inverting 10 times immediately before incubation.
- Tubes must be incubated upright at 37 °C for 16-24 hours in ambient air.
- After incubation, tubes may be held for *up to 3 days* at 4-27 °C prior to centrifugation.

- Centrifugation of incubated tubes is performed to obtain plasma – the gel plug in the tubes will separate the cells from the plasma; if this does not occur, tubes must be centrifuged again at a higher speed.
- Avoid any mixing of plasma prior to harvesting, and do not disturb material on the surface of the gel plug.
- Only harvest plasma samples using a pipette.
- Plasma samples may be loaded immediately into the QFT-GIT ELISA plate or can be stored for *up to 28 days* at 2-8 ^{o}C, or harvested plasma samples may be stored at –70 ^{o}C for extended periods

Testing (analytical)

- Plasma samples and reagents (except conjugate 100x concentrate) must be brought to room temperature (22 ^{o}C $\pm$5 ^{o}C), equilibrating with room temperature for at least 60 minutes.
- During the assay performance, thorough washing is key – each test well must be completely filled with wash buffer for each wash cycle. *An automated plate washer is recommended.*

Quality control

- QFT-ITG has analysis software available from Cellestis that can be used to analyze the raw data and calculate results; use of the software is recommended.
- The QFT analysis software performs a quality control check of the assay, generates the standard curve and provides a test result for each subject.
- Accuracy of the test results depends on the *generation of an accurate standard curve.*
- The standard curve must be examined before interpretation of the test sample result to determine whether the results meat the expected values.[41]
- If the standard curve criteria are not met, the run is considered invalid and must be repeated.
- If the “zero standard” has a mean optical density that is high (>0.15), then plate washing must be investigated.
- Laboratories should include external quality control samples for testing with patient samples; quality control samples can consist of pooled patient sera for specimens that are known mitogen negative or TB antigen positive and negative, or diluted assay standards.[42]

Result reporting and interpretation (post-analytical), taken from manufacturer’s package insert[41]

Table 5.

Nil [IU/mL]	TB Antigen minus Nil [IU/mL]	Mitogen minus Nil [IU/mL][1]	QFT Result	Report/Interpretation
≤ 8.0	< 0.35	≥ 0.5	**Negative**	*M. tuberculosis* infection NOT likely
	≥ 0.35 and < 25% of Nil value	≥ 0.5		
	≥ 0.35 and ≥ 25% of Nil value	Any	**Positive**[2]	*M. tuberculosis* likely
	< 0.35	< 0.5	**Indeterminate**[3]	Results are indeterminate for TB Antigen responsiveness
	≥ 0.35 and < 25% of Nil value	< 0.5		
> 8.0[4]	Any	Any		

Responses to the Mitogen positive control (and occasionally TB Antigen) can be commonly outside the range of the microplate reader. This has no impact on test results.

Where *M. tuberculosis* infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QFT ELISA. If repeat testing of one or both replicates is positive, the individual should be considered test positive.

Refer to Trouble Shooting section for possible causes.

In clinical studies, less than 0.25% of subjects had IFN-γ levels of >8.0 IU/mL for the Nil Control.

- While the QFT assay cut-off is interferon(IFN)-gamma 0.35 IU/mL, it is important to provide to clinicians who have requested this test the actual numerical value of the result (quantitative value) as well as the interpretation (positive, negative, indeterminate). This information is critical to the interpretation in individuals. Because of recent studies on high rates of IGRA conversions and reversions, and emerging literature on reproducibility, it is recommended that IFN-g values of 0.20-1.00 IU/mL for QFT be interpreted cautiously, as nonspecific variation can result in false conversions and reversions if the initial value falls within this borderline zone (see Chapter 4. Diagnosis of Latent Tuberculosis Infection).

- Reports should include information for the clinician to consider interpretation of the results in light of epidemiologic and clinical findings when assessing the probability of TB infection and disease.

- Guidance should be provided for an indeterminate result related to the following:
    - high Nil (high background interferon production) – does not allow an interpretation to be made
    - low Mitogen (lack of response to antigen stimulation) – does not allow an interpretation to be made and may indicate immunosuppression

Interpretation issues

- Unreliable or indeterminate results may be due to
  - technical failure, including improper protocol
  - excessive levels of circulating IFN-gamma or the presence of heterophile antibodies
  - greater than 16 hours between time of blood draw and incubation at 37 ^{o}C
  - storage of blood outside ambient temperature range (22 ^{o}C $\pm$5 ^{o}C)
  - insufficient mixing of blood collection tubes
  - incomplete washing of the ELISA plate.
- If an indeterminate result is suspected as a result of technical protocol issues (e.g. plate washing), repeat testing.
- Laboratories may consider a repeat test if the result is close to assay cut-off:
  - 0.35-1.0 for positives
  - 0.20-0.34 for negatives.[42]

T-SPOT[45-47]

- The T-SPOT assay uses the ELISPOT technique, which involves incubating peripheral blood mononuclear cells (PBMC) with antigens specific for *Mycobacterium tuberculosis*.

