

6<sup>TH</sup> EDITION

# CANADIAN TUBERCULOSIS STANDARDS



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# CANADIAN TUBERCULOSIS STANDARDS

6<sup>th</sup> Edition • 2007

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# Preface

## Preface

The first edition of the *Canadian Tuberculosis Standards* was published in 1972, with a pediatric supplement in 1974. The second, third, fourth and fifth editions were published in 1981, 1988, 1996 and 2000, respectively.

The fifth edition of the *Standards* represented a substantial revision to its predecessor and was the first to be jointly produced by the Canadian Thoracic Society (CTS) of the Canadian Lung Association (CLA) and Health Canada. The sixth edition is also a joint production, this time of the CTS/CLA and the Public Health Agency of Canada (PHAC), and again represents a substantial revision to its predecessor. Its contents reflect solicited feedback on the quality and utility of the fifth edition, and joint editing by the Chair of the Tuberculosis Committee of the CTS and the Manager, Tuberculosis Prevention and Control, PHAC. While the *Standards* have been jointly funded and produced by both PHAC and CLA/CTS, it is important to note that clinical recommendations are those of the CTS Tuberculosis Committee. In addition to three new chapters, expanded bibliographies and several new appendices, the text is populated throughout by a series of Web site resources that will be regularly updated by PHAC and other agencies. As in the previous edition, treatment recommendations are rated using a roman numeral (I, II, III), which indicates the quality of evidence supporting the recommendation (Gross PA, Barrett TL, Dellinger EP. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. *Clin Infect Dis* 1994;18:421). The rating of non-treatment recommendations is not provided, although at a minimum they are based upon Level III evidence, (opinions of respected authorities, clinical experience, descriptive studies or reports of expert committees). The *Standards* are meant to be a definitive resource on issues pertaining to tuberculosis prevention and control in Canada. In contrast to provincial/territorial guidelines, which describe *how* an action is to be accomplished and frame the structure of care, the *Canadian* (national) *Tuberculosis Standards*, like the *International Standards for Tuberculosis Care* (see Appendix H), provide the foundations on which care can be based, presenting what *should* be done.

PHAC and the CLA/CTS acknowledge that the advice and recommendations set out in the *Standards* are based upon the best currently available scientific knowledge and medical practice. PHAC and CLA/CTS are disseminating this document for information purposes to the medical and public health communities involved in tuberculosis prevention and control activities. These recommendations are intended to inform but not replace consultation with local/provincial/territorial TB authorities with respect to a particular patient or circumstance.

The text is in four sections, **Epidemiology** (Chapter 1), **Medical Aspects of Tuberculosis** (Chapters 2-10), **Public Health Aspects of Tuberculosis** (Chapters 11-17), and **International Aspects** (Chapter 18). Each chapter is now preceded by a table of contents. Key changes are outlined below.

Chapter	Key changes since 5 <sup>th</sup> edition
<b>1. Epidemiology of Tuberculosis in Canada</b>	<ul style="list-style-type: none"> <li>• Canadian goals and targets addressing specific high-risk populations are presented within the context of the targets of the international Stop TB Partnership's Global Plan to Stop TB, 2006-2015.</li> <li>• Reporting forms have been revised (see Appendix B).</li> <li>• The potential contribution of molecular epidemiology is discussed.</li> </ul>
<b>2. Mycobacteriology Laboratory Standards: Services and Policies</b>	<ul style="list-style-type: none"> <li>• This chapter focuses upon laboratory standards and not diagnostic testing. The latter is discussed in Chapter 4, <i>Diagnosis of Tuberculosis Infection and Disease</i>.</li> <li>• The role of provincial/territorial versus national laboratory services is described.</li> <li>• New methodologies, such as DNA fingerprinting, are described along with the standards around their use.</li> <li>• The expectations of reference laboratories with respect to susceptibility testing to first- and second-line antituberculosis drugs are described. Proficiency testing is emphasized.</li> </ul>
<b>3. Transmission and Pathogenesis of Tuberculosis</b>	<ul style="list-style-type: none"> <li>• The role of molecular epidemiology in understanding the dynamics of TB transmission is explained.</li> <li>• Primary TB disease is defined.</li> <li>• The role of host (susceptibility) and pathogen (virulence) genetics in transmission and pathogenesis is considered.</li> </ul>
<b>4. Diagnosis of Tuberculosis Infection and Disease</b>	<ul style="list-style-type: none"> <li>• Tuberculin skin testing (TST) methodology is described in detail and includes illustrations.</li> <li>• The interpretation of the TST is described in three dimensions: size, positive predictive value and risk of development of active TB disease.</li> <li>• The table on risk factors for the development of active tuberculosis among persons infected with <i>Mycobacterium tuberculosis</i> has been revised.</li> <li>• A section on the use of interferon-gamma release assays is included.</li> <li>• The role of nucleic acid amplification tests (NAAT) is described in detail.</li> </ul>
<b>5. Nonrespiratory Tuberculosis</b>	<ul style="list-style-type: none"> <li>• The emphasis continues to be on the high proportion of nonrespiratory tuberculosis among the foreign-born; tables that relate to this are updated.</li> <li>• New information on the diagnosis and treatment of disease in specific sites is provided.</li> <li>• The role of NAAT in the diagnosis of nonrespiratory tuberculosis and the role of molecular epidemiology in nonrespiratory tuberculosis are described.</li> </ul>



Chapter	Key changes since 5 <sup>th</sup> edition
<b>6. Treatment of Tuberculosis Disease and Infection</b>	<ul style="list-style-type: none"> <li>• Where possible the recommendations made in this chapter are consistent with the American Thoracic Society/U.S. Centers for Disease Control and Prevention/Infectious Diseases Society of America statement on Treatment of Tuberculosis (<i>Am J Respir Crit Care Med</i> 2003;167:603-62).</li> <li>• There is an expanded discussion of directly observed therapy.</li> <li>• A position on the use of rifampin plus pyrazinamide for the treatment of latent tuberculosis infection is taken.</li> <li>• A protocol for the follow-up of patients who have completed treatment of active tuberculosis is provided.</li> </ul>
<b>7. Drug-resistant Tuberculosis</b>	<ul style="list-style-type: none"> <li>• New tables on antituberculosis drug resistance in Canada are provided.</li> <li>• There is a revised section on the predictors of drug-resistant tuberculosis.</li> <li>• The section on the management of drug-resistant TB emphasizes multidrug-resistant tuberculosis. It has been updated to take into account several major contributions in the international literature.</li> <li>• The category “extensively drug-resistant” tuberculosis is introduced.</li> </ul>
<b>8. Pediatric Tuberculosis</b>	<ul style="list-style-type: none"> <li>• The layout of the chapter has changed with different headings.</li> <li>• Updated information on diagnostics is taken from several recent reviews.</li> <li>• The role of ethambutol in the treatment of pediatric tuberculosis is discussed in detail.</li> <li>• Contact tracing and aggressive treatment of latent tuberculosis infection are emphasized.</li> <li>• Methods to improve treatment adherence are suggested.</li> </ul>
<b>9. Tuberculosis and Human Immunodeficiency Virus</b>	<ul style="list-style-type: none"> <li>• The Canadian recommendations for the screening and prevention of tuberculosis in patients with HIV and the screening for HIV in tuberculosis patients and their contacts are referenced (<i>Canadian Communicable Disease Report</i>, 15 December 2002;28[ACS-7]).</li> <li>• The important contribution of antiretrovirals to reducing the morbidity and mortality of HIV-coinfected patients is emphasized.</li> <li>• New information on antituberculosis drug–antiretroviral drug interactions and the immune reconstitution inflammatory syndrome is provided.</li> <li>• The importance of HIV testing of contacts of HIV-coinfected tuberculosis patients is emphasized.</li> </ul>
<b>10. Nontuberculous Mycobacterial Disease</b>	<ul style="list-style-type: none"> <li>• New information on the syndromes of disease due to nontuberculous mycobacteria is provided.</li> <li>• The importance of opportunistic nontuberculous mycobacterial disease in those with underlying immunodeficiency is emphasized.</li> <li>• Another area of focus relates to the latest treatment regimens for nontuberculous mycobacterial disease.</li> </ul>
<b>11. The Role of Public Health in Tuberculosis Control</b>	<ul style="list-style-type: none"> <li>• The text of this chapter has been revised in response to two important international documents: 1) U.S. Centers for Disease Control and Prevention. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America (<i>Morbidity and Mortality Weekly Report</i> 2005;54[No. RR-12]:1-81); and 2) Tuberculosis Coalition for Technical Assistance. <i>International standards of tuberculosis care (ISTC)</i>. The Hague: Tuberculosis Coalition for Technical Assistance, 2006.</li> <li>• The role and responsibility of the Public Health Department in tuberculosis prevention and control are clarified.</li> <li>• There is new discussion of the public health challenges in select populations.</li> </ul>

Chapter	Key changes since 5 <sup>th</sup> edition
<b>12. Contact Follow-up and Outbreak Management in Tuberculosis Control</b>	<ul style="list-style-type: none"> <li>The text is revised in response to several new documents, most notably Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and the U.S. Centers for Disease Control and Prevention (<i>Morbidity and Mortality Weekly Report</i> 2005;54[RR-15]:1-37).</li> <li>The table describing the expected prevalence of TST results of <math>\geq 10</math> mm among various Canadian populations has undergone major revision. It is based upon data collected in an independent survey.</li> </ul>
<b>13. Surveillance and Screening in Tuberculosis Control</b>	<ul style="list-style-type: none"> <li>There has been major revision to the section on screening of specific populations, namely those with HIV infection, immigrants, the homeless and underhoused, children and adolescents, First Nations and Inuit communities, correctional facilities and travelers.</li> <li>There is a new section on “Ethical and Legal Considerations for Surveillance and Screening”.</li> </ul>
<b>14. Tuberculosis Control in First Nations and Inuit Populations</b>	<ul style="list-style-type: none"> <li>New</li> </ul>
<b>15. Immigration and Tuberculosis Control in Canada</b>	<ul style="list-style-type: none"> <li>New</li> </ul>
<b>16. Tuberculosis Control within Institutions</b>	<ul style="list-style-type: none"> <li>This chapter was critically reviewed by Steering Committee members of the Public Health Agency of Canada Guidelines Development Program.</li> <li>Major revisions have been introduced into the sections on engineering controls and personal respiratory protection.</li> </ul>
<b>17. Bacille Calmette-Guérin (BCG) Vaccination in Canada</b>	<ul style="list-style-type: none"> <li>This chapter has been revised in accordance with the National Advisory Committee on Immunization statement on bacille Calmette-Guérin vaccine published in <i>Canada Communicable Disease Report</i> (2004;30[ACS 5]). That statement does not recommend routine use of BCG vaccination in any Canadian population. However, it allows that, in some settings, consideration of local epidemiology and access to diagnostic services may lead to the decision to offer BCG vaccination.</li> </ul>
<b>18. Canada and International Tuberculosis Control</b>	<ul style="list-style-type: none"> <li>New</li> </ul>

### New Appendices:

- An Advisory Committee Statement by the Canadian Tuberculosis Committee on the use of interferon-gamma release assays
- Tuberculosis education and training resources
- A summary of provincial and territorial usage of BCG vaccine over time
- Recommendations for the screening and prevention of tuberculosis in patients with HIV and the screening for HIV in tuberculosis patients and their contacts
- A summary of the International Standards for Tuberculosis Care (ISTC)

## Acknowledgements

The editors and associate editors are very grateful to the many persons and groups who contributed to the completion of this edition of the Canadian Tuberculosis Standards. These include, but are not limited to, the following:

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- Steering Committee members of the Public Health Agency of Canada Guidelines Development Program for their thoughtful and critical review of Chapter 16, Tuberculosis Control Within Institutions;
- Other colleagues in tuberculosis prevention and control programs throughout Canada, many of whom served as authors or coauthors (see Appendix A, Contributors), others of whom provided data or peer review;
- Tuberculosis Prevention and Control Program, Public Health Agency of Canada (PHAC), including Jennifer Allison (Administrative Assistant), Kathryn Dawson (Clerical Assistant), Victor Gallant (Data Manager), Linda Gardiner (Production Assistant), Manon Fiset (Administrative Assistant), Melissa Phypers (Senior Epidemiologist), Derek Scholten (Epidemiologist), Dr. Rob Stirling, (Medical Specialist) and Dr. Tom Wong, (Director, Community Acquired Infections Division);
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- Dr. Madhukar Pai, Department of Epidemiology, McGill University;
- Cover photograph of Canadian tuberculosis physicians Drs. R.G. Ferguson and David A. Stewart taken in Saskatchewan in 1935, © 1991 C. Stuart Houston, M.D., R.G. Ferguson, Crusader Against Tuberculosis, page 39, photo by Henry Daneleyko, used with permission.
- many others whose contributions, though less conspicuous, were nonetheless critical to the finished project.

# Epidemiology of Tuberculosis in Canada

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## Background

The World Health Organization (WHO) estimates that one-third of the world population is infected with *Mycobacterium tuberculosis* (TB). In 2004, there were an estimated 8.9 million incident cases and over 15 million prevalent active cases of TB disease. An estimated 1.7 million deaths were attributable to the disease. Approximately 95% of incident cases reported every year occur in the developing world. The spread of the human immunodeficiency virus (HIV), particularly in sub-Saharan Africa, and the emergence of drug-resistant strains threaten to make some cases incurable. No doubt, the original declaration of WHO in 1993 that TB is a “global emergency” remains true today.<sup>1</sup> TB is not a disease of the past!<sup>2</sup>

All provinces and territories legally require reporting of TB to public health authorities. For those cases that meet the Canadian case definition (see Appendix B, Canadian Tuberculosis Surveillance Systems), selected non-nominal demographic, clinical, radiographic, mycobacteriologic, treatment and outcome information is then forwarded to the Canadian TB Reporting System (CTBRS) at the Public Health Agency of Canada (see Appendix B for the current Canadian reporting forms).

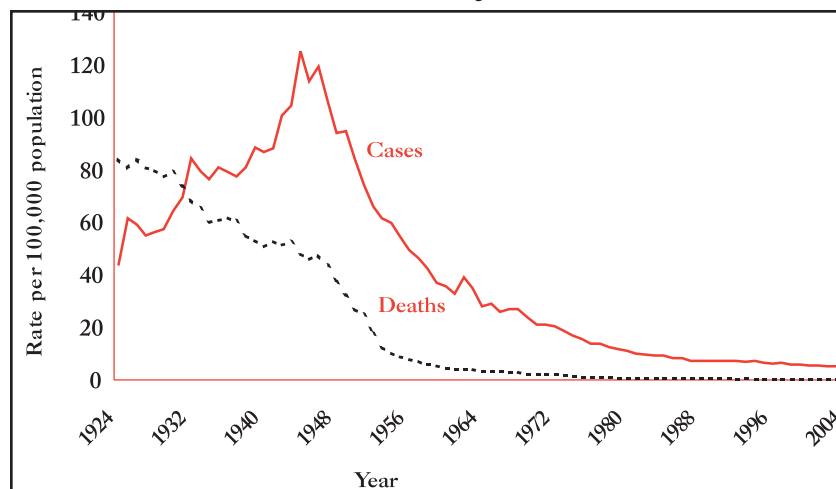
The latest TB reports for Canada are available at:  
<http://www.publichealth.gc.ca/tuberculosis>

The latest WHO reports on TB are available at:  
<http://www.who.int/tb/publications/en/>

## Incidence and Mortality

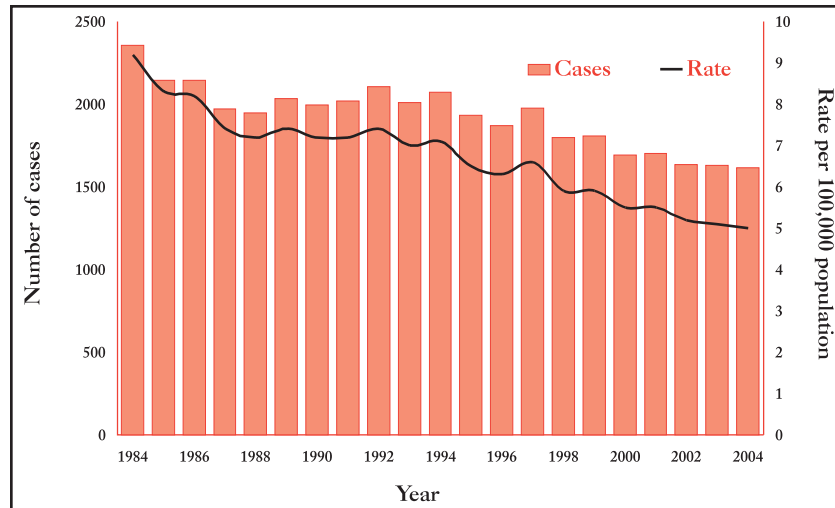
TB was a major cause of morbidity and mortality in Canada throughout the first half of the 20th century. Thereafter, Canadian TB disease and death rates declined rapidly for the most part as a result of improvements in general living conditions and public health measures to interrupt transmission, followed later by effective drug treatment (Figure 1).

Figure 1.  
Tuberculosis incidence and mortality rate in Canada, 1924-2004



Over the past two decades the reported incidence rate and number of cases of TB have continued to decrease (Figure 2). In 2004, the incidence rate of new active and relapsed TB cases was 5 per 100,000 population, reflecting 1,613 new active and relapsed cases (see Appendix C, Definition of Terms for definitions of active and relapsed cases).

Figure 2.  
Tuberculosis cases and incidence in Canada, 1984-2004



In 1997, participants in a National Consensus Conference on Tuberculosis agreed that the Canadian goal of TB prevention and control would be to reduce the annual number of new TB cases by 5% per year.<sup>3</sup> From 1997 through 2004, the annual average rate of decline in cases was 3.0%. In 2006, there was recognition by the Canadian Tuberculosis Committee (CTC) that a more realistic goal was required. Hence, the CTC set a goal to reduce the incidence rate of TB in Canada to 3.6 per 100,000 by 2015. This goal supports the target set in the *Global Plan to Stop TB 2006-2015* to reduce the burden of the disease by 50% as compared with the 1990 rate.<sup>4</sup> Achieving the goal will require a 3% annual reduction in the incidence rate and targeted efforts in the high-risk, origin-based groups.

## Origin Distribution

In Canada most cases of TB occur in two groups: Aboriginal peoples and the foreign-born.

### Canadian-born Aboriginal peoples

The incidence rate of TB in the Aboriginal population, which includes Status and non-Status Indians, Inuit and Métis, has been shown to vary inversely with the time of first contact with European settlers, being higher in those areas last exposed.<sup>5,6</sup> In Manitoba, Northwest Territories, Nunavut, Saskatchewan and Yukon, TB in Aboriginal peoples represents the majority of cases. While

the number of TB cases among Aboriginals has decreased in the past decade, the proportion of TB cases in this population is unchanged. Canadian-born Aboriginal peoples constituted 3.5% of the overall population in 2004 but accounted for 17% of the disease burden.<sup>7</sup> Age-standardized rates revealed a rate of disease 5-fold greater than the national rate and as much as 20 times the rate of non-Aboriginal Canadians. The TB incidence rate has declined slowly over the past decade, resulting in a 2004 rate of 23.8 per 100,000.

While the overall incidence of TB in Aboriginal populations as a whole is higher than among Canadian-born non-Aboriginal peoples, there is wide variation in levels of disease and infection among regions and communities. In 2004, the incidence rate of active TB among Status Indians ranged from 0 per 100,000 in the Atlantic region (Newfoundland and Labrador, Nova Scotia, Prince Edward Island and New Brunswick) to 72.7 per 100,000 in Manitoba. Among the Inuit in Quebec, the incidence rate was 95 per 100,000. For Inuit peoples in the three territories (Yukon, Nunavut and Northwest Territories) the incidence rate was 102.2 per 100,000. Tuberculin surveys and contact investigations among Aboriginal persons > 30 years of age living on reserve demonstrate a heterogeneous prevalence of TB infection, ranging from 12% in British Columbia to 55% in Saskatchewan.<sup>8</sup>

TB is more common in younger age groups of the Aboriginal population than in the Canadian-born non-Aboriginal population. In 2004, the percentages of TB cases less than 15 years of age in the Aboriginal and the Canadian-born non-Aboriginal populations were 21% and 6% respectively, 71% and 52% for those aged 15 to 64 years and 8% versus 42% for people 65 years or older.

### The foreign-born

Over the past decade, an average of 225,000 immigrants and refugees have come to Canada every year, 80% of them originating from countries with a high TB incidence.\* Despite this, the number of cases reported annually in the foreign-born in Canada has not increased substantially since 1970 (Figure 3). The incidence of disease has declined over the past 10 years to a rate of 16/100,000 in 2004, reflective of the larger foreign-born population (Figure 4).

\* High incidence TB countries are defined in Canada as having a rate of sputum smear-positive pulmonary TB (3 year average), as estimated by the WHO, of 15 per 100,000 or greater (<http://www.publichealth.gc.ca/tuberculosis>).



Figure 3.  
Number of tuberculosis cases by origin in Canada, 1970-2004

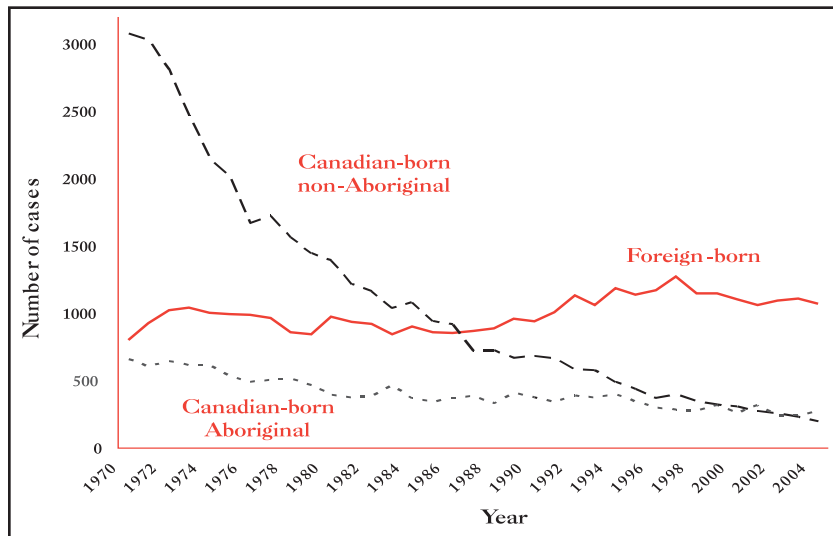
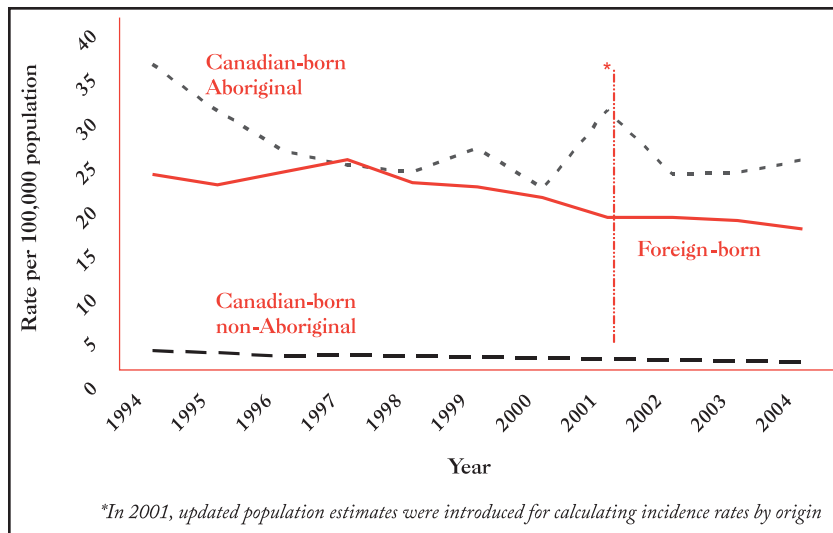


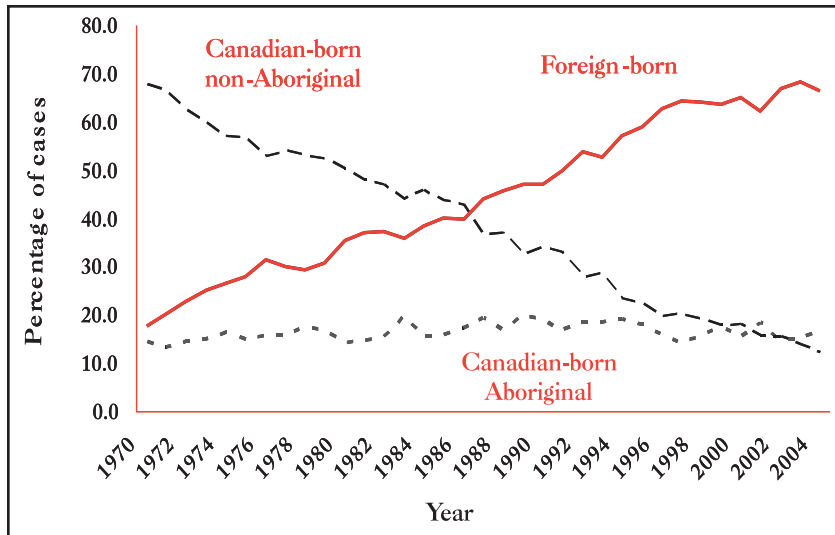
Figure 4.  
Tuberculosis incidence rate by origin, 1994-2004



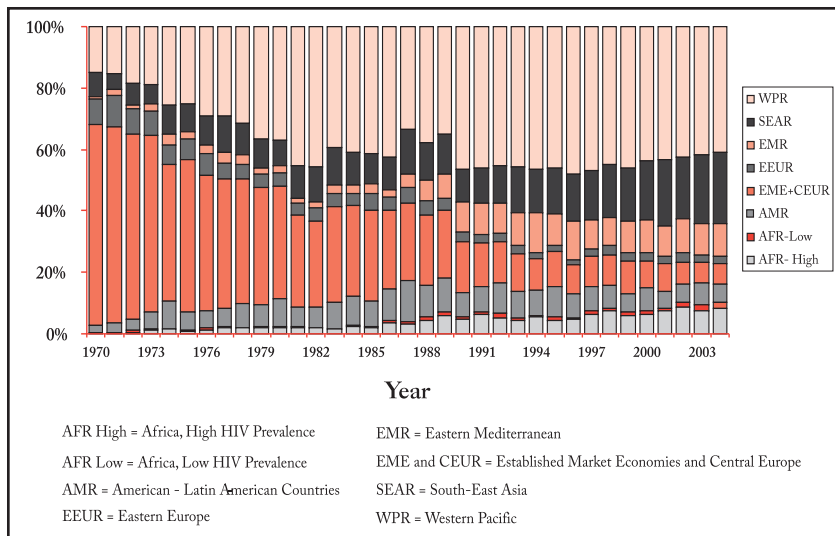
There has, however, been a significant increase in the *proportion* of TB cases among foreign-born persons, rising from 18% of all cases in 1970 to 67% in 2004 (Figure 5). The increased proportion of foreign-born TB cases in Canada is consistent with the shift in immigration patterns over the past 45 years, from countries whose TB rates were similar to Canada's to countries that have much higher rates (Figure 6), as well as with a substantial reduction in the burden of disease among Canadian-born non-Aboriginals (Figure 5). From 1994 to 2004, the proportion of TB cases attributable to the foreign-born population exceeded 50% for the leading immigrant-receiving provinces (Ontario – 82%, British Columbia – 68%, Alberta – 60%, Quebec – 52%). Most foreign-born TB cases

in Canada are reported from major metropolitan areas. Toronto, which received 42% of all immigrants to Canada in 2004, reported that 82% of TB cases were foreign-born.<sup>9</sup>

**Figure 5.**  
Proportion of tuberculosis cases by origin in Canada, 1970-2004



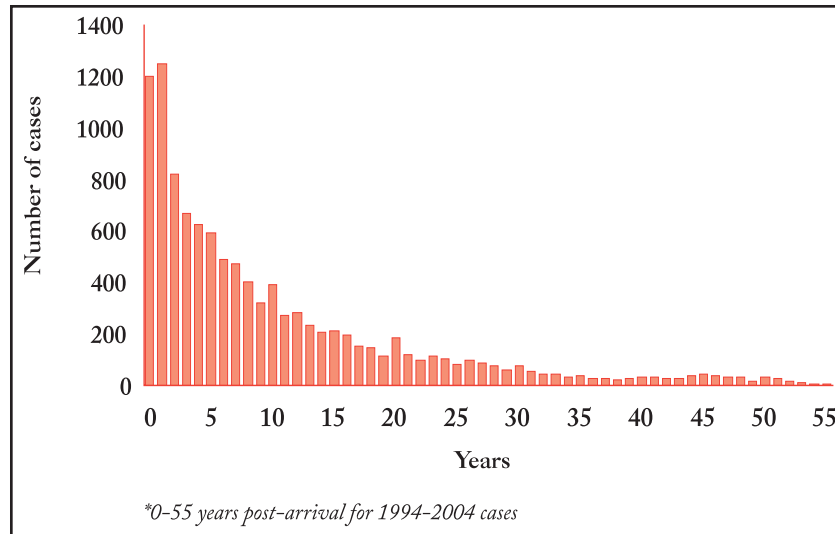
**Figure 6.**  
Foreign-born tuberculosis cases in Canada by WHO TB epidemiologic region, 1970-2004



Immigrants and refugees with latent TB infection (LTBI) are at highest risk of TB disease within the first 5 years of their arrival.<sup>10-12</sup> Of foreign-born TB cases in Canada reported from 1994 to 2004 for which date of arrival was known,

11% were reported to have had TB disease within 1 year, 22% within 2 years and 41% within 5 years of arrival. The risk of TB disease persists for many years after arrival, dropping at a rate of approximately 10% a year (Figure 7).

Figure 7.  
Foreign-born tuberculosis cases in Canada: time from arrival in Canada to diagnosis in years\*



### Canadian-born non-Aboriginal

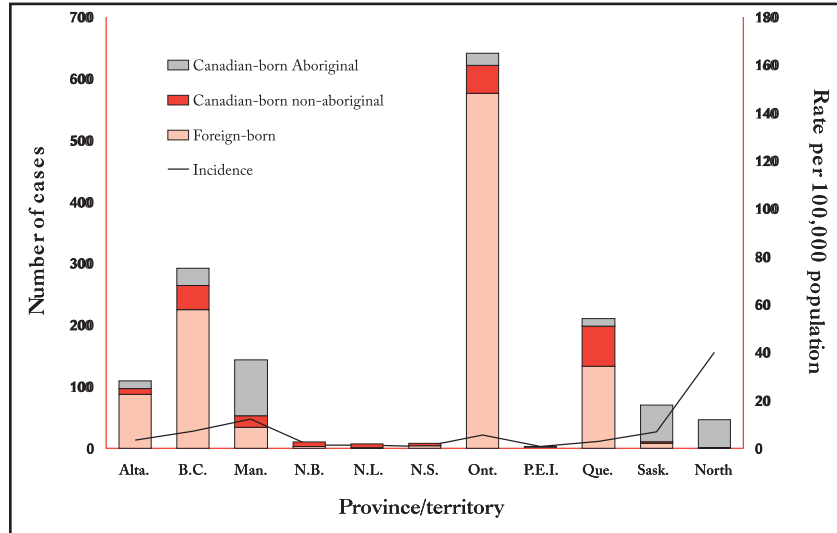
Case reporting among Canadian-born non-Aboriginal individuals continues to fall rapidly. The 2004 incidence rate in this population was 0.8 per 100,000.

### Geographic Distribution

In addition to the above-noted separation along ethnic lines, there are clear delineations in the presentation of TB cases along geographic lines. Whereas the national TB incidence rate was 5.0/100,000 in 2004, provincial/territorial rates varied considerably, from 0.7/100,000 in Prince Edward Island to 107.8/100,000 in Nunavut. The three most populous provinces (British Columbia, Ontario and Quebec), which collectively make up 75% of Canada's population, accounted for 76% of the total reported cases. In the Atlantic provinces (New Brunswick, Newfoundland and Labrador, Nova Scotia and Prince Edward Island), the reported numbers and incidence rates were very low, and cases occurred predominantly in the Canadian-born non-Aboriginal population (Figure 8).

Increasingly in developed countries TB is an urban disease. In 2004, 66% of all TB cases in Canada were reported from the 11 census metropolitan areas of 500,000 persons or more (Calgary, Durham Region [Ontario], Edmonton, Hamilton, Montreal, Ottawa, Peel, Toronto, Vancouver, Winnipeg and York Region [Ontario]).

Figure 8.  
Distribution of tuberculosis cases by origin and incidence,  
provinces/territories, 2004



### Age and Sex Distribution

While the number of reported cases and incidence rates have always been higher among males, there has been a noted decrease in the differential between males and females over the past several years (Figure 9). In 2004, the reported number of cases was highest for those aged 65 years and older, although this varied by origin (Figure 10).

Figure 9.  
Tuberculosis incidence rate by sex in Canada, 1984-2004

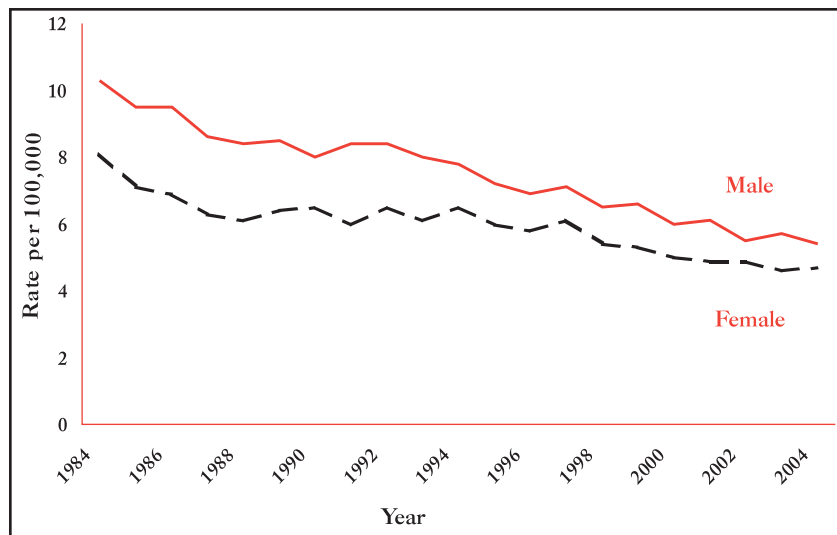
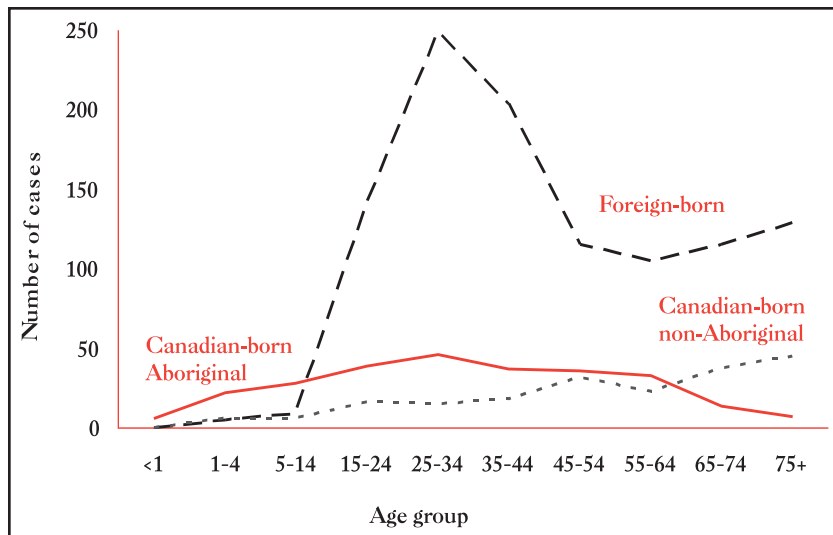


Figure 10.  
Tuberculosis cases by age group and origin in Canada, 2004

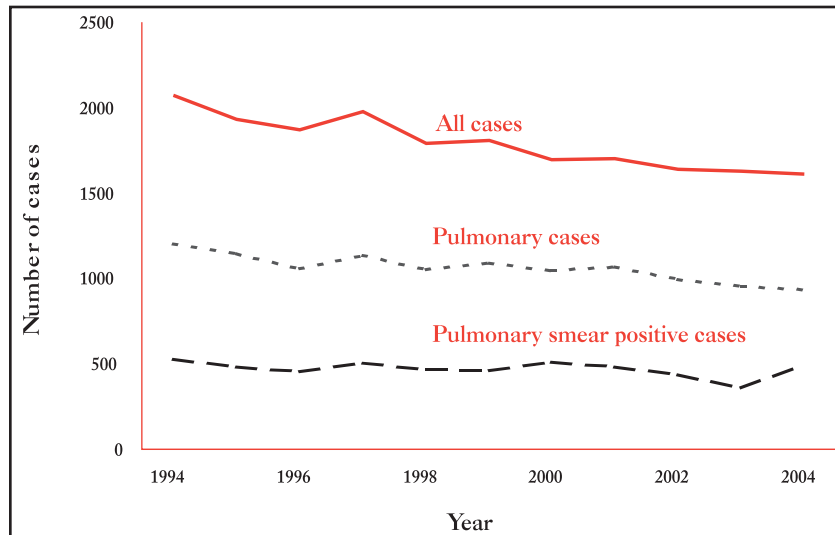


### Disease Site

Overall, respiratory TB (see Appendix C, Definition of Terms) was the most frequently reported diagnostic site, representing 70% of 1,613 reported cases in 2004. The proportion of TB cases by diagnostic site and origin varied considerably. Whereas respiratory TB accounted for 85% of Canadian-born non-Aboriginal cases, this proportion was considerably lower for Canadian-born Aboriginal cases (78%) and foreign-born cases (65%). The foreign-born present more often with nonrespiratory TB, whereas the Canadian-born Aboriginal population accounts for the majority of primary TB. More severe forms of disease, such as central nervous system TB, are rare, accounting for only 1% of reported cases. Similarly, miliary/disseminated TB is infrequently diagnosed, representing 2% of reported cases.

Most TB cases in Canada are diagnosed by culture: in 2004 this number was 1,305 (81%). In that year, of the 936 cases of pulmonary TB reported, 465 (49%) were smear positive, denoting the most infectious form of the disease. Over the past decade, the proportion of TB cases reported as pulmonary, smear positive, has been approximately 30% of the total reported cases and 50% of the reported pulmonary cases (Figure 11).

Figure 11.  
Pulmonary sputum smear-positive tuberculosis cases in Canada, 1994-2004



### Method of Detection

The three main methods of TB detection are (1) the recognition of presenting symptoms, (2) contact investigation and (3) screening. The vast majority of cases in 2004 were detected as a result of symptoms referable to the site of disease (75%). The method of detection differed by origin (Table 1).

Table 1.  
Origin and Principal Methods of Detection  
of TB Cases: Canada, 2004

Method	Origin (% of cases)		
	Canadian-born Aboriginal	Foreign-born	Canadian-born non-Aboriginal
Presentation of symptoms	57	81	69
Screening and contact investigation	32	6	12
Immigration screening	0	6	0
Other	11	7	19

### *Mycobacterium tuberculosis*-HIV Coinfection

The HIV epidemic has had a dramatic impact on TB rates and control globally. It is estimated that one-third of the 40 million people living with HIV/AIDS worldwide are coinfecting with TB.<sup>13</sup> Globally, TB is the most common cause of death among HIV-infected individuals, accounting for approximately one-third of AIDS deaths annually.<sup>1</sup> Conversely, in 2004, 15% of persons dying from TB were coinfecting with HIV.<sup>2</sup>

In Canada, there have been limited data so far on the prevalence of *M. tuberculosis*-HIV coinfection at the national level. A study that examined the interaction through the Canadian AIDS surveillance system found that 5.6% of the cumulative AIDS cases reported in Canada between the years 1994 and 2003 also had TB. Of these, two-thirds were foreign-born and almost one-tenth were of Aboriginal origin.<sup>14</sup> In another study, of TB cases diagnosed in 1997 and 1998, 22% had a record of an HIV test, and among those whose test results were known the prevalence of HIV infection was 15%. For the entire cohort, the prevalence of HIV was 3%. When HIV status was known, cases were more likely to be coinfecting if they were either 15 to 49 years of age, male, Canadian-born non-Aboriginal or had both pulmonary and extrapulmonary TB disease and known HIV risk factors.<sup>10,15</sup> Within the CTBRS, 374 TB cases (23% of all TB cases) included a report of HIV status in 2004. Of these, 38, (10%) were positive. Reports of testing are likely biased toward testing in persons with pre-existing risk factors for HIV. The WHO estimated that 8.7 % of new adult TB cases in Canada were coinfecting with HIV in 2004.<sup>2</sup>

## Drug Resistance

Drug-resistant strains of TB are a global threat to prevention and control efforts. A report produced by the WHO and the International Union Against Tuberculosis and Lung Disease describes resistance patterns in 77 geographic settings in 62 countries. The median prevalence of resistance to any of isoniazid, rifampin, ethambutol or streptomycin was 10.4%: 10.2% in new cases and 18.4% in previously treated cases. The median prevalence of multidrug resistance (MDR) was 1.7%: 1.1% in new cases and 7.0% in previously treated cases.<sup>16</sup>

The Canadian Tuberculosis Laboratory Surveillance System (CTLSS) found that 12.4% (168) of *M. tuberculosis* isolates were resistant to one or more of the antituberculosis drugs isoniazid, rifampin, ethambutol, pyrazinamide or streptomycin in 2004. Resistance to isoniazid was reported in 100 cases (7.4%), and MDR was reported in 12 cases (0.9%). In addition, Alberta, British Columbia, Manitoba and Ontario reported isolates with other patterns of resistance to multiple drugs. Six provinces and territories (Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island and Yukon) reported that all isolates tested were susceptible to first-line antituberculosis drugs. There has been no significant increase in reported drug resistance since this reporting system began in 1998.<sup>17</sup>

The CTBRS has similar information on TB drug resistance but with the addition of epidemiologic information. For cases reported in 2004, 5% of all cases and 7% of foreign-born cases were resistant to a first-line drug. Overall, foreign-born cases are 6 times more likely to be drug resistant and 10 times more likely to be MDR than Canadian-born cases (1997-2004). All previous Canadian studies have noted foreign birth to be a significant factor associated with drug resistance.<sup>10,18-23</sup>

Resistance acquired during treatment is rare in Canada. From 1997 to 2004, less than 1% of all cases were reported as having acquired drug resistance, and isoniazid accounted for 73% of all such resistance.

Extensively drug-resistant (XDR) TB is MDR-TB that is also resistant to any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin). Tuberculosis Prevention and Control, Public Health Agency of Canada, began collecting information on second-line drug resistance for all MDR isolates in 2006. Future reports of the CTLSS will include data on the extent of XDR-TB in Canada.

## Treatment Outcomes

Of the 1,613 cases diagnosed in 2004, 1,284 cases had a treatment outcome reported in 2005. When treatment outcome status was known, the majority of cases were reported as cured or treatment completed (973 cases, 76%).

Drug regimen reporting was complete for 632 cases. Of these cases 83% were given three or more antituberculosis drugs. Fifty-five percent of individuals were reported to have received directly observed therapy (DOT), 40% self-administered therapy (SAT) and 5% an unknown treatment method. No significant difference in treatment outcome has been observed between those who received DOT and those who received SAT. This may be due to selective use of SAT for individuals who are more adherent to treatment.

The Public Health Agency of Canada provides outcome data to the WHO on an annual basis. This reporting focuses on pulmonary smear-positive cases and the treatment outcome of these cases by major mode of treatment (e.g. DOTS or non-DOTS). The WHO 2015 global targets for TB include 70% detection of all pulmonary smear-positive cases and an 85% cure or treatment completion of these cases. In 2003, the WHO adjusted its reporting to include laboratory-confirmed pulmonary cases in those countries that routinely use cultures or other laboratory methods. For cases beginning treatment from 1997 through 2004, the average cure/treatment completion rate for Canada was 79%.

Of the 1,284 cases with an outcome reported, 139 (11%) were reported to have died during treatment. TB was the underlying cause of death in 27 cases (20%). TB contributed to death but was not the underlying cause in 55 cases (40%).

## Insights from Molecular Epidemiology

In recent years, the combination of conventional epidemiologic data with molecular genotyping of *M. tuberculosis* isolates has permitted the development of the discipline called molecular epidemiology. Since the incubation period from acquisition of TB infection to the development of TB disease can vary from weeks to decades, the use of molecular genotyping to infer transmission patterns has proven to be an efficient means of addressing epidemiologic questions not amenable to standard epidemiologic investigation. While the methods are provided in Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies, this section describes some of the epidemiologic lessons learned from *M. tuberculosis* genotyping that have been performed in two Canadian settings: (1) research groups pursuing defined epidemiologic questions and (2) provincial laboratories and the National Microbiology Laboratory, Winnipeg, in response to specific queries about patient and outbreak management.



Molecular typing has been very useful for identifying identical or near identical isolates (called clusters) within geographic areas or specific populations. Inferences about transmission can be made by linking this information with conventional epidemiology. Two studies of TB in the Inuit indicate significant clustering with likely recent transmission. One study found only a single case of inter-village transmission, while the other found inter-village transmission to be surprisingly common.<sup>24,25</sup> These findings suggest that optimal TB control needs to be tailored to the local transmission patterns.

Population-based studies have been performed in Montreal, Vancouver, Alberta and western Canada in order to infer the proportion of TB in the community attributable to chains of transmission. In Montreal, only 4% to 18% of cases represented recent transmission, depending on the criteria used for matching of molecular types.<sup>26</sup> However, ongoing spread has been demonstrated in the Haitian community, suggesting that this a group that may benefit from more targeted attention.<sup>27</sup> In Greater Vancouver, molecular typing showed that about 12% of cases represented recent transmission.<sup>28</sup> Only 8% of clusters were identified by conventional epidemiology. In this study, the risk factors for being a member of a molecular cluster were being Aboriginal less than 60 years old, being Canadian-born non-Aboriginal over 60 years old, and using intravenous drugs. Again, there was evidence of transmission within certain high-risk groups that may benefit from intensified contact tracing and surveillance. Since these studies found that the majority of cases result from reactivation, overall reductions in rates would likely require interventions aimed at persons with LTBI.

In a population-based study of 5 years of TB cases in Alberta, clustering and a transmission index were highest in Status Indians and lowest in the foreign-born, even though the number of cases was greatest in the foreign-born.<sup>29</sup> A study of four western provinces demonstrated similar clustering trends.<sup>30</sup> Multivariate analysis indicated that Aboriginal origin, living in a shelter the previous year and HIV coinfection were risk factors for clustering. Again, molecular typing permits identification of likely transmission and will allow TB control programs to focus resources according to these analyses.

## Conclusions

Although the TB incidence rate and the number of cases continue to decline in Canada, the concentration of the disease in groups that are defined by geographic region and demographic features creates new challenges that must be addressed in prevention and control strategies, both nationally and at a provincial/territorial level. The high proportion of TB cases that are foreign-born and the higher burden of drug resistance in this population demand increased efforts at global control of the disease, enhanced surveillance activity among immigrants and refugees, and targeted treatment of LTBI. As this population ages, the impact on the disease burden may increase.

Similarly, the limited decline in the incidence rate of TB among Canadian Aboriginal peoples, particularly in the Prairie provinces and the territories, calls for increased attention and resources targeted at this unacceptable level of disease. Ancillary health care services, which include TB control programs, have

been delivered to individuals on reserve by the First Nations and Inuit Health Branch of Health Canada. As responsibility for these activities is gradually transferred to individual Aboriginal communities, it is critical to maintain and coordinate TB control activities among the various jurisdictions dealing with mobile Aboriginal populations.

Molecular typing has helped confirm that most TB in this country appears to be due to reactivation disease. However, clear evidence of ongoing spread has been demonstrated in certain communities, where more intensive TB control might be of relatively immediate value.

Finally, the spread of HIV into populations at high risk of being infected with *M. tuberculosis* is considered a legitimate threat to TB control in Canada. In order to accurately assess the extent of TB-HIV coinfection in Canada and to ensure that effective treatment and the delivery of appropriate care and prevention programs are delivered, a further increase in testing and reporting is essential.

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# Mycobacteriology Laboratory Standards: Services and Policies

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## Mycobacteriology

The *Mycobacterium tuberculosis* complex (MTBC) is a genetically related group that currently encompasses *M. tuberculosis* (including *M. tuberculosis* subsp. *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 (TB) (see Appendix B). The species differ in host preference; hence species identification can contribute to the epidemiologic picture (see Chapter 1, Epidemiology of Tuberculosis in Canada).

In general, the MTBC has an infectious dose of 1-10 bacteria and is transmissible by the aerosol route. The organism is observed microscopically as an acid-fast bacterium and is remarkable for its serpentine cording formation in liquid media. However, as other members of the genus can exhibit this characteristic, laboratories should be wary of using cellular morphology for identification. Recently, newer testing methods have evolved, such as nucleic acid amplification tests and nucleic acid probes. They have been implemented in most mycobacteriology laboratories to rapidly identify the MTBC in processed clinical samples and cultures.

This chapter outlines the general services offered by a mycobacteriology laboratory with emphasis on the importance of state-of-the-art technologies with rapid turnaround times, reporting procedures and regionalization of services. The roles of laboratory services in training, decision-making and policies for TB control are also addressed. A section on standards for the future mycobacteriology laboratory considers assessment of capacity, capability and cost.

## Laboratory Services

### Specimen receiving and transport

Samples are to be carefully packaged before being sent to the laboratory. Most specimens submitted for mycobacterial culture originate from the respiratory tract, but tissue, sterile body fluids, urine and gastric aspirates are also commonly submitted (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease). If a laboratory does not have processing facilities, specimens should be referred to a laboratory with such a capability. This should be done promptly – within 24 hours of specimen collection – to avoid overgrowth by other microorganisms.

Laboratories are required to adhere to the *Transportation of Dangerous Goods Act and Regulations* (TDG) (Canada), (<<http://www.tc.gc.ca/acts-regulations/GENERAL/T/tdg/menu.htm>>), when transporting clinical specimens or cultures to another facility. This legislation is administered by Transport Canada and defines the labelling, packing and documentation requirements that are necessary for shipping infectious substances, including diagnostic specimens, within Canada. In addition to any requirements of the *Act*, the accepting facility must be able to accept and process the incoming specimens.\* Requisitions

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\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

should be sent with the package. Minimum information to be provided includes a unique identifier (i.e. patient and/or referring laboratory identifier), the date of collection/subculture, the specimen type and site, the requested test and the ordering physician. All types of clinical specimens and cultures are potentially contagious and must be handled appropriately and transported in accordance with the *Transportation of Dangerous Goods Act and Regulations* (TDG) (Canada).

## Biosafety

Compared with the general population, laboratory personnel have a three to nine times greater risk of acquiring latent TB infection.<sup>1,2</sup> Compliance with biosafety practices as outlined in the Laboratory Biosafety Guidelines and other standards for working with cultures of MTBC is critical.<sup>2-5</sup>

- Preparation of primary smears and cultures can be done in a containment level 2 (CL2) physical environment with CL3 operational practices, while manipulation of positive cultures must be carried out under CL3 physical and operational constraints.\*
- A biosafety cabinet must be used for all manipulations (clinical specimens and cultures).\*
- Centrifuges should be equipped to provide aerosol containment by having safety caps for each bucket.
- As demonstrated by in-house testing,<sup>6,7</sup> it is strongly recommended that fixation of slides render the material nonviable.
- All risk group 3 material leaving the CL3 area for shipping to another laboratory should be contained as per TDG regulations.
- All risk group 3 material should be deemed “nonviable” before being manipulated in CL-2 conditions.<sup>7</sup> This applies particularly to molecular work performed on any biomolecules extracted from specimens.<sup>7</sup>
- MTBC is noted to be resistant to many disinfectants. The most effective disinfectants for mycobacteria are phenolics, glutaraldehyde and formaldehyde (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease).
- It is the responsibility of a laboratory supervisor in conjunction with a Biosafety Officer to have in place a formal training program with standard operating procedures (SOPs) reflecting stringent adherence to safety guidelines. An official program of medical surveillance should be in place to monitor the tuberculin skin test (TST) and health status of all staff.<sup>2,4,8</sup> All biosafety failures should be documented and reviewed to prevent recurrence.

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\* A recommendation of the Canadian Thoracic Society’s Tuberculosis Committee



## Digestion, decontamination and concentration of specimens

Digestion, decontamination and concentration of a clinical specimen are commonly performed using the established NALC-NaOH procedure.<sup>9</sup> The concentration of NALC is critical, as a high concentration can result in a lower yield of mycobacteria and a low concentration can result in overgrowth of the culture with contaminants. The time of exposure is also critical to organism viability.<sup>9</sup> Both these factors need to be taken into account, and a laboratory should devise a protocol based on recent information available from published articles and from verification studies done in house.

- For direction on collection of specimens, please see Chapter 4, Diagnosis of Tuberculosis Infection and Disease. All specimen concentrates should have a smear for acid-fast bacteria (AFB) microscopy and be inoculated into both liquid and solid media.
- Steps should be taken to eliminate laboratory cross-contamination during processing of samples.
- Access to genotyping services is required to confirm or discount suspected laboratory cross-contamination.

## The 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 referral laboratory where a concentrated (more sensitive) smear can be performed for confirmation. Overall, smears have a reported sensitivity of 22%-65%.<sup>10</sup> 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.<sup>11</sup> The following guidelines should be observed:<sup>5,12-16</sup>

- The American Thoracic Society (ATS), U.S. Centers for Disease Control and Prevention (CDC), Canadian Thoracic Society and the Public Health Agency of Canada recommend that laboratories not performing a minimum of 10 AFB smears/week should refer specimens to another laboratory.
- Mycobacteriology laboratories should include positive and negative control slides for both incoming specimens and each new batch of stains prepared for quality control purposes.
- Slides should be individually stained to prevent cross-contamination.
- The fluorochrome stain should be the primary stain to detect AFB.<sup>13</sup> All positive smears should be confirmed by either carbol fuchsin staining or reading by another qualified individual.

- For purposes of quality control, 10% of negative slides should be examined by a second qualified person.
- Caution should be exercised when interpreting smears. Observed AFB can be MTBC, nontuberculous mycobacteria (NTMs) or, on rare occasion, nonmycobacterial organisms, such as *Nocardia* and actinomycetes, which can be weakly acid fast.
- Smear results should be reported within 24 hours of specimen receipt.
- Smears should be reported following an established grading system (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease).
- Negative slides should be retained until the final culture report has been issued.
- All positive slides should be kept for at least 1 year.

### Mycobacterial culture

Culture, as the gold standard for a positive diagnosis, is highly recommended for laboratory diagnosis.<sup>5</sup> As outlined in the section on digestion, decontamination and concentration, at least one solid and one liquid medium should be inoculated for culturing of AFB.<sup>5</sup>

- Broth and solid media should be monitored for a minimum of 6 and 8 weeks respectively before reporting as culture negative.
- Contamination of a positive AFB culture in liquid media should be verified by a blood agar sterility check, and detection of a mixed species population can be determined by subculture to a Middlebrook plate.
- Resubmission of one or more samples is recommended in the event of a positive smear but negative culture.
- A positive culture should use a rapid method (i.e. genetic probes) to conclusively identify MTBC.
- The laboratory should stock all cultures for a minimum of 1 year.

It is important to remember that cultures can occasionally be falsely positive, largely because of cross-contamination within the laboratory.<sup>17,18</sup> A report of a single positive culture, especially with a long detection time and/or few colonies and when clinical suspicion is low, should raise the possibility of a false-positive culture. The laboratory reporting this culture should investigate, ideally performing DNA fingerprinting on the isolate and all other isolates detected within that time frame.

### Nucleic acid amplification testing

Positive smears can be tested by an amplification test. Nucleic acid amplification (NAA) tests, which amplify target sequences of DNA or RNA from the *M. tuberculosis* organisms, are complex and expensive tests but have several important advantages.<sup>19,20</sup> They are rapid, have excellent specificity and provide

results within 3 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 that are smear positive, although upon special request they can be used on other specimens (e.g. cerebrospinal fluid).

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.

- When the test is applied to airway secretions, it is recommended that only processed and concentrated specimens be used.
- Results may be “indeterminate” because of inhibitors in the specimen or a very low bacterial load. The test can be repeated on the original specimen and, if it is still indeterminate, a new specimen may be obtained for repeat NAA testing.
- NAA testing should be performed on specimens from untreated patients. It should not be used to assess response to treatment.
- Results should be reported within 24 hours. For more information on these tests, please refer to Chapter 4, Diagnosis of Tuberculosis Infection and Disease.

### In-house polymerase chain reaction (PCR) testing

Early studies of NAA tests for detection of MTBC were performed by research laboratories with “in-house” PCR kits targeting the IS6110 element in the genome of MTBC.<sup>21</sup> These are less costly but less reproducible, are nonstandardized 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. For example, a disclaimer should be attached to the report: “*The sensitivity of the in-house PCR testing is not well established, and a negative PCR result **does not** exclude the possibility of infection. There are many documented factors that can compromise the sensitivity of this PCR, including DNA degradation in stored material, insufficient extractions and/or inadequate sampling from the specimen.*”<sup>22,23</sup> Newer detection methods involving real-time PCR or single nucleotide polymorphism detection are currently being evaluated.

### Identification of mycobacterial species

Mycobacterial identification based on biochemical and/or physical characteristics is a labour-intensive, slow, often limited process.<sup>24,25</sup> Methods based on molecular gene target sequencing, such as 16S rRNA, provide rapid, concise, tangible data and can be used in the absence of organism propagation. Rapid, accurate species identification is a necessity for both epidemiologic studies and determination of general antimicrobial susceptibility patterns.

For these reasons, mycobacteriology laboratories performing susceptibility testing should differentiate *M. tuberculosis* from *M. bovis* and *M. bovis* BCG because of the intrinsic resistance of the latter two organisms to pyrazinamide and the impact on epidemiologic tracing. Current molecular approaches available for MTBC differentiation include analysis of polymorphisms of the *gyrB* gene,<sup>26</sup> regions-of-difference schemes<sup>27,28</sup> and spoligotyping.<sup>29</sup>

Similar criteria used for identification of the MTB complex should be used for the NTM species. For level II and III laboratories that can perform identification tests of the MTBC and other, nontuberculous mycobacteria, identification of the *M. avium* complex, *M. kansasii* and *M. goodii* can be accomplished by the use of AccuProbe kits (GenProbe); other mycobacteria can be identified by molecular sequencing targets such as the 16S rRNA gene.<sup>24,25,30</sup>

- Upon sequence analysis it is recommended that both amplified primer strands be examined for single nucleotide substitutions.
- For quality control of sequence data, consistent use of the reference sequence should be instituted into the test procedure.
- Culture identification should be completed before other testing, such as susceptibility testing, is carried out in order to apply the correct interpretation.

Culture identification of *M. tuberculosis* complex should be reported within 21 days of specimen receipt.<sup>2,13</sup> However, this time frame is dependent on the growth rate of the organism. Culture identification should make use of rapid, state-of-the-art technologies such as DNA probes or molecular-based techniques. In the absence of such resources, cultures should be sent to a reference laboratory for identification.<sup>31</sup> The following elements should be identified in the report:<sup>25</sup>

- the phenotypic/genotypic method used;
- the gene target and nucleotides analyzed; and
- the reference sequences and/or sequence databases used.

### ***Mycobacterium leprae* Detection**

The diagnosis of leprosy is routinely based on acid-fast staining of the specimen in the correct clinical context in conjunction with characteristic histopathological features.<sup>32</sup> As the organism cannot be cultivated and there are currently no approved blood tests for diagnosis in place, PCR for detection is a feasible option. In the absence of stringent methodological validation and the use of appropriate controls, specimens should be referred to a facility specializing in leprosy PCR, such as the National Hansen's Disease Program, Baton Rouge, Louisiana, U.S.A.<sup>32</sup>

### **Genotyping of *M. tuberculosis***

The current gold standard for DNA fingerprinting is restriction fragment-length polymorphism (RFLP) analysis based on the IS6110 transposable element.<sup>33</sup> RFLP has high discriminatory power and extensive application in

historical databases. There are, however, technical limitations to the method due to the nature of the test:<sup>34,35</sup>

- The procedure requires large amounts of DNA, is very labour intensive and requires strict adherence to established protocol.
- If strict adherence to the protocol is not followed, interlaboratory comparisons cannot be performed. Standard protocol recommends that control strain Mt. 14323 be run, which should flank the sample set as well as being present at a third position, in the approximate middle of the set.
- Small deviations in mobility can result in error when fragment sizes are being calculated in comparison to the standard used, resulting in misalignment during data processing.<sup>35</sup> This can be compensated for by decreasing tolerance and band-matching values, but by doing so one is allowing for a higher potential of incorrect matching in a large database.<sup>35</sup>
- Other technical factors that contribute to variability in band identification are gel mobilities and exposure time of film.
- For isolates with fewer than five copies of the *IS6110* insertion sequence, the sensitivity of this methodology is greatly reduced.

In addition to the fact that running conditions affect both the banding pattern and number of bands observed, interpretation of more intense or wider bands as either single or double remains difficult. Although software with stringent “shoulder” parameters can be used alone in band determination, visual interpretation is also often required, contributing to variations in results among individuals.

The current international trend is to move towards a rapid, PCR-based universal genotyping system that requires very small amounts of DNA and provides a numerical output for ease of comparison.<sup>36</sup> One method being adopted globally is based on mycobacterial interspersed repetitive unit-variable number tandem repeats (MIRU-VNTRs). This method has shown great promise, with a discriminatory power close to that of RFLP and the additional benefit of being able to discriminate isolates with low copy numbers of *IS6110*.<sup>37-39</sup> Currently, the CDC has implemented the MIRU-VNTR method as its first-line genotyping test, in conjunction with spoligotyping.<sup>40</sup>

Spoligotyping,<sup>29</sup> another commonly used PCR-based genotyping method, lacks the individual discriminatory power of the other two typing methods, but in conjunction with RFLP and MIRU it is very valuable in case cluster analysis. A proposal for standardization of optimized MIRU-VNTR typing of *M. tuberculosis* has been published.<sup>41</sup>

## Susceptibility Testing for Antituberculosis Drugs

Agar proportion is still considered the gold standard, but because of the length of time of the test, liquid media detection methods using continuous monitoring systems are now recommended.<sup>3,42</sup>

- Appropriate controls should be included with antimicrobial testing: a fully susceptible strain of *M. tuberculosis* at least once per week of use.
- Each new lot of antimicrobials should be tested against a fully susceptible, characterized reference strain of *M. tuberculosis* as well as against strains resistant to each antibiotic.
- A laboratory receiving an isolate of MTBC for susceptibility testing should confirm organism identification.
- All initial isolates of MTBC should at minimum be tested for the following recommended first-line antituberculosis drugs: rifampin (RMP), isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA).
- Although phenotypic susceptibility testing for PZA can be technically challenging, guidelines are available for both the BACTEC 460 and BACTEC 960 monitoring systems.<sup>42-46</sup> Laboratories lacking the capability or experiencing technical difficulties in performing the PZA drug testing should refer the isolate to another laboratory or to a reference centre for phenotypic testing and/or molecular confirmation of PZA drug sensitivity/resistance.
- Additionally, PZA resistance is a critical tool for laboratories (in the absence of molecular confirmation) to assist in differentiation of *M. tuberculosis* from *M. bovis* or *M. bovis* BCG. Speciation of the MTBC is becoming increasingly more important for epidemiologic investigations, contact tracing and guidance for clinical treatment.
- As PZA monoresistance in *M. tuberculosis* is rare, these isolates should have repeat testing performed, ideally by another technology, such as the enzymatic amidase test and/or by molecular methods.
- Strict adherence should be maintained to recommended guidelines for antimicrobial concentrations and parameters for testing that are applicable to the continuous monitoring system used.
- Caution should be exercised when reporting low-level EMB resistance. The recommended critical concentration for EMB has undergone adjustments over time and remains controversial.<sup>47,48</sup>
- All resistance to first-line antimicrobials should be confirmed by either another laboratory or another approved method.
- Reporting of initial results should not be delayed while repeat testing is being undertaken. The report should indicate that drug resistance findings are preliminary and that confirmation of the result has been initiated and will follow in a final report.
- Susceptibility testing should be repeated if the patient's specimen does not convert to culture negative within 4 months or earlier if there is other evidence (clinical or radiographic) of a failure to respond to therapy.<sup>47,49</sup>

- Results should be reported within 7 to 14 days of detection of a positive culture,<sup>13,36</sup> according to established guidelines.<sup>42</sup>

When resistance is encountered to the critical concentration of INH by the methodology used, the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards) recommends testing at a higher concentration.<sup>42</sup> If the isolate is found to be susceptible at a higher concentration, this could indicate low-level or emerging resistance. CLSI recommends the following comment be added to the report: *“These test results indicate low-level resistance to INH. Some experts believe that patients infected with strains exhibiting this level of INH resistance may benefit from continuing therapy with INH. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.”*

If resistance to one or more of the first-line antituberculosis drugs is encountered or the patient’s treatment is failing, additional testing may be required for recommended second-line drugs, which include injectable agents (streptomycin, amikacin, kanamycin, capreomycin), fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin), rifabutin, ethionamide, cycloserine, *p*-aminosalicylic acid and clofazimine.<sup>5,42</sup> Standardized methods for second-line drug susceptibility testing are available in Canada for the injectable agents, ofloxacin, rifabutin, ethionamide and *p*-aminosalicylic acid. Second-line drug susceptibility testing should be limited to accredited reference laboratories. CLSI does not recommend testing of cycloserine because of the instability of the drug. If testing is performed, the results should be interpreted with caution.

In 2005, the Canadian Tuberculosis Committee reclassified streptomycin as a second-line TB drug in Canada. It is recommended that each TB laboratory director consult with his or her jurisdictional TB control physicians and public health department to decide whether streptomycin should be routinely tested on the basis of the following:

- patient population;
- prevalence of drug resistance;
- use in community; and
- availability and timeliness of testing if resistance or intolerance is encountered.

In the context of genetic mutation testing associated with drug resistance, DNA sequencing may be the only technology option to identify known and novel insertion or deletion mutations and remains the gold standard for molecular work.<sup>50</sup> It is well recognized that confirmation of resistance to PZA and RMP is possible using molecular targets (*pncA* and *rpoB* genes respectively).<sup>51-53</sup> Over 95% of isolates with phenotypic RMP resistance have a mutation in the 80 bp “hot spot” region of the *rpoB* gene.<sup>51,52</sup> Approximately 95% of PZA-resistant isolates have documented mutations in the *pncA* gene.<sup>52,53</sup>

Reporting of molecular gene targets for drug resistance requires the following information:<sup>25</sup>

- nucleotide and amino acid affected;
- analytic limitations (i.e. limits of sensitivity and processing); and

- interpretative limitations (i.e. a negative result/no mutation does not rule out phenotypic resistance).

## Serum Drug Levels

Serum drug level testing is useful for patients who may be failing therapy despite appropriate antituberculosis medication (see Chapter 6, Treatment of Tuberculosis Disease and Infection). Currently, this test is not available in Canada. Samples should be sent to a reference laboratory specializing in mass spectrometry analysis, such as the National Jewish Medical and Research Center, Denver, Colorado, website: <<http://www.njc.org>>. <sup>49</sup>

## Interferon-Gamma Release Assays (IGRA)

IGRA are new, in vitro T-cell based assays that measure interferon-gamma (IFN- $\gamma$ ) production. They operate on the basis that T-cells previously sensitized to TB antigens produce high levels of IFN- $\gamma$  when re-exposed to the same mycobacterial antigens. Two tests, Quantiferon TB Gold In-Tube<sup>®</sup> (Cellestis Ltd.) and T-SPOT. TB<sup>®</sup> (Oxford Immunotec) are registered with Health Canada for use in Canada. These tests demonstrate significant promise as an alternative to TST. They are discussed in detail in Chapter 4, Diagnosis of Tuberculosis Infection and Disease, and in Appendix D, Advisory Committee Statement on interferon-gamma based assays. Until the precise role of these assays has been established, it is recommended that they be performed in reference or public health laboratories and positive results reported to public health authorities.

## Quality and Proficiency Testing

All laboratories should be accredited by a recognized national/international accrediting organization and participate in internal and external quality assurance/quality control activities in conjunction with a reference laboratory. These results will assess the reproducibility and the interlaboratory variability of the methods used and help to ensure that there is 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. <sup>36,50</sup>

Validation of any new or adapted test methods should be completed to evaluate performance characteristics (i.e. reproducibility, repeatability, sensitivity, specificity) and demonstrate in-house competence. The feasibility of conducting the test method should be verified as being appropriate and adequate before being undertaken.

The design of validation studies should include the following: <sup>54</sup>

- techniques to be used (i.e. comparison of results with a “gold-standard” test, use of reference strains/materials and interlaboratory comparisons);



- number of samples/isolates determined by a mathematical model;
- samples/isolates exhibiting a range of known, characterized values; and
- performance characteristics to be evaluated by statistical analysis.

Further support for in-house validations can include documented acceptance of a test method from the scientific community. This may be provided through reference to public or private documentation on similar or related techniques or publication pertaining to the in-house method in peer-reviewed journals.

## Reporting Criteria and Turnaround Times

The following are suggested for each laboratory reporting system:

- Reporting SOPs should contain established turnaround times (TATs) and reporting parameters for each testing methodology.
- Reports should be date stamped and initialed.
- Reported information should be disseminated by telephone, facsimile or e-mail within 24 hours of test completion and the original hard copy mailed within the following 24 hours.
- Reported results should not be transcribed onto other reporting formats. Original reports should be forwarded to the appropriate personnel.
- Anticipated reporting/test TAT delays should be counteracted by preliminary reporting.
- Reports on nonstandardized testing (such as antimicrobials not recommended by CLSI for susceptibility testing) should include a disclaimer.
- TATs 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)<sup>13</sup>

Procedure	Turnaround time to completion/ report
Specimen collection and arrival at the laboratory	24 hours
AFB smear microscopy	24 hours from specimen receipt
NAA testing for MTBC detection	24 hours from smear result
Bacteriological diagnosis – culture	Up to 6 weeks for broth cultures and 8 weeks for solid media cultures from specimen receipt
Identification of mycobacterial species	21 days from specimen receipt
Primary susceptibility testing	7-14 days from a positive culture
Reporting of all test results (electronically)	24 hours from test completion
Reporting of all test results (mailed hard copy)	48 hours from test completion

## Progressive Standards for the Future of the Modern Mycobacteriology Laboratory

### Guiding principles

- The mycobacteriology laboratory has an essential role in the prevention and control of TB.
- Effective TB control depends on an integrated system that includes clinicians, the public health department and laboratories.
- An integrated system will establish prompt, reliable laboratory testing and provide an effective flow of information with established lines of communication.
- Each province/territory should have access to high-quality TB testing and complete reporting in a timely manner.

Historically, challenges to the development of such a system have been the lack of laboratory testing standards, inefficient laboratory information systems and communication gaps, as well as underfunding, leading to work force shortages and loss of expertise.

### Benchmarks of improvement in laboratory TB services

#### *Capacity and capability assessments*

The diagnosis of TB is a team effort between clinicians, the public health department and mycobacteriology laboratories. Before offering mycobacteriology services, each laboratory should assess the capacity and capability of the level of performed services.<sup>12,13</sup> It is prudent to consider alternatives to performing in-house testing if the laboratory does not meet the volumes and expectations outlined in Table 2. Regionalization of services and/or referral of specimens should be considered as per the CDC and ATS guidelines.<sup>12,13</sup>

The three-level structure endorsed by the ATS is based on a balance of laboratory capacities and timely availability of results.

**Table 2**  
Levels of Service Provided by Mycobacteriology Laboratories<sup>3,12</sup>

Level	Services
I	Specimen collection, acid-fast bacteria (AFB) smears
II	AFB smears, specimen processing, identification of MTBC and first-line susceptibility testing
III	As above, identification of NTM, second-line susceptibility testing

Table 3  
Laboratory Capacity/Capability Assessment Criteria<sup>12,13</sup>

Assessment of Workload and Testing Capacities	Yes/No
<p>Does the laboratory do/have the following:</p> <p>Prepares/examines &gt; 10 AFB smears/week</p> <p>Maintains current technology, e.g.</p> <ul style="list-style-type: none"> <li>fluorescent microscopy</li> <li>liquid media detection/recovery systems</li> <li>susceptibility testing methods</li> <li>rapid identification testing</li> </ul> <p>Has access to genotyping and analysis methodologies</p> <p>Ensures compliance with recommended biosafety practices and facility design (physical and operational requirements)</p> <p>Conducts medical surveillance of staff</p> <p>Has specimen transport capabilities that meet the <i>Transportation of Dangerous Goods Act</i> regulations</p> <p>Reports positive tests within 1 day</p> <p>Has the ability to disseminate information rapidly using standard electronic technology such as faxes, email, etc</p> <p>Has current SOPs in place and available for use by staff</p> <p>Has written criteria for acceptance/rejection of specimens</p> <p>Undertakes an accreditation program for staff training and tests offered by the laboratory</p> <p>Participates in an approved/recognized proficiency testing program</p> <p>Maintains quality control records for 2 years</p> <p>Maintains specimen repository capabilities and a tracking system</p> <p>Possesses contingency plans for surge capacity for outbreaks</p> <p>Has turnaround times for tests offered by the laboratory evaluated annually</p> <p>Maintains available resources for training and consultation for physicians and TB controllers</p>	

### *Cost analysis*

As the number of TB cases declines, the costs of maintaining testing in low-volume laboratories is challenging.

Cost assessments evaluate the efficiency and relevance of the provision of esoteric testing in all laboratory facilities and determine the appropriateness of concentrating resources in laboratories that can deliver such services with attendant workforce skills.

### *Strategic planning*

- Development of partnerships and collaborations in Canada, including the Canadian Tuberculosis Laboratory Technical Network, the Canadian Public Health Laboratory Network and the Canadian Tuberculosis Committee

- Continuation of support for a state-of-the-art core national mycobacteriology reference laboratory
- Development of a contingency plan for surge capacity in the event of an emergency, such as a TB outbreak, that would affect laboratory services
- Instituting the use of new technologies as they become available
- Maintaining a prompt and efficient reporting and tracking information system

### *Outcome measures and performance indicators*

- Continued decrease in the national incidence rate of TB disease
- Timeliness of AFB smear, culture and susceptibility testing
- Availability of SOPs, monitoring of proficiency testing results and participation in an approved laboratory accreditation program
- Efficient and complete flow of information for optimal patient care
- Measurement and assessments of training programs
- Evidence-based appropriate funding available for laboratories.

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# Transmission and Pathogenesis of Tuberculosis

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## Transmission

Tuberculosis (TB) is caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex, predominantly acquired through inhalation and rarely through ingestion or percutaneous inoculation (laboratory or hospital accident). Bovine TB, which in the past was caused by ingestion of infected (unpasteurized) milk and tended to involve the tonsils and intestines, has been largely eradicated as a result of the tuberculin testing of cattle and the subsequent slaughter of those found to be infected. Sporadic cases may result from inadvertent exposure of abattoir workers, veterinarians and wild game handlers to infected animals. Immigrants may harbour *M. bovis*, and occasionally this organism may be reactivated in older persons who acquired the infection before milk-borne disease had been controlled.

The reservoir for *M. tuberculosis* is humans. Animals may be infected but are rarely a source of infection. Infection is transmitted almost exclusively by the airborne route in minute droplets of moisture that become increasingly reduced by evaporation, creating “droplet nuclei”. Droplet nuclei are created by forceful expiratory efforts, such as coughing, sneezing, singing and playing wind instruments. Certain procedures, for example, bronchoscopy, sputum induction, 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. They are neither filtered out by simple gauze masks nor adequately stopped when the patient covers the mouth and nose during coughing. Large particles settle quickly and are either not inhaled 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.<sup>1-5</sup>

The rate of transmission can be measured by the percentage of close contacts (household and non-household) whose tuberculin skin test (TST) 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 susceptible 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.<sup>6</sup>

In patients with epidemiologically unrelated TB there is broad variability in the DNA fingerprints of *M. tuberculosis* isolates, whereas the DNA fingerprints of isolates from patients who were infected by a common source are identical or nearly identical. Therefore in “clustered” cases of TB, defined as those in which the isolates have identical or closely related DNA fingerprints, infection has

usually been recent. In contrast, cases in which the isolates have distinctive DNA fingerprints generally represent a reactivation of infection acquired in the distant past.<sup>6-8</sup>

Important caveats to these generalizations include the following. First, DNA fingerprinting data should be interpreted together with epidemiologic data, as shared DNA fingerprints from individuals that live in relatively closed communities may simply reflect the contemporaneous reactivation of a common strain that had been circulating in the community many years earlier and may not represent recent transmission.<sup>8-10</sup> Second, the accurate identification of clustered cases requires the evaluation of a large percentage of TB cases in the population over a long period of time. If DNA fingerprinting is performed in only a minority of cases, many clustered cases will be missed.<sup>11</sup> In addition, if DNA fingerprinting is performed over a short period, some clustered cases will be overlooked, as insufficient time will have elapsed for TB to have developed in infected persons. Third, there is always the possibility that the recovery of identical isolates represents laboratory cross-contamination.

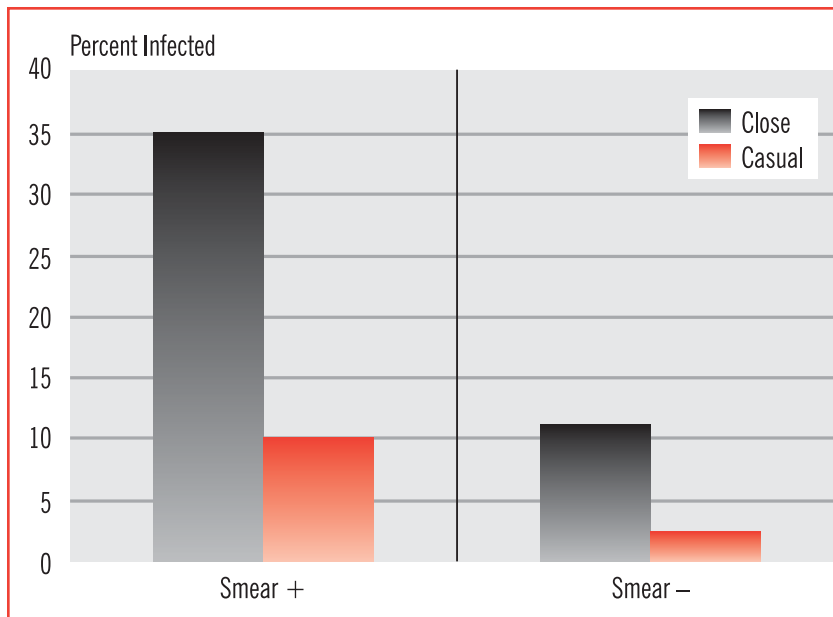
To paraphrase Barnes and Cave,<sup>6</sup> molecular epidemiologic studies have shown that the dynamics of the transmission of TB vary greatly geographically. Therefore local efforts to identify high-risk populations and transmission sites are crucial for the effective control of TB.

### Patient characteristics affecting the number of infectious droplet nuclei per volume of air

For successful transmission to take place, a TB patient must be able to produce airborne infectious droplets. This most often limits the potential for transmission to adolescent or adult patients with TB of the respiratory tract, although younger children can, on occasion, be highly infectious.<sup>7</sup> Among patients with TB of the respiratory tract not all are equally efficient at transmission.

1. *Viable bacteria in the sputum of the source case.* Patients whose sputum smears are positive for acid-fast bacteria have 5,000 or more organisms per millilitre of sputum and have the potential to infect many of their close contacts, whereas those who are smear-negative but culture-positive infect far fewer contacts<sup>9-11</sup> (Figure 1). Smear-positive patients often have cavitory pulmonary or laryngeal TB. 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 of all transmissions.<sup>12,13</sup> In addition to the greater infectivity of smear-positive cases, there are data to suggest that the risk of disease after infection from a smear-positive case is greater than it is after infection from a smear-negative case. In one study, more than one-third of children living in close contact with smear-positive patients, and infected by them, had disease. In contrast, only 18% of children having a comparable degree of contact with, and infected by, smear-negative patients had active disease.<sup>14</sup> These and other data lend support to the hypothesis that multiple discrete infections may occur during the period of time that it takes for immunity to mature after infection (18-24 months), and each may carry an independent risk of disease.<sup>15</sup>

Figure 1  
Infectiousness of tuberculosis by bacteriologic status of and proximity to source case\*



\*Data from reference 12

- Aerosolization of sputum by cough or other mechanisms.* One of the most important findings of the sentinel transmission studies of Wells and Riley was the extraordinary heterogeneity of infectiousness among patients with smear-positive pulmonary TB.<sup>16-18</sup> They went on to evaluate the aerial infectivity of the droplets from smear-positive patients by artificially atomizing sputum and exposing guinea pigs to a “standard dose”, and were able to show a marked variability in the infectivity of aerosolized sputum. Thus, although patients may appear to have an equal number of bacteria in their sputum, the physical and chemical properties of one patient’s sputum may be more suitable than those of another’s for the production of large numbers of droplet nuclei. In addition, the number of organisms put into airborne suspension by a patient depends upon his or her effectiveness as an “aerosolizer”; this, in turn, is related to the force and vigour of the coughing maneuver and the shape of the mouth and upper airway during coughing.<sup>19</sup> Tenacious sputum containing clumps of bacteria does not yield as many tiny infectious particles as does watery sputum containing more dispersed organisms. In normal breathing the number of infectious particles produced by diseased individuals is very low, but a bout of coughing produces up to 3,500 particles with infective potential, a number that equates with speaking for five minutes in a normal tone.<sup>19,20</sup> A sneeze dispenses up to a million particles. The likelihood that household contacts will be infected increases with the frequency of cough in the source case.<sup>21-23</sup>

On the basis of a study by Styblo et al,<sup>24</sup> the duration of cough at the time of diagnosis could be determined in 430 smear-positive patients: 30% of them had

been coughing for not more than 1 month, 60% for less than 3 months and 84% for less than 6 months.

### Environmental factors affecting the number of infectious droplet nuclei per volume of air

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 poor access to sunlight (ultraviolet rays). Ventilation dramatically dilutes the concentration of infectious droplet nuclei. At 1 air change per hour (a volume of fresh air equal to the room volume each hour), it will take 276 minutes to reduce the concentration by 99%, whereas a ventilation rate of 6 air changes per hour takes only 46 minutes, assuming that no one in the room is generating an aerosol and that perfect mixing of air is occurring within the space<sup>25</sup> (see Chapter 16, Tuberculosis Control Within Institutions, for further information on clearance times).

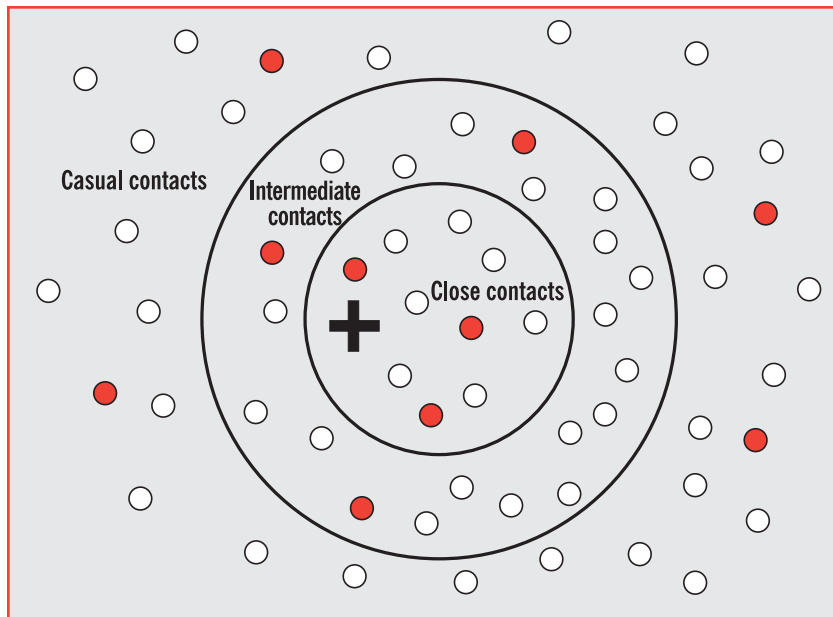
Although the probability of being infected after contact with an infectious source decreases with decreasing duration and closeness of contact with the source case, the absolute number of casual contacts that an infectious case infects may exceed the number of infected close contacts. As Rieder explains, this occurs when the number of casual contacts of an infectious case far exceeds that of susceptible close contacts.<sup>21</sup> This is illustrated schematically in Figure 2, in which the probability of infection among the closest, first circle contacts was 3 out of 10, in the next to closest contact circle was 3 out of 20, and in casual contacts beyond these two circles was much lower.<sup>21</sup> The absolute number of infected casual contacts, however, exceeded the absolute number of infected close contacts. DNA fingerprint data have highlighted the limits of contact tracing in settings where there is exposure of a large number of persons unknown to source cases, and in settings where social connections are tenuous at best.<sup>26,27</sup>

2. *Proximity to the source case.* Proximity to the source case, or to exhausted or ducted air from the room in which the source case is situated, is also an important determinant of transmission. The human host is social by nature; children (susceptible hosts) live with their parents for a prolonged period of time, allowing ample opportunity for transmission should a parent have active respiratory disease.

### Duration of exposure of susceptible individuals

Because of the dilution of infected air, the duration of exposure required to ensure that transmission occurs is commonly prolonged (days, months or even years), and yet documented and anecdotal reports have confirmed that exposures as short as seconds or 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.

Figure 2  
Example of the risk of infection among close contacts (inner circle), intermediate contacts (outer circle), and casual contacts\*



\*The index case is indicated by a cross, infected contacts by filled circles, and uninfected contacts by hollow circles

As a result of the systematic DNA fingerprinting of *M. tuberculosis* isolates, the conventional wisdom that until now has placed most close contacts within the home is undergoing revision. Within many large U.S. cities much of the ongoing transmission has been demonstrated to be occurring in an inner city population, many of whom are homeless. Under such circumstances it may be necessary to think in terms of “locations” of transmission,<sup>26</sup> e.g. shelters, social gathering places, rather than a home in the conventional sense.<sup>25</sup>

### Susceptibility of those exposed

Persons with no prior exposure to *M. tuberculosis* are at risk of becoming infected if exposed. Prior infection, and especially prior infection giving rise to TB disease, provides a measure of protection against reinfection, at least in immunocompetent persons. This protection is not, however, perfect. In highly endemic areas of South Africa, reinfection of immunocompetent persons with progression to disease has been documented.<sup>27</sup> Reinfection with progression to disease has also been documented in inner city persons whose immunologic status may be compromised by substance abuse and malnutrition.<sup>28</sup> The loss of cellular immunity in HIV-infected persons may permit reinfection from a different source, even in the presence of active TB disease.<sup>29</sup> Epidemiologic and autopsy data suggest that BCG (bacille Calmette-Guérin) vaccination does not prevent the establishment of infection in an exposed subject.<sup>30,31</sup> Interferon- $\gamma$  release assay data, however, indicate that BCG, while not preventing the establishment

of infection in everyone, will prevent it in some.<sup>32</sup> If infection is established, BCG limits the subsequent multiplication and dissemination of the bacteria and the development of lesions.

### Infectivity of one strain of *M. tuberculosis* versus another

Data are beginning to emerge suggesting that one or more virulence properties of *M. tuberculosis* may affect its ability to be transmitted. For example, one strain may be better suited than another to overcoming the innate resistance of the host. Drug-resistant strains have shown reduced virulence in animal models<sup>33</sup> but for practical purposes should be considered just as transmissible as drug-susceptible strains.

### Effect of treatment upon the contagiousness of the patient

Effective treatment rapidly reduces cough frequency<sup>34</sup> and sputum bacillary counts.<sup>35</sup> Moreover, the rate of decrease of bacillary counts in cough-generated aerosol cultures is considerably more rapid than that in sputum cultures.<sup>36</sup> Those bacteria that continue to be expectorated may be less metabolically active and/or are inhibited by antituberculosis drugs, two effects that may be anticipated to decrease the chances of the organism establishing an infection in the host.<sup>17,37</sup> However, in theory, any residual viable bacteria in respiratory secretions could be transmitted, although the chances of this occurring decrease rapidly with effective treatment.<sup>38</sup>

### Measures to prevent transmission

The highest priority should be given to early diagnosis and prompt, effective treatment of the source case together with the isolation of the patient when necessary and to the degree appropriate. 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 (e.g. isolation protocols, room ventilation devices, ultraviolet light fixtures) that aim to reduce exposure in health care and other congregate settings complement—but cannot replace—prompt diagnosis and appropriate therapy.