Specimen collection

- Does not require special collection tubes. Blood may be collected in sodium citrate, sodium heparin or lithium heparin containers.
- If T-Cell *Xtend* product will be used, DO NOT use cell preparation tubes (CPT).
- EDTA tubes are NOT acceptable.
- If blood is collected by a syringe and needle, the needle must be removed prior to transferring the blood into a blood collection tube to avoid cell lysis.
- CPT have anticoagulant, separation gel and density gradient liquid, which allow blood collection and PBMC separation to be conducted in one tube.
- Invert tubes 8-10 times to ensure that whole blood is mixed thoroughly with the anticoagulant, and store at room temperature (18-25 ^{o}C) before processing; do not refrigerate or freeze.
- For immunocompetent adults, one 8 mL tube or two 4 mL tubes should be sufficient to obtain enough cells.

Specimen transportation, incubation and processing

- Blood specimens must be processed on the day of blood collection (within 8 hours).
- If using the T-Cell *Xtend* product, whole-blood specimens collected in lithium heparin tubes and stored at room temperature (18-25 ^{o}C) may be processed within 0-32 hours of specimen collection; a gradient separation method (Ficoll) is required for processing.
- Centrifugation is an extremely important step to ensure that enough cells are obtained for the assay; the centrifuge must be able to maintain samples at room temperature.

- After centrifugation, the PBMCs must be isolated immediately using a large-bore pipette tip; if using a CPT, avoid transferring any of the separation gel, which may block the pipette.
- PBMCs must be washed twice in serum-free media (e.g. GIBCO™ AIM-V) and immediately resuspended and mixed in the media that will be used for the overnight incubation.
- Cells must be counted to determine numbers of viable cells available prior to incubation with test wells.

Testing

- T-SPOT requires 2.5 x 10^5 viable PBMCs per test well, and a total of four wells are required for each patient sample (for a total of 1 x 10^6 viable PBMCs per patient):
  - Nil Control
  - Panel A (ESAT-6 antigen)
  - Panel B (CFP-10 antigen) and
  - Positive Control (phytohaemagglutinin [PHA]), which tests for PBMC functionality.
- A new pipette tip must be used for every addition of each patient's cells to avoid cross-contamination between wells.
- Test plates must be incubated at 37 °C with 5% CO_2 in a humidified incubator for 16-20 hours; plates must not be stacked in the incubator as this may lead to uneven temperature distribution and ventilation.
- After incubation, plates must be washed with phosphate buffered saline (PBS) and developer reagents added; pipette tips must not touch the wells, or artifacts may be produced and misinterpreted as spots.
- Medium is removed from the plates by inverting the plate and shaking contents out into an appropriate container; DO NOT remove well contents by pipetting.
- Avoid the use of detergents (e.g. Tween™) in the PBS as this can cause high background counts in the test wells.
- Plates must be allowed to dry completely either in an oven at up to 37 °C for a minimum of 4 hours or overnight at room temperature.
- Counting cells (distinct dark blue spots on the membrane of each well) should be performed by visualizing with a magnifying glass, plate microscope or an ELISPOT plate reader instrument.

Quality control and test result interpretation

(See Figure 1)

- Typical results have few or no spots in the Nil Control.
- A Nil Control spot count in excess of 10 spots should be considered as "Indeterminate".
- If a high numbers of spots or a dark background is observed in the Nil Control wells, the assay reagents and culture media should be checked for contamination.
- Greater than 20 spots should be counted in the Positive Control.

- When the Positive Control is less than 20 spots, it is considered “Indeterminate” (unless panel A or B are “Reactive” as per the Result Reporting below); check to ensure that recommended incubation conditions were used. Weak PHA responsiveness may reflect anergy in the patient.