### Pathogenesis

The pathogenesis and transmission of TB are inseparably linked. *M. tuberculosis* is dependent upon human hosts for its survival. A successful host–pathogen interaction is one that results in pathogen transmission. Primary infection is usually self-limited and followed by a variable period of latency, which ultimately, in a proportion of those infected, results in infectious postprimary disease.

## Primary infection

At the time of the initial infection the distribution of inhaled droplet nuclei in the lung is determined by the pattern of regional ventilation. It thus tends to favour the middle and lower lung zones, although any lobe may be the site of implantation.<sup>39</sup> Infecting dose may be a factor in determining whether exposure to bacteria results in infection, but this has not been firmly established.<sup>40</sup> In immunocompetent hosts, it is theorized that alveolar macrophages ingest the *M. tuberculosis* organisms, and depending upon the degree to which phagocytosing cells are nonspecifically activated, host genetic factors and resistance mechanisms in the bacteria may or may not destroy them.<sup>40</sup> When innate macrophage microbicidal activity is inadequate to destroy the initial few bacteria of the droplet nucleus they replicate within the macrophage. When their numbers become sufficiently large (estimated to be  $10^3$ - $10^4$  bacteria), cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH) are stimulated.<sup>40</sup> The former involves CD4 receptor-bearing lymphocytes that are stimulated to secrete cytokines, in particular interferon- $\gamma$ , which in turn enhance the capacity of macrophages to ingest and kill the mycobacteria. The latter is thought to involve cytolytic T lymphocytes and may be protective or harmful to the host depending upon the circumstances.<sup>40</sup> At the site of implantation the lesion is usually insignificant, the infection is usually contained, and TB does not develop. The emphasis is on regional lymphatic spread and a self-limited, occult bacteremia, which seeds respiratory and nonrespiratory sites favoured by high blood flow and increased oxygen tension, e.g. the lung apex, the renal cortex and the metaphysis of long bones.

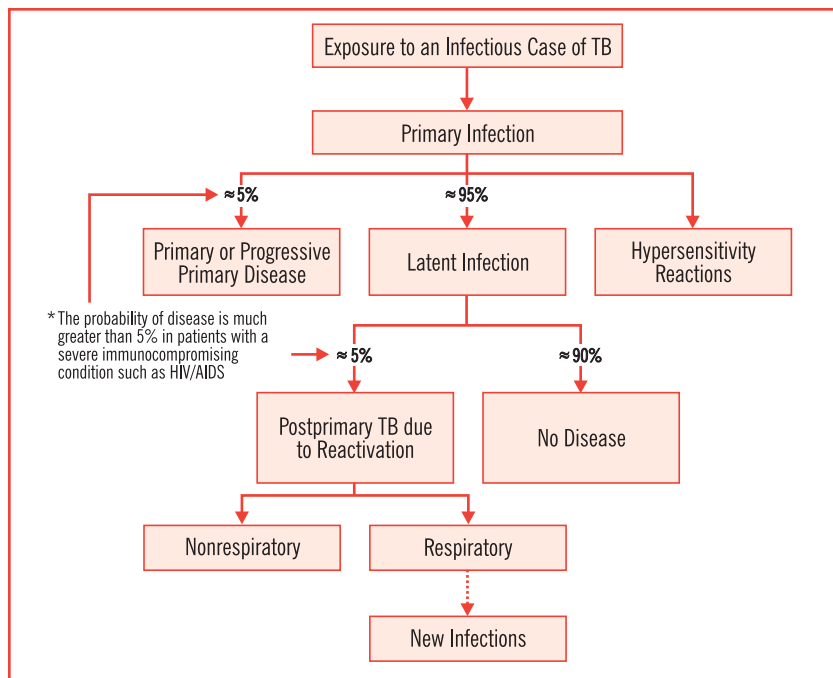
As alluded to earlier, there is epidemiologic evidence to suggest that it takes 18 to 24 months after first infection for cellular immunity to completely mature, and during that time repeated exposure may result in repeated infection. Each such infection may carry its own independent risk of disease.<sup>15</sup>

On average, approximately 5% of newly infected immunocompetent persons are unable to satisfactorily limit replication of the bacteria despite the stimulation of CMI and DTH, and infection develops into primary or progressive primary disease within 18 to 24 months. In a very small proportion, erythema nodosum (a cutaneous immunologic response to an extracutaneous tuberculosis infection) or phlyctenular conjunctivitis (a hypersensitivity reaction) may develop. Those newly infected persons not developing primary disease will either be left with latent tuberculosis infection (LTBI) and will never have postprimary disease (90%) or, after a variable period of latency, the infection will progress to reactivation or postprimary TB at some time in their lives (5%) (Figure 3). LTBI may be identified through conversion of the TST or sometimes the development of radiographically demonstrable fibrocalcific residua at the primary site of infection (Ghon focus) or primary site of infection and draining lymph nodes (Ghon complex). Newer blood tests (interferon- $\gamma$  release assays) detect CMI to mycobacterial antigens through changes in serum interferon- $\gamma$  levels following *in vitro* stimulation<sup>41</sup> (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, for further details).



Although this outline is a useful generalization, it does not always apply, nor are the factors that determine the fraction of infected persons in whom the disease will develop completely understood. Age and sex appear to directly affect resistance: mortality and morbidity is much greater among infants, among females in the early adult years and among males during old age. Poor nutrition probably has an effect, but in experimental animals nutritional deficiencies must be extreme to reduce resistance. Racial differences have been offered as factors determining native resistance, with some support,<sup>42</sup> but differences among races in all clinical forms of TB are probably best explained as phase differences in an epidemic wave.<sup>43</sup> All races initially exposed in an epidemic as a group are equally susceptible, but eventually the death and survival outcome select out a set of persons relatively more resistant. A growing body of evidence suggests that host genetic factors are important in determining susceptibility to TB.<sup>44-46</sup> Other factors that bear upon native resistance include the immunologic status of the host. This is most evident among persons infected with HIV. DNA fingerprinting of *M. tuberculosis* isolates from TB outbreaks has shown that, among patients with AIDS exposed to an infectious source case, progressive primary TB will develop in 37% within 5 months of exposure.<sup>47</sup> Among HIV-infected patients known to have acquired TB infection more than 2 years earlier, the annual risk of reactivation TB is closer to 10%, in contrast to lifetime risks of reactivation of 5% in immunocompetent hosts.<sup>48</sup>

Figure 3  
The pathogenesis of tuberculosis in the infected host



## Primary disease

Depending upon the immunocompetence of the host, primary TB is, as already mentioned, most often a subclinical or mild self-limited illness. Infants and young children may be asymptomatic or may present with fever and non-productive cough, and chest radiography may demonstrate unilateral, patchy parenchymal infiltrates, or paratracheal or hilar adenopathy, or both. Such patients should receive full antituberculosis treatment when the diagnosis is made, as their immune systems are relatively immature and there is a real risk of progression to life-threatening nonrespiratory disease, notably disseminated TB or central nervous system (CNS) TB. The term “primary pulmonary TB” refers to a pulmonary implantation site or draining lymph node site of disease in those recently infected (within the preceding 18-24 months) with bacteria. If, for whatever reason, bacteria within the primary focus continue to divide, massive tissue destruction may result (progressive primary TB).<sup>49</sup>

Under the low TB incidence conditions that prevail in Canada the majority of Canadian-born non-Aboriginal persons reaching adulthood have not been infected. When TB infection occurs for the first time in such adults the disease, if any, that follows may present as in childhood, with non-specific lung infiltrates and/or lymphadenopathy or, as is very often the case, pleurisy.<sup>49</sup> Patients with primary tuberculous pleurisy often have elevated temperatures, cough, pleuritic chest pain and, sometimes, dyspnea. Chest radiography reveals a unilateral pleural effusion, often without identifiable parenchymal lesions. Pleural biopsies show paucibacillary granulomatous pleuritis. The diagnosis should be suspected if there is a recent history of exposure to TB. Primary tuberculous pleurisy will usually resolve spontaneously, yet without therapy reactivation TB develops in up to 60% of patients. Treatment, as for disease, is therefore indicated in all patients. Complications are rare, and surgery is almost never indicated. In summary, “primary tuberculous pleurisy” refers to a disease state characterized by pleuritis and pleural effusion, usually in an adolescent or young adult but possibly in any age group, due to recent (within the preceding 18-24 months) infection with bacteria.

Please see Appendix C, Definition of Terms, for the definition of primary TB.

## Latent tuberculosis infection

*M. tuberculosis* bacteria are able to survive for years in the small granulomas or solid caseous material of lymphohematogenously 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.<sup>50</sup> 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 an oxygen gradient.<sup>51,52</sup> 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. The ability to

withstand anaerobic conditions would appear to be essential to the survival of this pathogen.

The highly variable latency period makes it difficult to precisely document transmission using currently available tools. Persons found to have “positive” TSTs during contact investigation may have been infected in the past (remotely) rather than by the source case of concern—though for contact management and public health purposes they are treated as though they were recently infected when there is no way to know the duration of infection. DNA fingerprinting techniques will only detect transmission to the small group of persons in whom active disease develops following transmission from other patients of interest during the study time frame. Public health strategies will reflect the relative burden of disease attributed to recent/ongoing transmission—implying that the first priority is to prevent further transmission—versus reactivation of remotely acquired infection, in which the priority shifts to identification of persons with LTBI, notably those at increased risk of reactivation.

### Postprimary tuberculosis

In populations whose natural immunity is high and the TB epidemic is receding, reactivation of infection, in any of the various sites in which bacteria have been seeded, is the favoured explanation for the pathogenesis of postprimary TB. Hence the terms “reactivation” and “postprimary” are sometimes used interchangeably. However, in populations in which the epidemic is still peaking, the role of reinfection may be of considerable importance because the natural resistance to TB is not as developed in this population, and the risk to persons who inhale bacteria on several separate occasions is high.<sup>53</sup> In adolescents, postprimary or reactivation-type pulmonary TB may occur within 1 or 2 years of infection.<sup>54</sup>

In Canada, in 2004, 63% of all cases of TB were pulmonary or “other respiratory”.<sup>55</sup> The tendency for postprimary TB to localize in the lung, particularly the upper lung, is probably related to the higher oxygen tension in this region, resulting from the effect of gravity on the ventilation–perfusion ratio in the upright lung.<sup>39</sup> This oxygen tension effect may be indirect and arise through the unfavorable effect that high oxygen tension has on the macrophage, thereby permitting intracellular growth. Others incline toward the view that the upper lung localization of postprimary disease is less related to oxygen tension than it is to the combination of lowered blood flow and consequently lowered lymph flow, together with reduced respiratory movement at the apex, all of which result in reduced lymphatic drainage and antigen removal.<sup>1</sup>

These theoretical considerations aside, from the standpoint of public health as well as the organism’s survival, the lungs are the most important site of postprimary disease. Patients with postprimary pulmonary TB, particularly those whose smears are positive for acid-fast bacteria, can spread the organism to the lungs of others by coughing, sneezing, laughing or even talking.<sup>11</sup> Infants and young children with primary disease, adolescents or adults with primary tuberculous pleurisy and those with TB in non-respiratory sites are unlikely to infect others.<sup>11</sup>

## Pathogenetic factors enabling the communicability and survival of *M. tuberculosis*

1. *The aerobic nature of the species.* The growth of *M. tuberculosis* is favoured in the oxygen-rich environment of the human lung, from which the organism is transmissible to other humans.
2. *Liquefaction and lung cavity formation.* Although, as mentioned earlier, in immunocompetent persons whose CMI fails to control primary TB the infection may progress to cavitary disease (progressive primary disease), cavity formation is usually associated with postprimary disease. The exact causes of liquefaction and cavity formation are unknown, but hydrolytic enzymes and DTH to tuberculin-like proteins are thought to be important factors.<sup>56</sup> Within the unique extracellular environment of cavities, host defences are ineffectual, and bacteria multiply in great 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.
3. *Interruption of perfusion in parallel with ventilation in lung tissue.* Physiologic and radiologic data are consistent with the concept that postprimary TB is an endobronchial disease that causes parallel reductions in ventilation and perfusion. This concurrent involvement of both airways and contiguous pulmonary blood supply offers an explanation for the minimum respiratory limitation experienced by these patients despite often extensive lung disease. No doubt this serves to extend the life of the host within the community, creating an opportunity for transmission before the patient either seeks medical attention or succumbs.<sup>57</sup>
4. *Virulence of the infecting strain of *M. tuberculosis*.* Some data suggest that the virulence of infecting strains may vary. In Manitoba, the dominant “type 1” strain and in the Western Pacific the dominant “Beijing/W” family of strains may be hypervirulent.<sup>58,59</sup> U.S. investigators suspected a hypervirulent strain in a rural outbreak that led to a particularly high number of secondary cases and infected casual contacts, though the virulence factors that led to infection and those that favour progression to active disease may not be the same.<sup>60</sup>

Postprimary disease may involve a nonrespiratory site alone or occur in combination with respiratory disease. Please see Chapter 5, Nonrespiratory Tuberculosis, for additional information on nonrespiratory TB.

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# Diagnosis of Tuberculosis Infection and Disease

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## Diagnosis of Tuberculosis Infection

The main tool to diagnose tuberculosis (TB) infection is the tuberculin skin test (TST). This test consists of the intradermal injection of a small amount of purified protein derived from *Mycobacterium tuberculosis* bacteria. In a person who has cell-mediated immunity to these tuberculin antigens, a cell-mediated, 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. In persons who are newly exposed and become infected with TB, this cell-mediated reaction to tuberculin will develop 3 to 8 weeks later.<sup>1</sup>

New tests that measure cell-mediated reactions to tuberculin antigens *in vitro* have been developed for the diagnosis of TB infection over the past decade. The test characteristics and potential indications for these new interferon-gamma release assays (IGRA) are reviewed in this chapter. Chest radiography for the diagnosis of infection is briefly reviewed, although its major utility is for the diagnosis of active disease.

## Indications for Tests to Diagnose TB Infection

In general, testing for latent TB infection (LTBI) is indicated when the risk of development of disease, if the patient is infected, is increased. There are three general situations when risk of disease is increased:

1. Recent infection, most commonly contacts of a patient with a recent diagnosis of active, contagious respiratory TB or immigrants and visitors from countries of high TB incidence within 2 years of arrival in Canada.
2. Increased risk of reactivation due to impaired immunity. This includes HIV infection and other immunosuppressed conditions, diabetes, renal failure, immunosuppressant medication and pulmonary silicosis.
3. When there is radiographic evidence of old, healed inactive TB but no prior treatment.

The TST has been used in epidemiologic surveys to define the prevalence of infection in populations and to estimate subsequent incidence of active TB. To date however, the newer *in vitro* tests have not been applied in this manner.

NOTE: Screening for LTBI in persons or groups who are healthy and have low risk of development of active disease is discouraged, since the positive predictive value of the TST is low and the risks of treatment are likely to 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.

The following persons should not receive a TST:

1. Those with 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.

2. 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.
3. Those with major viral infections.
4. Those who have received measles immunization within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results. No data are available regarding the effect on TST of other live virus immunizations – mumps, rubella, varicella (chickenpox) and yellow fever – but it would seem prudent to follow the same 4 week guideline. 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.<sup>2</sup>)

The following persons can receive a TST:

1. Those with a common cold.
2. Those who are pregnant or are breast-feeding.
3. Those immunized with any vaccine on the same day.
4. Those immunized within the previous 4 weeks with vaccines other than the ones listed earlier.
5. Those who give a history of a positive TST reaction (other than blistering) that is not documented.
6. Those taking low doses of systemic corticosteroids, < 15 mg prednisone (or equivalent) daily. It generally takes a steroid dose equivalent to  $\geq 15$  mg prednisone daily for 2-4 weeks to suppress tuberculin reactivity.<sup>3,4</sup>

## Types of Tuberculin Skin Tests

Mantoux: this is an intradermal test and is the most accurate, consistent and reliable.

Multi-puncture tests, such as the Tine or Heaf tests: these tests may have significant false-negative rates, and readings are very difficult to standardize. The tests are not recommended.<sup>5,6</sup> The Heaf test is no longer available.

## The Mantoux Technique of Tuberculin Skin Testing

### Administration

#### *Handling the tuberculin solution*

- Tubersol® 5 tuberculin units (5-TU) (0.1 mL) of PPD-S (purified protein derivative – standard), manufactured by sanofi pasteur, is used in Canada. Use of one tuberculin unit (1-TU) is not recommended in Canada as there are 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.<sup>7</sup>

- Store at 2°–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 with the arm extended. Explain the procedure. Instruct the person not to scratch the area afterwards as the resulting inflammation would make the result difficult to read. The area may be bathed but should not be scrubbed.
- 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 that make TST result difficult to read. 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 the area dry.
- Do not use EMLA<sup>®</sup> cream (or similar local anesthetic cream), as 10% of those applying this cream report localized edema,<sup>8</sup> which could easily be confused with a positive TST result.

#### *Injecting the PPD tuberculin solution*

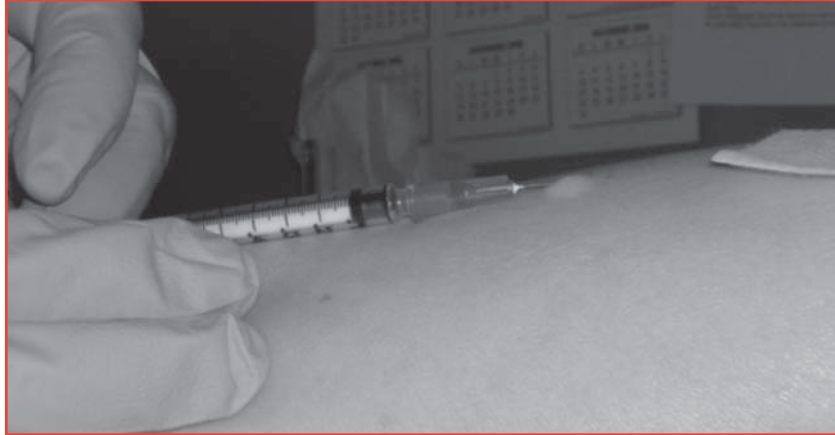
- Use a 0.6 to 1.3 cm ( $\frac{1}{4}$  to  $\frac{1}{2}$  inch), 26- or 27-gauge needle with a disposable plastic tuberculin syringe.

- 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.
- Without aspirating, administer the PPD by the slow **intra**dermal injection of 0.1 mL of 5-TU.
- Withdraw the needle quickly and look for a discrete, pale elevation of the skin (a wheal) 6-10 mm in diameter. 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 10 cm (2 inches) from the previous injection.
- 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 an intramuscular injection, this should not pose a serious problem. It is theoretically possible that tuberculin-sensitive persons 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 must be administered again *but using proper intradermal technique* on the volar surface of the forearm.\*
- Record the following:
  - date of injection
  - dose (5-TU, 0.1 mL)
  - manufacturer
  - lot number
  - expiration date of solution
  - site of injection
  - person administering the TST.

---

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

Figure 1  
Technique of administration of TST



#### *Precautions*

- Acute allergic reactions, including anaphylaxis, angioedema, urticaria and/or dyspnea, have been very rarely reported following skin testing with Tubersol<sup>®</sup>, see “Risk of Serious Allergic Reactions Following Tubersol<sup>®</sup> [Tuberculin Purified Protein Derivative (Mantoux)] Administration” (available from: <[http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/tubersol\\_hpc-cps\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/tubersol_hpc-cps_e.html)>).
- These reactions may occur in persons without a prior 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 (NACI) for monitoring of 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.

#### *Measuring induration*

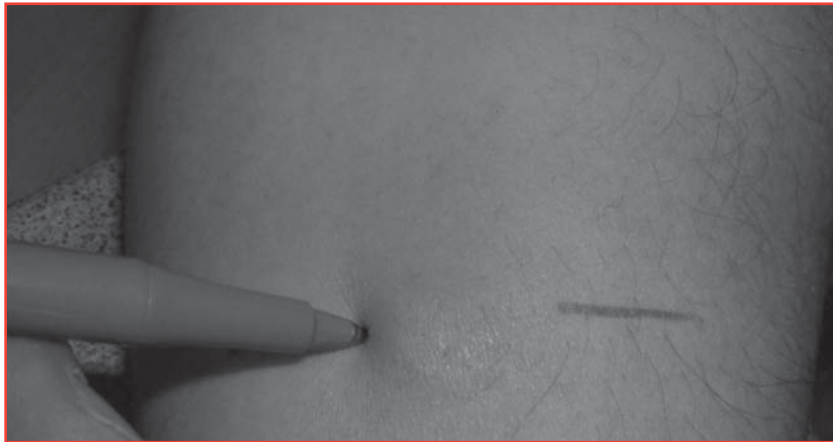
- The TST should be read by a trained health professional, (see Appendix E, Tuberculosis Education and Training Resources). Individuals without experience in reading a TST may not feel slight induration, and the TST would be mistakenly recorded as 0 mm.
- Self-reading can be very inaccurate and is strongly discouraged.<sup>9</sup>
- 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.<sup>10</sup> If the TST cannot be read within 72 hours because of unforeseen circumstances, it should be repeated at a location far enough from 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.
- 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.<sup>11</sup>
- 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 persons tested will have localized redness or rash (without induration) that occurs within the first 12 hours. These are allergic reactions, are not serious and do not indicate TB infection. They are not a contraindication to future TSTs.<sup>12</sup>
- Blistering, which can occur in 3% to 4% of subjects with positive tests, should be recorded.
- Record the result in millimeters (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



### *Recording the results*

Record the following:

- date the induration was read
- measurement of the induration, if any, in millimetres (mm)
- any adverse reactions, e.g. blistering
- name of 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.

1. Technical: poor injection technique<sup>13</sup> – this should be avoidable.
2. Biologic:
  - Immune suppression due to advanced age, treatment with corticosteroids (at least 15 mg/day of prednisone or equivalent for 1 month or more), cancer therapy agents, HIV infection, especially if the CD4 count is  $< 500 \times 10^6/L$ , and possibly tumor necrosis factor (TNF)-alpha inhibitors. Whether ribavirin-peginterferon alfa-2b (Pegetron<sup>®</sup>) will affect the TST result has not been reported.
  - Malnutrition, particularly when there has been recent weight loss.<sup>14</sup>
  - Severe illness, which can include active TB.<sup>15</sup>
  - Major viral illness (mononucleosis, mumps or measles, but NOT the common cold) or immunization within the previous 4 weeks

with measles, mumps, rubella, varicella (chickenpox) or yellow fever vaccine.

- Very young age (less than 6 months). The validity of the TST in infants aged less than 6 months is unknown.

### 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 must decide whether the test is positive. This is based on the size, using the criteria listed in Table 1. 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 that was properly performed and read is considered positive.

**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.

### 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 – size, positive predictive value and risk of disease if the person is truly infected. A Web-based interactive algorithm is available to assist in TST interpretation, available at <http://www.meakins.mcgill.ca/respepi/homeE.htm>.

#### *First dimension – size*

This dimension is the easiest to understand (but the least important). 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 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.

**Table 1**  
The First Dimension of Interpretation of the TST - Size

TST Reaction Size (mm induration)	Situation in Which Reaction is Considered Positive
0-4	HIV infection with immune suppression AND the expected likelihood of TB infection is high (e.g. patient is from a population with a high prevalence of TB infection, is a close contact of an active contagious case, or has an abnormal x-ray)
5-9	HIV infection Close contact of active contagious case Children suspected of having tuberculosis disease Abnormal chest x-ray with fibronodular disease Other immune suppression: TNF-alpha inhibitors, chemotherapy
≥ 10	All others

Please see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, Table 2, for further information on interpreting the TST result in the context of a contact investigation.

### *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, with previous exposure to nontuberculous mycobacteria (NTM) or previous BCG vaccination, each of which can reduce the specificity of the TST.

**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 persons 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.<sup>16</sup> 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.<sup>17,18</sup> This is why, in Canada, 10 mm remains the standard cut-point to determine whether TB infection is present.

**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.<sup>19</sup> In Canada, many Aboriginal Canadians have been vaccinated, as have persons born in Quebec and Newfoundland and Labrador between the 1940s and the 1970s (see Appendix F for a summary of the provincial and territorial usage of BCG vaccine over time).<sup>20</sup>

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  $\geq 10$  mm if tested  $>10$  years later. Therefore, a history of BCG vaccination received in infancy can be ignored in all persons aged 10 years and older when interpreting an initial TST reaction of 10 mm or greater.<sup>21-25</sup>

If the BCG vaccination was received after 12 months of age, 42% had a false-positive TST of  $\geq 10$  mm after 10 years. If it 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.<sup>24</sup> 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.<sup>22,26,27</sup> 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%.

#### *Summary Points:*

- ▶ BCG vaccination can be ignored as a cause of a positive TST if
  - 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 (see Table 2).
- ▶ BCG should be considered the likely cause of a positive TST if
  - BCG vaccine was given after 12 months of age AND the person is either Canadian-born non-Aboriginal OR an immigrant/visitor from a low TB incidence country.

International TB incidence rates are available at <http://www.publichealth.gc.ca/tuberculosis>.

Some tips to identify BCG scars, “Recognition of BCG (versus smallpox) scars”, may be viewed at <http://www.publichealth.gc.ca/tuberculosis>.

BCG vaccination coverage in different countries is summarized at [http://www.who.int/immunization\\_monitoring/data/en/](http://www.who.int/immunization_monitoring/data/en/).

#### *Third dimension – risk of development of active TB disease*

Following 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 following infection. Certain factors increase the risk of TB

reactivation because of diminished local or systemic immunity, as summarized in Table 2.

**Table 2**  
**Risk Factors for the Development of Active TB among Persons Infected with *Mycobacterium tuberculosis***

Risk Factor	Estimated Risk of TB Relative to Persons with No Known Risk Factor	References
<b>HIGH RISK</b>		
Acquired immunodeficiency syndrome (AIDS)	110-170	28,29
Human immunodeficiency virus (HIV) infection	50-110	30,31
Transplantation (related to immunosuppressant therapy)	20-74	32-35
Silicosis	30	36,37
Chronic renal failure requiring hemodialysis	10-25	38-41
Carcinoma of head and neck	16	42
Recent TB infection ( $\leq 2$ years)	15	43,44
Abnormal chest x-ray – fibronodular disease	6-19	45-47
<b>INCREASED RISK</b>		
Treatment with glucocorticoids	4.9	48
Tumor necrosis factor (TNF)-alpha inhibitors	1.5-4	49-50
Diabetes mellitus (all types)	2.0-3.6	51-54
Underweight ( $< 90\%$ ideal body weight; for most persons this is a body mass index $\leq 20$ )	2-3	55
Young age when infected (0-4 years)	2.2-5.0	56
Cigarette smoker (1 pack/day)	2-3	57
Abnormal chest x-ray – granuloma	2	47,58
<b>LOW RISK</b>		
Infected person, no known risk factor, normal chest x-ray (“low risk reactor”)	1	59

Among persons with TB infection, dual infection with HIV is the most important risk factor for the development of disease. The annual risk of active disease varies from 3% to 13% and is highest when the CD4 counts falls below  $200 \times 10^6/L$ . TB is often the earliest manifestation of HIV-associated immune deficiency and will occur with increasing frequency when CD4 counts fall below  $500 \times 10^6/L$ .

Immune suppression may also occur following treatment with cancer chemotherapeutic agents. The risk from glucocorticoids appears to be dose dependent, in that the risk is much higher if treatment is with prednisone (or equivalent) of 15 mg/day or more (odds ratio [OR] = 7.7, 95% confidence interval [CI] 2.8-21.4) than if the dose is  $< 15$  mg/day (OR = 2.8, CI 1.0-7.9) or  $< 7.5$  mg/day (OR = 2.3, CI 0.7-7.5).<sup>48</sup>

Persons who drink alcohol daily may be at increased risk of acquiring or developing TB. However, given the many other risk factors that commonly occur among such persons, it is difficult to know whether daily alcohol use is an independent risk factor for TB. Similarly, injection drug use is associated with increased risk of TB disease, but it is unclear whether this is solely because of the greater risk of infection, malnutrition, HIV infection and presence of other confounding risk factors.

Certain tumours, such as T-cell lymphomas, increase the risk of reactivation of LTBI.<sup>60,61</sup> Pulmonary silicosis (simple or complicated) will increase the risk of reactivation substantially but only for pulmonary forms of TB. Tuberculin reactors whose weight is less than 90% of ideal body weight will have twice the risk of reactivation of tuberculin reactors whose weight is in the ideal range and four times the risk compared with tuberculin reactors whose weight is more than 110% of ideal.

**Table 3**  
Examples of Interpretation of TST in Three Dimensions

Condition	Relative Risk of Disease	TST Size (in mm)	BCG Vaccination After 12 Months of Age	Positive Predictive Value	Annual Risk of Active TB
Low risk reactors	1.0	5-9 mm	NO	100%	0.04%
	1.0	10+ mm	NO	100%	0.10%
Abnormal chest x-ray, fibronodular disease	6.0	5-9 mm	NO	100%	0.24%
	6.0	10+ mm	NO	100%	0.60%
Abnormal chest x-ray, fibronodular disease	6.0	5-9 mm	YES	25%	0.06%
	6.0	10+ mm	YES	25%	0.15%
Recent TST	15.0	10+ mm	NO	100%	1.50%
conversion	15.0	10+ mm	YES	25%	0.38%

As an example, a young woman is 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 immigrated to Canada from a country with high TB incidence and is asymptomatic. The TST reaction measured 8 mm. Her risk of disease is 0.24% per year, considerably higher than a “low-risk” reactor with a TST of 10+ mm.

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 Tuberculosis Disease and Infection).

### Interpretation When Sequential TST is Performed

#### Non-specific variation

Because of differences in 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.<sup>1</sup>

### 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.

If there is a documented previous TST result less than 5 mm, conversion is usually defined as a TST of 10 mm or greater. However the circumstances of the contact should be taken into account. For example, if the source case is highly infectious, if there was close or prolonged contact, if the contact is under age 5 or if the contact has impaired immunity, then an increase of 6 mm from the previous TST result may be considered a conversion. Decisions in this regard need to be individualized.

If there is a documented previous TST result 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 situation.
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.<sup>1</sup>

TST conversion occurs within 8 weeks of exposure and infection. The traditional concept was that conversion occurred in up to 12 weeks. However, all available experimental and epidemiologic evidence consistently shows that this interval is less than 8 weeks.<sup>1</sup> 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 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. This phenomenon is important to detect, as it could be confused with TST conversion. The booster effect was first described in older persons in whom it was felt to show LTBI acquired many years before (remotely) with subsequent waning of immunity.<sup>62</sup> It has also been described in persons with prior BCG vaccination<sup>18,63</sup> or sensitivity to nontuberculous mycobacterial antigens.<sup>18,64</sup>

### *Indications for 2-step testing*

A two-step TST should be performed if subsequent TSTs will be conducted at regular intervals or following exposure to an infectious TB case, for instance among health care or correctional service workers (see Chapter 16, Tuberculosis Control Within Institutions). This is to reduce the chance of a false-positive TST conversion when the TST is repeated. One controversial area is whether travelers should be given two-step TST before and/or after travel to a region with high TB incidence. Please refer to Chapter 13, Surveillance and Screening in Tuberculosis Control, 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.

In a contact investigation, two-step TSTs (to detect boosting) should not be performed. A single TST is performed soon after the contact is identified. If this TST is negative and it is performed less than 8 weeks after contact with the source case was broken, then a second TST is performed. This second TST is performed no sooner than 8 weeks after the contact was broken. It is performed to detect TST conversion from infection that occurred just before contact was broken, as a positive TST can develop any time within 3 to 8 weeks of the infection.

### *Technique*

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 persons 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.<sup>15,65</sup> 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 whose first TST response was 10 mm or more.<sup>65</sup> Therefore, 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. 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 whose 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 persons whose second TST increased by at least 6 mm. The decision to give INH should be individualized, but it seems unlikely to provide substantial benefit.

### Interferon-Gamma Release Assays (IGRAs)

Please see Appendix D, Interferon-gamma Release Assays for Latent Tuberculosis Infection: Canadian Tuberculosis Committee Advisory Committee Statement (2007). For subsequent versions, see <http://www.publichealth.gc.ca/tuberculosis>.

Recently, *in vitro* T-cell based assays that measure interferon-gamma (IFN- $\gamma$ ) production have been developed. These assays operate on the basis that T-cells previously sensitized to TB antigens produce high levels of IFN- $\gamma$  when re-exposed to the same mycobacterial antigens.<sup>66</sup> Two available tests are Quantiferon-TB Gold In-Tube<sup>®</sup> (Cellestis) and T-SPOT.TB<sup>®</sup> (Oxford Immunotec). For Quantiferon-TB Gold In-Tube<sup>®</sup>, whole blood is incubated with *M. tuberculosis* antigens, and the resulting production of IFN- $\gamma$  is measured using an enzyme-linked immunosorbent assay (ELISA). In the T-SPOT.TB<sup>®</sup> assay peripheral blood mononuclear cells are incubated with *M. tuberculosis* antigens and the number of T-cells producing IFN- $\gamma$  measured using an enzyme-linked immunospot (ELISPOT) assay.

While early IGRAs used PPD as the stimulating antigen, newer assays use *M. tuberculosis*-specific proteins – the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP10) – encoded by genes located within the RD-1 segment of the *M. tuberculosis* genome. These antigens are not found in BCG and many NTM species.

### Sensitivity, specificity and reproducibility

As shown in Table 4, IGRAs have shown variable sensitivity when assessed in patients with newly diagnosed active TB. The best sensitivity is with the Quantiferon tests using two RD-1 antigens (ESAT6 and CFP10) or ELISPOT using ESAT6. Interestingly, the sensitivity has been even lower in patients who have completed treatment of active TB. In only five studies have TSTs and IGRAs been concurrently used in patients with newly diagnosed TB; TST

sensitivity ranged from 86% to 93%. On the other hand, in previously treated patients the sensitivity of the TST was much higher than that of the IGRA assay; the 95% average sensitivity was similar to that reported in earlier studies in previously treated patients.<sup>67</sup>

**Table 4**  
Sensitivity of Interferon- $\gamma$  Release Assays  
in Patients with Active TB – Summary

Test	Studies (N)	References	Subjects (N)	IFN- $\gamma$ Sensitivity	TST Sensitivity
Quantiferon-PPD	7	68-71 72-74	278	76%	86%*
Quantiferon					
• ESAT6	3	70,75,76	97	57%	93%†
• ESAT6 + CFP10	4	73,76-78	205	86%	–
ELISPOT with ESAT-6 and/or CFP10	6	79-82 83,84	223	88%	–
<b>Cured active TB</b>					
Quantiferon-PPD	3	68,72,85	149	64%	95%‡

\* Only 2 studies<sup>69,72</sup> performed TST with adequate technique

† Only 1 study<sup>75</sup> performed TST with adequate technique

‡ Only 2 studies<sup>72,85</sup> performed TST with adequate technique

The major advantage of the new IGRAs is their potential for improved specificity in detecting LTBI in BCG-vaccinated populations. In populations that have received BCG vaccination before the age of 12 months, there is little discernable effect on either the TST reaction or on the results of Quantiferon assays using PPD. However, as shown in Table 5, specificity is superior with IGRAs using RD-1 antigens in populations that have received BCG vaccination after the age of 12 months, such as those in many European countries. In this population the specificity of ELISPOT or Quantiferon with RD-1 antigens has been excellent, at 97%–98%. In BCG-vaccinated populations, however, the specificity of the TST and IGRA using PPD has been much lower.

**Table 5**  
Specificity of Interferon- $\gamma$  Release Assays in  
Populations at Low Risk of TB Infection – Summary

Test	Studies (N)	References	Subjects (N)	IFN- $\gamma$ Sensitivity	TST Sensitivity
Quantiferon-PPD	8	68,70,72,86 73,74,85,87	1,079 No BCG 73 BCG	96.2% 73.0%	99.1%* 87.0%
Quantiferon	5	70,73,77 76,78	105 No BCG 353 BCG	98.0% 98.0%	97.0% 46.0%†
ELISPOT – ESAT6	4	79-82	145 BCG‡	97.0%	–‡

\*TST performed with adequate technique in all but one study.<sup>73</sup>

†TST performed with adequate technique in three studies.<sup>70,73,78</sup>

‡In the four studies with ELISPOT, 123/145 or 85% had received BCG. Results not presented separately. No TST done

When TSTs and IGRAs have been performed in the same subjects whose probability of TB infection was defined clinically, it has been possible to estimate concordance of the TST with the newer assays. As seen in Table 6, there is very substantial discordance in both high- and low-risk populations. Some of the discordance in TST-positive and IGRA-negative subjects is explained by

sensitivity to NTM and prior BCG vaccination. However, there are a large number of IGRA-positive yet TST-negative individuals in whom no explanation for this phenomenon has been found. In low-risk populations the number of positive but discordant reactions far exceeds the number of concordant positive reactions. Use of IGRA in screening low-prevalence populations may lead to a significant number of positive IGRA tests. The significance of such positive tests in a population at low risk is not yet known; this will make interpretation and management difficult.

**Table 6**  
Agreement between New Interferon- $\gamma$  Release Assays and Tuberculin Testing

Test (references)	TST		Agreement	Concordant* as % of All Positive	
	+	-			
Populations at increased risk of TB infection					
QFT-PPD <small>68,69,72,74,85</small>	+	501	212	79%	55%
	-	204	1,042		
QFT-ESAT6 + CFP10 <small>88,89</small>	+	251	63	83%	64%
	-	76	414		
ELISPOT-ESAT6 or CFP10 <small>82,90-92</small>	+	306	108	79%	51%
	-	184	815		
Populations at very low risk of TB infection					
QFT-PPD <small>72,86</small>	+	3	31	97%	6%
	-	16	1,511		

\* Percentage of subjects with any test positive who had both tests positive.

Five studies have compared ELISPOT with the TST when evaluating contacts with a gradient of exposure.<sup>92-96</sup> In four of the studies ELISPOT was better correlated with exposure than the tuberculin test used.<sup>92-94,96</sup> However, in two of these studies, in Great Britain, the Heaf test was used,<sup>92,96</sup> which has now been discontinued. In four studies a high proportion of the subjects had been BCG vaccinated.<sup>92,94,96</sup> In the only study in a largely non-BCG vaccinated population that employed an internationally accepted TST, reactions to the tests were inexplicably low in all exposure groups. These studies provide limited evidence of the superiority of ELISPOT over the standard TST, except in BCG-vaccinated populations, in which the greater specificity of the ELISPOT (and presumably Quantiferon) enhances precision of identification of infected contacts. In one study of household contacts in subSaharan Africa the TST was better correlated with exposure than an in-house Quantiferon test.

The reproducibility of results from IGRAs has been examined in several studies to date. In two studies performed by the manufacturer, the reproducibility of test results over time was high.<sup>97</sup> In a multicentre study in the United States there was substantial variability between centres in the degree of discordance between TST and Quantiferon results, which the authors attributed to differences in TST reading,<sup>72</sup> although this was later disputed.<sup>85</sup> In a fourth study a large group of health care workers with positive TST had serial Quantiferon assays every 2 months for up to 1 year; 37% of positive tests were followed by a negative test, and 16% of negative tests were followed by a positive result, for an overall weighted kappa of 0.51.<sup>71</sup> This evidence of substantial variability in Quantiferon

results raises important concerns regarding the validity of serial testing with these assays for detection of new TB infection in exposed groups.

### Summary: TST versus IGRA

In the diagnosis of latent TB infection, IGRAs have a number of potential advantages over the TST. Current commercially available assays that are based on combinations of RD-1 antigens such as ESAT-6 and CFP-10 appear to minimize false-positive test results due to vaccination with BCG and sensitization by certain NTM. Other benefits of these tests are that they require only a single visit by the patient and pose no risk of serious skin or allergic reactions.

A major advantage of the TST is that results have been validated through follow-up of large cohorts to determine subsequent incidence of active TB. On the basis of these studies, risk of disease in an individual with certain risk factors and a given TST reaction can be predicted with some accuracy. However, as of mid-2006, none of the IGRAs had been validated prospectively in this way.

The initial material costs of an IGRA are greater than those of the TST. Rigorous cost-benefit analyses are needed to compare the TST with either of the two available IGRAs. The occurrence of many reactions that are discordant with TST reactions is of concern, because this phenomenon of discordance remains largely unexplained. Therefore, individuals who are IGRA positive and TST negative will be difficult to manage appropriately.

It is important to note that IGRAs, like TSTs, are not recommended for the diagnosis of active TB. The precise indications for use and interpretation of results, particularly with regard to future risk of active TB disease, remain uncertain at this time. Future research is needed to define the ability of these assays to predict the development of TB, to determine their reproducibility, and to assess the health and economic implications of their use. At present it is difficult to recommend routine use of the assays for the diagnosis of LTBI. However further studies, particularly prospective studies with simultaneous performance of TSTs and IGRAs, will be of great interest.

### Chest Radiography for Diagnosis of LTBI

Chest radiography is not usually considered a tool to diagnose LTBI. However, it is quite common that chest radiography is done for some other reason, and radiographic abnormalities consistent with previous TB infection are detected. Individuals are considered to have inactive TB in Canada when the chest x-ray shows certain abnormalities consistent with TB infection AND a TST reaction of at least 5 mm. These individuals have an increased risk of reactivation and may be considered for treatment of LTBI (see Table 1 and Chapter 6, Treatment of Tuberculosis Disease and Infection).

The following radiographic findings are commonly believed to represent inactive TB. While some are associated with increased risk of reactivation of active TB disease in future, others are not.

1. Granulomas that may be calcified or not: this doubles the risk of reactivation resulting in active TB disease.
2. Calcified hilar lymph nodes: if there are no parenchymal lesions, these individuals do not appear to have an increased risk relative to those who are TST positive and have normal chest x-rays.
3. Costophrenic angle blunting: this is due to past pleural effusion or pleurisy, which can have many causes. The most common cause in individuals from countries with high TB incidence and other TB-endemic areas is previous primary TB. Such individuals have an increased risk of reactivation.
4. Apical pleural capping: this is not considered to be related to TB infection and is a nonspecific finding that is more common in older individuals.
5. Apical fibronodular disease: this is associated with increased risk of reactivation ranging from 6 to 19 times greater than those who are TST positive and have normal chest x-rays. Individuals with more extensive abnormalities have greater risk of disease.

### Diagnosis of Respiratory TB Disease

In Canada, respiratory TB includes primary TB, pulmonary TB, tuberculous pleurisy (non-primary) and TB of 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 pneumothorax, isolated tracheal or bronchial TB and tuberculous laryngitis.

### Clinical picture of pulmonary TB

1. Epidemiologic risk group: 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.
2. Symptoms: the classic symptom of pulmonary TB disease is a chronic cough of at least 3 weeks' duration. This cough is initially dry but after several weeks to months will become productive. 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.
3. 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.

## TST

For diagnosis of active disease in adults, the TST and an IGRA are *not* recommended. There is a limited role for TSTs in the diagnosis of pediatric TB (see Chapter 8, Pediatric Tuberculosis). TST results will be falsely negative in 20% to 30% of patients with active TB at the time of initial diagnosis.<sup>15</sup> In addition, because TB disease occurs in epidemiologic groups with a high prevalence of TB infection, TSTs and IGRAs will often be positive even when TB disease is not present, i.e. the predictive value of a positive test for *active disease* is very low.

## Chest radiography

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

1. Typical findings: a triad of classic findings are seen in non-immunocompromised adults.
  - Position – 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 may not be seen in severely immunocompromised individuals.
2. Atypical features: these will be seen in patients with immunocompromising conditions such as HIV infection, diabetes, renal failure or corticosteroid use.
  - Hilar and mediastinal lymphadenopathy, particularly in HIV-infected individuals.
  - Non-cavitary infiltrates and lower lobe involvement.
3. Radiographic signs of complications:
  - 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 diagnosis of active TB based on the abnormalities listed above. If *any* abnormality is considered, it will have more than 95% sensitivity.<sup>98</sup> Approximately 10% of HIV-positive persons or close contacts with active pulmonary disease will have normal x-rays.
2. Specificity is relatively poor, in the range of 60% to 70%.<sup>98</sup> If the sensitivity were improved (any abnormality considered possible TB), then the specificity would be much lower.
3. Inter-reader variability: one of the greatest problems of chest x-ray reading is that the interpretation is highly variable. There is very poor agreement between readers regarding the presence of cavitation, hilar lymphadenopathy and the likelihood of active disease.<sup>98</sup>

In summary, chest radiography is not considered the gold standard for diagnosis of pulmonary TB.

### Microbiology (see also Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies)

The role of the mycobacteriology laboratory is to isolate, identify and perform susceptibility tests on clinically significant mycobacteria. Mycobacterial culture, using both solid and liquid media, is considered the gold standard for diagnosis. 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, new molecular-based techniques for the detection and identification of mycobacterial species are being introduced, enabling more rapid identification of individuals with disease due to *M. tuberculosis*.<sup>99</sup>

Standards for the diagnosis of *M. tuberculosis* recommended by the U.S. Centers for Disease Control and Prevention (CDC) are that an AFB smear result should be reported within 24 hours of the laboratory's receipt of the specimen; if the AFB smear is positive, a positive culture result should be reported within 14-21 days; and primary drug susceptibility tests should be reported within 7-14 days after culture positivity.<sup>100,101</sup>

Mycobacteria can be cultured on solid media, such as Lowenstein-Jensen medium, and on liquid media, such as those used in the radiometric Bactec 460 (Becton Dickinson, Sparks, MD) or the continuous monitoring nonradiometric systems Bactec 960 and the MB/BacT systems. It is highly recommended that liquid media be used for primary culture of all clinical specimens. The length of time before cultures show positive results depends on whether the culture medium is liquid or solid, and the number and metabolic activity of mycobacteria in the original specimen. With use of broth culture media most mycobacteria, including *M. tuberculosis*, can now be detected within an average of 9-14 days.<sup>102-105</sup> Therefore, in order to achieve the goals described above, it is necessary for specimens to be processed daily, a liquid medium to be used for

culture and a rapid technique used for identification, either chromatography or an amplification method, such as polymerase chain reaction (PCR). Besides work load, expertise and biosafety requirements, the high cost of these new techniques justifies greater centralization of mycobacteriology services. Each health care facility must decide which procedures will be performed on site and which will be referred to a reference laboratory.<sup>101,106 \*</sup>

### Collection of respiratory specimens

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.

Once collected, specimens should be transported to the laboratory promptly. If processing within 1 hour is not possible, samples should be refrigerated at 4°C (not frozen) and protected from light. Clinical specimens, such as sputum, are not more contagious than any other clinical specimens and, therefore, can be handled with the same procedures. However, cultures of *M. tuberculosis* are much more hazardous and require careful procedures for packaging and shipment.

#### *Sputum*

Three sputum specimens of 5-10 mL each should be collected.<sup>98</sup> These can be collected 8-24 hours apart (or longer if necessary). At least one should be collected in the early morning upon awakening. Twenty-four-hour collections are unacceptable because of the lower sensitivity and significantly increased bacterial contamination.

#### *Induced sputum*

This technique was first introduced for the diagnosis of TB more than 35 years ago. Induced sputum has a sensitivity of 90%,<sup>107</sup> better than gastric aspirate (77%)<sup>108-110</sup> or bronchoscopy (also 77%). 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. With the use of this, virtually all patients will produce sputum, and a single sputum induction will have equivalent or better yield than fiberoptic bronchoscopy.<sup>107</sup> Sputum induction has been performed successfully in children as young as 2 years of age. 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 is spontaneously expectorated sputum.

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee



### *Bronchoscopy*

Bronchoscopy may be used to confirm the diagnosis of TB when spontaneous sputum and induced sputum are unavailable, or all samples are smear negative. Bronchoscopy is very useful if other pulmonary diseases, such as lung cancer, are also suspected. However, bronchoscopy for the diagnosis of active TB entails risk and discomfort for the patient, is expensive and can contribute to nosocomial spread of TB. In addition, the overall yield of bronchoscopy in prospective series of patients is only 77%.<sup>111-114</sup> If bronchoscopy is done, postbronchoscopy sputum should be sent for AFB testing, as this has a yield similar to that of bronchial washings and lavage.

### *Gastric aspirate*

This technique was introduced more than 70 years ago and is still used in some centres.<sup>115</sup> The primary indications are investigation of possible TB in children who cannot expectorate sputum or, for the same reason, elderly demented patients. In children less than 2 years old, 70% sensitivity for gastric washings has been reported, which compares with a sensitivity of 30%-40% in children between the ages of 2 and 12 years.<sup>116</sup>

The technique is relatively simple (see Chapter 8, Pediatric Tuberculosis, Table 2). The child needs to have had nothing to eat or drink for at least 6 hours before the test. When the individual first wakes, a nasogastric tube is introduced to the stomach, and the contents are aspirated. If nothing is obtained, small quantities (20-50 mL) of sterile water can be instilled and aspirated. The fluid has to be adjusted to neutral pH within 4 hours of collection because acid is detrimental to mycobacteria. If the sample cannot be processed rapidly within less than 4 hours, it should be placed in a container with 100 mg of sodium carbonate.

However, this technique is uncomfortable and unpleasant for patients, and may be difficult to implement because it is usually performed immediately upon awakening. This often means that the patient must be kept overnight in hospital, although it can be done at home.

### **Acid-fast staining and microscopic examination (AFB smear)**

Specimens must be homogenized and then concentrated.\* The fluorochrome stain auramine is the most widely used staining method for initial AFB smears because it can be read at a lower magnification than the classical Ziehl-Neelsen stain, and thus readings are much quicker. A positive fluorochrome stain must be confirmed with a fuchsin stain – meaning Kinyoun or Ziehl-Neelsen stain. 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  $10^5$  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. By contrast, as few as 10-100 viable bacteria can be detected by culture.<sup>98</sup>

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

The overall sensitivity of the direct (unconcentrated) AFB smear varies from 22% to 80%,<sup>117-119</sup> depending on the type of specimen, patient population, staining technique and experience of the technologist. The sensitivity is higher for respiratory than for nonrespiratory specimens, particularly body fluids.

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 *Actinomyces*, can be weakly acid-fast, but these are very rare. Therefore, a positive AFB smear almost always indicates the presence of mycobacteria, but not necessarily *M. tuberculosis*.

When acid-fast organisms are seen, the number of bacteria is reported semiquantitatively, as shown in Table 7. There are different scales in use, one used by most laboratories in Canada<sup>104</sup> and another recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD).<sup>120</sup> The latter is relevant if interpreting smear results from countries that use that system.

**Table 7**  
**Number of Bacteria Seen on Microscopy and Laboratory Interpretation**

Number of AFB Seen by Staining Methods			
Fuchsin stain (Ziehl-Neelsen) (1,000-fold magnification)	Fluorochrome (250-fold magnification)	Laboratory report, Canadian <sup>104</sup>	Laboratory report, IUATLD <sup>120</sup>
0 in 100 fields	0 in 30 fields	Negative	Negative
1-2 per 300 fields	1-2 per 30 fields	Indeterminate, repeat	Report exact number
1-9 per 100 fields	1-9 per 10 fields	1+	1+
1-9 per 10 fields	1-9 per field	2+	2+
1-9 per field*	10-90 per field	3+	3+
> 9 per field†	> 90 per field	4+	

\* Consistent finding in at least 50 fields

† Consistent finding in at least 20 fields

### Mycobacterial culture

Culture for *M. tuberculosis* is considered the gold standard in diagnosis. For pulmonary TB, the sensitivity of three sputum cultures exceeds 90%, although six specimens are required to achieve 100% sensitivity.<sup>98</sup> Three sputum cultures are recommended, as this represents the best balance between high sensitivity and efficiency. A single positive culture for *M. tuberculosis*, in general, is considered to define active disease. However, it is important to remember that cultures occasionally can be false positive, largely because of cross-contamination within the laboratory.<sup>121,122</sup> 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, ideally performing DNA fingerprinting on the isolate and all others isolates detected at the same time.

## Identification of mycobacterial species<sup>103-105</sup>

1. Biochemical tests: historically, mycobacteria were identified on the basis of their rate of growth and pigmentation as well as through biochemical tests. For example, *M. tuberculosis* is a nonchromogenic mycobacterium. These tests were well standardized and inexpensive, but results were available only 2 to 4 weeks after growth was first detected. Therefore, they are rarely performed in Canadian laboratories nowadays.
2. High performance liquid chromatography (HPLC): HPLC analyses the cell wall lipids of mycobacteria. This is technically complex and requires expensive equipment, and so it is available in only a few reference laboratories in Canada.
3. DNA probes: DNA probes are now available for the identification of many mycobacterial species, including *M. tuberculosis* complex, *M. avium* complex, *M. avium*, *M. intracellulare*, *M. goodii* and *M. kansasii*. These results are available within 3 hours but can be used only to test positive cultures, as they are not sensitive enough to detect mycobacteria in clinical specimens. In Canada, the probes for mycobacteria other than *M. tuberculosis* are available only in reference laboratories, and they are very expensive.
4. Sequence-based identification: 16S *Hsp65*, ITS (internal transcribed spacer), etc.

## Nucleic acid amplification techniques

Nucleic acid amplification (NAA) tests, which amplify target sequences of DNA or RNA from the *M. tuberculosis* organisms, have been introduced into clinical use over the past 15 years. Commercially available NAA tests detect *M. tuberculosis* in clinical specimens in two steps. First specific segments of *M. tuberculosis* DNA are amplified, then the amplified DNA is detected with DNA probes. These tests are complex and expensive but have several important advantages. They provide results within 3 to 24 hours, are more sensitive than AFB smears, although less sensitive than TB cultures, and have excellent specificity. Most early studies of NAA tests were performed by research laboratories with “in-house” PCR kits. These were less costly but were less reproducible and required much greater technical skill. Several tests are now commercially available:

1. The Amplicor<sup>®</sup> (Roche Diagnostics, Inc.) test amplifies and detects the 16S ribosomal RNA using conventional polymerase chain reaction technology. This assay takes about 6 hours to complete.
2. The Cobas Amplicor<sup>®</sup> test, also produced by Roche Diagnostics, Inc., is an automated version of the original Amplicor test and is more practical for laboratories processing large numbers of specimens.
3. The MTD<sup>®</sup> and the enhanced MTD<sup>®</sup> (Gen-Probe, Inc.) system utilizes transcription-mediated amplification of the same 16S rRNA. This test takes approximately 3 hours to complete.
4. The Ligase Chain Reaction (LCx)<sup>®</sup> (Abbott Laboratories).

NAA tests have been extensively evaluated in the United States and Europe, and a few studies have been conducted in developing countries. As summarized in Table 8, in studies that used TB culture as their gold standard, the sensitivity of NAA tests ranged from 70% to 100% with an average of approximately 80%. Sensitivity in smear-positive respiratory specimens averaged 95% but was considerably lower in smear-negative specimens. In extrapulmonary disease, sensitivity has ranged from 40% to 80% and averaged between 50% and 60%. Specificity exceeds 95% in almost all studies. However false-positive rates can be very high without careful attention to proper technique by highly trained and closely supervised laboratory staff. At present, these tests are recommended only for smear-positive respiratory specimens. Their usefulness could increase in the near future if the sensitivity were improved and the cost lowered. In situations in which a biopsy was done and no culture sent, the utility of NAA has been evaluated in pathologic specimens. A sensitivity of 73% has been reported.<sup>123</sup> This is not optimal but better than no confirmation at all (when cultures were inadvertently not sent).

**Table 8**  
**Nucleic Acid Amplification Tests for Diagnosis**  
**of Active TB – Summary**

Test	Studies N (References)	Specimens (N)		Sensitivity (%)			Specificity (%) Overall
		Not TB	Active TB	Overall	Respiratory		
					Smear Positive	Smear Negative	
"In house" PCR	5 124-128	2,319	451	84-98	88-100	50-71	96-99
Roche-Amplicor®	4 90,124,129,130	3,531	309	70-95	95-98	40-86	98-99
Roche Cobas Amplicor®	2 131,132	5,051	466	84-94	96-99	72-75	99-100
Gen Probe-MTD®	6 90,132-136	1,922	434	71-98	92-100	65-85	99-100
Ligase Chain Reaction LCx®	4 136-139	1,180	405	76-94	92-99	48-73	92-99

### DNA fingerprinting of strains

This is not really a diagnostic test but, rather, an epidemiologic tool used to study transmission events (see Chapter 1, Epidemiology of Tuberculosis in Canada).

### Serology

A serologic test for the diagnosis of TB was first described in 1898. However, after a century of efforts, there is still no accurate serologic test for the diagnosis of active TB. While interferon- $\gamma$  release assays (see above) require the drawing of blood, they are not serologic tests.

Earlier serologic assays were quite crude and unstandardized, resulting in poor sensitivity and specificity.<sup>140</sup> Newer antigens used with ELISA techniques have better specificity,<sup>141-143</sup> although sensitivity is still suboptimal. Sensitivity is highest in smear-positive patients, particularly those with symptoms of long duration, but lower in smear-negative or extrapulmonary disease.

At present, the use of a serologic test for the diagnosis of TB cannot be recommended. However, this remains an active area of research, because an ELISA test with sensitivity and specificity equivalent to AFB smears would have enormous advantages because of its rapidity, simplicity and low cost.

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# Nonrespiratory Tuberculosis

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## Definition

The diagnostic classification of tuberculosis (TB) in Canada is based upon the *International Classification of Diseases*, 9<sup>th</sup> and 10<sup>th</sup> editions. For each case of TB, up to five individual diagnoses are captured for reporting purposes. Effective from 2003, the main diagnostic site is determined by the following hierarchy: primary, pulmonary, other respiratory, miliary/disseminated, meninges/central nervous system (CNS), peripheral lymph node and other sites.

Primary TB includes primary respiratory TB and tuberculous pleurisy in primary progressive TB (see Appendix C, Definition of Terms, for precise definitions). In Canada, pulmonary TB includes TB of the lungs and the conducting airways, which includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia, tuberculous pneumothorax, isolated tracheal or bronchial TB and tuberculous laryngitis. Other respiratory includes tuberculous pleurisy (nonprimary) and TB of intrathoracic lymph nodes, mediastinum, nasopharynx, nose (septum) and sinus (any nasal).

Although the terms “pulmonary” and “extrapulmonary” are more commonly used (e.g. in the United States), the terms “respiratory” and “nonrespiratory” are judged to be more practical as they distinguish between all forms of the disease that are potentially communicable and those that are almost never communicable. Further confusion exists when reports are compared that involve both a respiratory and a nonrespiratory diagnostic site. Some sources have chosen to report only the most prominent or major site of disease. Others have reported both, with emphasis on the respiratory site because of its public health implications. The Canadian TB Reporting System encourages coding of all diagnoses that apply and identification of the main diagnostic site through the previously mentioned hierarchy.

## Epidemiology

Canadian data from the early 1970s indicated that approximately 17% of all TB cases involved primarily a nonrespiratory site.<sup>1,2</sup> 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.<sup>3</sup> U.S. data showed that the proportion of extrapulmonary disease among all patients with TB by age was largest among children (and generally decreased with increasing age); larger among black, Asian and American Indians than among non-Hispanic white patients; larger among female than male patients; and larger among foreign-born patients than those born in the United States.<sup>4</sup> More recent U.S. data, including the results of DNA fingerprinting of *M. tuberculosis* isolates, have shown young age, female sex and HIV infection to be independent risk factors for extrapulmonary TB.<sup>5</sup>

Between 1980 and 2004, the number of reported cases of respiratory TB in Canada decreased by 49%, whereas the number of nonrespiratory cases decreased by 11%. As a result, the proportion of total cases that were nonrespiratory rose to approximately 30% in 2004, by far the most common site of involvement

being the superficial lymph nodes.<sup>6</sup> Similar trends have been reported in the United States.<sup>7</sup>

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 European) to those with high TB incidence (Africa, Asia, Central and South America, Eastern Europe). Foreign-born persons are disproportionately more likely to have nonrespiratory than respiratory TB compared with Canadian-born persons (Table 1), a finding that may reflect, in part, 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. TB patients with HIV infection are more likely to have nonrespiratory TB alone or concurrent with respiratory TB than are those without HIV<sup>8-11</sup> (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus).

**Table 1**  
**Anatomic Site of Disease and Ethnic Origin of Patients with TB, Canada 2004**

Disease Site	Aboriginal*		Canadian-born (other)		Foreign-born		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%
Respiratory†	229	85	156	78	698	65	44	59	1,127	70
Nonrespiratory	39	15	42	21	374	35	30	41	485	30
Unknown	0	0	1	0	0	0	0	0	0	0
<b>TOTAL</b>	<b>268</b>	<b>100</b>	<b>199</b>	<b>100</b>	<b>1,072</b>	<b>100</b>	<b>74</b>	<b>100</b>	<b>1,613</b>	<b>100</b>

\* Includes Status and Non-Status Indians, Metis and Inuit.

† Includes primary, pulmonary, pleural, "other" respiratory TB.

## Pathogenesis

*M. tuberculosis* is almost exclusively a human pathogen. Its survival as a species depends upon its transmission from one human to another. This transmission is facilitated by the occurrence of respiratory disease in the host. From the perspective of the pathogen, nonrespiratory disease is a failed phenotypic expression, as it almost never results in transmission to new hosts. On the other hand, from the point of view of the human host, nonrespiratory TB has important consequences. A disproportionately large number of nonrespiratory compared with respiratory cases may be life-threatening, mainly on account of a delay or failure altogether to make the diagnosis. Although nonrespiratory disease does not contribute significantly to the transmission of TB, infection control precautions are nevertheless strongly recommended if there is any possibility of aerosolization of bacteria, as may be the case in wound care, surgical procedures and postmortem examination.

As described in Chapter 3, Transmission and Pathogenesis of Tuberculosis, nonrespiratory sites are seeded at the time of primary infection as a consequence of bacteria gaining access to the circulation through the lymphatic system

and then seeding distant capillary beds. In most instances the cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH) stimulated by the infection result in the containment of these foci, and active disease does not develop. Occasionally in immunocompetent hosts, and not uncommonly in immunocompromised hosts, CMI and DTH fail to contain these foci of infection, and localized or generalized (disseminated) disease develops within a year or two of the primary infection.<sup>12</sup> The majority of nonrespiratory TB is acquired through the reactivation of latent infection.<sup>5</sup>

Seeding of respiratory and nonrespiratory sites at the time of primary infection favours organ systems with high blood flow and increased oxygen tension, such as the lung apices, renal cortex, brain and growing ends of long bones.<sup>12</sup> For reasons that are not known, certain reticuloendothelial organs, such as the liver, spleen and bone marrow, may be seeded but seldom give rise to disease, presumably because the organisms are effectively eradicated, whereas in the superficial lymph nodes disease is very common. This and other observations, such as the high incidence of cervical lymphadenitis due to *Mycobacterium bovis* prior to the pasteurization of milk, have led to debate over the local versus generalized nature of superficial lymph node disease.<sup>13</sup>

Even if the foci of infection are contained at the time of primary infection, reactivation may occur many years later after a prolonged period of latent infection. Many risk factors for reactivation have been described (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease); none is more important than HIV/AIDS. Patients with HIV/AIDS who are coinfecting with *M. tuberculosis* bacteria have a high frequency of nonrespiratory involvement (usually with concurrent respiratory disease) and lower cure rates.<sup>8,14</sup> Some studies have found this to correlate with the CD4 cell count, whereas others have found no such correlation.<sup>15-17</sup> In general, nonrespiratory TB is associated with lower CD4 cell counts.<sup>15,18</sup> TB lymphadenitis and disseminated disease are frequent forms of nonrespiratory TB in persons with HIV/AIDS. Involvement of the bone marrow, genitourinary system and CNS are also common. Nonrespiratory TB is more common in other immunocompromised patients, such as those with end stage renal disease.<sup>19</sup> There is even some evidence to suggest that those who contract nonrespiratory TB and are overtly immunocompetent may actually have abnormal innate immune responses.<sup>20</sup>

## Diagnostic Considerations

A high index of suspicion is paramount to the rapid diagnosis of nonrespiratory TB. Given that nonrespiratory TB made up 30% of all reported cases of TB in 2004 in Canada, any delay in diagnosis could subsequently increase morbidity in a significant proportion of TB cases.<sup>21</sup> Delays in nonrespiratory TB diagnosis may be related to the often nonspecific (e.g. fever, night sweats, weight loss) or organ-specific presentation compounded by the absence of an abnormal chest radiograph or positive sputum samples. When evaluating at-risk patients with fever of unknown origin, with fever and site-specific signs and symptoms or patients with biopsy-proven granulomatous inflammation, appropriate steps should be taken to secure the diagnosis of TB. With a diagnosis of nonrespiratory TB established, confirmation of HIV status is imperative.

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

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. Biopsy material for mycobacterial culture should be submitted fresh or in a small amount of sterile saline. Histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further attempts to culture. Common histopathologic findings include necrotizing and non-necrotizing granulomatous inflammation, giant cells or epithelioid cells, with variable numbers of AFB. Host immune status can influence the findings on histopathology with, greater suppurative response, less well-formed granulomas and numerous AFB seen with loss of immune function.<sup>22</sup>

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.<sup>23-25</sup> For now, the diagnosis of nonrespiratory TB is dependent upon clinical acumen and culture confirmation.

## Clinical Presentations

### Peripheral TB lymphadenitis

Almost all forms of TB involve regional lymphatics and nodes. Intrathoracic lymph nodes are commonly involved in primary disease and advanced pulmonary disease, and in patients with HIV/AIDS. Rarely, intrathoracic nodes may be the major site of disease in immunocompetent patients. Peripheral TB lymphadenitis involves extrathoracic nodes, in particular the cervical nodes, which are by far the most commonly affected nonrespiratory site.<sup>3</sup> Only extrathoracic lymph node involvement will be discussed in this section. Peripheral TB lymphadenitis made up 16% of all cases of TB in Canada in 2004 (Table 2).

Table 2  
Number of TB Cases and Incidence per 100,000 Population  
by Main Diagnostic Site, Canada 2004

Disease Site	Cases		Incidence per 100,000 Population
	<i>n</i>	%	
<i>Respiratory</i>	1,127	70	3.5
<i>Nonrespiratory</i>			
Peripheral lymph nodes	251	16	0.8
Miliary/disseminated	30	2	0.1
Meninges/central nervous system	19	1	0.1
Abdominal	38	2	0.1
Bones and joints	44	3	0.1
Genitourinary	36	2	0.1
Other*	67	4	0.2
<i>Unknown</i>	1	0	0.0
Total	1,613	100	5.0

\* Includes 2 cases with more than one extrapulmonary site identified.

Tuberculous involvement of the lymph glands can be secondary to infection from *M. tuberculosis* as well as nontuberculous mycobacteria. *M. bovis*, when isolated from peripheral lymph nodes, has been associated with ingested contaminated milk directly infecting the lymph nodes through contiguous spread.<sup>26</sup> Atypical or nontuberculous mycobacteria (NTM) are most commonly isolated from the cervical lymph nodes and submandibular glands of young (< 5 years) Caucasian children.<sup>27</sup> The high incidence of TB lymphadenitis in the foreign-born may reflect the incidence of TB lymphadenitis in the country of origin, yet the reasons for this geographic variability remain unknown. It may be due to specific TB strains found in the country of origin or a genetically conditioned response to infection with TB.

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 3).<sup>3,8,28</sup> Presentation can be at a single nodal site or in multiple sites. A recent study of TB lymphadenitis in Manitoba found that 18% of cases also had a concurrent diagnosis of TB elsewhere in the body.<sup>28</sup> In general, the disease is most often indolent, and the patient usually presents with an isolated, unilateral, nontender neck mass. With time, the nodes may become fluctuant and drain spontaneously with sinus tract formation irrespective of treatment. The term “scrofula” has been used historically to describe tuberculous involvement of a cervical lymph node with sinus tract formation or ulceration. Non-nodal symptoms are rare except in individuals infected with HIV/AIDS.<sup>9,10,13</sup> Peripheral lymphadenitis is particularly common among immigrants to Canada from Asian countries such as China, Viet Nam and the Philippines.<sup>28,29</sup> Among these immigrants, young women are especially prone to isolated lymph node involvement.<sup>28,30</sup> High rates of tuberculous lymphadenitis in the foreign-born are well documented in the developed world.<sup>13,30-32</sup> In Manitoba, the highest incidence of peripheral lymphadenitis has been reported among older Aboriginal women.<sup>28</sup> The reason(s) for this age-, sex- and ethnicity-related organotropism is unknown.

**Table 3**  
**Lymph Node Site and Symptoms at Presentation in Cases of Tuberculous Lymphadenitis in Manitoba (n = 147)\***

Anatomic site	n	%
Cervical	111	76
Supraclavicular	39	27
Axillary	14	10
Inguinal	9	6
Intra-abdominal	9	6
<i>Symptoms: lymph node</i>		
Swelling	121	82
Pain	32	22
Drainage	16	11
Ulceration	6	4
<i>Symptoms: other</i>		
Constitutional	25	17
Other	24	16

\* Percentage more than 100 because some patients had multiple nodal sites and symptoms.<sup>28</sup>

The best diagnostic procedure is an excisional biopsy, which yields the diagnosis in 80% of cases. Fine needle aspiration (FNA) biopsy is a useful initial procedure with a reported sensitivity of 77%, specificity of 93% and diagnostic accuracy of 62%.<sup>33</sup> In the developing world, FNA is most valuable in HIV-infected individuals.<sup>34,35</sup> 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.<sup>36</sup>

As stressed earlier, specimens must be submitted for both mycobacteriologic and histopathologic analysis.\* Differentiation of *M. tuberculosis* from the *M. avium* complex (MAC) is imperative, as treatment is very different. Surgical excision of an MAC-affected node or gland is usually curative, whereas *M. tuberculosis* of the superficial lymph nodes requires antituberculosis drug treatment, which leads to an uneventful resolution of the condition in up to 80% of patients.<sup>28</sup> The optimal duration of treatment ranges from 6 to 9 months depending on resistance patterns and response to treatment.<sup>37-39</sup> 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.<sup>40</sup> At the end of treatment, 10% may be left with residual nodes, and, if after treatment the nodes enlarge or reappear afresh, this is usually transient.<sup>41</sup> Such events do not necessarily imply relapse, nor does the persistence of nodes presage relapse. Surgical procedures, other than diagnostic, should be reserved for the relief of discomfort caused by enlarged nodes or tense, fluctuant nodes.<sup>42</sup>

### Genitourinary TB

Genitourinary TB made up 2% of all cases of TB in Canada in 2004 (Table 2). At the time of primary infection, or in the case of dissemination associated with reactivation, *M. tuberculosis* seeds the vascular renal cortex. Healed

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

granulomatous lesions in the glomeruli can rupture into the renal tubule and become mechanically caught up at the loop of Henle, where, in the medullary portion with its poor host defence, granulomatous progression, necrosis and cavitation is likely to ensue. Although both kidneys are usually seeded, severe renal involvement is often asymmetric or unilateral (25%), so that renal failure is uncommon.<sup>43-45</sup> Subsequently, through descending infection, the infundibulum, ureter, bladder, prostate, epididymis and testes may be involved. A combination of upper and lower tract disease is highly suggestive of TB. Urinary tract disease has also been associated with secondary amyloidosis and interstitial nephritis.

Most often, onset of the disease is insidious, and patients present with asymptomatic sterile pyuria, gross hematuria, frequency and dysuria. Back pain or flank pain, resembling acute pyelonephritis, often reflects calyceal or ureteral obstruction though renal colic is uncommon. Other symptoms may be due to defects of urinary concentration, bladder involvement with resultant diminished bladder capacity and inability to empty completely, or complicating nonmycobacterial infection. Antibiotics such as fluoroquinolones, used to treat the latter, may compromise the laboratory's ability to recover *M. tuberculosis* and therefore should be administered no later than 48 hours before urine specimens for mycobacteriologic tests are collected.

Many patients with genitourinary TB remain asymptomatic, and early in the course of the disease have no radiologic signs, though the urinary sediment is rarely normal.<sup>46</sup> The clinical suspicion for genitourinary TB increases in a symptomatic patient with a history of previous TB or a positive tuberculin skin test result. Of patients with urinary tract disease, 80% to 90% will have positive cultures to confirm 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).<sup>43,47,48</sup> AFB smears alone are less reliable, and concurrent bacteriuria or nonpathogenic mycobacteria does not exclude the diagnosis of TB. Prior administration of intravesical BCG vaccine should be considered when diagnosing genitourinary TB.

Intravenous pyelography (IVP) is the radiologic procedure of choice, but ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are also useful. The earliest lesions seen on IVP are distorted or eroded calyces, overt papillary necrosis, parenchymal scarring and calcification, which can mimic the changes seen in chronic pyelonephritis.<sup>47,49,50</sup> Occasionally, in highly suspect cases that are bacillary negative, FNA of the kidney under ultrasound guidance may be indicated. 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. Hence, radiologic follow-up and intervention to maintain lumen patency may be necessary.<sup>44,51</sup>

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. 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.<sup>43</sup> Pelvic TB is most commonly diagnosed during

a work-up for infertility or during evaluation of abnormal uterine bleeding, pelvic pain or adnexal masses. The diagnosis of female genital TB requires a combination of microbiologic, histologic and radiologic techniques. Findings on hysterosalpingography may suggest TB, though, as with renal TB, imaging is often nonspecific and findings are observed later in the disease process. Cultures of *M. tuberculosis* can be obtained from several sources, especially endometrial biopsy specimens, menstrual fluid, vaginal discharge or, less commonly, peritoneal fluid. Male genital TB usually presents with scrotal swelling, sometimes with rectal or pelvic pain and less commonly with epididymitis, hydrocele or discharging sinus (“watering can” perineum). 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. Epididymal or prostate biopsies are often necessary for diagnosis. FNA has been successfully applied in this setting as well. A good prognosis is associated with early detection of disease and full sensitivity to first-line antituberculosis medications.

### 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. 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.<sup>52</sup> The disease may manifest as a miliary pattern on the chest radiograph or, among those without a miliary pattern on chest radiograph, as a bone marrow aspirate/biopsy or blood culture positive for *M. tuberculosis*, or generalized TB at postmortem examination.<sup>53</sup> For this discussion, the terms miliary and disseminated are interchangeable.

The proportion of all TB cases that were miliary or disseminated was 2% in Canada in 2004 (Table 2). While the incidence of miliary TB in Canada has remained relatively stable for the last decade, it has risen in the United States largely on account 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 the elderly, malnourished, HIV-infected and those with other conditions associated with impaired CMI, such as solid organ transplantation, renal failure 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.<sup>53</sup> Choroidal tubercles seen on fundoscopy may suggest the diagnosis. Most often, the presentation is subacute or chronic, though acute fulminant presentations can occur, such as shock and acute respiratory distress syndrome.<sup>54</sup> The nonspecific and often variable presentation frequently leads to a delay or lack of diagnosis and a high mortality rate.<sup>55</sup>

Diagnosis of miliary TB is difficult, and a high index of suspicion, with institution of therapy prior to a confirmed diagnosis, is required to prevent morbidity and death.<sup>56</sup> 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.<sup>57</sup> 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. Transbronchial, thoracoscopic or surgical biopsies of lung (if imaging is abnormal) and biopsy of liver (highest yield > 90%) and bone marrow will frequently demonstrate caseating granulomas or AFB on special stains, justifying the early commencement of antituberculosis therapy. In children, gastric washings may be positive. In cases in which hematogenous dissemination is suspected, particularly those associated with HIV infection, blood cultures may be positive. The yield 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  $100 \times 10^6/L$ . Liquid culture media specifically designed for the growth of *M. tuberculosis* (e.g. BACTEC 13A) must be used, which are different from the blood culture bottles used for the isolation of other bacteria.<sup>15,58 \*</sup>

Standard antituberculosis treatment regimens will achieve microbiologic and clinical cure, but longer therapy (i.e. 12 months) should be considered for children and the immunocompromised (e.g. those with HIV/AIDS), as well as patients with a slow response to treatment or with drug-resistant disease. Despite appropriate treatment, mortality from miliary TB remains as high as 20%.<sup>59,60</sup> Negative prognostic indicators include meningeal disease, hematologic abnormalities, late presentation, concomitant diseases and anergy.

### Bone and joint TB

Bone and joint TB made up approximately 3% of all reported cases of TB in Canada in 2004 (Table 2), a proportion that has not changed significantly for decades. Most bone and joint TB is presumed to arise as osteomyelitis from granulomatous foci in the growth plates of bones, where the blood supply is richest. Because these growth plates or metaphyses are typically near joints, the infection can then spread locally into joint spaces, resulting in tuberculous arthritis.<sup>61</sup> Local manifestations, such as pain, predominate, and soft tissue collections (cold abscesses) may occur at or near the bone and joint focus. Constitutional symptoms are relatively uncommon. Spinal or vertebral TB (Pott's disease) involvement is noted in approximately 50% of the cases of bone and joint TB. Vertebral bodies remain highly vascular into adulthood, which explains the propensity for bone and joint TB to develop at this site. When the incidence of TB is high, bone and joint TB occurs most commonly in childhood, usually within 1 year of primary infection; when the incidence of TB is low, it is mainly a disease of adults and is associated with reactivation.

Two distinct patterns of spinal disease are recognized: the classic form of spondylodiscitis and an increasingly common atypical form characterized by spondylitis without disc involvement.<sup>62,63</sup> 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. Paraspinal collections with typically a fusiform appearance may develop and track distally

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

into the groin. In children and adolescents the lower thoracic vertebrae are most often diseased; among adults, disease more commonly involves the lumbar vertebrae. Spinal angulation as well as compression and vascular damage to the spinal cord may occur with devastating consequences. Surgical intervention may be necessary, and its indications have recently been reviewed.<sup>64</sup> Appropriate airborne precautions should be taken in the surgical suite, as well as by health care workers involved in wound care, if bone and joint TB is suspected or has been diagnosed.

Tuberculous arthritis is usually a mono-arthritis affecting large weight-bearing joints such as the hip or knee. Multifocal lesions are noted in 15% to 20% of cases. Symptoms can include swelling, pain and loss of function (“cold joints”). 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. Synovial fluid microscopy has a low yield, but cultures have been reported as positive in 79% of cases.<sup>65</sup> Synovial biopsy with culture may be required and is highly sensitive in the diagnosis.<sup>66</sup> Osteomyelitis affecting other sites in the skeleton is very infrequent but is known to occur. Multifocal presentations can be misinterpreted as metastasis.

The diagnosis of bone and joint TB is often delayed because of the insidious nature of the illness, physician failure to consider the diagnosis, bacterial/fungal coinfections and a failure to obtain the appropriate specimens for laboratory testing. The radiologic features of bone and joint TB are relatively nonspecific. MRI is valuable in evaluating spinal cord compression. As in all other forms of nonrespiratory TB, the diagnosis is confirmed only with microscopy and culture. A CT-guided needle biopsy is the recommended approach to obtain tissue for testing. Standard antituberculosis treatment regimens will achieve microbiologic and clinical cure, but longer durations are suggested (i.e. 12 months) because of concerns about poor penetration into bony tissues. Shorter courses of treatment (6 months) have been reported with results comparable to those of longer regimens but only when combined with radical surgical resection.<sup>67</sup> It should be noted that the radiologic features of disease may initially appear to progress despite treatment, which in isolation should not prompt changes to the regimen.<sup>68</sup>

### Abdominal TB

Abdominal TB made up approximately 2% of all reported cases of TB in Canada in 2004 (Table 2), a proportion that has not changed significantly for decades. 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 or ingestion of contaminated milk, hematogenous spread from initial primary foci in the lung or later dissemination of reactivated disease or, rarely, contiguous spread from adjacent organs.

Gastrointestinal involvement usually occurs in the ileocecal, jejunoileal or anorectal area. A minority of cases are made up of mesenteric adenitis alone.

These patients often present with abdominal masses. The macroscopic appearance of lesions may be ulcerative (60%), hypertrophic (10%) or a combination of both (ulcero-hypertrophic, 30%). 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%). The differentiation of enteric TB from Crohn's disease is difficult, though it should be noted that patients with Crohn's disease rarely have ascites or circumferential ulcers, while "cobblestoning" on colonoscopy is rarely seen with enteric TB. Suspected Crohn's disease in Aboriginal Canadians and the foreign-born from countries with a high TB incidence should always raise the possibility of enteric TB. Confirmation of the appropriate diagnosis is essential, given the implications of immunosuppressing treatment for suspected Crohn's disease that is, in fact, TB. Radiographic features of enteric TB are nonspecific, though the most common finding on CT scan is concentric mural thickening of the ileocecal region (with or without proximal dilation) and characteristic adjacent mesenteric lymphadenopathy with hypodense centres.<sup>69</sup> Although colonoscopy and biopsy for histopathology and culture may be the procedure of choice (up to 80% diagnostic yield), the diagnosis is frequently made only after laparotomy.<sup>70</sup> It should be noted that in Crohn's disease, caseating granulomas are rarely found. Empiric treatment is also an option prior to laparotomy, as the response to antituberculosis treatment can be followed. Appropriate respiratory protection should be worn by health care workers in endoscopy or surgical suites if enteric TB is suspected.

In those with peritoneal involvement, common presenting symptoms are abdominal swelling (particularly in patients with coexisting alcoholic liver disease), abdominal pain, fever, weight loss and diarrhea.<sup>71-74</sup> 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"). Ascitic fluid is exudative with a predominance of lymphocytes, although when TB peritonitis complicates chronic peritoneal dialysis, neutrophils may predominate. Culture yields of a large volume of ascitic fluid (1 L) after centrifugation are high (> 80%), though smears are often negative.<sup>74</sup> Laparoscopy with peritoneal biopsy is the single best diagnostic procedure. Targeted biopsies of the typical white nodules or tubercles seen in tuberculous peritonitis lead to positive histopathologic and smear results in the majority of cases. Radiologic features are nonspecific, though peritoneal thickening, omental caking and septated ascites are suggestive of the diagnosis.

Treatment for abdominal TB follows the standard approach and is highly effective. Surgery is generally advised only in the face of serious complications, such as perforation, bleeding or obstruction.

### CNS TB

CNS TB includes tuberculous meningitis, tuberculous myelitis and brain and/or meningeal tuberculoma. In Canada, CNS TB made up approximately 1% of all reported cases of TB in Canada in 2004 (Table 2).

Meningitis, with or without tuberculoma, occurs in approximately 75% and tuberculoma alone in 25% of patients with CNS TB.<sup>75</sup> Cerebral tuberculomas are thought to be more common in patients with HIV/AIDS and in developing countries.<sup>76</sup> 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. TB meningitis alone is frequently associated with devastating consequences: 25% morbidity (i.e. permanent neurologic deficit) and 15% to 40% mortality despite available treatment.<sup>75,77,78</sup> It is believed that the initial lesion is a tubercle in the superficial cortex (subependymal) or meninges that ruptures into the subarachnoid space. Brain and cranial nerve damage results from the effects of a granulomatous basal exudate (proliferative arachnoiditis), which may cause obstructive hydrocephalus and raised intracranial pressure as well as periarteritis and thrombosis of blood vessels, especially those supplying the basal ganglia and brainstem.<sup>78,79</sup> This is the most rapidly progressive form of TB: 50% of cases are ill for less than 2 weeks before diagnosis. 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. Outcomes are known to be affected by age, whether hydrocephalus is present at diagnosis, cerebrospinal fluid (CSF) protein levels and, most important, the clinical stage of disease at diagnosis.<sup>80,81</sup>

At presentation, the CSF pressure is often normal. CSF findings 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/ $\mu$ L; normal 0-5 white blood cells/ $\mu$ L and 0 red blood cells/ $\mu$ L). 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.<sup>82</sup> 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 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). NAA is commercially available to identify mycobacteria directly from CSF. Its major advantage is a rapid diagnosis, generally within 48 hours, and it is most useful in diagnosing meningeal TB.<sup>23-25</sup> 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.<sup>74,83</sup> Empiric therapy should be initiated immediately on suspicion of the diagnosis to prevent complications. A CT scan of the brain showing basilar meningeal enhancement and hydrocephalus is highly suggestive of TB meningitis, while MRI will better delineate abnormalities in the spinal cord, brainstem and posterior fossa.

Treatment for CNS TB follows the standard approach and is highly effective. Isoniazid, rifampin and pyrazinamide all penetrate the CSF well, and treatment duration should be extended for at least 12 months with drug-susceptible disease. Neurosurgical intervention may be indicated for complications such as hydrocephalus or, less likely, large local collections. Adjunctive corticosteroid treatment reduces the incidence of neurologic complications and

mortality.<sup>80,84,85</sup> Specific indications for steroid use include severe or deteriorating clinical presentation, acute encephalitis, elevated CSF opening pressure or hydrocephalous, cerebral edema and evidence of clinical deterioration upon initiation of antituberculosis treatment. The use of corticosteroids in TB is discussed in Chapter 6, Treatment of Tuberculosis Disease and Infection.

### Ocular TB

The epidemiology of ocular TB has not been well described in Canada. The diagnosis is often problematic given the difficulty in obtaining clinical specimens for mycobacteriologic and histopathologic testing.<sup>86,87</sup> Evidence of TB disease elsewhere in the body can help to confirm the diagnosis. Ocular TB can be characterized by direct infection of external and internal eye structures, as well as an inflammatory hypersensitivity response to mycobacterial antigen, which can lead to vasculitis and progressive loss of vision. 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. Clinical specimens are more easily obtained from external eye structures, leaving intraocular disease often a clinical diagnosis. Intraocular disease, specifically choroidal TB, is the most common form of ocular TB. 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 systemic TB (i.e. miliary TB). There may be a role for clinical sampling of the anterior chamber fluid for PCR<sup>88</sup> as well as a therapeutic trial to support the diagnosis. Treatment of ocular TB includes antituberculosis therapy, though systemic steroids are often added for those with retinal disease.

### Tuberculous pericarditis

In developed countries, the incidence of TB pericarditis has declined alongside the decline in TB incidence. 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 usually accompanied by tuberculous disease at another site. The earliest clinical presentation of TB pericarditis is of a serosanguinous exudative effusion that may resolve spontaneously over a few weeks, but can heal with constriction. Large pericardial effusions with signs of both tamponade and inflammation have been associated with TB, but, in general, clinical features are generally nonspecific and subtle. Imaging, including radiographs and echocardiograms, are nondiagnostic. Diagnostic yield is improved if pericardial fluid and tissue are sent for AFB smear and culture (~ 50% positive) as well as histopathologic analysis, especially in symptomatic patients. Antituberculosis treatment has reduced the incidence of constrictive pericarditis (10% to 20% of treated cases) and mortality associated with tuberculous pericarditis. Empiric treatment should be considered, especially in the immunocompromised. Adjunctive corticosteroid treatment is felt to reduce the incidence of complications and improve mortality.<sup>89-92</sup> The recommended adult steroid 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 6, Treatment of Tuberculosis Disease and Infection. In patients with recurrent

effusions or persistently elevated central venous pressures despite removal of pericardial fluid and use of antituberculosis drugs, early pericardiectomy is suggested.

### 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.<sup>93</sup> 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 (direct infection of the skin) and tuberculids (cutaneous reactions to noncutaneous TB infection).<sup>94</sup> 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. Patients with pulmonary TB are not uncommonly found to have active disease elsewhere, which can often complicate treatment. For example, subclinical liver involvement is common in patients with chronic pulmonary TB whereas primary hepatic TB is an uncommon, but potentially fatal, form of nonrespiratory TB.

### 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, though the latter is capable of doing so in the form of respiratory insufficiency due to far advanced disease, pneumothorax and massive hemoptysis, especially if associated with underlying lung disease.<sup>95</sup> 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. 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.<sup>96</sup> 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. 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.

### Treatment

As a general rule, nonrespiratory TB responds to the same regimens used to treat respiratory TB<sup>97,98</sup> (see Chapter 6, Treatment of Tuberculosis Disease and Infection). 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. CNS TB, disseminated TB, and bone and joint TB are notable exceptions, in that a longer course of therapy is suggested, especially in children, in whom 2 months of at least three drugs in the initial phase and 10 months of two or more drugs in the continuation phase are recommended, assuming that the initial isolate is fully drug sensitive. 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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## Introduction

Effective chemotherapy taken over an adequate period of time is the guiding principle of treatment for all forms of tuberculosis (TB) – respiratory and nonrespiratory. The objective of anti-TB therapy is to achieve a lifetime cure of the disease while preventing drug resistance. This chapter deals with the treatment of TB that is proven or presumed to be due to *Mycobacterium tuberculosis* and is susceptible to four first-line drugs: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB)<sup>1</sup> (Table 1). Streptomycin (SM) (not readily available in Canada), rifapentine and rifabutin are classified as second-line drugs in Canada.\* Rifabutin is used in special situations, such as in cases of HIV/AIDS and drug resistance. Rifapentine and the fluoroquinolones are very promising drugs and in time may be reclassified as first-line (see Chapter 7, Drug-resistant Tuberculosis, and Chapter 9, Tuberculosis and Human Immunodeficiency Virus).