Result reporting

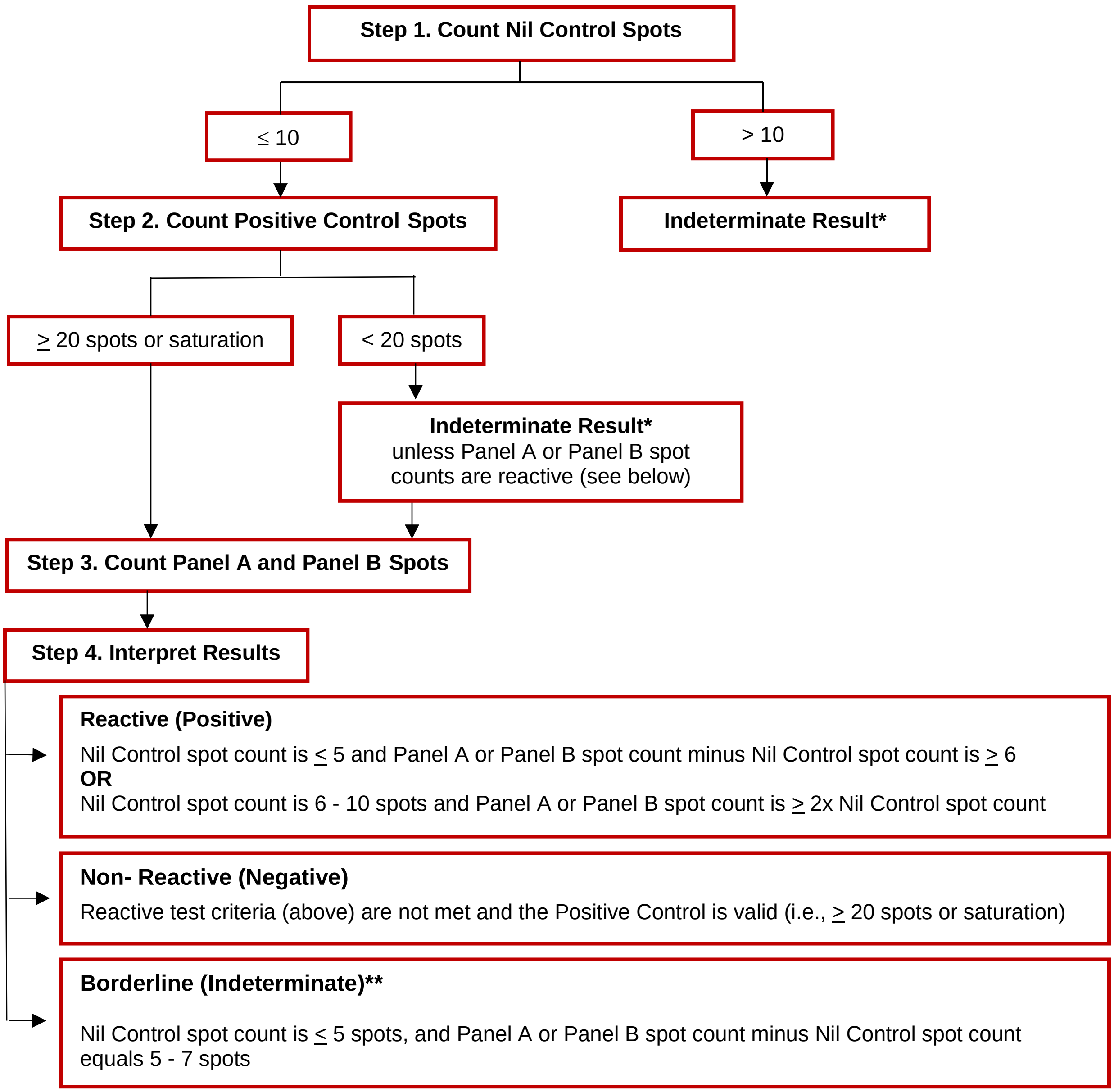
- A test is considered *Reactive*[††] *Positive* if either or both Panel A and Panel B show the following:
  - Nil Control has 0 – 5 spots and (Panel A or Panel B spot count) – (Nil Control spot count) ≥ 6;
  - Nil Control has 6 – 10 spots and (Panel A or Panel B spot count) ≥ 2x (Nil control spot count).

- A test is considered *Non-Reactive* if the above criteria are not met and the Positive control is valid.

- A test is considered *Indeterminate* if:
  - the Positive Control is “*Indeterminate*” and both Panel A and Panel B are “*Non-reactive*” and should be repeated;
  - the Nil Control has 0 – 5 spots and (Panel A or Panel B spot count) – (Nil Control spot count) = 5 – 7.

[††] It is possible that a “Reactive” result may be due to infection with non-tuberculous mycobacteria (M. *kansasii*, M. *szulgai*, M. *marinum* or M. *gordonae*). Alternative tests are required if infection with these organisms is suspected.

Figure 1. Algorithm for interpretation of T-SPOT® .*TB* assays



*Refer to the T-SPOT®.*TB* Technical Handbook for possible causes (may be downloaded from www.oxfordimmunotec.com). It may be necessary to collect a further sample and re-test the individual.

**Result should be considered in conjunction with all available clinical information. It may be necessary to collect a further sample and re-test the individual.

The T-SPOT®.*TB* Package Insert[45] interpretation guide provides an algorithm for interpretation; please refer to package insert for more details and tables (www.oxfordimmunotec.com/CANpageinsert).

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