## Bacteriologic Basis of Short-Course Chemotherapy

Anti-TB drugs are theoretically described by their action in three areas:

- prevention of drug resistance
- rapidity of improvement
- prevention of relapse

The efficacy of the first-line anti-TB drugs in these actions is summarized in Table 1, in which a strong effect is reported as 3+ and no effect as 0.

One of the goals of effective chemotherapy is to prevent acquired drug resistance. Acquired resistance occurs during therapy when resistance to one or more drugs develops in organisms that were originally susceptible to the drug(s) (see Chapter 7, Drug-resistant Tuberculosis). Drug resistance is prevented by using drugs that eliminate all mycobacterial populations and thus do not allow the emergence of resistant organisms.<sup>1-3</sup> The best protection against acquired drug resistance is the use of at least two bactericidal drugs to which the organisms are sensitive.

Bactericidal activity is the ability of a drug to kill rapidly replicating bacteria. In therapeutic doses, the bactericidal first-line drugs are INH, RMP and PZA.<sup>2,3</sup> The bactericidal activity of a drug is dependent upon factors such as oxygen tension. In extracellular areas of high oxygen tension, the mycobacteria grow rapidly and reach high numbers. In these populations, the drugs with the most bactericidal activity are INH and RMP followed by high-dose EMB. PZA has little to no activity in this population and therefore will not protect against the development of resistance (Table 1).<sup>1</sup> Conversely, in areas of low oxygen tension, such as inside cells (acid pH) and in areas of fibrosis (neutral pH), the mycobacteria grow more slowly. In intracellular populations, the drug with the least bactericidal activity is INH, followed in order of increasing activity by RMP and PZA. Low-dose EMB is bacteriostatic. In areas of fibrosis, where

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee



organisms are thought to grow intermittently, RMP is the only drug that has bactericidal activity.<sup>1</sup>

Sterilizing activity is the ability of a drug to kill the last viable, often semi-dormant, bacterium inside the host. The best measure of sterilizing activity is the proportion of patients with negative cultures after 2 months of treatment and the proportion who relapse within 2 years following completion of treatment.<sup>2</sup> RMP and PZA are the most effective sterilizing drugs;<sup>4</sup> INH is intermediate, and EMB is the least effective (Table 1).

### Summary Point:

- Drugs vary in the ability to reduce the bacteria count, prevent resistance and kill the last remaining bacterium. LEVEL II

**Table 1**  
Activity of First-Line Anti-TB Drugs

Drug	Resistance Effect*	Bactericidal Effect		Sterilizing Effect
		Rapid Replication Rate	Slow Replication Rate	
INH	++	++	+	++
RMP	++	++	+	+++
EMB	+/-	+/-	+/-	0
PZA	0	0	++	+++

\*The effect in preventing resistance is similar to the bactericidal effect in rapidly replicating organisms; 0 = no effect, 3+ = greatest effect, +/- little or no effect.

## Treatment Regimens for Active TB

Treatment is divided into two phases: (1) the initial or intensive phase, when drugs are used in combination to kill rapidly replicating populations of *M. tuberculosis* and to prevent the emergence of drug resistance, followed by (2) the continuation phase, when drugs are used to kill slowly and intermittently replicating populations.<sup>5-8</sup> During the intensive phase, drugs are prescribed daily. The bactericidal effect leads to rapid bacteriological sputum conversion and decreasing clinical symptoms. During the continuation phase, when typically only INH and RMP are prescribed either daily or twice-weekly, the sterilizing effect of therapy eliminates the remaining bacteria and prevents subsequent relapse.<sup>2</sup>

The regimen options for the initial phase of treatment of adult and pediatric TB are shown in Tables 2, 3 and 4. Regimens that include INH and RMP but not PZA can be discontinued after 9 months,<sup>10-12</sup> and regimens that include INH, RMP and PZA can be discontinued after 6 months,<sup>5, 13-18</sup> provided in both instances that the patient has been adherent. In the case of 6-month regimens, the duration should be extended to 9 months in patients with cavitary pulmonary disease and positive cultures after 2 months of treatment.<sup>9,19,20</sup> Any regimen that does not include INH and RMP throughout its course should

be extended to a minimum of 12 months. If uncertainties about the duration of treatment arise, it is recommended that referral be made to a TB specialist, who may be defined as a physician, usually but not always with training in respiratory or infectious disease, who has taken a special interest in TB and has become knowledgeable and experienced in the prevention and treatment of TB. For assistance in identifying a TB specialist, consult the local/provincial/territorial TB control program or public health department.

**Table 2**  
**Drug Regimen Options for Treatment of TB**

Regimen	Duration (months)			Number of doses
	Intensive	Continuing	Total	
INH/RMP/PZA ± EMB	2	4	6	95*
INH/RMP ± EMB	1-2	7-8	9	120†

\* See Table 3

† See Table 4

**Table 3**  
**Dosing Interval Options for INH, RMP and PZA regimens\***

Option 1: 95 doses	Option 2: 60 doses
Administer daily INH, RMP and PZA for 2 months, followed by INH and RMP daily or 2×/wk for 4 months.	Administer daily INH, RMP and PZA for 2 weeks, followed by INH, RMP and PZA 2×/wk for 6 weeks, followed by INH and RMP 2×/wk for 4 months.†

\* Adapted from reference 9; 2×/wk dosing is not recommended in patients with HIV infection and low CD4 counts, < 100 × 10<sup>6</sup>/L (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus).

† All regimens administered 2×/wk (two times a week) should use DOT for the duration of therapy.

Medication dosages for daily and twice weekly administration are listed in Table 4. Treatment of patients who are at increased risk of disease due to drug-resistant organisms is described in Chapter 7, Drug-resistant Tuberculosis.

EMB should be added to the initial regimen until such time as drug susceptibility tests establish that it is not necessary<sup>9,19</sup> (an injectable agent or a third- or fourth-generation fluoroquinolone may be used when EMB is not an option), or initial therapy should be based on prevailing drug susceptibility patterns in the community.<sup>21</sup> Therefore, it is essential that all patients be questioned carefully about risk factors for drug resistance. In all cases of suspected drug resistance, the patient should be referred to a TB specialist.

**Table 4**  
Dosing Interval Options for INH and RMP Regimens\*

Option 1	Option 2	Option 3
Administer daily INH and RMP for 2 months, followed by INH and RMP 2×/wk for 7 months†	Administer daily INH and RMP for 1 month, followed by INH and RMP 2×/wk for 8 months†	Administer INH and RMP daily for 9 months

\*Adapted from reference 9. These regimens should only be considered in patients found to have fully drug-susceptible isolates or as initial therapy (before drug susceptibility test results are available) only if the prevailing rate of primary INH resistance is less than 4%. Twice weekly dosing is not recommended in patients with HIV infection and low CD4 counts,  $< 100 \times 10^6/L$ .

†All regimens administered two times a week should be DOT for the duration of therapy

#### Summary Points:

- ▶ Short-course regimens consist of a daily intensive phase and an intermittent continuation phase. Provided patients are adherent
  - INH, RMP regimens may be discontinued after 9 months
  - INH, RMP, PZA may be discontinued after 6 months. Level I-II
  - 6-month regimens should be extended to 9 months in patients with the combination of cavitory disease and positive cultures after 2 months of treatment. LEVEL III

## Nonrespiratory TB

Although less common than respiratory TB, nonrespiratory TB (see Chapter 5, Nonrespiratory Tuberculosis) accounts for a significant proportion of all cases in Canada, 485/1613 (30%) in 2004.<sup>22</sup> Nonrespiratory TB is even more prevalent among persons with HIV/AIDS<sup>23</sup> and immigrants from Asian countries.<sup>24</sup> The fundamental principles that underlie the treatment of respiratory TB also apply to nonrespiratory TB.<sup>25</sup> Reports of treatment of nonrespiratory TB are limited, but reports on pleural, lymphatic, renal, abdominal, meningeal, and bone and joint TB show that outcomes are similar to those of respiratory forms of TB using similar regimens.<sup>26-30</sup> However, since ideal therapy for meningitis, miliary/disseminated disease or spinal disease with neurological complications has not yet been defined with certainty, some authorities have recommended longer courses of treatment.<sup>9,19,27</sup> If there is uncertainty about the duration of treatment, referral to a TB specialist is recommended.

#### Summary Point:

- ▶ With three possible exceptions, CNS (central nervous system) TB, miliary/disseminated TB, and bone and joint TB, nonrespiratory TB is treated with the same regimens as respiratory TB. LEVEL II

## Program Responsibility for Patient Adherence

The responsibility for successful treatment lies with the TB program/public health department in cooperation with the treating physician, rather than the patient. The overall goals of treatment are (1) to cure the individual patient and (2) to minimize the transmission of *M. tuberculosis* to other persons. Successful treatment benefits the patient and the community. For this reason the treating physician has the responsibility of prescribing an appropriate regimen, preferably within 24 hours of diagnosis, particularly for infectious cases. A case manager, either the physician or public health nurse, is recommended to monitor the treatment response, adherence and drug toxicity at least monthly and completion of therapy. Treatment completion is a fundamental principle in TB control. It is most successful within a comprehensive framework that addresses both the clinical and social issues of the patient. The guiding principle of patient-centred care is making a plan based on each patient's circumstances.<sup>9,19</sup>

Despite the availability of highly effective drug regimens, TB cure rates are not always satisfactory. The most important reason for these failures is that patients do not take the prescribed drugs regularly or long enough to achieve cure.<sup>31-33</sup> In particular, regular intake of drugs in the initial phase of treatment is often not achieved. While shortening the duration of treatment to 6 months may diminish the default rates somewhat, this initiative alone has not consistently overcome patient nonadherence.

Another element of treatment nonadherence is partial adherence to a prescribed regimen. When some drugs are selectively discontinued, there is a risk of acquired drug resistance. The likelihood of acquired drug resistance is greatest when patients take only one effective drug (i.e. a drug to which the bacteria are susceptible) during the time when the bacterial count is still high.<sup>34</sup> It is the responsibility of the TB/public health department and treating physician to ensure that this risk is minimized.

Daily regimens, even as short as 6 months, remain effective in the presence of minor irregularity of drug ingestion because of the relatively high number of doses. On the other hand, regimens that are partly intermittent may be less effective if enough doses are skipped. Other more unlikely causes of treatment failure, such as malabsorption of drugs, are discussed below.

### *Summary Point:*

- ▶ Failure of treatment and relapse are most commonly due to inadequate treatment. LEVEL II

## Directly Observed Therapy

Poor adherence to prescribed anti-TB therapy is the most common cause of treatment failure. Patient-centred care includes an adherence plan that emphasizes directly observed therapy (DOT) and is an effective way to monitor adherence to therapy.

DOT is the process whereby a health care worker or pill dispenser watches the patient swallow each dose of medication, helping to ensure that higher treatment completion rates are achieved.<sup>19</sup> Note that in international TB control, the DOTS strategy includes additional elements (see Chapter 18, Canada and International Tuberculosis Control).

Several treatment outcomes have been reported using varying definitions of DOT. DOT may be subclassified as modified, standard or enhanced. Modified DOT refers to DOT for only part of the treatment period, typically during the initial phase, followed by self-administered therapy during the continuation phase, with reported completion rates of about 80%.<sup>19</sup> Standard DOT refers to DOT throughout the initial phase and the continuation phase, with completion rates of about 85%.<sup>19</sup> Enhanced DOT also refers to DOT throughout both phases but also includes incentives and enablers, with completion rates of about 90%.<sup>19</sup> These DOT rates may be compared with completion rates after self-administered therapy of about 60%.<sup>19</sup> For the best outcomes, all doses should be given DOT with incentives and enablers when needed to complete treatment.

In addition to significantly increased completion rates, the use of DOT has been shown to reduce the rate of drug resistance and relapse when compared with self-administered therapy.<sup>35,36</sup> DOT may be given daily, twice weekly, or thrice weekly.<sup>9,37-40</sup> Intermittent regimens are clinically effective and have similar toxicity to that of daily regimens.<sup>37-42</sup> DOT allows the number of doses to be reduced and, importantly, allows patient defaulting to be quickly identified. All intermittent regimens must be directly observed.\* If self-administered therapy is the only option for drug delivery, the drugs must be taken daily.\*

DOT with a suitable regimen should ideally prevent the emergence of drug resistance. Since resistance rates of  $\leq 2.1\%$  have been reported in program DOT evaluations,<sup>35,43</sup> this rate is the recommended program standard with adherence rates that should aim for at least 80% of the total prescribed doses.<sup>12</sup> Treatment should continue until a *minimum* of 76 doses have been taken for a 95-dose, 6-month regimen or 96 doses have been taken for a 120-dose, 9-month regimen, even if the regimen extends beyond the intended 6 or 9 months.

There are program conditions under which DOT has not contributed to improved treatment outcome.<sup>43,44</sup> DOT may be selectively used when not all patients are being treated with DOT and yet at least 90% of patients complete treatment (no culture done at the end of treatment) or are cured (negative culture at the end of treatment).<sup>44</sup> When adherence is difficult to predict,<sup>45,46</sup> the most effective method of drug delivery is DOT rather than self-administered therapy. If universal provision of DOT is currently not feasible because of resource limitations, the following circumstances should be given priority:

- suspected or proven drug-resistant organisms
- treatment failure
- documented re-treatment disease
- injection drug users/homeless patients
- suspected nonadherence or previous nonadherence

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

- psychopathology
- sputum smear positive for acid-fast bacteria<sup>44</sup>
- HIV infection
- children

When DOT is not feasible in these circumstances, clinicians may consider the use of self-administered, fixed-dose combinations (adjusted for body weight) whenever the drugs are self-administered. Fixed-dose drug combinations of INH/RMP (unavailable in Canada except through application to Health Canada's Special Access Program) and INH/RMP/PZA (available in Canada) make selective monotherapy impossible and thus eliminate the potential risk of patients taking only some of their medication.

A comprehensive patient-centred treatment program consists of an individual treatment regimen and additional considerations that incorporate the prescription into the patient's daily routine – bedtime dosing for drowsiness; flexible clinic hours; taking sufficient time for questions; coordinating social service support for child care, eye glasses and other medical appointments; treatment incentives; housing assistance; referral for treatment of substance abuse; and providing transportation where possible. Prescriptions for longer than 1 month, and therefore clinic reviews less frequent than one per month, are strongly discouraged.

#### *Summary Point:*

- ▶ DOT for all doses is strongly recommended in a patient-centred treatment plan when self-administered therapy fails to meet treatment standards. **LEVEL II - III**

### Adverse Reactions

The prompt recognition and appropriate management of adverse drug reactions is an essential part of the treatment program, and physicians and nurses responsible for drug therapy need to be well acquainted with these reactions (Table 5). Toxicity and hypersensitivity reactions require that the offending drug(s) be discontinued. However, this should be accompanied by careful evaluation of the reaction and identification of the offending drug(s) to avoid unnecessary cessation of a first-line drug. In Canada, drug intolerance is a more likely reason to withhold a drug than is drug resistance. For practical purposes the effect on treatment planning is the same.

A number of field trials for short-course chemotherapy reported significant adverse reactions.<sup>5,11-13,17,18,35-42,47-51</sup> The most common are listed in order of decreasing frequency: skin rash, hepatitis, gastrointestinal upset, thrombocytopenia, 'flu-like syndrome, vestibular symptoms, fever, arthralgia and neuropsychiatric symptoms. Patients with regimens containing SM have the highest rate of any adverse reactions (up to 22%) and the highest rate of stopping drug(s) (up to 5.3%). Regimens containing INH, RMP and PZA without SM result in lower rates of adverse reactions (up to 18%), but a similar rate of discontinuation (up

to 4.7%). INH- and RMP-containing regimens without PZA or SM have the lowest rates of any adverse reactions (7%).

**Table 5**  
**Doses and Common Adverse Reactions to Anti-TB Drugs**

Drug	Daily Dose Adults [Children] mg/kg*	Usual Adult Daily Dose, mg*	Twice Weekly Dose, mg*	Common Adverse Reactions†
INH	5 [10-15]	300	900	Asymptomatic elevation of aminotransferases, hepatitis, paresthesias
RMP	10 [10-20]	600	600	Hepatitis, 'flu-like illness, orange discoloration of body fluids, drug interactions
PZA	18-26 [15-30]	1000-2000	2000-4000	Hepatitis, elevated uric acid levels, arthralgia
EMB	18-26 [15-20]	800-1600	2000-4000	Retrolbulbar neuritis

\*American Thoracic Society recommendations based on lean body mass.<sup>9</sup> Evidence Level III. Daily dosing of initial phase-medications and daily or thrice weekly dosing of continuation-phase medications are recommended in patients with HIV infection and low CD4 counts,  $< 100 \times 10^6/L$ . Usual adult thrice weekly doses are as follows: INH 600 mg; RMP 600 mg; PZA 1500-3000 mg; EMB 1200-2400 mg.

†All drugs may cause rash, nausea, and fever.

## INH

INH may produce liver dysfunction ranging from asymptomatic, mild elevation of the serum transaminases to overt hepatitis causing liver failure.<sup>52</sup> The incidence of liver toxicity increases with age and with daily alcohol consumption.<sup>9</sup> A feeling of being unwell may be the first sign of impending hepatitis, and patients should be instructed to report such symptoms without delay so that liver enzymes can be measured. INH as well as other hepatotoxic drugs (see RMP and PZA) should be withdrawn when the serum transaminase level (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) exceeds five times the upper limit of normal or when clinical jaundice develops.<sup>9</sup> While the offending drug(s) is being identified, and particularly if the subject has infectious TB, an injectable agent, a fluoroquinolone and/or EMB may be initiated. Once the liver enzymes normalize, therapy with each drug can be reintroduced sequentially to identify the offending drug. Often only one of the three hepatotoxic drugs will be responsible, and a modified regimen can continue. Mild elevation of the liver enzymes may occur in 10%-20% of patients, and this usually resolves even if treatment is continued.<sup>9</sup> Routine monitoring is not necessary. However, for patients who have pre-existing liver disease, who are taking other hepatotoxins or who develop abnormal liver function that does not require stopping the drug, liver function tests should be measured monthly or when symptoms occur.<sup>9</sup>

INH may interfere with pyridoxine metabolism and produce peripheral neuropathy and other significant reactions (i.e. psychotic episodes). Pyridoxine (vitamin B6), 25 mg daily, should routinely be added when prescribing INH to patients with diabetes, renal failure, malnutrition, HIV infection, substance abuse or seizure disorders or women who are pregnant or breastfeeding, because of the increased risk of symptoms related to pyridoxine deficiency in these patients.<sup>53</sup> A pyridoxine dose of 25 mg is sufficient; higher doses may interfere with INH

activity.<sup>53</sup> The interaction of INH and phenytoin may cause an increase in serum levels of both drugs.<sup>25</sup> In this instance, serum levels of phenytoin should be monitored and the dose of phenytoin adjusted accordingly.

Other reactions are less common or less clinically significant. Cutaneous allergic reactions may occur. For severe reactions INH should be discontinued. For mild reactions it can be continued with antihistamine treatment. Nausea and vomiting may occur during therapy, especially with twice weekly regimens administered in combination with RMP. Finally, patients may also note fatigue, drowsiness, headaches or mild hair loss. Patients with previous significant reactions to INH should not receive this medication.

### RMP

Adverse reactions to RMP include hepatotoxicity, renal toxicity, memory impairment and altered immune responses. Hypersensitivity reactions to RMP include skin rash, fever, abdominal pain, thrombocytopenia and a rare hypotensive reaction similar to anaphylactic shock.<sup>48</sup> 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. When RMP is combined with INH, there is a slightly increased incidence of liver toxicity than with either drug alone.<sup>54</sup>

Because RMP induces hepatic microsomal enzymes, it may accelerate the clearance of drugs metabolized by the liver. These include estrogens, coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonyleureas, theophylline, cyclosporin, methadone, ketoconazole and others.<sup>9</sup> By accelerating estrogen metabolism, RMP may interfere with the effectiveness of oral contraceptives. Where appropriate, patients should be advised to use alternative forms of birth control while receiving RMP.

### PZA

Hepatotoxicity can occur with PZA and should be managed as outlined in the INH section. PZA can cause elevation of serum uric acid levels through its inhibition of renal tubular secretion of uric acid. While hyperuricemia can occur in up to 64% of patients, arthralgias occur infrequently, and acute gout is rare.<sup>13</sup> Routine monitoring is not required. Hypersensitivity reactions and gastrointestinal upset may also occur with PZA.

### EMB

Optic neuropathy manifested by either decreased visual acuity, decreased visual fields or colour blindness is the most significant adverse effect of EMB and usually occurs after the patient has been taking the medication for months.<sup>55</sup> This adverse effect is most commonly seen in patients receiving a daily dose of  $\geq 25$  mg/kg but can occur in patients on a daily dose of 15 mg/kg ( $< 1\%$ ), particularly in those with impaired renal function.<sup>9</sup> Patients should be advised to report any change in vision immediately and should ideally be referred to an ophthalmologist at the outset of therapy for accurate baseline assessment of



visual acuity, colour vision and visual fields.<sup>55,56</sup> Monthly assessment of visual acuity and red-green colour discrimination is recommended while the patient continues to receive EMB.<sup>55</sup> Fortunately, EMB-related optic neuritis is usually reversible within weeks to months of discontinuing the drug.<sup>55-57</sup> 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.<sup>58</sup>

Other side effects, such as cutaneous reactions, may also occur. Because EMB is excreted via the kidneys, the dose should be adjusted in renal failure.<sup>9,59</sup>

When the appropriate management of side effects is uncertain, consultation with a TB specialist is recommended.

#### **Summary Point:**

- ▶ For adverse effects of first-line anti-TB drugs see Table 5.  
LEVEL II

### **Alternative Routes of Administration**

The 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.<sup>60</sup> Either the tablet formulations can be crushed or suspensions of the medication can be made up to make delivery easier. Only INH, RMP, the injectable agents and the fluoroquinolones are available in parenteral form. In patients for whom oral medication is not feasible, consultation with a TB specialist is recommended.

### **Serum Drug Concentration Measurements**

There are several clinical situations in which the monitoring of serum drug concentration might be helpful. These include cases of HIV/AIDS, multidrug resistance or acquired drug resistance (see Chapter 7, Drug-resistant Tuberculosis), severe liver dysfunction, severe renal dysfunction and gastrointestinal disease/malabsorption. At the present time Canada does not have the capacity to measure serum drug levels. Serum samples must be sent to the National Jewish Medical and Research Center in Denver, CO. Information about the timing of blood draws, processing and shipping of samples to Denver is available from the literature and the Web site <http://www.njc.org>.

### **Special Situations**

#### **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. In Canada in 2004 there were 371

TB patients 65 years of age and older (23% of the total of 1,613 patients).<sup>22</sup> Hospitalized TB patients should be admitted to appropriate facilities designated for the treatment of infectious TB and capable of providing adequate airborne isolation (see Chapter 16, Tuberculosis Control Within Institutions). It is important that these institutions be staffed by personnel knowledgeable and experienced in the management of TB.

Indications for hospitalization in this population include the following:

- investigation and/or treatment of symptoms, i.e. fever, life-threatening hemoptysis, malaise/cachexia;
- establishment of an acceptable therapeutic regimen in patients with significant side effects from drugs or with known/suspected drug resistance;
- socio-economic reasons, i.e. homelessness;
- 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 may be necessary when other measures such as DOT are unsuccessful);
- drug desensitization.

### TB patients with hepatic disease

Since there is a risk of hepatotoxicity with INH, RMP and PZA, the use of these drugs must be carefully considered and patients closely monitored in the presence of hepatic disease.\* Patients with infectious or life-threatening TB and severe hepatitis may be treated with either INH or RMP with the addition of EMB and usually one of either a fluoroquinolone or an injectable agent. Patients with noninfectious or non-life-threatening TB and severe hepatitis may be treated with an injectable agent, EMB and a fluoroquinolone.<sup>25</sup> In all cases, close monitoring of liver enzymes is recommended. A similar approach is recommended in the elderly, who may have a narrow therapeutic index with TB drugs. If INH and/or RMP are not tolerated, the patient should be referred to a TB specialist.

### TB patients with impaired renal function

INH and RMP are given in the usual doses since these drugs are metabolized mostly by the liver.<sup>61</sup> The use of aminoglycosides (streptomycin, amikacin, kanamycin) and polypeptides (capreomycin) should be avoided if possible in patients with impaired renal function. The routine use of EMB should also be avoided, because the clearance of this drug decreases with impaired renal function and predisposes to toxic effects. However, if it is important that EMB

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

be continued despite renal insufficiency, the dose should be adjusted (standard doses but given three times per week) and serum levels monitored carefully.<sup>9,61</sup> In patients undergoing dialysis, INH and RMP may be given in the usual doses since they are not appreciably affected by dialysis. In contrast, EMB<sup>61,62</sup> is given in standard doses three times per week. PZA is dialyzable, and therefore, as with EMB, a longer interval between doses with three times per week administration is recommended; i.e. 25-35 mg/kg per dose three times per week after dialysis. Ideally, all doses are given after dialysis to maintain DOT. When uncertainties arise, the patient should be referred to a TB specialist.

### TB patients with HIV infection (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus)

With respect to the treatment of TB itself, daily doses of medication are recommended in the initial phase and thrice weekly (3x/week) doses in the continuation phase whenever the CD4 count is  $< 100 \times 10^6/L$  (see Table 5). Use of combination antiretroviral therapy during TB treatment is complicated by 1) the adherence challenge of polypharmacy, 2) overlapping side-effect profiles of the anti-TB drugs, antiretroviral therapy and drugs used to prevent or treat opportunistic infections, 3) drug-drug interactions and 4) the occurrence of immune reconstitution inflammatory syndromes.

### Pregnancy/breastfeeding

The risk of untreated TB to a pregnant woman and her fetus is far greater than the risk of toxic effects from the drugs used in its treatment.<sup>63,64</sup> In a pregnant woman with TB it is essential that prompt, effective therapy be administered. TB is not an indication for the termination of pregnancy.

The use of INH, RMP and EMB has been well studied during pregnancy, and they are safe in this setting.<sup>64</sup> The use of aminoglycosides (streptomycin, amikacin, kanamycin) and the polypeptide capreomycin during pregnancy is contraindicated because of the effects on the fetus, including eighth cranial nerve palsies, deafness and teratogenicity.<sup>65</sup> No studies have been undertaken to assess the safety of PZA during pregnancy. Therefore while its routine use has been approved by international TB agencies, recommendations for the general use of PZA during pregnancy cannot be made because of inadequate teratogenicity data.<sup>18</sup> Little is known about the safety of second-line agents during pregnancy. These drugs should only be considered for use in specific instances after consultation with a TB specialist.

The initial treatment regimen in pregnancy should consist of INH, RMP and EMB<sup>9</sup> unless the prevailing rate of primary INH resistance is known to be less than 4%, in which case EMB need not be continued (see Treatment Regimens for Active TB). Pyridoxine is recommended for pregnant and breastfeeding women receiving INH.<sup>53</sup>

A mother receiving treatment for TB should not be discouraged from breastfeeding, as the very small concentrations of anti-TB drugs in the breast milk do not produce toxic effects on the newborn. It should also be emphasized

that the small amount of medication that may be found in breast milk should not be considered effective treatment or prophylaxis in a nursing infant.<sup>66</sup>

**Summary Point:**

- ▶ In uncommon/special situations patients should be referred to a TB specialist for their treatment. **LEVEL II-III**

### Corticosteroids

Corticosteroids should be used only when adequate anti-TB therapy is also being administered.<sup>67</sup> Randomized controlled trials show improved survival with the use of corticosteroids in patients with all stages of severity of TB meningitis,<sup>68-70</sup> and improved survival and less need for pericardiectomy in patients with TB pericarditis.<sup>71,72</sup> Corticosteroids may also be of clinical value in cases of TB-caused adrenal insufficiency and in cases of life-threatening disseminated disease, particularly when there is concern about adrenal insufficiency.<sup>68</sup> In patients with tuberculous pleurisy, both the symptoms and the pleural fluid may resolve more quickly with corticosteroids, but there are no long-term benefits to these patients from the adjunctive use of corticosteroids. Two reviews suggest that prednisone in doses of 40-80 mg/day for 6-12 weeks is likely to be effective,<sup>68,72</sup> but the optimal dose and duration of treatment are unknown.

**Summary Points:**

- ▶ Adjunctive corticosteroid treatment may
  - improve survival in meningitis at all stages of severity **LEVEL I**
  - improve survival and reduce morbidity in pericarditis **LEVEL I-II**
  - provide benefit in life-threatening cases **LEVEL III**

### Response to Treatment and Treatment Failure

In order to monitor sputum conversion and treatment outcome, all patients with smear- and culture-positive sputum should have repeat sputum examinations performed at the end of the second month of treatment.<sup>2</sup> Approximately 80% of pulmonary TB cases with drug-susceptible bacteria who are started on four-drug treatment will have a negative sputum culture by then.<sup>9</sup> If the culture is still positive, repeat after 4 months of treatment. In order to report treatment outcome as “cure”, there must be a negative culture at the completion of treatment.\* If sputum cannot be obtained at that time, treatment outcome is reported as “treatment completed.” More frequent monitoring is recommended when the clinical or radiographic response is unfavourable.

\* A recommendation of the Canadian Thoracic Society’s Tuberculosis Committee

While it is theoretically possible to cure or at least complete treatment of all cases of TB, in practice there are failures. The most common causes are patients not taking the prescribed drugs (nonadherence or because of toxicity), development of drug resistance, inadequate regimens (another form of nonadherence) and, rarely, malabsorption.<sup>43,73,74</sup>

Treatment failure is defined as positive sputum cultures after 4 or more months of treatment<sup>9</sup> or two positive sputum cultures in different months during the last 3 months of treatment, even if the final culture is negative.<sup>5,13,75</sup> Treatment failure should be suspected before the intended completion date. Failure of symptom resolution and/or poor radiographic response combined with persistently positive sputum smears or cultures should raise the question of failure as early as the third month of therapy. In these instances, the reason(s) for failure ought to be identified, and drug susceptibility tests should be repeated. If the patient's bacteria are resistant to INH and/or RMP, or the patient does not tolerate either drug, second-line drug susceptibility testing is almost always necessary. If drug resistance is suspected, the treatment regimen will need to be modified (see Chapter 7, Drug-resistant Tuberculosis). For all instances of known or suspected treatment failure, referral to a TB specialist is recommended.

### Program Performance Standards for Treatment of TB Disease

The ideal anti-TB drug regimen and drug delivery system for any patient will result, at a minimum, in the following:

- convert sputum cultures to negative after 4 months of treatment;
- achieve re-treatment rates of less than 3% within 2 years following cessation of treatment;
- achieve acquired drug resistance rates of 0%;
- be cost-effective (since DOT is the optimal mode of drug delivery, intermittent regimens of 120 doses [9 months] or 95 doses [6 months] are recommended);
- be tolerated by the patient (< 5% of patients will discontinue or modify therapy because of adverse effects); and
- achieve at least a 90% cure (negative sputum culture at the end of treatment) or treatment completion (treatment completed but no sputum culture at the end of treatment) rate within 12 months of starting treatment for patients who did not die or transfer out during treatment.

Treatment regimens should be chosen and their efficacy assessed using these principles.

## Additional Components of TB Management

### Treatment completion

TB control programs need to find patients with active disease in a timely manner and to persuade them to complete treatment in order to establish a cure. Through the use of incentives, increased sensitivity to psychological, cultural and behavioral factors,<sup>76</sup> and the expanded use of DOT patients may remain in treatment longer to achieve a lasting cure. Treatment protocols should continue for 6 or 9 months or until a minimum of 80% of the prescribed doses have been taken.<sup>13</sup>

### Prevention of transmission

It is important to recognize that the management of the patient with TB includes more than effective chemotherapy. While TB patients are largely managed in the outpatient setting, measures to reduce the risk of transmitting infection are indicated. Timely contact tracing is essential. Appropriate education for both patients and their families is also necessary. In certain instances, this education may be extended beyond the family to include co-workers and employers. These specific aspects of TB management can best be delivered by a centralized and coordinated, multi-disciplinary TB program that recognizes the importance of close linkage between the clinical and public health arms.

### Follow-up after treatment

As a general rule, patients who have achieved cure or treatment completion (see Appendix C, Definition of Terms) do not need follow-up after treatment.<sup>77</sup> The likelihood of relapse after treatment is reduced by the use of DOT throughout. For patients with inadequate regimens or who are nonadherent, regular follow-up either 6 monthly or annually for up to 3 years is recommended. Regular follow-up should also be provided to those whose incident episode of TB was polydrug-resistant, multidrug-resistant or extensively drug-resistant (see Chapter 7, Drug-resistant Tuberculosis, and Appendix C for the definition of drug-resistant TB) and considered for those who are HIV coinfecting. Finally, any patient who reports having symptoms that suggest disease relapse, such as persistent cough or fever, should undergo follow-up examination.

### Treatment Regimens for Latent TB Infection

Chemoprophylaxis or preventive therapy refers to the treatment of TB infection before disease has occurred. The term latent TB infection (LTBI) replaces TB infection, and treatment of LTBI replaces chemoprophylaxis or preventive therapy. Treatment of LTBI is started only after active TB disease has been excluded. Failure to do so may result in the development of drug-resistant TB disease.

## Rationale

In persons infected with TB bacteria the risk of active TB varies according to the time since infection, age and other factors. Without risk factors, TB develops in about 10% of infected, otherwise healthy adults in their lifetime, 5% within 2 years of infection and 5% after 2 years.<sup>78</sup> In young children the risk of disease after infection is inversely related to age, with very high risk (up to 40%) in infants.<sup>79</sup> In both children and adults, a number of immunocompromising conditions will increase the risk of disease after infection (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease). With treatment of LTBI, the number of persons who go on to have TB can be significantly diminished.

## Background

TB prevention has been a cornerstone of TB control in industrialized countries for over 45 years. The effectiveness of INH alone to treat LTBI was first reported in 1957 by Ferebee et al<sup>79</sup> and subsequently confirmed by others.<sup>80-83</sup> INH was suitable because it was safe, cheap, easy to take, well tolerated and effective. Effectiveness, however, was a function of adherence and duration of treatment. In completers/compliers ( $\geq 80\%$  of doses) daily INH for 1 year provided 93% protection, and daily INH for 6 months provided 69% protection.<sup>83</sup>

## Indications, dose and duration

Treatment of LTBI is recommended for persons with an increased risk of TB disease (Table 6). INH is recommended in a dose of 10-15 mg/kg per day for children up to a maximum of 300 mg per day. For adults the dose is 5 mg/kg to a maximum of 300 mg daily. Twice weekly therapy, particularly when adherence may be a concern, is also effective with a dose of 20-30 mg/kg to a maximum of 900 mg per dose in children and 900 mg per dose in adults. The addition of vitamin B6 (pyridoxine) in a dose of 25 mg is indicated when there is poor nutrition, alcoholism, HIV coinfection, pregnancy, diabetes or uremia, or other disorders that might predispose to neuropathy.<sup>84</sup> As there are no side effects to low-dose vitamin B6, many centres routinely prescribe it to prevent the development of neuropathy.

Nine months of daily INH is more effective than 6 months, but 12 months is not much more effective than 9 months (Tables 7 and 8). The optimal protection is probably achieved by 9 months, and this is the recommended benchmark. The important variable is total doses rather than continuity, i.e. extend treatment long enough to achieve the equivalent of 9 months of 100% adherence (270 doses).<sup>85</sup> INH daily for 6 months (180 doses) is an acceptable alternative when 9 months daily is not feasible.<sup>83</sup> INH twice weekly for 9 months (78 doses) is an acceptable alternative to 9 months daily. INH twice weekly for 6 months (52 doses) may be used when INH twice weekly for 9 months is not feasible. In order to guarantee effectiveness, directly observed prophylaxis (DOP) is recommended for all intermittent regimens (Table 7).

**Table 6**  
**Tuberculin Skin Test (TST) Cut Points for Treatment**  
**of Latent TB Infection in High-Risk Groups**

TST Result	Indication
< 5 mm	<ul style="list-style-type: none"> <li>• HIV infection and high risk of TB infection (contact with infectious TB, from high TB incidence country or abnormal chest x-ray)</li> <li>• Other severe immunosuppression and high risk of TB infection</li> <li>• Child less than 5 years and high risk of TB infection*</li> </ul>
≥ 5 mm	<ul style="list-style-type: none"> <li>• HIV infection</li> <li>• Recent contact with infectious TB</li> <li>• Fibronodular disease on chest radiograph (healed TB but not previously treated, or if treated, not adequately treated)</li> <li>• Organ transplantation (related to immune suppressant therapy)</li> <li>• 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)</li> </ul>
≥ 10 mm	<ul style="list-style-type: none"> <li>• Converters (within 2 years)</li> <li>• Other immunosuppression               <ul style="list-style-type: none"> <li>• silicosis</li> <li>• end-stage renal disease</li> <li>• carcinoma of head and neck<sup>†</sup></li> </ul> </li> <li>• Consider treatment for those who have resided or traveled in a high TB incidence country (see Chapter 13, Surveillance and Screening in Tuberculosis Control) or Canadian Aboriginal community within the past 2 years, are HIV-seronegative injection drug users, are workers or residents in a health care facility or correctional facility, or are homeless and can be treated with directly observed prophylaxis.<sup>‡</sup></li> <li>• Others, not listed above, may, at the discretion of the treating physician, also be considered for treatment; for example, those identified as being at “increased risk” in Table 2, Chapter 4, Diagnosis of Tuberculosis Infection and Disease.</li> </ul>

\* Skin test immediately and repeat at least 8 weeks after last exposure to an infectious TB case. Begin treatment immediately. Treatment can be stopped in a healthy child if repeat TST is negative. 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.

† Other tumours, such as T-cell lymphomas, may also increase the risk of reactivation of LTBI (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease).

‡ Age alone (e.g. ≥ 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.

RMP-containing regimens have also been used to treat LTBI.<sup>86-88</sup> Regimens of daily INH for 6 months or daily RMP for 3 months in adults with silicosis resulted in 41% and 51% protection respectively.<sup>87</sup> A twice weekly directly observed 6-month regimen with INH and RMP resulted in 90% protection.<sup>89</sup> It has been shown to be a suitable regimen. RMP daily for 4 months is an acceptable alternative when INH cannot be used on account of toxicity, if there is exposure to an INH-resistant source case or when a regimen of longer duration is not feasible.<sup>84,90,91</sup> Table 7 compares the regimens (drugs, duration, number of doses) and Table 8 compares the protective effects.

In HIV-seropositive persons 2 months of daily RMP plus PZA was found to be comparable to 12 months of INH in protecting against TB, and there did not appear to be an increased risk of toxicity.<sup>92,93</sup> On the basis of these results, the 2-month RMP-PZA regimen was recommended by the American Thoracic Society/U.S. Centers for Disease Control and Prevention (ATS/CDC) as an alternative regimen in HIV-seronegative persons.<sup>84</sup> However, the administration



of this regimen to HIV-seronegative persons resulted in rates of hepatitis and death that were significantly higher than those associated with INH regimens.<sup>94,95</sup> The revised ATS/CDC guidelines recommend that this regimen not be used in HIV-seronegative or seropositive persons.<sup>19,94,95</sup> If a patient has a high risk of developing TB and is unlikely to complete a longer course of treatment of LTBI, he or she should be referred to a TB specialist. For more details on the U.S. guidelines, the reader is referred to the cited references.<sup>19,94,95</sup>

**Table 7**  
Regimens for Treatment of Latent TB Infection

Drugs	Duration	Interval	Mode*	Level of Evidence†
INH	9 mo	Daily	SAP	I
INH	6 mo	Daily	SAP	I
INH	9 mo	2×/wk	DOP	III
INH	6 mo	2×/wk	DOP	III
RMP‡	4 mo	Daily	SAP, ± DOP	III
INH, RMP	6 mo	2×/wk	DOP	II

\*SAP = self-administered preventive therapy; DOP = directly observed preventive therapy

†I = randomized controlled trial, II = nonrandomized trial, III = expert opinion.

‡For INH resistance or intolerance.

**Table 8**  
Outcome of Treatment of Latent TB Infection in HIV-Seronegative or HIV Status Unknown Populations

Regimen	Duration, months	Adherence, %	Protection, %	Follow-up, months	Study Group	Level of Evidence
INH*	12	68	75	60	20-64 yrs	I
INH*	12	> 80	93	60	20-64 yrs	I
INH*	6	78	65	60	20-64 yrs	I
INH*	6	> 80	69	60	20-64 yrs	I
INH†	6	Unknown	41	60	26-34 yrs silicosis	I
RMP‡	6	Unknown	100	30	20-50 yrs converters	II
RMP†	3	Unknown	51	60	25-64 yrs silicosis	I
INH, RMP§	6,9	Unknown	88	15	0-15 yrs	II
INH, RMP¶	6	> 80	90	40	0-35 yrs	II
INH, RMP‡	4	Unknown	100	30	20-50 yrs converters	II
INH, RMP†	3	Unknown	37	60	25-64 yrs silicosis	I
RMP¶	6	Unknown	100	24	15-23 yrs students	III

\* IUAT<sup>83</sup>

† Hong Kong, drug resistance unknown<sup>10</sup>

‡ INH resistant, HIV status unknown<sup>11</sup>

§ Children<sup>86</sup>

*e Canadian Aboriginal<sup>12</sup>*

*¶INH resistant, presumed protection<sup>13</sup>*

## Resistance to INH alone or to INH plus RMP

Resistance to INH may be anticipated in contacts of a source case with known INH resistance. Alternative regimens have been suggested, such as RMP or INH and RMP, but these have been insufficiently studied. Daily RMP for 6 months showed 100% protection over 27 months, and a combination of INH and RMP for 4 months showed 100% protection over 29 months in 86 homeless adults who were presumed to be infected with INH-resistant organisms.<sup>88</sup> In persons infected with an INH-resistant organism and at high risk of TB disease, RMP daily for at least 4 months is an acceptable alternative regimen.<sup>84,91</sup>

Bacteriostatic drugs are unsuitable for treatment of LTBI since they do not sterilize the lesion.<sup>1</sup> For the treatment of LTBI in persons thought to be infected by an organism resistant to both INH and RMP, see Chapter 7, Drug-resistant Tuberculosis.

## Improving adherence to treatment of LTBI

Poor adherence is the most important reason for the failure of treatment to prevent TB disease. DOP, also known as directly observed preventive therapy (DOPT), is a method of drug delivery to improve adherence,<sup>96</sup> especially for infected persons who are at very high risk of disease, such as those coinfecting with HIV and children under age 5 years.

However, a great deal can be accomplished by developing a relationship that is based on trust and support between a health care worker and a patient and that takes into account cross-cultural sensitivities.<sup>97</sup> Incorporating the prescription into the patient's daily routine is recommended – bedtime dosing for drowsiness, flexible clinic hours, taking sufficient time for questions, coordinating solutions to other problems (such as child care, eye glasses, other medical appointments) and providing transportation where possible.

Prescriptions for longer than 1 month, and therefore clinic reviews less frequently than once per month, are strongly discouraged.

## Pregnancy

Except for patients coinfecting with HIV or those with recent TB infection, treatment of LTBI during pregnancy is not recommended.<sup>84,98</sup> Outside of these two categories, the small benefits of INH treatment of LTBI in pregnancy are not thought to outweigh the small risks attendant upon the administration of the drug.<sup>64,84,99</sup> Treatment of LTBI should be reconsidered in the postpartum period, assuming of course that active disease has been excluded. There is no conclusive evidence that pregnant women or women in the first postpartum year are at increased risk of INH hepatotoxicity.<sup>98</sup> Nevertheless, pregnant women, women in the first postpartum year and breastfeeding women who are recommended an INH-containing regimen should undergo careful clinical

and laboratory monitoring for hepatitis.<sup>84</sup> They should also receive pyridoxine (vitamin B6).

### Renal failure/dialysis

The standard regimen is recommended in patients who have renal failure or who undergo dialysis. Both INH and RMP are metabolized in the liver, so serum drug levels do not rise in the presence of renal failure. Both drugs are not dialyzed, so that the regimen does not need modification.

### Management of persons exposed to infectious TB after previous LTBI treatment

Very high risk, severely immunocompromised persons (e.g. those who are HIV coinfecting) who are re-exposed to infectious TB after having already completed a satisfactory course of treatment for LTBI in the past should be considered for a repeat course of treatment of LTBI (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus). If questions arise regarding risk of TB following repeat LTBI, referral to a TB specialist is recommended.

### Side effects associated with treatment of LTBI

#### *INH*

Hepatitis, defined as an AST or ALT level exceeding five times the upper limit of normal without symptoms or exceeding three times the upper limit of normal in the presence of symptoms, and, rarely, death have been reported in association with INH.<sup>98,100,101</sup> Hepatitis occurs most commonly in adults, but it has been reported in children as young as 2 years.<sup>102</sup> Amendments to early INH treatment guidelines were designed to diminish the risk of hepatitis.<sup>103</sup>

Although old age at the time of administration, pre-existing liver disease and alcoholism are known to increase the risk of hepatitis, the occurrence of this complication is not always predictable.<sup>104,105</sup> It is rare in persons under the age of 20 but increases to over 2% in patients over age 50. It is more frequent in persons with daily alcohol consumption<sup>32,33</sup> or viral hepatitis.<sup>106,107</sup> INH-induced hepatitis is usually, but not always, reversible upon discontinuation of the drug.<sup>108</sup> It presents with nausea, anorexia and an elevation of the hepatocellular enzymes AST or ALT.

Patients with INH-induced hepatitis, especially those who go on to liver failure, often give a history of having continued to take the drug despite being symptomatic or of not having adequate follow-up with the public health nurse or physician.<sup>108</sup>

The side effects/reasons for which INH was stopped in 143/1,000 patients<sup>52</sup> and 4/38 patients<sup>88</sup> included rash, nausea, malaise, fever, nervousness, headache and pregnancy. INH should not be used if there is a previous history of adverse reaction to the drug. It should be avoided

in the presence of acute liver disease. Patients receiving phenytoin (e.g. Dilantin™) or carbamazepine (e.g. Tegretol™) will require dose adjustment of these agents because INH inhibits the enzymes responsible for their metabolism.<sup>109</sup>

### *RMP*

Side effects for which RMP was stopped in 2/157 patients<sup>90</sup> included anorexia, gastrointestinal upset, abdominal pain, diarrhea, fatigue, headache, dizziness, blurred vision, rash, joint pain, bruising (probably due to thrombocytopenia) and scleral icterus. Additional side effects were related to induction of hepatic enzymes and accelerated clearance of estrogens, cyclosporins, coumadin, glucocorticoids and sulfonylureas.<sup>110</sup> Dose adjustment of these drugs or, in the case of estrogens, the use of alternative forms of contraception is required when RMP is prescribed.

### *INH and RMP*

Side effects for which medication was stopped in 8/167,<sup>87</sup> 6/37,<sup>88</sup> and 39/591<sup>89</sup> patients include hepatitis, gastrointestinal upset, fatigue, rash, dizziness, headache, sleepiness, insomnia and paresthesia.

### *Monitoring*

Baseline liver function testing (AST or ALT level) is recommended before INH therapy is started and at least monthly during therapy in those with pre-existing liver disease, those with concomitant use of hepatotoxic drugs, a history of ethanol abuse or prior INH hepatitis, and those who are older than 34 years, pregnant or within 3 months postpartum. The patient should be advised of potential toxic effects and asked to report symptoms such as nausea, anorexia, dark urine or scleral icterus. In the event that they have such symptoms but cannot reach a caregiver, they should stop the INH on their own. Minor elevations in transaminase levels are common while taking INH and are not a reason to discontinue treatment unless the patient is symptomatic. Reintroduction of INH, despite previous enzyme elevation, is frequently successful. For those receiving self-administered treatment of LTBI the prescription for medication should not exceed the number of doses for 1 month.

INH should be withheld if the AST or ALT level exceeds five times the upper limit of normal without symptoms or when the AST or ALT level exceeds three times the upper limit in the presence of symptoms.<sup>84,111</sup>

### **Management of LTBI when treatment is refused, contraindicated or stopped before completion**

In patients who cannot or will not start or complete LTBI treatment yet in whom the risk of TB disease is high, regular follow-up for 2 years is recommended (for example at 6, 12 and 24 months). This is the period of highest risk.

## Program performance standards for treatment of LTBI

The ideal LTBI treatment regimen and drug delivery program for any patient will achieve, at a minimum, the following:

- result in 80% acceptance of treatment among persons with LTBI at high risk of progressing to active TB disease and without contraindications to INH or RMP;
- result in at least 80% of patients completing the required number of doses;
- result in drug discontinuation rates due to adverse effects of less than 5%; and
- result in less than 5 cases of active TB disease per 1,000 adequately treated patients at 2 years of follow up.

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# Drug-Resistant Tuberculosis

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## Introduction

Since their discovery in the mid 20<sup>th</sup> century, antituberculosis drugs have accelerated the natural decline in the incidence of tuberculosis (TB) within epidemics. Latterly, two forces have conspired to reverse this trend. One is a natural phenomenon, the human immunodeficiency virus (HIV). The other is a man-made phenomenon, antituberculosis drug resistance.<sup>1</sup> Patients are said to have drug-resistant TB if the strain of *Mycobacterium tuberculosis* causing their disease is resistant to one or more of the four first-line drugs: isoniazid (INH), rifampin, pyrazinamide and ethambutol. Streptomycin was once, but is no longer, considered a first-line drug in Canada. The impact of drug resistance on the outcome of treatment of TB varies according to which drug, or combination of drugs, is resistant and reflects the different but complementary role each agent plays in the treatment of TB.<sup>2</sup>

The third 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 (IUATLD), describes resistance patterns in 77 geographic settings in 62 countries from 1999 to 2002. The median prevalence of resistance to any of INH, rifampin, ethambutol or streptomycin was 10.4%: 10.2% in new cases and 18.4% in previously treated cases. The median prevalence of multidrug resistance (MDR) (defined as resistance to at least INH and rifampin, the two most important antituberculosis drugs) was 1.7%: 1.1% in new cases and 7.0% in previously treated cases.<sup>3</sup> Data from the second global report<sup>4</sup> plus multiple logistic regression analysis was used to estimate the number of MDR-TB cases in countries where no resistance surveys had been carried out. Overall, 3.2% of all new TB cases in 2000 were multidrug-resistant.<sup>5</sup>

## TB Drug Resistance Monitoring in Canada

TB drug resistance is monitored by the Public Health Agency of Canada through two systems:

1. Canadian Tuberculosis Reporting System (for reporting of new and re-treatment TB cases)\*

Between 2000 and 2004, drug-resistant TB was reported most commonly in persons with a past history of TB (“relapsed” cases – roughly equivalent to previously treated cases – see below) and in foreign-born persons (see Tables 1 and 2).<sup>6</sup> Of 5,542 new active cases of TB, 5.0% had an INH-resistant/rifampin-sensitive strain and 0.7% had an MDR strain. Of 501 cases of relapsed TB, 7.6% had an INH-resistant/rifampin-sensitive strain and 4.8% had an MDR-TB strain. Between 2000 and 2004, foreign-born persons with TB were 3.5 times more likely to have INH-resistant TB and almost 4 times more likely to have MDR-TB than Canadian-born persons. Higher rates of drug resistance in foreign-born persons correspond to higher rates of drug resistance in their country or region of birth.<sup>7</sup> Countries in

\* Prior to 2008, cases were reported as new or relapsed cases. Effective 2008, they are reported as new or re-treatment cases, (see Appendix B, Canadian Tuberculosis Surveillance Systems, and Appendix C, Definitions and Terms).

which the majority of the population has access to the DOTS strategy (see Chapter 18, Canada and International Tuberculosis Control) have lower rates of drug resistance.<sup>3</sup> Most TB cases (74.6%) and most MDR-TB cases (88.7%) in Canada were reported in three provinces: British Columbia, Ontario and Quebec.

**Table 1**  
Patterns of Susceptibility and Resistance to Isoniazid (INH) and Rifampin (RMP) in the Initial Positive Culture from TB Cases by Disease Type and Patient Country of Birth, Canada, 2000-2004\*

Resistance Pattern	Disease Type	Country of Birth			Total No. (%)
		Canadian-born	Foreign-born	Unknown	
		No. (%)	No. (%)	No. (%)	
Susceptible to INH and RMP	New Active	1,639 (85.1)	3,366 (82.8)	114 (75.0)	5,119 (83.4)
	Relapse	188 (9.8)	235 (5.8)	4 (2.6)	427 (7.0)
	Unknown	13 (0.7)	65 (1.6)	29 (19.1)	107 (1.7)
Resistant to INH with or without resistance to another drug except RMP	New Active	31 (1.6)	276 (6.8)	3 (2.0)	310 (5.0)
	Relapse	9 (0.5)	29 (0.7)	0 (0.0)	38 (0.6)
	Unknown	0 (0.0)	3 (0.1)	1 (0.7)	4 (0.1)
Resistant to INH and RMP with or without resistance to another drug (MDR-TB)	New Active	2 (0.1)	35 (0.9)	0 (0.0)	37 (0.6)
	Relapse	5 (0.3)	19 (0.5)	0 (0.0)	24 (0.4)
	Unknown	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Unknown	New Active	34 (1.8)	29 (0.7)	0 (0.0)	63 (1.0)
	Relapse	5 (0.3)	5 (0.1)	0 (0.0)	10 (0.2)
	Unknown	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.0)
<b>Total</b>		<b>1,926 (100)</b>	<b>4,063 (100)</b>	<b>152 (100)</b>	<b>6,141 (100)</b>

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

**Table 2**  
Type of TB Drug Resistance By Country of Birth for New and Relapsed Cases in Canada and Internationally Reported MDR-TB Rates by Country

Country of Birth	New Cases Diagnosed in Canada: 2000-2004*				Internationally Reported MDR-TB Rates by Country, 2004 <sup>§</sup> %
	Total No. of Positive Cultures <sup>†</sup>	Any Resistance <sup>‡</sup>	INH Resistant/ RMP Sensitive	MDR-TB	
		Cases (%)	Cases (%)	Cases (%)	
TOTAL	5,542	525 (9.5)	310 (5.6)	37 (0.6)	-
Afghanistan	47	9 (19.1)	4 (8.5)	2 (4.3)	1.7
Albania	1	0	0	0	1.4
Algeria	7	0	0	0	1.2
Andorra	0	0	0	0	0
Angola	7	1 (14.3)	1 (14.3)	0	1.6
Antigua and Barbuda	0	0	0	0	1.3
Argentina	3	0	0	0	1.8
Armenia	0	0	0	0	6
Australia	1	0	0	0	0.8
Austria	1	0	0	0	0.4
Azerbaijan	2	1 (50)	1 (50)	0	14.8
Bahamas	0	0	0	0	1.2



Bahrain	0	0	0	0	1.2
Bangladesh	41	2 (48.8)	0	0	1.8
Barbados	1	0	0	0	–
Belarus	0	0	0	0	7.4
Belgium	1	0	0	0	1.2
Belize	0	0	0	0	1.5
Benin	1	0	0	0	0.3
Bhutan	0	0	0	0	1.8
Bolivia	1	0	0	0	1.2
Bosnia and Herzegovina	1	0	0	0	0.1
Botswana	2	0	0	0	0.8
Brazil	5	2 (40.0)	1 (20.0)	0	0.9
Brunei Darussalam	1	0	0	0	1.2
Bulgaria	2	0	0	0	5.6
Burkina Faso	2	0	0	0	2.0
Burundi	14	0	0	0	1.6
Cambodia	39	3 (7.7)	3 (7.7)	0	0
Cameroon	12	1	0	1 (8.3)	1.6
<b>Canada</b>	<b>1,712</b>	<b>75 (4.3)</b>	<b>31 (1.8)</b>	<b>2 (0.1)</b>	<b>0.7</b>
Cape Verde	0	0	0	0	1.6
Central African Republic	1	0	0	0	1.1
Chad	6	0	0	0	1.6
Chile	5	1 (20.0)	0	0	0.7
China	458	57 (12.4)	37 (8.1)	4 (0.9)	5.3
China, Macao	5	0	0	0	1.4
Colombia	7	1 (14.3)	0	0	1.5
Comoros	0	0	0	0	1.6
Congo	30	2 (6.7)	1 (3.3)	0	1.5
Congo, Democratic Republic of	11	5 (45.5)	5 (45.5)	0	2.0
Costa Rica	3	0	0	0	1.2
Croatia	1	0	0	0	0.1
Cuba	1	0	0	0	0.3
Cyprus	0	0	0	0	0.9
Czech Republic	1	0	0	0	1.1
Denmark	2	1 (50.0)	0	0	0.3
Djibouti	2	1 (50.0)	1 (50.0)	0	1.6
Dominica	1	0	0	0	1.5
Dominican Republic	6	0	0	0	6.6
Ecuador	4	0	0	0	4.9
Egypt	4	1 (25.0)	1 (25.0)	0	2.2
El Salvador	10	2 (20.0)	2 (20.0)	0	0.3
Eritrea	6	0	0	0	1.7
Estonia	0	0	0	0	17.1
Ethiopia	44	14 (31.8)	7 (15.9)	0	1.7
Ethiopia (former)	51	9 (17.6)	4 (7.8)	0	–
Fiji	9	0	0	0	1.4
Finland	3	0	0	0	0.3
France	10	1 (10.0)	1 (10.0)	0	0.8
French Polynesia	0	0	0	0	1.7
Gabon	0	0	0	0	1.3
Gambia	2	0	0	0	0.5
Georgia	0	0	0	0	15.6
Germany	11	0	0	0	0.8
Ghana	2	0	0	0	1.6
Greece	13	1 (7.7)	1 (7.7)	0	1.0
Grenada	1	0	0	0	–
Guam	0	0	0	0	1.2
Guatemala	4	0	0	0	3.0
Guinea	4	0	0	0	0.6
Guinea-Bissau	1	0	0	0	2.1
Guyana	15	0	0	0	1.5
Haiti	113	9 (8.0)	9 (8.0)	0	1.4
China, Hong Kong	159	14 (8.8)	5 (3.1)	0	0.8
Honduras	4	0	0	0	1.8
Hungary	5	2 (40.0)	0	0	1.7

India	583	47 (8.1)	28 (4.8)	4 (0.7)	2.4
Indonesia	15	1 (6.7)	1 (6.7)	0	1.6
Iran	14	2 (14.3)	0	0	5
Iraq	5	0	0	0	1.7
Ireland	4	0	0	0	0.7
Israel	1	0	0	0	2
Italy	32	0	0	0	1.2
Ivory Coast	3	0	0	0	5.3
Jamaica	10	0	0	0	1.2
Japan	9	0	0	0	0.9
Jordan	0	0	0	0	1.5
Kazakhstan	1	0	0	0	14.2
Kenya	35	0	0	0	0.0
Korea, Democratic Peoples Republic of, (North Korea)	30	5 (16.7)	4 (13.3)	0	2.8
Korea, Republic of (South Korea)	56	10 (17.9)	8 (14.3)	1 (1.8)	2.2
Kiribati	0	0	0	0	1.5
Kuwait	0	0	0	0	1.0
Kyrgyzstan	0	0	0	0	8.2
Lao People's Democratic Republic	16	3 (18.8)	1 (6.3)	0	2
Latvia	2	0	0	0	9.3
Lebanon	9	1 (11.1)	0	1 (11.1)	1.2
Lesotho	0	0	0	0	0.9
Liberia	2	0	0	0	–
Lithuania	2	0	0	0	9.4
Libyan Arab Jamahiriya	0	0	0	0	1.1
Luxembourg	0	0	0	0	0.0
Madagascar	3	0	0	0	1.8
Malawi	1	0	0	0	1.7
Malaysia	9	0	0	0	0.1
Maldives	0	0	0	0	1.5
Mali	2	0	0	0	1.4
Malta	0	0	0	0	0.9
Marshall Islands	0	0	0	0	1.6
Mauritius	0	0	0	0	1.1
Mexico	10	0	0	0	2.4
Micronesia	0	0	0	0	2.5
Moldova, Republic of	0	0	0	0	15.2
Mongolia	0	0	0	0	1.0
Morocco	22	1 (4.5)	0	0	2.2
Mozambique	0	0	0	0	3.5
Myanmar	22	1 (4.5)	1 (4.5)	0	4.4
Namibia	0	0	0	0	1.3
Nepal	4	3 (75.0)	1 (25.0)	1 (25.0)	1.3
Netherlands	11	3 (27.3)	1 (9.1)	0	0.9
New Caledonia	0	0	0	0	0.0
New Zealand	0	0	0	0	0.0
Nicaragua	3	0	0	0	1.2
Niger	0	0	0	0	2.1
Nigeria	17	1 (5.9)	1 (5.9)	0	1.7
Northern Mariana Islands	0	0	0	0	2
Norway	0	0	0	0	1.9
Oman	0	0	0	0	0.0
Pakistan	128	11 (8.6)	5 (3.9)	1 (0.8)	1.9
Palau	0	0	0	0	1.9
Panama	1	0	0	0	1.7
Papua New Guinea	1	0	0	0	2.3
Paraguay	0	0	0	0	2.1
Peru	28	2 (7.1)	1 (3.6)	0	3.0
Philippines	450	70 (15.6)	57 (12.7)	8 (1.8)	1.5
Poland	30	1 (3.3)	1 (3.3)	0	1.2

Portugal	18	2 (11.1)	0	0	1.7
Puerto Rico	0	0	0	0	2
Qatar	0	0	0	0	0.4
Romania	38	2 (5.3)	1 (2.6)	0	2.8
Russian Federation	6	1 (16.7)	1 (16.7)	0	10
Rwanda	15	1 (6.7)	1 (6.7)	0	1.9
Saint Lucia	0	0	0	0	1.6
Samoa	0	0	0	0	2.4
Saudi Arabia	3	2 (66.7)	2 (66.7)	0	1.2
Senegal	3	0	0	0	1.9
Serbia and Montenegro	1	0	0	0	0.4
Seychelles	0	0	0	0	1.1
Sierra Leone	9	2 (22.2)	2 (22.2)	0	0.9
Singapore	1	0	0	0	0.5
Slovakia	0	0	0	0	1.1
Slovenia	0	0	0	0	0
Solomon Islands	0	0	0	0	1.7
Somalia	92	16 (17.4)	12 (13.)	1 (1.1)	1.4
South Africa	6	0	0	0	1.8
Spain	5	0	0	0	1.2
Sri Lanka	65	7 (10.8)	4 (6.2)	0	1.7
St. Vincent	0	0	0	0	1.6
Sudan	22	4 (18.2)	1 (4.5)	0	1.6
Suriname	1	0	0	0	–
Swaziland	0	0	0	0	0.9
Sweden	0	0	0	0	1.2
Switzerland	1	1 (100.0)	1 (100.0)	0	0
Syrian Arab Republic	1	0	0	0	1.6
Taiwan	22	3 (13.6)	1 (4.5)	1 (4.5)	–
Tanzania, United Republic of	9	0	0	0	1.8
Tajikistan	0	0	0	0	8.6
TFYR Macedonia	0	0	0	0	1.6
Thailand	10	0	0	0	0.9
Timor-Leste	1	0	0	0	1.6
Trinidad and Tobago	7	1 (14.3)	0	0	–
Togo	2	0	0	0	1.7
Tonga	1	0	0	0	2.4
Tunisia	2	0	0	0	1.4
Turkey	13	3 (23.1)	2 (15.4)	0	2.8
Turkmenistan	2	0	0	0	3.8
Uganda	11	0	0	0	0.5
Ukraine	9	0	0	0	10.1
United Arab Emirates	1	0	0	0	1.2
United Kingdom	27	2 (7.4)	1 (3.7)	1 (3.7)	0.9
Uruguay	3	0	0	0	0.3
United States of America	17	0	0	0	1.1
U.S.S.R. (former)	17	4 (23.5)	1 (5.9)	2 (11.8)	–
Uzbekistan	0	0	0	0	13.2
Vanuatu	0	0	0	0	1.5
Venezuela	0	0	0	0	0.5
Vietnam	331	77 (23.3)	46 (13.9)	4 (1.2)	2.3
West Bank and Gaza Strip	0	0	0	0	1.6
Yemen	2	0	0	0	1.8
Zambia	2	1 (50.0)	0	1 (50.0)	1.8
Zimbabwe	14	2 (14.2)	1 (7.1)	1 (7.1)	1.9
All other countries	262	18 (7.3)	8 (3.2)	1 (0.4)	–

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

† The totals for positive cultures will differ between Table 1 and Table 2. Table 2 does not include the data for the 112 patients for whom it was not known if the case was new, active or a relapsed one.

‡ Some laboratories do not routinely report pyrazinamide or streptomycin resistance.

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Country of Birth	Relapsed Cases Diagnosed in Canada: 2000-2004*				Internationally
	Total No. of Positive Cultures <sup>1</sup>	Any	INH Resistant/ RMP Sensitive	MDR-TB	Reported MDR-TB Rates by Country, 2004 <sup>5</sup>
		Resistance <sup>1</sup> Cases (%)	Cases (%)	Cases (%)	%
TOTAL	488	81 (16.6)	38 (7.8)	24 (4.9)	–
Afghanistan	7	3 (42.9)	3 (42.9)	0	28.3
Albania	1	0	0	0	8.8
Algeria	0	0	0	0	8.7
Andorra	0	0	0	0	8.8
Angola	0	0	0	0	8.3
Antigua and Barbuda	0	0	0	0	9.0
Argentina	0	0	0	0	9.4
Armenia	0	0	0	0	28.5
Australia	0	0	0	0	8.6
Austria	0	0	0	0	1.5
Azerbaijan	0	0	0	0	30.5
Bahamas	0	0	0	0	8.4
Bahrain	0	0	0	0	28.2
Bangladesh	2	0	0	0	14.4
Belarus	0	0	0	0	28.9
Belgium	0	0	0	0	5.1
Belize	0	0	0	0	8.5
Benin	0	0	0	0	8.6
Bhutan	0	0	0	0	14.5
Bolivia	0	0	0	0	4.7
Bosnia and Herzegovina	0	0	0	0	2.0
Botswana	1	0	0	0	10.4
Brazil	0	0	0	0	5.4
Brunei Darussalam	0	0	0	0	14.5
Bulgaria	0	0	0	0	28.7
Burkina Faso	0	0	0	0	8.1
Burundi	1	1 (100.0)	0	1 (100.0)	7.6
Cambodia	1	1 (100.0)	0	1 (100.0)	3.1
Cameroon	0	0	0	0	7.8
<b>Canada</b>	<b>207</b>	<b>19 (9.1)</b>	<b>9 (4.3)</b>	<b>5 (2.4)</b>	<b>3.4</b>
Cape Verde	0	0	0	0	8.9
Central African Republic	0	0	0	0	18.2
Chad	0	0	0	0	8.0
Chile	1	0	0	0	3.8
China	67	11 (16.4)	7 (10.4)	2 (3.0)	27.2
China, Macao	0	0	0	0	14.7
Colombia	0	0	0	0	8.6
DR Congo	1	1 (100.0)	0	1 (100.0)	8.1
Comoros	0	0	0	0	8.8
Congo	1	0	0	0	8.0
Costa Rica	0	0	0	0	8.7
Croatia	0	0	0	0	1
Cuba	0	0	0	0	2.6
Cyprus	0	0	0	0	8.7
Czech Republic	0	0	0	0	9.1
Denmark	0	0	0	0	3
Djibouti	1	0	0	0	8.4
Dominica	0	0	0	0	9.0
Dominican Republic	0	0	0	0	19.7
Ecuador	0	0	0	0	24.3
Egypt	1	1 (100.0)	1 (1.00)	0	38.2
El Salvador	0	0	0	0	7.0
Eritrea	0	0	0	0	8.2

Estonia	0	0	0	0	35.4
Ethiopia	1	0	0	0	8.2
Ethiopia (former)	3	1 (33.3)	0	0	—
Fiji	2	0	0	0	14.3
Finland	1	0	0	0	3.4
France	1	0	0	0	8.5
French Polynesia	0	0	0	0	14.9
Gabon	0	0	0	0	7.8
Gambia	0	0	0	0	0.0
Georgia	0	0	0	0	30.5
Germany	0	0	0	0	5.9
Ghana	0	0	0	0	8.2
Greece	0	0	0	0	8.6
Guam	0	0	0	0	14.3
Guatemala	0	0	0	0	26.5
Guinea	1	0	0	0	28.1
Guinea-Bissau	0	0	0	0	8.2
Guyana	1	0	0	0	8.3
Haiti	4	0	0	0	7.7
China, Hong Kong	25	5 (20.0)	2 (8.0)	1 (4.0)	11.2
Honduras	2	0	0	0	6.9
Hungary	0	0	0	0	9.1
India	22	7 (31.8)	1 (4.5)	1 (4.5)	14.7
Indonesia	1	0	0	0	14.3
Iran	0	0	0	0	48.2
Iraq	0	0	0	0	28.5
Ireland	0	0	0	0	3.8
Israel	0	0	0	0	28.2
Italy	2	0	0	0	24.1
Ivory Coast	0	0	0	0	7.8
Jamaica	0	0	0	0	8.5
Japan	4	0	0	0	19.7
Jordan	0	0	0	0	28.2
Kazakhstan	1	0	0	0	56.4
Kenya	2	0	0	0	0.0
Korea, Democratic Peoples Republic of, (North Korea)	6	0	0	0	15.1
Korea, Republic of, (South Korea)	10	3 (30.0)	2 (20.0)	1 (10.0)	7.1
Kiribati	0	0	0	0	14.3
Kuwait	0	0	0	0	27.9
Kyrgyzstan	0	0	0	0	28.9
Lao People's Democratic Republic	1	0	0	0	14.5
Latvia	0	0	0	0	27.1
Lebanon	0	0	0	0	28.0
Lesotho	0	0	0	0	5.7
Libyan Arab Jamahiriya	0	0	0	0	27.8
Lithuania	0	0	0	0	53.3
Luxembourg	0	0	0	0	0.0
Madagascar	0	0	0	0	8.5
Malawi	0	0	0	0	7.1
Malaysia	1	0	0	0	0.0
Maldives	0	0	0	0	14.5
Mali	0	0	0	0	8.2
Malta	0	0	0	0	0.0
Marshall Islands	0	0	0	0	14.6
Mauritius	0	0	0	0	8.7
Mexico	0	0	0	0	22.4

Micronesia	0	0	0	0	15.1
Moldova, Republic of	0	0	0	0	30.3
Mongolia	0	0	0	0	14.5
Morocco	0	0	0	0	28.2
Mozambique	0	0	0	0	3.3
Myanmar	3	1 (33.3)	0	1 (33.3)	15.5
Namibia	0	0	0	0	6.8
Nepal	0	0	0	0	20.5
Netherlands	2	0	0	0	1.1
New Caledonia	0	0	0	0	0.0
New Zealand	1	0	0	0	0.0
Nicaragua	0	0	0	0	8.9
Niger	0	0	0	0	8.7
Nigeria	0	0	0	0	7.9
Northern Mariana Islands	0	0	0	0	15.0
Norway	1	1 (100.0)	1 (100.0)	0	0.0
Oman	0	0	0	0	58.3
Pakistan	5	1 (20.0)	0	1 (20.0)	28.3
Palau	0	0	0	0	15.0
Panama	1	0	0	0	8.9
Papua New Guinea	0	0	0	0	14.6
Paraguay	0	0	0	0	3.9
Peru	2	0	0	0	12.3
Philippines	30	11 (36.7)	5 (16.7)	6 (2.0)	14.4
Poland	2	0	0	0	8.5
Portugal	2	1 (50.0)	0	1 (50.0)	18.8
Puerto Rico	0	0	0	0	8.0
Qatar	0	0	0	0	28.2
Romania	5	1 (20.0)	0	1 (20.0)	14.4
Russian Federation	0	0	0	0	47.8
Rwanda	1	0	0	0	8.0
Saint Lucia	0	0	0	0	9.0
Samoa	0	0	0	0	15.0
Saudi Arabia	0	0	0	0	28.2
Senegal	0	0	0	0	8.8
Serbia and Montenegro	0	0	0	0	0.0
Seychelles	0	0	0	0	8.8
Sierra Leone	0	0	0	0	23.1
Singapore	0	0	0	0	0.8
Slovakia	0	0	0	0	1.8
Slovenia	0	0	0	0	0.0
Solomon Islands	0	0	0	0	14.5
Somalia	4	0	0	0	8.5
South Africa	1	1 (100.0)	0	0	6.7
Spain	0	0	0	0	11.1
Sri Lanka	0	0	0	0	14.5
St. Vincent	0	0	0	0	9.0
Sudan	1	1 (100.0)	1 (100.0)	0	8.4
Swaziland	0	0	0	0	9.1
Sweden	0	0	0	0	4.5
Switzerland	0	0	0	0	1.8
Syrian Arab Republic	0	0	0	0	28.3
Taiwan	4	1 (25.0)	1 (25.0)	0	-
Tajikistan	0	0	0	0	28.9
Tanzania, United Republic of	1	0	0	0	7.6
TFYR Macedonia	0	0	0	0	9.0
Thailand	1	1 (100.0)	1 (100.0)	0	20.3
Timor-Leste	0	0	0	0	14.3
Togo	0	0	0	0	8.2

Tonga	0	0	0	0	15.0
Tunisia	1	0	0	0	28.1
Turkey	1	0	0	0	9.5
Turkmenistan	0	0	0	0	18.4
Uganda	2	0	0	0	4.4
Ukraine	1	0	0	0	28.9
United Arab Emirates	0	0	0	0	28.2
United Kingdom	4	2 (50.0)	2 (50.0)	0	4.2
Uruguay	0	0	0	0	8.8
United States of America	3	0	0	0	5.2
U.S.S.R. (former)	4	0	0	0	–
Uzbekistan	0	0	0	0	40.2
Vanuatu	0	0	0	0	14.4
Venezuela	0	0	0	0	13.5
Vietnam	17	4 (23.5)	2 (11.8)	0	14.5
West Bank and Gaza Strip	0	0	0	0	28.2
Yemen	0	0	0	0	28.2
Yugoslavia (former)	5	0	0	0	–
Zambia	0	0	0	0	2.3
Zimbabwe	0	0	0	0	8.3
All other countries	13	2 (15.4)	0	1 (7.7)	–

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

† The totals for positive cultures will differ between Table 1 and Table 2. Table 2 does not include the data for the 112 patients for whom it was not known if the case was new, active or a relapsed one.

‡ Some laboratories do not routinely report pyrazinamide or streptomycin resistance.

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## 2. Canadian Tuberculosis Laboratory Surveillance System

In 1998, Tuberculosis Prevention and Control, at the Public Health Agency of Canada, in collaboration with the Canadian Tuberculosis Laboratory Technical Network and participating laboratories (representing all provinces and territories) in the Canadian Tuberculosis Laboratory Surveillance System, established a laboratory-based national surveillance system to monitor TB drug resistance patterns in Canada. Please see Table 3 for the overall pattern of TB drug resistance in Canada, 2000–2004, as reported by this system. For additional reports, see <<http://www.publichealth.gc.ca/tuberculosis>> for annual *Tuberculosis Drug Resistance in Canada* reports.

Drug resistance is detected by the performance of in vitro drug susceptibility tests on pure cultures of *M. tuberculosis* complex grown from clinical specimens collected from patients (see Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies). 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 drugs.<sup>8–11</sup> Newer tests, such as molecular beacons, line probe assays and phage-based assays, hold the promise of earlier detection of drug resistance.<sup>12</sup>

What follows is a brief account of drug resistance theory, a summary of the predictors of drug-resistant TB and a review of the management of drug-resistant TB.

Table 3  
Overall Pattern of Reported TB Drug Resistance in Canada  
for Initial and Follow-up Cultures (2000-2004)\*

	2000		2001		2002		2003		2004	
	Total	%	Total	%	Total	%	Total	%	Total	%
Total number of isolates	1,491	100.0	1,476	100.0	1,420	100.0	1,428	100.0	1,358	100.0
Isolates susceptible	1,323	88.7	1,328	90.0	1,241	87.4	1,248	87.4	1,190	87.6
Any resistance†										
INH	111	7.4	102	6.9	116	8.2	135	9.5	100	7.4
RMP	18	1.2	16	1.1	25	1.8	25	1.8	14	1.0
EMB	21	1.4	10	0.7	27	1.9	17	1.2	11	0.8
PZA	24	1.6	20	1.4	31	2.2	29	2.0	26	2.4
SM	65	5.6	68	5.7	74	7.2	73	6.2	88	7.8
Resistance to one or more drugs	168	11.3	148	10.0	179	12.6	180	13.1	168	12.4
Monoresistance	121	8.1	101	6.8	131	9.2	117	8.5	113	8.3
MDR-TB	15	1.0	15	1.0	22	1.5	23	1.7	12	0.9
Other patterns	32	2.1	32	2.2	26	1.8	40	2.9	43	3.2

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

\* Based on the Canadian Tuberculosis Laboratory Surveillance System drug susceptibility results for *Mycobacterium tuberculosis* clinical isolates. These numbers are higher than those in Table 1 (sensitivity of the initial positive culture) as they also include sensitivity results for follow-up cultures.

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

## Drug Resistance Theory

Epidemiologically, drug resistance in TB is classified into three types.<sup>13</sup>

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.
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.
3. *Initial drug resistance*: when drug resistance occurs in patients who deny previous treatment but whose prior drug use history cannot be verified. In reality it consists of true primary resistance and an unknown amount of undisclosed acquired resistance. Primary drug resistance is uncommon in the Canadian-born unless they have travelled abroad to a country with high TB incidence. Acquired drug resistance is also uncommon in the Canadian-born, perhaps because directly observed therapy (DOT) is used to secure treatment adherence.<sup>15</sup> Drug resistance in the foreign-born who deny previous drug use is best classified as *initial* rather than primary, unless

\* Drug-resistant TB in **epidemic** areas (not Canada) has recently been reclassified.<sup>14</sup> The term “primary drug resistance” has been replaced by “drug resistance among new cases” and the term “acquired drug resistance” has been replaced by “drug resistance among previously treated cases”. This reclassification arose because of the inability to know for certain whether previously treated patients have always been infected with drug-resistant strains, became drug-resistant while receiving treatment or were re-infected with a new drug-resistant strain, unless drug susceptibility testing and DNA fingerprinting of original and subsequent isolates are performed. In Canada, up to the end of 2007, the terms “new case” and “relapsed case” have been used to describe disease type, with “relapsed case” approximating “previously treated case”. Beginning in 2008, the terms “new case” and “re-treatment case” will be used to describe disease type in Canada (see Appendix C, Definition of Terms).



their prior drug use history can be verified. The following theory relates to acquired drug resistance.

An understanding of acquired drug resistance theory is the 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.<sup>16,17</sup> Random mutations that confer resistance to each of the major antituberculosis drugs occur at predictable frequencies in *notreated* populations of tuberculosis bacteria (Table 4). A 2 cm TB cavity harbouring  $10^8$  bacteria may contain a few (10-1,000) bacteria resistant to INH, a few (0-10) resistant to rifampin, a few (10-1,000) resistant to ethambutol and a few (10-1,000) resistant to streptomycin, etc. This does not imply 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 must be resistant to the drug. 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.<sup>16,18,19</sup>

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 rifampin resistance, 1 in  $10^6 \times 1$  in  $10^8$  equals 1 in  $10^{14}$ . Because the total number of bacteria in the body, even with far advanced cavitary disease, rarely approaches this number ( $10^{14}$ ), spontaneous evolution of a multidrug-resistant bacterium is very rare. As Iseman and Madsen have enunciated so clearly,<sup>19</sup> “This is the salient principle of modern tuberculosis 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. Owing to the relative weakness of streptomycin and *para*-aminosalicylic acid (PAS), triple rather than double therapy was the standard until the advent of rifampin. The success of the two-drug (INH and rifampin) “Arkansas” regimen<sup>20</sup> substantially validated the aforementioned model for drug-susceptible tuberculosis.”

**Table 4**  
Spontaneous Occurrence of Drug-Resistant Mutants in  
Wild Strains of *Mycobacterium tuberculosis*<sup>13</sup>

Drug	Probability of Resistance
Rifampin	$10^{-8}$
Isoniazid, streptomycin, ethambutol, kanamycin, <i>para</i> -aminosalicylic acid	$10^{-6}$
Ethionamide, capreomycin, viomycin, cycloserine, thiacetazone	$10^{-3}$

Although two-drug (INH and rifampin) treatment of drug-susceptible disease is possible, standard short-course therapy with a pyrazinamide-containing regimen is generally preferred (see Chapter 6, Treatment of Tuberculosis Disease and Infection).

If infection (latent TB infection or LTBI) and not disease is present, then it is safe to assume that a small population of bacteria (probably fewer than  $10^6$ ) are present in the body and that a single drug, usually INH, may be used as treatment.

The emergence of drug resistance is due to the selection of pre-existing resistant mutants in the original bacterial population by “drug pressure”. For example, if INH alone is prescribed (or is the only drug actually taken in a prescribed multidrug regimen) to a patient with cavitary pulmonary TB, then it will kill all of the organisms susceptible to it, including those random mutants resistant to drugs such as rifampin and ethambutol, 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 occurring 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.<sup>21</sup> If rifampin alone is now added to the regimen, then by the same mechanism an MDR strain (i.e. resistance to both INH and rifampin) will emerge; rifampin 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 rifampin. Fixed dose combinations (FDCs) reduce the likelihood of monotherapy but so far are not proven to reduce the risk of drug resistance.

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.<sup>22-24</sup> 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 sensitive 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.

### Predictors of Drug-Resistant TB

The possibility of drug-resistant TB should be considered simultaneously with specimen collection and selection of the initial treatment regimen. Failure to consider the possibility of drug-resistant TB until drug susceptibility tests return weeks to months later can result in unnecessarily inadequate treatment regimens.

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

1. Previous treatment for TB disease or treatment for LTBI, even if that treatment lasted only 1 month.

When treatment in the past was for cavitary pulmonary TB, if the treatment regimen was inadequate or self-administered, or the patient was non-adherent, then the level of suspicion for drug-resistant TB should be especially high. Conversely, if the patient has a history of defaulting on multidrug, directly observed treatment (i.e. stops all medications at the same time) or has relapsed after completion of a directly observed, standardized regimen, then the likelihood of the isolate being drug-resistant is much lower.<sup>25</sup>

To quote the Francis J. Curry National Tuberculosis Center,<sup>26</sup> “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 provincial/territorial/local TB control program. Foreign-born persons 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 can be retrieved by the Health Management Branch of CIC (see Chapter 15, Immigration and Tuberculosis Control in Canada).

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 the foreign-born are more likely to be harbouring drug-resistant strains, the in-Canada transmission of drug-susceptible and drug-resistant strains from the foreign-born to the Canadian-born is relatively uncommon.<sup>15,27</sup>

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,<sup>28-37</sup> other data suggest that any reduced virulence of drug-resistant bacteria is offset by longer periods of infectiousness in drug-resistant cases<sup>37,38</sup> or compensatory mutations in drug-resistant bacteria.<sup>39</sup> 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 susceptibility test 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 warranted from the outset.

Global surveys suggest that HIV is not an independent risk factor for the development of drug resistance.<sup>7</sup> However, numerous MDR-TB outbreaks have been documented in HIV patients, and in some areas of the world HIV is a risk factor for MDR-TB.<sup>40</sup>

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

- when the treatment regimen is inadequate to begin with,
- when there is intermittent or erratic ingestion of the prescribed antituberculosis drugs,
- when the patient is malabsorbing one or more of the drugs in the treatment regimen,
- when the patient has cavitory pulmonary TB – cavities contain large numbers of bacteria, and large numbers of bacteria include many naturally occurring resistant mutants,
- when the patient's disease is sequestered, e.g. TB empyema, a rare condition in which differential penetration of antituberculosis drugs may lead, in effect, to monotherapy.

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

Approximately 80% of patients with pulmonary TB caused by drug-susceptible organisms who begin standard four-drug therapy will have negative sputum cultures 2 months after initiation of treatment. Progressive clinical and/or radiographic deterioration or failure of cultures to convert in a timely fashion while the patient is receiving TB treatment should lead to anticipation of treatment failure, defined as continued or recurrent positive cultures after 4 or more months of treatment in patients in whom medication ingestion was confirmed<sup>41</sup>, and acquired drug resistance. Prior drug susceptibility test results should be reviewed and repeat drug susceptibility tests performed. Self-administered treatment should be abandoned in favour of DOT and, in the event of possible drug malabsorption, serum drug levels should be measured.<sup>41</sup> 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 must be added – a single drug must

never be added to a failing regimen. The new drugs should be chosen from those to which the organism is known to be susceptible or those that the patient has never received.<sup>26\*</sup>

**Summary Point:**

- ▶ Within programs, priority should be given to the prevention, not to the management, of drug-resistant TB. To prevent resistance from occurring it is necessary to (a) prescribe, in proper dosage, at least two and preferably three drugs to which the isolate is proven or anticipated to be susceptible, (b) provide assurance that the prescribed regimen is adhered to and that those who abscond from treatment are identified early – best achieved by supervising the ingestion of each dose and (c) never introduce a single drug to a failing regimen.

## Management of Drug-resistant TB

The optimal management of drug-resistant TB, particularly MDR-TB, requires the timely performance of state-of-the-art drug susceptibility testing, an uninterrupted supply of first- and second-line antituberculosis 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 drug supply should begin 6 months or more in advance of anticipated need, and drug needs should be estimated as accurately as possible.<sup>40</sup>

Second-line drug susceptibility testing should be ordered for any patient whose *M. tuberculosis* is resistant to INH and rifampin or who is unable to take INH and rifampin due to side-effects etc.

Among patients with the various patterns of drug resistance, definitive, randomized or controlled studies have not been performed. Recommendations for treatment are based upon general principles, extrapolations and expert opinion. With few exceptions the treatment regimens for drug-resistant nonrespiratory TB are the same as those for respiratory TB.<sup>40</sup> The regimens assume that the pattern of drug resistance has not changed between the time of submission of the specimen for drug susceptibility testing and the time of reporting of drug resistance. If there is reason to believe this assumption is incorrect then further adjustments in the regimen, as appropriate to the circumstances, may be necessary. Detailed information on the treatment of drug-resistant TB in special conditions or situations is not provided here but is available in recent reviews.<sup>26,40</sup>

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

## Resistance to INH with or without resistance to streptomycin

In Canada, the initial isolate of *M. tuberculosis* from all newly diagnosed cases of TB is tested for resistance to INH, rifampin and ethambutol. Routine testing for resistance to pyrazinamide is strongly encouraged (see Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies). Resistance to INH is more common than resistance to any other first-line anti-TB drug; relapsed cases and foreign-born persons are at increased risk of INH-resistant TB (Table 1). Resistance to INH is important because it is a potent bacteriocidal drug, capable of destroying the metabolically active and potentially communicable population of bacteria in cavities.<sup>2</sup> Resistance to INH is due to mutations at one of two main sites in either the *katG* or *inhA* genes.<sup>8,9</sup>

In general, patients suspected of having TB resistant to INH (with or without streptomycin) should be started on at least four first-line drugs while awaiting drug susceptibility test results. An initial four-drug regimen should also be used whenever the prevailing rate of INH resistance among those in whom there is no history of antituberculosis drug use is 4% or more (see Tables 1 and 2).<sup>42</sup>

A number of regimens have been proven to cure INH-resistant TB (see Table 5). The presence of streptomycin resistance does not affect the efficacy of these regimens. Ideally each of the regimens should be regarded as the *minimum* effective therapy, and each should be directly observed. Direct observation of treatment is especially important in patients with sputum smear-positive pulmonary disease or HIV co-infection. Some strains of *M. tuberculosis* demonstrate resistance at low concentrations of INH (0.2 µg/mL using solid media [agar proportion method]; 0.1 µg/mL using liquid media [indirect proportion method]) but are susceptible at higher concentrations (1.0 µg/mL using solid media, 0.4 µg/mL using liquid media). In these situations, high-dose (900 mg) intermittent therapy may be indicated.<sup>26</sup>

Table 5  
Regimens for the Treatment of INH-resistant TB

Initial Phase	Continuation Phase
2 months daily or thrice weekly (H) RZE*†	4 months daily or thrice weekly RZE <sup>43</sup>
2 months daily (H) RZE*†	7 months twice weekly RZE <sup>44,45</sup>
2 months daily (H) RZE†‡	10 months daily or intermittent RE <sup>46-48</sup>

H = isoniazid, R = rifampin, Z = pyrazinamide, E = ethambutol

\* If treatment was started with a standard 4-drug regimen, INH can be stopped when resistance is documented.

† If a patient has extensive disease a fluoroquinolone may be added to the regimen, especially during the initial phase of treatment.

‡ Pyrazinamide is recommended here, but in most field trials this drug was not included in the regimen.

## Isolated resistance to rifampin

Resistance to rifampin is nearly always due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase.<sup>10</sup> With one exception, i.e. the occurrence of acquired rifamycin resistance in HIV-infected patients, rifampin monoresistance is uncommon. It has been described in AIDS patients taking rifabutin as prophylaxis against *M. avium* complex<sup>49</sup> and in HIV co-infected TB patients, in whom the consistent associations are advanced HIV disease (CD4 counts in cases of acquired rifamycin resistance have all been

< 200 cells  $\times$  10<sup>6</sup>/L and usually < 50 cells  $\times$  10<sup>6</sup>/L) and the use of an intermittent regimen during the initial phase of treatment.<sup>50-55</sup> In general, twice or thrice weekly intermittent treatment should be avoided altogether in the initial phase and twice weekly intermittent treatment avoided in the continuation phase of treatment of HIV co-infected TB patients, especially those with advanced HIV or TB disease. Treatment options for patients determined to be rifampin monoresistant are outlined in Table 6.

**Table 6**  
**Regimens for the Treatment of Rifampin-Monoresistant TB**

Initial Phase	Continuation Phase
2 months HZEF*	10-16 months HEP <sup>26,41</sup>
2 months HZS (or other aminoglycoside/ polypeptide daily or thrice weekly)	7 months daily or thrice weekly HRS <sup>56</sup>
2 months HZE daily†	16 months daily or twice weekly HE <sup>57,58</sup>

H = isoniazid, Z = pyrazinamide, E = ethambutol, S = streptomycin, F = fluoroquinolone

\* In patients with extensive cavitory 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 pyrazinamide or ethambutol

Isolated resistance to pyrazinamide or ethambutol is rare. Isolated pyrazinamide resistance occurs genotypically in *M. bovis*. Recently, pyrazinamide monoresistance has been described in isolates of *M. tuberculosis* from Quebec.<sup>59</sup> In patients with disease due to pyrazinamide-resistant isolates, the total duration of treatment must be 9 months or more.\* Ethambutol monoresistance will not change the efficacy or duration of treatment with standard regimens.

### Resistance to two or more first-line drugs (polyresistant TB) not including MDR-TB

Polyresistant TB refers to resistance to two or more first-line drugs. It is not common in Canada (see Table 2); the range of possible resistance patterns and treatment options have been described in several recent reviews.<sup>26,40,41</sup>

### Multidrug resistant (MDR) TB and Extensively Drug-resistant (XDR) TB

MDR-TB is defined as TB due to bacteria resistant to INH and rifampin with or without resistance to other first- or second-line drugs. MDR-TB represents a grave threat to TB control. In the United States in the late 1980s and early 1990s, the nosocomial spread of MDR-TB contributed to a renewed interest in TB research and antituberculosis drug development.<sup>60</sup> Two MDR-TB case series have been reported in Canada.<sup>61-63</sup> In both, a high proportion of cases were foreign-born, and a high proportion had acquired drug resistance (Table 7). HIV co-infection of MDR-TB cases was uncommon in the jurisdiction of these studies. MDR-TB, unrelated to HIV, has been reported in Tibetan refugees in Ontario.<sup>64</sup> Second-line drugs are used to treat MDR-TB, and they

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

are more expensive, less effective, need to be given for longer periods of time and have more side effects than first-line drugs (see Table 8).<sup>40,41,65-68</sup> In the United States and Hong Kong 30% and 19% of MDR-TB patients, respectively, had to discontinue drugs suspected of causing adverse events.<sup>69,70</sup>

**Table 7**  
**MDR-TB Experience in Canada**

Reference	Jurisdiction (Time Period)	No. of Cases	No. (%) Foreign-born	No. (%) Acquired resistance	No. (%) HIV Co-infected	Mean No. of First-Line Drugs to Which the Isolate Was Resistant*
61,62	AB & BC (January 1989 to June 1998)	24	20 (83.3)†	16 (67.7)	1/17 (5.9)	3.25
63	ON (January 1986 to June 1999)	40	38 (95.0)	26 (65.0)	6/46 (13.0)‡	3.20

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.

Standardized, proficiency-tested methods for second-line drug susceptibility testing in Canada are available for the injectable agents (streptomycin, amikacin, kanamycin and capreomycin), ofloxacin, ethionamide, *para*-aminosalicylic acid, and rifabutin. There is currently no international consensus on methodology for second-line drug susceptibility testing.<sup>71</sup>

#### Summary Point:

- 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.

Genetic probes that detect drug resistance to rifampin do so with > 95% accuracy and are very suggestive of MDR-TB. Less than 10% of rifampin resistance is monoresistance, and so rifampin resistance is a marker for MDR-TB in > 90% of cases.<sup>11</sup>

In Europe, and with few exceptions elsewhere, the strongest determinant of MDR-TB is previous treatment.<sup>72</sup> Presumably some combination of physician error and patient nonadherence to treatment turned fully susceptible organisms, or those with less complex resistance patterns, into MDR-TB. In this regard it is noteworthy that among patients referred to the National Jewish Medical and Research Center (Denver, Colorado) with MDR-TB there were an average of 3.9 physician treatment errors per case.<sup>73</sup> 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.<sup>74-76</sup>

**Table 8**  
**Doses of and Common Adverse Reactions to Second-Line Antituberculosis Drugs<sup>26,40,41</sup>**

Drug*	Usual Adult Daily Dosage (Pediatric Doses)	Peak Serum Concentration, ug/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	15 mg/kg (15-30 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.
Kanamycin	15 mg/kg (15-30 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.
Capreomycin	15 mg/kg (15-30 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.
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, pharmacokinetics of cycloserine	Avoid in patients with epilepsy, mental illness or alcoholism. <sup>†</sup>
Ciprofloxacin	750 mg BID (20-40 mg/kg daily divided BID) (MAX 2 gm)	3-5	Hepatic enzymes, symptoms	GI disturbance, headache, anxiety, tremulousness, prolonged Q-T interval. Avoid in pregnant women or growing children.
Ofloxacin	400 mg BID (15-20 mg/kg daily divided BID) (MAX 800 gm)	8-10		
Levofloxacin	500-1000 mg OD ( $<$ 5 yrs, 15-20 mg/kg daily divided BID) ( $\geq$ 5 yrs, 10 mg/kg OD)	8-12		
Moxifloxacin	(MAX 500 mg) 400 mg OD (10 mg/kg daily OD)	2.5-4.5		
Gatifloxacin	(MAX 400 mg) 400 mg OD (10 mg/kg daily OD)	3.5		
Rifabutin	(MAX 400 mg) 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 discoloration, conjunctiva, ichthyosis, GI intolerance (occasionally severe), rare ocular changes.

BID = twice a day, TID = three times a day, OD = once daily, TSH = thyroid-stimulating hormone, GI gastrointestinal

\* *Second-line drugs are more difficult to manage than first-line drugs. They should be administered and monitored by health care providers experienced in their use. In general, anti-TB drugs should be dosed according to body weight. Monthly monitoring of body weight is therefore especially important in children, with adjustment of doses as they gain weight.*<sup>66,67</sup>

† *Vitamin B6 is recommended to prevent the central nervous system toxicity of cycloserine; 50 mg of vitamin B6 for every 250 mg of cycloserine in adults; a dose of vitamin B6 proportionate to their weight in children.*

MDR-TB has been associated with reduced rates of cure and treatment adherence and increased rates of fatality and relapse.<sup>77,78</sup> In the original series of Goble, Iseman and Madsen,<sup>69</sup> the overall response rate was only 56%. Factors associated with adverse outcome in univariate analysis included previous use of a greater number of drugs, in vitro resistance to more drugs, regimens containing fewer previously unused drugs, and male sex.<sup>69</sup>

More recently the term “extensively drug-resistant TB” (XDR-TB) has been coined. Originally, this term was used to describe patients with TB whose isolates are resistant to INH, rifampin and at least three of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and *para*-aminosalicylic acid).<sup>79-82</sup> More recently, the term has been used to describe patients with TB whose isolates show resistance to at least INH and rifampin from among the first-line drugs plus resistance to any fluoroquinolone and to at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).<sup>83</sup> XDR-TB carries a worse prognosis than MDR-TB.<sup>79</sup> The global scale and molecular epidemiology of XDR-TB are unknown and require urgent assessment. As well, laboratory capacity needs to be greatly increased within a network of sentinel sites.

Patients with MDR-TB can be cured with early detection and prompt, appropriate administration of second-line drugs and any remaining first-line drugs. The best outcomes, in the range of 70%-90% cure, have been associated with the absence of a history of previous treatment, resistance to fewer drugs at the outset, inclusion of a fluoroquinolone and HIV seronegativity.<sup>63, 70,74-76,84-87</sup> Conversely, the worst outcomes have been associated with previous treatment of MDR-TB, fluoroquinolone resistance and low body mass index (< 18.5 kg/m<sup>2</sup>), a marker of advanced disease.<sup>87,88</sup> In the United States, HIV-infected MDR-TB cases initially had a 100% mortality, but with the availability of highly active antiretroviral therapy, greater awareness and earlier diagnosis, survival rates up to 60% have been reported.<sup>89</sup> Whereas INH and/or streptomycin resistance probably has no detrimental effect on the outcome of TB meningitis when patients are treated with first-line drugs, the combination of INH and rifampin resistance is strongly predictive of death in this population.<sup>90</sup>

### The management of MDR-TB

Many questions related to the management of MDR-TB remain unanswered.<sup>91</sup> However, most would agree that individualization of therapy based on drug susceptibility test results plus the adaptation of treatment strategy to changing clinical situations are key to successful management.<sup>92</sup> No MDR treatment regimen will be successful unless the patient actually takes the medications. For this reason, all patients with MDR-TB should be treated with DOT. Treatment must be daily for most medications (DOT for 5 days per week with self-medication on weekends is acceptable if there are no problems with weekend

adherence).<sup>\*</sup> The effectiveness of intermittent regimens for TB treatment of MDR has not been demonstrated to date.

**Summary Point:**

- ▶ The key to successful management of MDR-TB is individualization of therapy and the ability to adapt treatment strategy in response to changing clinical situations.<sup>92</sup> No MDR treatment regimen will be successful unless the patient actually takes the medications. For this reason, essentially all patients with MDR-TB should be treated with DOT.

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, cycloserine and ethionamide, can be introduced under direct observation, central lines can be inserted for administration of injectable agents, psychosocial issues can be addressed,<sup>93</sup> and the patient and family can be educated. This may have the effect of reducing complications and improving adherence over the long haul, justifying the expense of hospitalization.<sup>89</sup> Hospitalization is an especially important consideration when the patient is highly infectious (smear positive) and effective home isolation cannot be provided, when the patient is resistant to many more drugs than just INH and rifampin, and when the patient is HIV co-infected. For 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.<sup>86</sup> Ideally, patients who require hospitalization should be admitted to specialized centres that meet strict criteria (see Table 9).

**Table 9**  
**Specialized Centre 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,<sup>85</sup> 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.

<sup>\*</sup> A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

## Patients suspected of having MDR-TB

Before the results of antituberculosis drug susceptibility tests become available, MDR-TB should be suspected in specific circumstances:

- patients who have failed treatment with a standard four-drug (INH, rifampin, pyrazinamide and ethambutol) regimen,
- patients who were treated for TB in the past and were nonadherent,
- patients who were treated in the past for INH-resistant TB,
- patients who may or may not have been treated in the past but were close contacts of patients who were known to have infectious MDR-TB.

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 the taking of a meticulous history and the assembly of all available information concerning previous treatment and drug susceptibility testing. Patients may recognize drugs as having been taken in the past when they are shown pictures of the drugs or the drugs themselves. As informed a prediction as possible should be made about precisely which drugs are likely to be effective in the individual. Great care must be taken to avoid a circumstance whereby an empiric regimen inadequate in number or effectiveness of drugs allows the emergence of further drug resistance.\* Once drug susceptibility test results are available for the current episode, unnecessary drugs prescribed in an initial surfeit regimen can always be stopped. Drugs to which there is known *in vitro* resistance are not recommended. An exception to this may be low-level INH resistance. The strain W variety of MDR-TB is susceptible to higher concentrations of INH, and when INH is administered to patients with this strain survival rates are improved.<sup>94</sup> Previous use of a drug may be associated with reduced clinical response, despite apparent susceptibility *in vitro*.<sup>21,69</sup>

## Suggested treatment regimens for patients with suspected or proven MDR-TB

There is currently no consensus on the number of drugs necessary to achieve good outcomes of individualized treatment for MDR-TB. Until drug susceptibility test results are available it is generally recommended that patients be given at least four drugs that are certain or highly likely to be effective (three previously unused drugs). One of the previously unused drugs should be an injectable agent, and ideally at least two of the previously unused drugs should be bacteriocidal. If other previously unused drugs are likely to be active then one and up to three of these should be added. In patients with MDR-TB in whom there was resistance to other first-line drugs in addition to INH and rifampin, regimens employing four to six drugs have been associated with good outcomes.<sup>69,75,76</sup> In designing an empiric regimen for suspected MDR-TB, the potential toxicities (see Table 8), cross-resistances and drug interactions (see Table 10) should be taken into account.

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

**Table 10**  
**Cross-Resistance and Interactions Among Antituberculosis Drugs**

Cross-resistance	<ul style="list-style-type: none"> <li>• Resistance to amikacin induces cross-resistance to kanamycin and vice versa.<sup>95</sup></li> <li>• Resistance to streptomycin does not induce cross-resistance with amikacin-kanamycin, or capreomycin.<sup>95</sup></li> <li>• Strains resistant to streptomycin, amikacin and kanamycin are still susceptible to capreomycin.<sup>95</sup></li> <li>• Resistance to one fluoroquinolone induces class-effect cross-resistance to all other fluoroquinolones, though the fourth generation fluoroquinolones, which may have more than one gene target, may continue to demonstrate activity despite in vitro resistance to ofloxacin.<sup>26</sup></li> <li>• Most isolates resistant to rifampin (approximately 80%) are also resistant to rifabutin.<sup>95</sup></li> <li>• Cross-resistance to ethionamide may occur when there is low-level resistance to INH.<sup>26</sup></li> </ul>
Drug interactions	<ul style="list-style-type: none"> <li>• Increased risk of neurotoxicity from cycloserine has been associated with concomitant use of INH,<sup>96</sup> ethionamide<sup>96</sup> and fluoroquinolones.<sup>97</sup></li> <li>• <i>Para</i>-aminosalicylic acid and ethionamide have each been associated with hypothyroidism. The probability of hypothyroidism is increased when both agents are used together.<sup>22</sup></li> <li>• Rifabutin does not induce catabolic enzymes or alter the pharmacokinetics of other drugs to the extent that the related compound rifampin does. Nevertheless, the potential for rifabutin to affect the metabolism of other drugs needs to be considered.<sup>22</sup></li> </ul>

Once drug susceptibility test results are available a more tailored regimen can be fashioned. If the isolate is susceptible to pyrazinamide and/or ethambutol these agents should be included in the regimen.<sup>84</sup> A third or fourth generation fluoroquinolone should also be included, as should an injectable agent. The latter should be given daily or five times weekly until culture conversion (see below) and then thrice weekly for at least 3 additional months. Administration of injectable agents through a central venous line may avoid irritation and persistent pain at the injection site. If an isolate is resistant to rifampin, testing for in vitro susceptibility to rifabutin should be requested. If cross-resistance is not present, rifabutin should be added. Rifabutin is as effective as rifampin in the treatment of drug-susceptible TB,<sup>98,99</sup> but data on its use for MDR-TB are controversial and limited. If the isolate is resistant to rifabutin then most practitioners would add another second-line agent, either ethionamide, *para*-aminosalicylic acid, clofazimine or cycloserine. If one of these agents is not tolerated then another may be tried (see Table 11). At a minimum the regimen should contain at least four drugs with either certain, or almost certain, effectiveness.<sup>40</sup>

**Table 11**  
Suggested Regimens for the Treatment of MDR-TB

Pattern of Drug Resistance	Suggested Regimen	Dosage*	Duration and Timing
INH, RMP ± SM	FLQ (moxifloxacin or gatifloxacin) (levofloxacin)	400 mg OD 750 mg OD	24 months
	IA (AK, KM, CM)	15 mg/kg OD	From 0-3 months
		25 mg/kg 3×/wk	From 3-6 months
	PZA	15-25 mg/kg OD	24 months
	EMB	25 mg/kg OD	From 0-2 months or until culture conversion
		15 mg/kg OD	After 2 months, or culture conversion, to a total of 24 months
	Rifabutin (if available)	300 mg/OD	24 months
	Otherwise one of ETM, CF, PAS or CS		24 months
INH, RMP, PZA, EMB ± SM	FLQ (moxifloxacin or gatifloxacin) (levofloxacin)	400 mg OD 750 mg OD	24 months
	IA (AK, KM, CM)	15 mg/kg OD	From 0-3 months
		25 mg/kg 3×/wk	From 3-6 months
	Rifabutin (if susceptible)	300 mg OD	24 months
	ETH CF PAS CS } two to four of these drugs	500-750 mg (OD divided doses)	24 months
		100-300 mg OD	24 months
		4-8 gm (OD divided doses)	24 months
		500-750 mg (OD divided doses)	24 months

INH = isoniazid, RMP = rifampin, SM = streptomycin, FLQ = fluoroquinolone, IA = injectable agent, AK = amikacin, KM = kanamycin, CM = capreomycin, PZA = pyrazinamide, EMB = ethambutol, ETM = ethionamide, CF = clofazimine, PAS = para-aminosalicylic acid, CS = cycloserine

\* Incremental dosing, i.e. starting with a low dose and increasing to the recommended dose over a period of days to a few weeks, of ETH, CF, PAS, and CS is recommended.

If the initial isolate is resistant to all first-line antituberculosis drugs then it is recommended that the regimen include at least five second-line drugs, the strongest drugs being a third or fourth generation fluoroquinolone and an injectable agent. Other drugs of necessity would be at least three of either ethionamide, para-aminosalicylic acid, clofazimine or cycloserine. When extensive resistance to first and second-line drugs has been documented better outcomes have been reported in those who received more than five drugs.<sup>88</sup> In both of these highly resistant groups consideration should also be given to surgery (see below) or use of experimental drugs. Whenever drugs such as ethionamide, para-aminosalicylic acid, clofazimine or cycloserine are used one should begin with a small dose and increase gradually to the planned dose over a period of several days.<sup>26</sup> The patient may otherwise experience severe drug intolerance and refuse to continue to take the drugs. Pharmacokinetic studies to place dosages of second-line drugs in the therapeutic range and to minimize toxicity should be performed whenever possible.<sup>100</sup> In general, high-end dosing is preferred.<sup>92</sup>

In addition to being followed closely for adverse reactions patients should be instructed to report immediately any symptoms of drug toxicity.<sup>40</sup> The bacteriologic response to treatment should also be monitored closely. Patients with smear- and/or culture-positive respiratory tract disease should have sputum submitted at least weekly and remain in airborne isolation until three consecutive specimens are culture negative after 6 weeks of incubation in broth or 8 weeks in

solid media. The World Health Organization uses a slightly different definition of sputum conversion: 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 negative consecutive cultures.<sup>40</sup> Even after culture conversion specimens should be submitted at least monthly to document the stability of the mycobacteriologic response.

Independent predictors of a longer sputum culture conversion time include previous treatment of MDR-TB, high initial sputum culture colony count, bilateral cavitation on chest radiography and the number of drugs the initial isolate was resistant to at treatment initiation.<sup>101</sup> Treatment outcomes are worse for patients whose sputum culture has not converted within 2 months.<sup>101</sup>

Treatment outcome definitions for MDR-TB have been developed by the World Health Organization and partners: an MDR-TB patient is not considered cured until he or she has completed treatment according to the program's protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.<sup>40,102</sup> A total of 18 months of treatment, after culture conversion, is generally recommended.<sup>40</sup>

From the outset it should be made clear to patients, families and staff that meticulous adherence to the prescribed regimen is critical to cure. Patients should try to tolerate any unpleasant side effects in order to achieve cure, agree to remain under direct observation with each dose supervised, and receive in their own language clear and complete instructions before treatment begins plus consistent psychological support during treatment. Traditional roles and responsibilities within families may need to change and social support may need to be provided to secure adherence.

Pregnancy may complicate the management of MDR-TB, and experience is necessary with the issues involved. 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.<sup>40,103,104</sup>

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

### 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 pharmacological cure decreases. Unfortunately for many patients the extent of disease and/or the severity of the underlying lung function abnormality precludes 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.<sup>105,106</sup>

The selection of surgical candidates and the timing of adjunctive surgery should be performed on a case-by-case basis. 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. The optimal timing of surgical intervention is after 3 to 4 months of therapy and eradication of bacteria from the sputum. 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 prior to surgery to ensure the absence of endobronchial TB, which if present is associated with poor healing and a persistent broncho-pleural fistula.<sup>92,107</sup> Surgical outcomes are generally good.<sup>87,106</sup> Antituberculosis drug treatment should be continued for at least an additional 18 to 24 months after surgery.<sup>92,106</sup>

### Management of contacts of MDR-TB

Contacts of patients with MDR-TB should be rapidly identified and evaluated, especially when the index case has cavitory pulmonary TB or laryngeal TB.<sup>40</sup> 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 with 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 preventive therapy.

There are no randomized controlled trials assessing the effectiveness of treatment of LTBI in persons exposed to MDR-TB.<sup>108</sup> In a systematic review of the literature on people treated and not treated for LTBI following exposure to MDR-TB only two observational studies met the inclusion criteria.<sup>109</sup> A prospective cohort study found individualized tailored treatment to be effective in preventing active TB in children,<sup>110</sup> and a retrospective cohort study found INH not to be effective.<sup>111</sup>

If preventive treatment is offered to individuals likely to be infected with an MDR-TB strain most authorities recommend that that it include two orally administered drugs to which the putative infecting strain is susceptible. Depending upon the relative strength of this regimen the duration of treatment of LTBI is usually between 6 and 12 months. Adverse events such as hepatotoxicity, gastrointestinal symptoms and musculoskeletal symptoms leading to termination of drug therapy in 58% or more of patients have been reported in small case series using the drug combinations of pyrazinamide/ethambutol and pyrazinamide/levofloxacin for treatment of LTBI. The risks and benefits of such regimens should be discussed with the patient beforehand; when accepted, such regimens should be carefully monitored for adverse events.<sup>108,112,113</sup>

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 receive periodic medical and radiographic



evaluation for the 2 years immediately following 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.<sup>114</sup>

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## Introduction

Pediatric tuberculosis (TB) is defined by the World Health Organization (WHO) as TB in persons less than 15 years of age. In Canada, pediatric TB is largely a disease of Aboriginal and foreign-born children, and Canadian-born children of foreign-born parents. Overall, the incidence of pediatric TB in Canada has declined from 6.6 per 100,000 in 1970 to 1.5 per 100,000 in 2004.<sup>1,2</sup> Global statistics, largely based on sputum smear examination, underestimate the incidence of pediatric TB.<sup>3,4</sup> Strategic planning aimed at the elimination of pediatric TB in Canada must take into account the increasing incidence of TB worldwide and the increased probability of drug resistance in the foreign-born.<sup>5,6</sup>

In general, children pose three unique challenges to TB control: (1) TB diagnosis in children, especially in children under 5 years of age, can be difficult because they often have nonspecific signs and symptoms and a paucity of mycobacteria, (2) TB in children is considered a sentinel event usually indicating recent transmission and (3) children, especially infants, are at increased risk of progressing from latent TB infection (LTBI) to active and sometimes severe TB disease.<sup>7-9</sup>

## Pathogenesis and Definitions

Details of the pathogenesis of TB are outlined in Chapter 3, Transmission and Pathogenesis of Tuberculosis. Children inhale *Mycobacterium tuberculosis* bacteria that have been expelled by persons with infectious pulmonary or laryngeal TB.<sup>10,11</sup> Rarely, children may acquire *Mycobacterium bovis* through the consumption of unpasteurized milk products. 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. The upper lobes drain to ipsilateral paratracheal nodes, whereas the rest of the lung drains to perihilar and subcarinal nodes, with dominant lymph flow from left to right.<sup>12</sup> Primary infection may be associated with complications, especially in children under 5 years of age.<sup>13,14</sup> 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 bacteremia may be complicated by severe forms of disease such as disseminated TB and CNS TB. This, again, is more apt to occur in children under 5 years of age. In general, the risk of TB disease and of severe forms of TB disease after infection is inversely related to age (Table 1).<sup>13</sup> When all age groups are taken into account, most infection does not result in disease. Rather, the primary focus heals, and the bacteria continue to survive in a dormant state that is referred to as LTBI. Children and adults with LTBI and an immunocompromising condition are at increased risk of TB disease.

For practical purposes a child with LTBI is considered to have a relatively small number of bacteria dormant in the body, a positive tuberculin skin test (TST), 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.<sup>14</sup> A central problem with this definition is the absence of a confirmatory test for LTBI.

TB disease, on the other hand, has a confirmatory test: recovery of *M. tuberculosis* in culture. However, because children may be too young to produce sputum or they have paucibacillary disease, recovery of the organism from them may be difficult and confirmation is not always possible. Thus, in many children the diagnosis of TB disease is based on a clinical case definition.<sup>8,15</sup> Clinical case definitions vary somewhat but most rely on the triad of (1) a positive TST, (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.

In recent years, existing concepts about what constitutes childhood pulmonary disease versus infection have been challenged and may ultimately change.<sup>16</sup>

**Table 1**  
Average Age-Specific Risk for Disease Development  
after Untreated Primary Infection\*

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

\*Adapted from Marais et al.<sup>12</sup>

### Clinical Presentation of TB Disease

Most children with TB are asymptomatic at presentation. Typically these children are identified by public health authorities as contacts of patients with infectious TB and when evaluated are found to have abnormal chest x-rays. This is especially true of children under 5 years of age.

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. As in adults, their physical findings are often minimal relative to their chest x-

ray abnormalities.<sup>17</sup> The latter include lung infiltrates, typically but not always in the upper zone(s), that may be cavitated. Delay in diagnosis of adolescents is common and may reflect a lack of suspicion by clinicians.<sup>18</sup>

Any extrapulmonary site may be involved, but the most common site is the extrathoracic lymph nodes. Miliary/disseminated disease and CNS disease, the most life-threatening forms of TB, are more likely to occur in young children and the immunocompromised.<sup>19,20</sup> Children with LTBI and HIV infection may have an accelerated progression from infection to disease.<sup>21</sup> The TST is often negative. A search for an infectious adolescent or adult is an important step towards diagnosis.

## Diagnostic Tests

### Tuberculin skin tests

Only the Mantoux tuberculin skin test should be used. Please see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, for details about administration and interpretation of the results of the TST. In children the TST is an important part of the clinical case definition of TB, especially if it is a TST conversion or a new positive TST.

### Interferon-gamma release assays

New tests referred to as interferon-gamma release assays (IGRA) have the potential to replace the TST.<sup>22</sup> They are relatively simple tests in which peripheral blood T-lymphocytes are exposed to antigens that are specific to *M. tuberculosis*. If the individual has had previous exposure to *M. tuberculosis* his or her T-lymphocytes will respond to the antigens by releasing interferon gamma. In infants and young children whose Th1-type T-cell responses are relatively immature, it remains to be seen how these tests perform.<sup>23</sup>

## Radiology

Chest radiography is an important part of the diagnostic workup of pediatric TB. The results may be difficult to interpret, especially if there has been inadequate inspiration or overpenetration. Facilities may vary in the quality of the films they produce; a facility with a good track record for pediatric radiography is desirable. Films should be reviewed by a radiologist experienced in reading pediatric chest x-rays.<sup>24,25</sup> A recent classification system relates radiographic appearances of primary pulmonary TB to complications of (1) the primary focus, (2) the regional lymph nodes or (3) both.<sup>12</sup>

To increase the chances of discerning intrathoracic adenopathy, a common radiographic feature of primary pulmonary TB, posterior-anterior and lateral chest radiographs are recommended.<sup>26</sup> Parenchymal lesions may be anywhere in primary disease and are typically, but certainly not always, apical in reactivation disease.<sup>13</sup> Follow-up is complicated by the fact that radiological abnormalities in children may, in the short term, worsen on treatment before they improve.<sup>7</sup>

Usually there has been some response by 2 months, but even at the end of a satisfactory course of treatment there may be residual lymphadenopathy.

Computed tomography (CT) scans are generally not recommended unless there is a questionable abnormality on the plain film and further definition is required.<sup>27</sup> The radiation risk of CT in children has recently been reviewed.<sup>28</sup>

CT and magnetic resonance may be very helpful in the evaluation of suspected active CNS disease or bone and joint disease.<sup>29-31</sup> CT can also be helpful in the evaluation of disease in other sites, such as the intra or extrathoracic lymph nodes, pericardium and peritoneum.

### Gastric aspirates, induced sputum, and nucleic acid amplification tests

Mycobacterial confirmation of the diagnosis of pediatric TB should be sought when (1) an isolate from a source case is not available; (2) the source case has drug-resistant TB; (3) the child is immunocompromised; or (4) the child has extrapulmonary TB.<sup>32</sup> Although mycobacterial confirmation of other cases is desirable it is less critical. Gastric aspiration (Table 2) has traditionally been the diagnostic procedure of choice in young children who are unable to produce sputum.<sup>7-9</sup> The yield of gastric aspirates in infants is up to 75%.<sup>33</sup> The child must usually be hospitalized for gastric aspirates to be obtained, although the procedure has been performed successfully in outpatients.<sup>34</sup> A recent report suggests that sputum induction may be performed successfully in young children.<sup>35</sup> The combination of sputum induction and gastric aspirate has yielded the organism in up to 90% of cases.<sup>36</sup> In older children or adolescents, sputum induction is preferable to bronchoscopy.<sup>37</sup>

Table 2  
Gastric Aspirates: Some Tips\*†

<ul style="list-style-type: none"> <li>• 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.</li> </ul>
<ul style="list-style-type: none"> <li>• Aspirates are obtained after at least 6 hours of sleep and before the stomach has emptied.</li> </ul>
<ul style="list-style-type: none"> <li>• 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.</li> </ul>
<ul style="list-style-type: none"> <li>• 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.</li> </ul>
<ul style="list-style-type: none"> <li>• The fluid has to be adjusted to neutral pH within 4 hours of collection because acid is detrimental to mycobacteria. If this adjustment cannot be done within 4 hours, it should be placed in a container with 100 mg of sodium carbonate.</li> </ul>

\*With thanks to Ann Loeffler, Oregon Health Sciences University

†See also <http://www.nationaltbcenter.edu/>

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.<sup>27,38,39</sup> NAA tests performed on cerebrospinal fluid are very specific (helpful in confirming the diagnosis) but insensitive (not very helpful in ruling out the diagnosis) of TB meningitis.<sup>40</sup>

## Treatment of TB 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 always include a pediatric TB specialist as well as nursing and support staff from the public health department. Treatment is aimed at reducing morbidity and mortality, interrupting transmission, preventing drug resistance and providing a lasting cure. The interruption of transmission and the prevention of drug resistance is less of a concern in young children who have paucibacillary disease.

The drugs used in the treatment of pediatric TB, their doses and side effects are summarized in Table 3. A common question is whether the first-line drug ethambutol (EMB) can be safely administered to children. EMB can cause retrobulbar neuritis, a side effect that is dose-dependent and renal-function-dependent. It manifests as decreased visual acuity or decreased red-green colour discrimination and is usually reversible upon discontinuation of the drug. Monitoring of vision is recommended monthly in older children and adults.<sup>39,41</sup> Past guidelines have advised against the use of EMB or have advised caution when using EMB in children who cannot verbalize symptoms of optic neuritis.

**Table 3**  
Drugs Used for Treatment of Tuberculosis in Children\*

Medication	Daily Dose**	Intermittent Twice Weekly Dose**†	Available Dosage Forms	Principal Adverse Reactions
Isoniazid	10-15 mg/kg‡ (max. 300 mg)	20-30 mg/kg (max. 900 mg)	10 mg/mL suspension 100 mg tablet 300 mg tablet	<ul style="list-style-type: none"> <li>• Mild hepatic enzyme elevation</li> <li>• Hepatitis</li> <li>• Gastritis</li> <li>• Peripheral neuropathy (see pyridoxine below)</li> <li>• Hypersensitivity</li> </ul>
Rifampin	10-20 mg/kg (max. 600 mg)	10-20 mg/kg (max. 600 mg)	10 mg/mL suspension (reconstituted shelf life = 1 month) 150 mg capsule 300 mg capsule	<ul style="list-style-type: none"> <li>• Orange discoloration of secretions</li> <li>• Vomiting</li> <li>• Hepatitis</li> <li>• Flu-like illness</li> </ul>
Pyrazinamide	15-30 mg/kg (max. 2 g)	50 mg/kg (max. 4 g)	500 mg scored tablet	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Hyperuricemia</li> <li>• Arthralgia</li> </ul>
Ethambutol	15-20 mg/kg§ (max. 1 g)	50 mg/kg (max. 2.5 g)	100 mg tablet 400 mg tablet	<ul style="list-style-type: none"> <li>• Optic neuritis with decreased visual acuity and decreased red-green colour discrimination</li> <li>• Gastrointestinal disturbance</li> </ul>

Medication	Daily Dose**	Intermittent Twice Weekly Dose**†	Available Dosage Forms	Principal Adverse Reactions
Pyridoxine	1 mg/kg p.o. (max. 25 mg)		25 and 50 mg tablets	<ul style="list-style-type: none"> <li>• Few</li> <li>• Used to prevent INH neuropathy for children on meat- and milk-deficient diets, those with nutritional deficiencies, children with symptomatic HIV infection and adolescents who are pregnant or breastfeeding</li> </ul>

\* Adapted from Blumberg et al.<sup>41</sup>

\*\*Dose per weight is based on ideal body weight.

† Intermittent doses should be prescribed only when directly observed therapy is available.

‡ Hepatotoxicity is greater when INH doses are more than 10–15 mg/kg daily.

§ Ethambutol at 15 mg/kg daily presents a very low risk of optic neuritis but may sometimes result in subtherapeutic serum drug levels in young children. When ethambutol is a very important part of therapy, 20 mg/kg can be considered after discussion of risks and benefits and with suitable monitoring (see text). At this dose, ethambutol is bacteriostatic, but it will help prevent the development of resistance. High-dose ethambutol (25 mg/kg daily) is bactericidal and sometimes used to treat drug-resistant TB but carries a higher risk of optic neuritis. Expert consultation is recommended in this situation.

Two reviews have now been published, neither of which reported visual toxicity in young children.<sup>42,43</sup> In children in whom toxicity cannot be monitored and for whom better or safer alternative drugs are not available, use of EMB in a dose of 15 mg/kg per day is acceptable and carries a very low risk of optic neuritis. A recent pharmacokinetic study suggests that drug levels may sometimes be subtherapeutic at this dose because of slow or incomplete absorption of EMB in young children.<sup>44</sup> For situations in which EMB is a cornerstone of therapy, for instance, in treating isoniazid (INH)- or rifampin-resistant strains, 20 mg/kg may be considered after suitable discussion of risks and benefits. Baseline serum creatinine levels should be measured to rule out occult renal impairment before or at the time of initiation of therapy. Many young children are able to be tested using pseudoisochromatic colour vision plates; this should be done with acuity testing at each monthly visit.

It is more difficult to isolate *M. tuberculosis* from a child with pulmonary TB than from an adult. Therefore, to guide the choice of drugs for the child it is frequently necessary to rely on the results of culture and susceptibility tests of specimens from the person presumed to be the source of the child's infection. For children in whom drug resistance is suspected or for whom no source-case isolate is available, attempts to isolate organisms by means of three early morning gastric aspirations, sputum induction, bronchial lavage, tissue biopsy or other specimen as appropriate should be considered.<sup>25</sup> Treatment should begin promptly for every child who is judged, by laboratory or clinical case definition, to have active TB.<sup>41</sup>

To quote the treatment guidelines of the American Thoracic Society/U.S. Centers for Disease Control and Prevention/Infectious Diseases Society of America:<sup>41</sup> "Several controlled and observational trials of 6-month therapy in children with pulmonary TB caused by organisms known or presumed to be susceptible to the first line drugs have been published.<sup>45–53</sup> Six months of therapy with isoniazid (INH) and rifampin has been shown to be effective for hilar adenopathy and pulmonary TB caused by drug-susceptible organisms.<sup>49,50</sup> However, most studies used 6 months daily treatment with INH and rifampin, supplemented during



the first 2 weeks to 2 months with pyrazinamide. In children with proven or presumed drug-susceptible disease this 3 drug combination has a success rate of greater than 95% and a rate of adverse events of less than 2%. Two studies used twice or three times weekly therapy from the beginning with good results.<sup>45,51</sup> Please refer to Chapter 6, Treatment of Tuberculosis Disease and Infection, Tables 3-5, for the recommended treatment of pediatric TB.

The American Association of Pediatrics recommends use of a four-drug empiric TB regimen for children who live in areas of more than 4% primary INH resistance or who are exposed to adults who come from an area with more than 4% resistance.<sup>32</sup> This applies to almost all foreign-born individuals suspected of having TB disease in Canada. (For TB drug susceptibility data in Canada, refer to *Tuberculosis: Drug Resistance in Canada* at <<http://www.publichealth.gc.ca/tuberculosis>>) The American Thoracic Society recommends the use of a four-drug empiric regimen for children with (1) adult type pulmonary disease, (2) disseminated or CNS disease, (3) a history of travel to an area of high prevalence of drug resistance or (4) a history of exposure to an individual at risk of resistance (known drug-resistant TB, history of previous TB treatment, residence in an area of high prevalence of drug resistance or poor response to therapy). Other children, it advises, can be treated with an initial three-drug TB regimen: in Canada this will be a select minority of patients.<sup>41</sup>

In general, antituberculosis drug doses should be adjusted in accordance with the weight (see Table 3) of the child. Monthly monitoring of body weight is therefore especially important in pediatric cases with adjustment of doses as children gain weight.<sup>54</sup>

For the treatment of children proven to have or suspected of having more complex patterns of resistance, see Chapter 7, Drug-resistant Tuberculosis; *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, produced by the Francis J. Curry National Tuberculosis Center and California Department of Health Services;<sup>55</sup> and the WHO guidelines for the programmatic management of drug-resistant tuberculosis.<sup>56</sup> It is strongly recommended that the advice of a physician experienced in the management of drug-resistant TB be sought in such cases.

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 reduced neurologic complications, neurologic sequelae and cognitive dysfunction. Corticosteroids may be considered for children with pleural or pericardial effusions (to hasten reabsorption of fluid), severe miliary disease (to mitigate alveolocapillary block) and endobronchial disease (to relieve obstruction and atelectasis). Corticosteroids should always be used in conjunction with effective antituberculosis therapy and should be tapered slowly over weeks to avoid a rebound reaction. Generally 1-2 mg/kg daily of prednisone (maximum 60 mg/day) or its equivalent tapered over 6 to 8 weeks is used.

The most important element of the treatment of TB is the actual ingestion of the drugs. Children are difficult to dose with TB drugs; they may not tolerate the pill burden, and the existing formulations are not particularly child friendly.<sup>7</sup>

Only INH comes as a commercially available liquid product. This product causes diarrhea and abdominal pain in more than half of children owing to the osmotic load of sorbitol in which it is suspended. INH crushed into sugary liquids is unstable and should be avoided. INH crushed into a semisoft vehicle such as pudding, baby food or yogurt is acceptable and often well tolerated. Rifampin 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. At the outset of treatment parents should be warned that there may be a several-week period of trial and error.<sup>7</sup>

Adherence to therapy is as much of an issue in children as it is in adults (see Table 4). Many factors contribute to poor adherence, not the least of which are the great difficulty in ensuring that the child ingests the medication and the long duration of treatment. To maximize the benefits of therapy, all children should be treated by directly observed therapy (DOT).<sup>39</sup> Parents should not be relied on to supervise DOT. In most children, response to treatment is assessed clinically and radiographically. In children, weight loss or, more commonly, failure to gain weight adequately is of particular concern and often one of the first (or only) signs of treatment failure.<sup>56</sup>

Extrapulmonary TB in children is 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. The optimal treatment of pulmonary TB in children and adolescents with HIV infection is unknown. The American Academy of Pediatrics recommends that initial therapy should always include at least three drugs (INH, rifampin and pyrazinamide for the first 2 months) and that the total duration of therapy should be at least 9 months.<sup>32</sup>

**Table 4**  
**Improving Adherence and Completion Rates for TB Therapy<sup>7</sup>**

• Use tablets crushed into semisoft vehicles 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 education regarding reasons for therapy and symptoms of TB and toxicity.
• Develop a small, dedicated and enthusiastic team of staff providers, nurses and interpreters.
• Develop systems to encourage adherence, such as having the child put a sticker on the calendar for each dose taken.
• Have 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.

### Management of Contacts

The most efficient way to prevent pediatric TB is to evaluate and treat those children exposed to an infectious adult source case. Missed opportunities to prevent cases of pediatric TB include delayed reporting of a source case to the local public health/TB control authority, failure to identify a child during

the contact investigation, failure to treat the source case with DOT despite indications of nonadherence, failure to document sterilization of cultures, failure to start INH preventive therapy or LTBI treatment in the child and failure to ensure that the child takes the treatment.<sup>57-60</sup>

All exposed children should be identified and ranked according to their risk of infection and progression to TB disease.<sup>61</sup> All exposed children should have a symptom inquiry and TST. Those less than 5 years of age 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 encouraged to complete primary or “window” 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 infected by a drug-susceptible isolate, INH either daily or twice weekly, directly observed, is recommended. The INH may be discontinued if, after a period of 8 weeks, the repeat TST is negative, and the child remains asymptomatic and is immunocompetent. If the child is an infant who is too young to mount the delayed-type hypersensitivity reaction required to document a positive TST, treatment should be prolonged past the 8 week period and until the child is at least 6 months of age.<sup>62</sup> If the repeat TST is positive the child should complete a 9-month course of INH.

If the initial TST is positive ( $\geq 5$  mm) and there is no clinical or radiographic evidence of disease, then a full course of preventive therapy is recommended. Loeffler has offered many helpful suggestions to improve adherence and completion rates (Table 3).<sup>7</sup> DOT should be strongly considered as the means of treating children who are newly infected.

When a child with new active TB is the index case it is very important that reverse contact tracing be undertaken, i.e. that a vigorous search 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 or day care workers. Molecular characterization of *M. tuberculosis* isolates can lead to identification of previously unrecognized source cases.<sup>63</sup> If the child is hospitalized it is important to screen adolescent or adult visitors for evidence of active TB.<sup>64</sup>

### Targeted Testing and Treatment of 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.<sup>65</sup> 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 Tuberculosis Infection and Disease), (4) children traveling or residing for 3 months or longer in an area with a high incidence of TB, especially if the visit is anticipated to involve contact with the local population (see Chapter 13, Surveillance and Screening in Tuberculosis Control) and (5) children who arrived in Canada from countries with a high TB incidence within the previous

2 years. 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.<sup>65-69</sup> In Canada, a school-based TB screening program and associated investigation targeting recently immigrated children has been evaluated and found to be effective.<sup>70</sup>

In general, LTBI should be treated with INH 10 mg/kg daily (maximum of 300 mg/day) or a 20-30 mg/kg dose twice weekly DOT (maximum of 900 mg/dose) 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 and are not taking other hepatotoxic drugs. Families should be educated to watch for the symptoms of hepatotoxicity and to stop the therapy and return to the clinic if the symptoms are consistent with drug toxicity. Lack of association with other viral symptoms and lack of improvement after a few days should suggest the possibility of hepatotoxicity rather than an intercurrent illness. Jaundice is often preceded by a period of days or weeks of malaise and nausea. Children should be seen in the clinic monthly, and questions should be asked about symptoms of toxicity as well as symptoms of active TB, adherence to therapy and results of skin testing of family members and other contacts.

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 the drug of choice is rifampin daily at 10-20 mg/kg daily (maximum of 600 mg/day) for 4 months.<sup>57</sup> US guidelines recommend the use of rifampin daily for 6 months,<sup>65</sup> but this is based on limited experience in adolescents and young adults aged 15 to 23 years.<sup>71</sup> Children taking anti-epileptic drugs and either INH or rifampin should be monitored closely because both of these drugs can affect the metabolism and serum levels of anti-epileptics.<sup>41</sup>

Children judged to be infected with a multidrug-resistant strain of *M. tuberculosis* should be referred to a TB specialist (refer also to Chapter 7, Drug-resistant Tuberculosis).

## 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.
- Administration of first-line TB drugs is not an indication for termination of pregnancy. If second-line drugs are used, advice from a TB expert should be sought.
- Women receiving first-line agents, including INH and rifampin, may continue to breastfeed. The concentrations of drugs in breast milk are insufficient to protect the fetus. Supplementary pyridoxine (vitamin B<sub>6</sub>) should be given to the nursing mother receiving INH and to her child.

Infants born to mothers with suspected TB need to be managed according to the categorization of the maternal infection:

**Mother with LTBI and no abnormality on chest x-ray**

- No special investigation or therapy for the newborn is required. However, household members should be screened for active disease.
- Mother and infant do not need to be separated.
- Mother may be a candidate for preventive therapy if she was recently infected or is HIV coinfecting.
- Non-HIV infected mothers may breastfeed when receiving first-line drugs.

**Mother with a chest x-ray abnormality consistent with active TB**

- Separate the infant and mother until it is established that the mother does not have infectious pulmonary TB; manage as outlined below.

**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, strongly encourage her to take preventive treatment. Induced sputum may be helpful in evaluating the mother.
- Follow the infant with a repeat TST at 3 and 6 months of age. If there is uncertainty about the status of the mother then the child should be provided with preventive treatment.

**Mother or household contact with clinical or radiographic evidence of infectious TB at or close to the time of delivery**

- If the mother has TB, submit the placenta for histology and TB culture. Attempt to conduct HIV serologic testing of the mother if not already done.
- Separate mother and child until mother is appropriately treated and no longer infectious.
- Evaluate the infant for congenital TB: chest radiology, gastric aspirates, abdominal ultrasound, lumbar puncture, TST.
- If congenital TB is present, initiate treatment promptly with the appropriate regimen.
- If congenital TB is excluded give treatment for LTBI until the infant is at least 3 months of age then repeat the TST. If the skin test is positive reassess the child for active TB. If disease is absent give a full course of treatment for LTBI based on the sensitivities of the index strain.
- If the TST result is negative at 3 months in a child receiving INH, continue INH and repeat the TST at 6 months. If TST is now positive, give an additional 3 months of INH; if negative, discontinue INH.

## Conclusions

TB continues to be an important disease in Canadian children. Although there is a pressing need for, and some promise of, a better test for LTBI, 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. Treatment of pediatric TB requires a team approach 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.<sup>65</sup>

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# Tuberculosis and Human Immunodeficiency Virus

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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. Globally, TB is the most common cause of death in HIV-infected individuals. In Canada, coinfection is likely to become more important, particularly in immigrants and refugees from TB- and HIV-endemic countries and in Aboriginal peoples.

## 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 *Mycobacterium tuberculosis*. The immune deficiency induced by HIV infection decreases the immunologic containment, most importantly of latent TB infection, but also of new infection or reinfection with *M. tuberculosis*. It also alters the delayed-type hypersensitivity (DTH) reaction involved in the tuberculin skin test (TST) and the clinical and radiologic features of TB, which are determined by the host response. Although TB can occur at any stage in the course of HIV infection,<sup>1</sup> the risk increases with advancing immunosuppression and decreases in patients receiving effective antiretroviral therapy (ART).<sup>2,3</sup> *M. tuberculosis* increases HIV replication *in vitro*, and active TB may enhance the progression of HIV disease.

## Diagnosis of HIV Infection in TB Patients

HIV prevalence is commonly much higher among patients with active TB than in the general population. Of 1,613 cases of TB diagnosed in Canada in 2004, HIV status was reported for only 23%. Of the 374 cases for which HIV status was reported, 38 (10%) were positive. Such data are inadequate to measure the incidence of HIV-seropositive TB nationally and to define subgroups of TB patients at higher risk of HIV infection. Thus, TB patients constitute a high-priority group for epidemiologic surveillance for HIV.

The advantages to the patient of identifying previously unrecognized HIV infection are substantial, including the opportunity for individual patients to benefit from ART and prevention of opportunistic infections, as well as opportunities for preventing future HIV transmission. HIV testing should be done at least once during the period between the date of TB diagnosis and the completion of treatment unless the HIV infection has already been diagnosed. Please see Appendix G, Recommendations for the Screening and Prevention of Tuberculosis in Patients with HIV and the Screening for HIV in Tuberculosis Patients and Their Contacts.

**Summary Points:**

- ▶ All patients with newly diagnosed TB should be strongly encouraged to undergo informed HIV serologic testing. **LEVEL II**
- ▶ HIV testing of contacts of patients with infectious TB should be considered if the contacts are at risk of HIV or the index case of TB is HIV co-infected.
- ▶ Additional information resources concerning HIV should be made available to patients for whom HIV testing is recommended, as well as to other patients seen through TB programs.

**Diagnosis of TB Infection in HIV-infected Individuals**

Of the known risk factors for the reactivation of latent TB infection, HIV is the most powerful. Among the HIV and TB coinfecting, the annual risk that active TB will develop may be as high as 10 per 100 person years.<sup>4,5</sup> Thus, identifying latent TB infection (LTBI) and preventing progression to active disease in those infected is a high priority in the care of HIV-infected individuals. Similarly, treatment of LTBI in HIV-infected persons should be a priority for TB control programs. Please see Appendix G, Recommendations for the Screening and Prevention of Tuberculosis in Patients with HIV and the Screening for HIV in Tuberculosis Patients and Their Contacts.

Although its sensitivity decreases in parallel with the CD4 cell count, the TST remains the standard method of diagnosing LTBI. New interferon- $\gamma$  release assays based on *in vitro* stimulation of the patient's lymphocytes with *M. tuberculosis*-specific antigens appear to be more specific than the TST.<sup>6</sup> However, there is little information on the ability of these tests to predict the development of active TB and limited experience with their use in immunocompromised patients.<sup>7</sup>

HIV-infected patients appear to be more likely to have active TB in the absence of typical clinical or radiologic features, such as cough or chest x-ray abnormalities;<sup>8</sup> hence the need, before initiating treatment of LTBI, for particularly rigorous measures to exclude active disease, including sputum culture even in the absence of chest x-ray abnormalities. In patients with absolute CD4 counts  $< 50-100 \times 10^6/L$  a blood culture for mycobacteria may be considered to exclude *M. avium* complex (MAC) infection and could identify occasional patients with disseminated TB whose symptoms are nonspecific.

**Summary Points:**

- ▶ Every newly identified patient with HIV infection should be assessed with regard to history of active TB and known or likely exposure to TB, including close contact with an infectious case or origin in a community with high TB prevalence, and results of any previous TST. A physical examination and chest radiography should be performed to investigate features of past or present TB. **LEVEL II**
- ▶ Except for those with a past history of active TB or a well-documented previous positive TST, 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. **LEVEL II**
- ▶ TST induration of  $\geq 5$  mm should be considered indicative of TB infection in HIV-infected individuals. **LEVEL III**
- ▶ Routine anergy testing is not recommended. **LEVEL I**
- ▶ A TST should be repeated annually in patients at increased risk of ongoing TB exposure. **LEVEL III**
- ▶ In patients with negative TST, repeat TST may be considered after institution of ART and immune reconstitution indicated by an increase in the CD4 cell count. **LEVEL III**
- ▶ HIV-infected patients found to be TST positive or who have a well-documented positive TST in the past should be evaluated for the presence of active TB by clinical assessment, chest radiography and other investigations suggested by the clinical findings. Even when the chest x-ray is normal, sputum should be obtained for TB smear and culture. **LEVEL II**
- ▶ If an interferon- $\gamma$  release assay is used, interpretation should take into consideration the results of concomitant standard TST testing until further information is available. **LEVEL III**

**Treatment of LTBI**

Treatment of LTBI in TST-positive, HIV-infected persons significantly reduced the risk of developing active TB in five of six reported studies, but a reduction in mortality has not been clearly shown.<sup>9-16</sup> Treatment of suspected LTBI in tuberculin-negative or anergic HIV-infected individuals has not been consistently shown to be beneficial.<sup>11,17</sup> The results of two studies suggest that protection may wane in the years following treatment of LTBI, possibly as a result of reinfection in communities with high rates of transmission.<sup>10,13</sup>

**Summary Points:**

- ▶ Except when there is a well-documented history of completed treatment of LTBI or active TB, treatment of LTBI should be strongly recommended for every HIV-infected patient with a TST reaction  $\geq 5$  mm, regardless of age or BCG vaccination status, after exclusion of active TB. **LEVEL I**
- ▶ HIV-infected persons felt to have had recent close contact with an infectious TB patient should receive treatment for presumed LTBI regardless of the TST result. **LEVEL III**
- ▶ On an individual basis, preferably with input from an expert in TB, consideration may be given to recommending preventive therapy for TST-negative HIV-infected individuals likely to be at increased risk of LTBI (e.g. high epidemiologic risk or chest radiographic features suggestive of past TB exposure) who are immunosuppressed to a degree likely to result in a false-negative TST. **LEVEL III**

Completion rates for a full course of preventive therapy in Canadian programs vary widely.<sup>18</sup> Many HIV-infected candidates for preventive therapy are likely to have one or more characteristics associated with poor adherence, such as substance abuse or unstable housing. Directly observed preventive therapy, for example in a methadone clinic or by an outreach worker, has been found to be cost-effective or cost-saving under a variety of conditions.<sup>19,20</sup>

**Summary Points:**

- ▶ When treatment of LTBI is indicated in an HIV-infected individual, consideration should be given to providing it in a directly observed fashion. **LEVEL II**
- ▶ For patients with predictors of poor adherence, such as unstable housing or active substance abuse, or those who have demonstrated poor adherence, directly observed preventive therapy should be provided whenever feasible. **LEVEL II**
- ▶ Twice weekly regimens should always be given under direct supervision. **LEVEL II**
- ▶ Attention should be given to practical measures such as clinic hours, staff attitudes, inducements and close follow-up, which may enhance adherence. **LEVEL II**

While twice weekly isoniazid (INH) has not been compared with daily chemoprophylaxis, it has been used in two studies<sup>10,13</sup> and, on the basis of its efficacy in treatment, is generally thought to be comparable. Six months has proven, but lower, preventive efficacy than 9 or 12 months.



Two studies of rifampin and pyrazinamide, one using daily and the other twice weekly dosing, for 2 months in HIV-infected individuals demonstrated efficacy comparable to 6 months of INH.<sup>10,12</sup> Subsequent experience with this regimen has revealed a high rate of serious hepatotoxicity.<sup>21-25</sup> This effect may be less common in the HIV-infected,<sup>26</sup> but experience to date is insufficient to recommend its use in any population.

A 4-month regimen with rifampin alone has not been studied in HIV-infected individuals but can be considered as an option if the patient is not receiving an incompatible antiretroviral regimen (see following Summary Points). On the basis of equivalence in three treatment studies,<sup>27-29</sup> it is thought that rifabutin is likely to be as effective as rifampin in preventive regimens.

### *Summary Points:*

- ▶ In HIV-infected individuals for whom treatment of LTBI is indicated, the regimens are the same as those recommended for HIV-uninfected patients:
  - Daily self-administered INH for 9 months. LEVEL I
  - or
  - Twice weekly directly observed INH for 9 months. LEVEL II (see Chapter 6, Treatment of Tuberculosis Disease and Infection, for dosages)
- ▶ Daily rifampin (or rifabutin) for 4 months is an alternative regimen for patients unable to tolerate INH, for patients infected with an INH-resistant strain or for patients in 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. LEVEL III.

The combination of rifampin and pyrazinamide should generally not be offered, regardless of HIV serostatus LEVEL II.

- ▶ HIV-infected persons 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. LEVEL III
- ▶ 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, *not* delayed until after the delivery. LEVEL III

## Diagnosis of Active TB

The clinical presentation of TB may be altered in the presence of HIV infection; extrapulmonary TB is more common. Lymph nodes are 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 or absent in approximate proportion to the individual's degree of immunosuppression.<sup>30</sup> Upper lobe predominance and cavitation are less common, and hilar adenopathy, pleural effusions, disseminated disease and a normal chest x-ray are more common in the HIV-infected.

Laboratory diagnosis may also be affected by the presence of HIV infection. Some studies have found the rate of sputum smear positivity to be lower in those infected with HIV.<sup>31</sup> Characteristic granulomas may be absent or altered on histologic examination of tissue.<sup>32</sup> *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.<sup>33</sup> Acid-fast bacilli staining of lymph node aspirates is relatively sensitive in HIV-coinfected patients with TB lymphadenitis.<sup>34</sup> Infection with nontuberculous mycobacteria is relatively common in advanced HIV infection; polymerase chain reaction techniques can provide a rapid means of confirming or excluding *M. tuberculosis* in a patient with acid-fast bacilli detected on sputum smear examination or in culture, with important clinical and public health implications.

### Summary Points:

- ▶ 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 recent or remote TB exposure, in the investigation of any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB. **LEVEL II**
- ▶ An HIV-infected patient in whom a respiratory tract specimen is found to contain acid-fast bacilli should be managed as a suspected TB case until such time as the organism has been shown *not* to be *M. tuberculosis*.

## Treatment of TB

Considerable experience indicates that TB cure rates are similar in HIV-infected and uninfected patients if the treatment regimen is appropriate and includes a rifamycin, if the organism is susceptible to first-line drugs and if adherence to treatment is certain.<sup>35-42</sup> However, two recent observational studies found lower rates of treatment failure<sup>43</sup> and recurrence<sup>44</sup> in patients treated for 9 months than in those receiving a shorter duration of treatment.

Overall, recurrence has been somewhat more common among the HIV-infected than non-infected in some studies. When molecular techniques have been used to distinguish between relapse and reinfection, 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 in communities with high levels of ongoing transmission.<sup>45</sup> Two studies 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 have been due to prevention of reinfection in a high-prevalence community.<sup>46,47</sup>

Mortality is higher among HIV-infected TB patients, largely on account of other HIV-related conditions rather than because of TB.<sup>38</sup> Combination ART seems to have reduced the mortality rate of TB patients with advanced HIV.

Several studies have suggested that HIV-infected patients are more likely to have inadequate serum levels of antituberculosis agents as a result of decreased absorption,<sup>48-51</sup> but other studies have failed to find a difference between HIV-infected and uninfected patients.<sup>52,53</sup> These inconsistencies may relate to differences in drug absorption between African and North American patients with TB. In the latest study from North America, HIV-infected patients with TB who were receiving rifampin and ethambutol commonly had low maximum concentrations of both drugs.<sup>54</sup>

The benefits of adjuvant corticosteroids on immune activation and CD4 positive T cell counts have not been found to outweigh the risks of adverse events in HIV-infected patients with TB and preserved immune function.<sup>55</sup>

### ART in TB Patients

Combination ART has resulted in dramatic improvements in the outcome of HIV infection, reflected in the 80% decrease in HIV-related mortality in some Canadian populations.<sup>56</sup> In the pre-ART era, HIV-infected individuals with a CD4 cell count of  $< 50 \text{ cells} \times 10^6/\text{L}$  showed an all-cause mortality of 7 deaths per 100 patient months.<sup>57</sup> Clinical and immunologic benefits from ART may be apparent very early after treatment initiation.<sup>58</sup>

### Drug Interactions

Antiretroviral drugs, particularly those in the protease inhibitor class but also the non-nucleoside reverse transcriptase inhibitor (NNRTI) group, demonstrate major and sometimes bidirectional interactions with rifamycin antituberculosis agents, mainly through the hepatic cytochrome P450 enzyme system. There is considerable variation among drugs within a class in terms of potential or observed interactions. Updated information on this rapidly evolving area can be found at [http://www.cdc.gov/tb/TB\\_HIV\\_Drugs/default.htm](http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm).<sup>59</sup>

Clinically important interactions with antituberculosis agents have not been found with any of the nucleoside or nucleotide analogues (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine or tenofovir).

Rifamycins, which are critical to the success of short-course TB treatment, are the only antituberculosis agents found to have clinically significant interactions with antiretroviral drugs. Lesser degrees of interaction are seen with rifabutin than with rifampin, which in turn interacts less than rifampin.<sup>60</sup>

Rifampin can be used concomitantly with the NNRTI efavirenz, although efavirenz levels are variably reduced.<sup>58</sup> A standard efavirenz dose of 600 mg daily appeared to be adequate in Thai patients with relatively low body weight.<sup>61</sup> The U.S. Centers for Disease Control and Prevention (CDC) advocates increasing the efavirenz dose to 800 mg/day. Rifampin can also be used with full-dose ritonavir as the sole protease inhibitor (but this regimen is very poorly tolerated and now rarely, if ever, used).<sup>62</sup> There is limited information on the interaction of rifampin with “boosted” protease inhibitors such as lopinavir/ritonavir.<sup>63</sup> Use of rifampin with ritonavir-boosted saquinavir was associated with unacceptable hepatotoxicity in one study.<sup>64</sup>

A regimen comprising three nucleoside/nucleotide analogues would not be expected to be associated with significant interactions with rifampin. However, the combination of zidovudine, lamivudine and abacavir, the only well-studied example of a triple nucleoside regimen, has been found inferior to standard ART regimens.<sup>65</sup> Therapy with the combination of four nucleoside/nucleotide reverse transcriptase inhibitors, zidovudine, lamivudine, abacavir (Trizivir) and tenofovir, appears comparable in early studies<sup>66</sup> to standard ART regimens and is not expected to be associated with significant drug interactions.

Kinetic data<sup>67</sup> and experience with small numbers of patients suggest that coadministration of rifampin and the NNRTI nevirapine may be acceptable.<sup>68</sup>

It has been reported that rifabutin can be substituted for rifampin in TB treatment.<sup>27-29</sup> Rifabutin levels are increased to varying degrees by concomitant therapy with different protease inhibitors, ocular toxicity being the most frequently observed adverse effect. Rifabutin, *with appropriate dose reduction*, can be used together with most protease inhibitors but should not be used with saquinavir because of reduced saquinavir levels. The rifabutin dose must be increased when used with efavirenz.<sup>69</sup> \*

Non-rifamycin-containing regimens such as INH, pyrazinamide and streptomycin given for 9 months or more had high initial cure rates and acceptable relapse rates in non-HIV-infected persons.<sup>70</sup> The efficacy of this regimen in HIV-infected individuals has not been studied, and a non-rifamycin-containing regimen was found to have higher relapse rates in HIV-infected than uninfected Africans.<sup>71</sup>

### Paradoxical or Immune Reconstitution Reactions

There is increasing recognition that paradoxical reactions (immune reconstitution [IR] disease or immune reconstitution inflammatory syndrome) may occur during TB treatment because of IR following initiation of effective ART.<sup>72</sup> These reactions may present as fever, and clinical and radiologic deterioration

\* A recommendation of the Canadian thoracic Society's Tuberculosis Committee

at involved sites, e.g. enlarging lymph nodes, worsening pulmonary infiltrates or exacerbation of inflammatory changes at other sites, and can be severe.<sup>73-75</sup> This phenomenon has been described in up to 36% of patients receiving both therapies.<sup>76</sup> Almost all affected patients have low initial CD4 cell counts.<sup>75-77</sup> Onset has been described between 2 and 40 days after ART initiation.<sup>75,76</sup> Paradoxical reactions can occur even when ART is initiated more than 2 months after starting TB treatment,<sup>78</sup> 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. 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 are usually effective. Most patients have been treated successfully without interruption of ART.

### Timing of Initiation of ART

In the HIV-infected patient with active TB, establishment of effective TB treatment is almost always the most urgent priority. The high likelihood of adverse effects, attributable to either anti-TB or antiretroviral drugs, could compromise the initiation of TB therapy if both treatments are started simultaneously. On the other hand, undue delay in the institution of effective ART could result in a significant risk of HIV-related death among patients with advanced disease. The optimal timing for the introduction of ART in patients receiving TB treatment is unknown.

On the basis of a recent observational study of 188 patients, the authors recommended initiating ART 2 weeks after starting anti-TB therapy in patients with CD4 cell counts of  $< 100 \times 10^6/L$ , 2 months after TB therapy if the CD4 cell count was  $> 100 \times 10^6/L$ .<sup>79</sup> A decision analysis concluded that outcome was improved by the early introduction of ART under a wide range of assumptions and initial CD4 cell counts.<sup>80</sup> CDC recommends that the interval be individualized and suggests 4 to 8 weeks as the usual range.<sup>81</sup>

Because of the possibility of reduced drug absorption, the potential for complex and incompletely understood drug interactions, and the serious consequences (treatment failure, drug resistance) of inadequate treatment of either infection, therapeutic drug monitoring of either antituberculosis<sup>82</sup> or antiretroviral drug levels might contribute to the management of selected patients, particularly when the response to therapy is poorer than expected or the therapies selected in an individual patient have been less well studied.<sup>83</sup>

### Rifampin Mono-resistance

The development of acquired rifampin mono-resistance has been observed during TB treatment in HIV-infected patients in a study of once weekly INH and rifapentine (not available in Canada) and in twice weekly rifampin-based regimens. When long-acting rifamycins (rifabutin and rifapentine) have been used the risk of resistance has been attributed to low serum INH levels.<sup>84,85</sup> For both rifampin and rifabutin regimens the risk appears to be greatest in patients with low CD4 counts and in those who receive twice weekly intermittent therapy during the initial phase of treatment. The CDC recommends that HIV-

infected patients with CD4 counts  $< 100 \times 10^6/L$  receiving rifamycin-containing therapy receive a daily or at least thrice weekly regimen.<sup>85,86</sup> Rifapentine is no longer recommended for HIV-positive TB patients in the United States.

HIV-infected individuals are at increased risk of neuropathy due to HIV or ART and may be more susceptible to INH-associated neuropathy.

#### *Summary Points:*

- ▶ 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 and should follow the most recent available information regarding drug interactions. Please see [http://www.cdc.gov/tb/TB\\_HIV\\_Drugs/default.htm](http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm).<sup>59</sup> LEVEL II
- ▶ Considerations related to ART should not delay the initiation of TB therapy immediately upon diagnosis. LEVEL II
- ▶ A standard rifamycin (rifampin or rifabutin)-containing regimen should be used unless the organism is rifamycin resistant or the patient is intolerant of rifamycins. LEVEL I
- ▶ Directly observed therapy should be given wherever possible, and other measures should be used to enhance adherence. LEVEL II
- ▶ A standard regimen including INH and rifampin for 6 months and pyrazinamide for 2 months may be considered adequate therapy in a patient with HIV infection when the organism is fully sensitive, adherence to therapy is assured and a satisfactory clinical and microbiologic response is observed. LEVEL I
- ▶ If cavitation is present on the chest x-ray and there is evidence of a delayed treatment response, such as a positive culture at 2 months, treatment should be continued for a total of 9 months. LEVEL II A 9-month course of treatment should also be considered for HIV-positive patients with *either* cavitation on chest x-ray *or* a delayed treatment response, although the evidence for this is not as strong
- ▶ In patients for whom protease inhibitor therapy incompatible with the use of rifampin is judged most appropriate, dose-adjusted rifabutin should be substituted for rifampin in standard treatment regimens. Rifampin should be switched to rifabutin 2 weeks before ART is initiated to allow for “washout” of the hepatic enzyme induction. LEVEL II
- ▶ Rifapentine should not be used in any HIV-infected individuals. Twice weekly rifampin or rifabutin therapy should not be used in patients with CD4 cell counts  $< 100 \times 10^6/L$ . LEVEL II

- In patients receiving effective combination ART at the time of TB diagnosis, the same antiretroviral regimen should generally be continued when possible, with rifabutin substituted for rifampin in the TB regimen if appropriate. **LEVEL III**
- In patients not receiving ART at the time TB treatment is initiated but who meet strict criteria for ART initiation<sup>87</sup> (i.e. absolute CD4 cell count  $\leq 200$ ), ART should be initiated at some point during the course of anti-TB therapy but not simultaneously with the initiation of TB therapy
- For most patients (except women at risk of pregnancy) receiving standard rifampin-containing TB therapy who are initiating ART for the first time, an efavirenz-based regimen with zidovudine, abacavir or tenofovir combined with lamivudine or emtricitabine (avoiding the potential synergistic neurotoxic effects of stavudine or didanosine) would be the first consideration. **LEVEL II.**
- The timing of ART initiation should be individualized depending on factors such as the CD4 cell count and how well anti-TB drugs are tolerated. The period of delay between initiation of TB treatment and ART initiation should usually be in the range of 2 to 8 weeks. **LEVEL III**
- A “paradoxical reaction” following initiation of ART should be suspected on the basis of fever and localized findings after exclusion of other possible causes. Corticosteroid therapy may be considered, if needed, to manage the effects of the reaction. Neither antituberculosis drugs nor ART should be stopped unless there is a high level of suspicion of a drug adverse effect through a mechanism other than a paradoxical reaction. **LEVEL II**
- In patients with chronic diarrhea and advanced HIV disease, or in whom a drug interaction is suspected to be lowering anti-TB drug levels (particularly if the patient is demonstrating a sub-optimal clinical or bacteriologic response to TB therapy), consideration should be given to measuring serum levels of antituberculosis agents after excluding poor adherence and drug resistance. **LEVEL III**
- In patients with a suboptimal viral load response to ART after exclusion of poor adherence and antiviral resistance, and in whom an interaction with a TB drug is a possible explanation, monitoring of antiretroviral drug levels may be considered. **LEVEL III**
- Patients with CD4 cell counts less than 200 cells  $\times 10^6/L$  should receive prophylaxis against *Pneumocystis* pneumonia according to current guidelines.<sup>88</sup> **LEVEL I**
- Pyridoxine supplementation, with or without other vitamins, should be given to HIV-infected TB patients receiving INH, particularly those who may be malnourished. **LEVEL III**

## Bacille Calmette-Guérin (BCG)

BCG vaccination can lead to disseminated BCG-related disease in immunodeficient individuals, although the overall risk appears to be small in those infected with HIV.<sup>89</sup> Estimates of the protective efficacy of BCG vaccine in the non-HIV-infected have varied widely, and vaccine efficacy has not been studied in HIV-seropositive subjects.

### Summary Point:

- ▶ BCG vaccine should not be given to individuals known or suspected to have HIV infection or to children of mothers known or suspected to have HIV infection. **LEVEL I**

## Control of TB Transmission to HIV-infected Individuals

Outbreaks of TB, including multidrug-resistant TB in HIV-infected individuals, have been associated with hospitals and clinics caring for HIV-infected patients and with correctional institutions.

### Summary Point:

- ▶ Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and guidelines 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. **LEVEL II**

## Collaborative TB/HIV Activities

The *goal* of collaborative TB/HIV activities is to decrease the burden of TB and HIV in populations affected by both diseases.<sup>90</sup>

The *objectives* of collaborative TB/HIV activities are as follows:

1. to establish and support collaboration between TB and HIV/AIDS prevention and treatment programs at all levels;
2. to decrease the burden of TB disease in people living with HIV/AIDS; and
3. to decrease the number of cases of unrecognized HIV infection and the burden of illness due to HIV in TB patients.<sup>90</sup>

To achieve the *goal* and *objectives* the Stop TB Department and the Department of HIV/AIDS of the World Health Organization have recommended a series of collaborative activities that address the interface of the TB and the HIV/AIDS epidemics. These recommendations were designed to be used in conjunction with a *Strategic framework to decrease the burden of TB/HIV*<sup>91</sup> and



the *Guidelines for implementing collaborative TB and HIV programme activities*.<sup>92</sup> They are complementary to and in synergy with the established core activities of TB and HIV/AIDS prevention and control programs.

For countries such as Canada, which may be said to be in a “low-level epidemic state”, many of the recommended collaborative activities are already in place and have been alluded to in this chapter. The threshold for starting other activities is relatively high. In this regard the European experience – in which priority has been given to populations at high risk of HIV and TB, such as injection drug users, sex workers, immigrants from high burden countries and those living in congregate settings – is instructive.<sup>93</sup>

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# Nontuberculous Mycobacterial Disease

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## Introduction

The term “nontuberculous mycobacteria” (NTM) includes all mycobacterial species except those that cause tuberculosis (TB) (*Mycobacterium tuberculosis* complex includes *M. tuberculosis* [including *M. tuberculosis* subsp *canetti*], *M. bovis*, *M. bovis* BCG strain, *M. africanum*, *M. caprae*, *M. microti* and *M. pinnipedii*) and leprosy (*M. leprae*). Mycobacteria that infect other species or are saprophytes were identified soon after the discovery of the tubercle bacillus in the late 19th century. In 1954, Timpe and Runyon published their NTM classification system based on the colonial morphology and growth characteristics of NTM collected in various parts of the United States.<sup>1</sup> In 1948, only 10 species of NTM were recognized. Largely as a result of better protocols for mycobacterial culture and advances in genetic techniques, more than 100 NTM species have now been identified, half in the last decade.<sup>2,3</sup> It has been suggested that the rapidly growing mycobacteria differ sufficiently from other mycobacteria to be assigned to a separate genus.<sup>4</sup> Approximately 30% of the positive NTM cultures are unidentifiable, suggesting that new mycobacterial species will continue to be described.

Other terms for NTM include “mycobacteria other than tuberculosis” (MOTT), “atypical”, “environmental” and “opportunistic” mycobacteria. The term suggested for diseases caused by NTM is mycobacterioses to differentiate them from TB.<sup>5</sup> NTM are common environmental saprophytes but infrequent human pathogens. Approximately 40% of NTM isolates are estimated to be associated with significant disease.<sup>6</sup> A clear indication of the presence of disease is essential in order to avoid treating nonsignificant isolates. On the other hand, NTM are opportunists and may cause significant disease in patients with localized or systemic immunosuppression.

### Summary Point:

- There are more than 100 species of NTM with varying degrees of pathogenicity and variable prevalence from one geographic region to the next. All are opportunists, producing more virulent lesions in the immunosuppressed host.

Unlike TB, NTM infection is not spread from person to person, and NTM disease is not notifiable to public health authorities. It appears to be acquired from the environment. NTM occur naturally in water, both fresh and salt, in soil and food, and also in association with animals. *M. avium* has been found in different cigarette components, including tobacco, paper and filters. The NTM are relatively resistant to chlorination and ozonization, and actually benefit from the eradication of competing microorganisms. The rapidly growing mycobacteria, including the *M. fortuitum*, *M. chelonae-abscessus* and *M. smegmatis* groups, are especially hardy and resist freezing, chemical disinfectants and even moderate heating.<sup>7</sup> NTM are present in tap water, and shower heads have often been found to be colonized. It has been suggested that showering instead of bathing may, by aerosolizing more water, be contributing to an increase in NTM disease.<sup>8</sup> The presence of NTM in the hospital water supply can be a source of disseminated

*M. avium* complex (MAC) in patients with AIDS.<sup>9</sup> Water colonization with NTM has also been implicated in outbreaks of NTM disease associated with dialysis units and dental practices.<sup>10</sup> As well, NTM may colonize solutions in the laboratory, resulting in pseudo-outbreaks of NTM.<sup>11</sup> Similarly, improved laboratory methods may increase the reported incidence rate.<sup>12</sup> Changes in the environment can influence shifts in the relative frequency of certain isolates in human specimens over time.<sup>13</sup>

NTM isolates are understood to have become more frequent as a result of a real increase, an increased recognition of NTM-associated disease, and the routine use of more supportive liquid and solid culture media. Approximately 21,000 NTM isolates were reported by state public health laboratories in the United States each year from 1993 to 1996.<sup>14</sup> About 40% of these were MAC, 10% were rapidly growing NTM of the *M. fortuitum-chelonae-abscessus* family, 15% were “unknown” or currently unknown species of NTM, and 25% were *M. gordonae*, a saprophyte and likely not responsible for disease. Only 2.5% of the isolates were *M. kansasii* and 1% were *M. xenopi*. In Alberta, during a similar period, NTM accounted for 70% of all mycobacterial isolates, of which 33% were MAC, 25% of the *M. fortuitum-chelonae-abscessus* family, and 1% each of *M. kansasii* and *M. xenopi* (Fanning EA, personal communication, 2005). These and data from other parts of the world suggest that MAC is the most common NTM isolated from humans. Certain species are commonly found in specific areas and occupations, including *M. xenopi* in Ontario;<sup>15,16</sup> *M. kansasii* in the midwestern United States, in the United Kingdom and among South African gold miners;<sup>17</sup> and *M. malmoense* in Scandinavia.<sup>18</sup> However, in addition to a general increase in prevalence, the patterns of NTMs in geographic areas are changing.<sup>19</sup>

The increase in NTM disease may be due, at least in part, to immunosuppression associated with medication and with AIDS, the aging of Western populations and the declining rates of BCG vaccination.<sup>20</sup> The elderly appear to be particularly susceptible to NTM, especially MAC. There has also been an increased awareness of NTM and their role in diseases such as cystic fibrosis and fibronodular bronchiectasis. NTM disease has also become relatively more prevalent because of the declining prevalence of TB in North America.

#### Summary Point:

- ▶ The common clinical syndromes associated with NTM are lymphadenopathy, chronic pulmonary disease, skin and soft tissue infections (often associated with trauma or a foreign body) sometimes with extension to bone and joint, and disseminated disease.

A report of caseating granulomata on tissue biopsy or acid-fast bacilli (AFB) in secretions or tissues should be interpreted to mean the presence of *M. tuberculosis* until proven otherwise and the patient treated accordingly. The process of determining whether the causative organism is *M. tuberculosis* or NTM is expedited in sputum samples by using polymerase chain reaction (PCR) assays that speciate the organism from the AFB smear. Once the organism has been

cultured, commercially available DNA probes can be used to reliably distinguish cultures of *M. tuberculosis* from NTM. Commercially available DNA probes are available to identify MAC, *M. kansasii* and *M. goodii*. NTM cultured on a single occasion from the sputum of patients undergoing treatment for TB are likely contaminants and do not require specific treatment if the patient is improving clinically.

The physician is advised to contact the laboratory to discuss time lines to further relevant laboratory information on the identification of the organism and its drug susceptibility pattern. NTM species are listed by site of disease in Table 1 (adapted, with permission, from Debrunner et al.<sup>5</sup>).

Table 1 Clinical Nontuberculous Mycobacteria Syndromes\*

Definition	Treatment (see Table 2)	Etiologic Agent	
		Common	Rare
<i>Pulmonary disease</i> (usually adults) <ul style="list-style-type: none"> <li>• Symptoms of cough, sputum production, weight loss</li> <li>• Two or more sputum isolates or one isolate from sterile site</li> <li>• Distribution of isolates varies regionally</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment with combined antimicrobials</li> <li>• Resection if localized</li> <li>• Attention to bronchial toilet</li> </ul>	<i>M. avium</i> complex (MAC)† <i>M. kansasii</i> † <i>M. abscessus</i> <i>M. xenopi</i> <i>M. malmoense</i>	<i>M. simiae</i> <i>M. szulgai</i> <i>M. fortuitum</i> <i>M. chelonae</i> <i>M. smegmatis</i>
<i>Lymph node disease</i> (usually < 5 years of age) <ul style="list-style-type: none"> <li>• Unilateral, submandibular site most common</li> <li>• Onset of symptoms subacute</li> <li>• Skin induration and sinus tract formation may occur</li> </ul>	<ul style="list-style-type: none"> <li>• Surgical resection is usually curative</li> </ul>	MAC† <i>M. kansasii</i> † <i>M. malmoense</i> <i>M. haemophilum</i>	<i>M. scrofulaceum</i> <i>M. fortuitum</i> / <i>peregrinum</i> <i>M. abscessus/chelonae</i>
<i>Skin/soft tissue/bone/joint and tendons</i> <ul style="list-style-type: none"> <li>• History of trauma or superficial laceration</li> <li>• Presence of a foreign body</li> </ul>	<ul style="list-style-type: none"> <li>• Debridement plus combined drug therapy</li> </ul>	<i>M. marinum</i> <i>M. fortuitum</i> / <i>peregrinum</i> <i>M. abscessus/chelonae</i> <i>M. ulcerans</i>	MAC <i>M. kansasii</i> † <i>M. terrae</i> <i>M. haemophilum</i>
<i>Disseminated</i> <ul style="list-style-type: none"> <li>• HIV or other immunosuppressive disease</li> <li>• Symptoms: fever, weight loss, diarrhea</li> <li>• Any site possible</li> <li>• No trauma necessary</li> </ul>	<ul style="list-style-type: none"> <li>• Prevention of MAC in HIV</li> <li>• Treat positive blood culture aggressively</li> </ul>	MAC† <i>M. genavense</i> <i>M. kansasii</i> †	<i>M. abscessus/chelonae</i> <i>M. haemophilum</i> <i>M. goodii</i> † Any mycobacterium may cause disease in association with significant immunosuppression, and any localized lesion may disseminate.

\* Adapted with permission from Debrunner et al.<sup>5</sup>

†DNA probe available

The treatment of NTM disease is problematic, because NTM are resistant to a wide range of antimicrobial agents. Communication with the laboratory will help to define the organisms for which susceptibility testing is useful (see Table 2). It must be remembered that even organisms considered “nonpathogens”

may occasionally cause disease in those who are severely immunocompromised. Drug treatment is most critical in these patients.

Resistance develops readily, hence single drug therapy must be avoided.\* If feasible, surgical resection (e.g. in lymph node disease) may be curative.

## Laboratory Methods

Please refer to Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies, for details of specimen submission. The identification of mycobacteria is best performed by experienced laboratory personnel, and careful quality assurance techniques need to be in place to detect laboratory NTM pseudo-outbreaks.<sup>11,12</sup>

Antibiotic susceptibility testing of NTM may be performed by the laboratory, at the request of the physician. However, susceptibility testing is not standardized except for clarithromycin in MAC, and the correlation between *in vitro* susceptibility testing and the clinical response to treatment is less well defined than with the *M. tuberculosis* complex.<sup>21</sup>

## Clinical Syndromes

The clinical syndromes most frequently associated with NTM are chronic lung disease, lymphadenopathy, skin and soft tissue disease and disseminated disease. Lung disease due to NTM is primarily a disease of the elderly, patients with underlying lung disease or patients who are immunocompromised. In most parts of the world, MAC is the most common cause of NTM lung disease. Lymphadenopathy is the most common type of NTM disease in children, and MAC the most common etiologic agent. Skin and soft tissue infection may occur after surgery or other trauma, is usually associated with the presence of foreign material and may extend to bones and joints. Disseminated disease may occur in patients with severe immunosuppression, such as those with advanced AIDS (CD4 lymphocyte counts less than  $50 \times 10^6/L$ ).

## Pulmonary disease

Approximately 75% of the NTM isolates reported by public health laboratories in the United States from 1993 to 1996 were from sputum or lung specimens. MAC is the most common cause of NTM lung disease, followed by the rapid growers of the *M. fortuitum-chelonae-abscessus* complex, *M. kansasii* and *M. xenopi*.<sup>14</sup>

In diagnosing pulmonary disease caused by *M. kansasii*, a single isolate, in the presence of characteristic disease, is usually considered diagnostic. For other NTM species, a diagnosis of pulmonary disease generally requires at least three positive sputum cultures, or two if one is smear positive.<sup>21</sup>

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

Although there may be some overlap between them, two patterns of lung disease are commonly described in association with MAC.<sup>22</sup> In the first, patients with underlying lung disease, such as previous TB, chronic obstructive pulmonary disease (COPD) and pneumoconiosis, often with a history of tobacco and alcohol abuse, tend to develop features similar to those of TB with cavitory disease primarily involving the upper lobes. The second pattern has been described as fibronodular bronchiectasis, which is seen in older patients, typically women, without a history of underlying lung disease.<sup>23,24</sup> It has a characteristic appearance of bronchiectasis associated with parenchymal nodules. The bronchiectasis is most evident in the lingular segment of the left upper lobe and in the right middle lobe. It is understood to be secondary to the MAC and not a primary, predisposing condition.

The treatment of MAC lung disease is centred upon a macrolide, either clarithromycin or azithromycin, and companion medications such as ethambutol, rifampin, fluoroquinolones and clofazimine, which have the specific role of preventing the organism from developing resistance to the macrolide.<sup>22</sup> The macrolide-containing regimens have not been subjected to formal study but are widely regarded as being more effective than rifampin and ethambutol with or without isoniazid, a regimen that has been tested in a randomized controlled trial.<sup>25</sup> In general, it has been recommended that treatment of MAC lung disease should continue for 12 months after the sputum culture becomes negative. Rapid growers, such as *M. abscessus*, may also cause fibronodular bronchiectasis. Treatment of *M. abscessus* lung disease has been disappointing.<sup>26</sup>

*M. kansasii* is the most pathogenic of the NTM and produces lung lesions that are similar to those seen in TB, including upper lobe involvement and cavitation.<sup>27</sup> There have also been reports of *M. kansasii* producing nodular bronchiectasis with features similar to those associated with MAC.<sup>27</sup> Patients may have no predisposing conditions for *M. kansasii* disease, although it was originally reported to occur in older men often with a history of alcoholism and cigarette smoking and with underlying lung disease such as COPD, previous TB or pneumoconiosis. Treatment for 9 months with rifampin and ethambutol was evaluated in a prospective study in Britain and found to be successful in 88% of 155 subjects.<sup>28</sup> In North America, treatment regimens generally include isoniazid, notwithstanding the organism's usual *in vitro* resistance to this drug, with rifampin and ethambutol. Treatment is generally continued for 18 months.<sup>21</sup> Clarithromycin has been recommended to replace rifampin when that drug cannot be tolerated<sup>21</sup> and has also been used together with rifampin and ethambutol in a thrice-weekly treatment regimen.<sup>29</sup>

*M. xenopi* causes cavitory disease in immunocompetent individuals, and a similar pattern has been reported in HIV-infected individuals receiving antiretroviral therapy. In a British study, rifampin and ethambutol appeared to be beneficial<sup>30</sup> but, in general, clarithromycin, ethambutol and a fluoroquinolone, with or without a rifamycin, appear to be favoured.<sup>21</sup>

Other pulmonary disorders associated with NTM include a hypersensitivity–pneumonitis-like syndrome in patients exposed to *M. avium* in hot tubs<sup>31</sup> and lung disease due to rapidly growing mycobacteria associated with chronic aspiration.<sup>32</sup>

*M. malmoense* was first isolated in Sweden but has occurred elsewhere in Europe and in North America.<sup>33</sup> It has an unusually slow growth *in vitro*, requiring more than 6 weeks for isolation. It is more common in older adults with chronic lung disease. Most strains are susceptible to ethambutol, cycloserine and ethionamide. Sensitivity to rifamycins and fluoroquinolones is variable.<sup>21</sup> There are reports of successful treatment with clarithromycin, rifampin and ethambutol.<sup>34,35</sup>

Lung disease due to NTM is rare in children unless they have cystic fibrosis. A recent multicentre study in the United States found that NTM were regularly cultured from the sputum of patients with cystic fibrosis.<sup>36</sup> Those patients from whom NTM were cultured were older, had better lung function and were less likely to have *Pseudomonas aeruginosa* cultured from their sputum than the other patients with cystic fibrosis. The most common NTM isolated was *M. avium* with *M. abscessus* a distant second. As determined by computed tomography, cystic fibrosis patients with NTM had greater progression of their parenchymal lung disease over the subsequent 15 months than did other cystic fibrosis patients.<sup>37</sup>

Specific medication regimens for NTM lung disease are listed in Table 2.

### Lymphadenopathy

Granulomatous lymphadenopathy due to NTM is most commonly seen in children between the ages of 6 months and 5 years.<sup>38,39</sup> The unilateral cervical lesion usually appears abruptly and is associated with minor upper respiratory symptoms, but the lymph node fails to resolve as the respiratory symptoms disappear. The lymph node is usually submandibular, submental or preauricular in location. It may be fluctuant, and produce skin inflammation and suppuration. The child is otherwise well. There is no history of contact with TB, and the chest x-ray is normal. Tuberculin skin testing usually, but not always, results in less than 10 mm of induration. In Canada, NTM accounts for childhood granulomatous lymphadenopathy more commonly than does *M. tuberculosis*, with the notable exception of children who are from First Nations or Inuit communities, who were born in a country with a high incidence of TB or who are in frequent contact with persons from such countries. Hence, after total surgical excision, it may be reasonable to withhold antituberculosis treatment, unless there is a suggestive history of TB contact, until the results of culture of surgically excised lymph node tissue are available. In Canada the majority of cases are caused by MAC. In Texas, *M. kansasii* accounts for some lymphadenopathy in children and adults. In Sweden, *M. malmoense* is an important cause of cervical lymphadenopathy in children. Rarely *M. fortuitum* and *M. chelonae* are reported to cause lymphadenopathy.<sup>40</sup>

In NTM lymph node disease, surgical excision is usually curative without drug treatment. Occasionally, lymph node proximity to the facial nerve makes surgical excision difficult, and treatment with clarithromycin and ethambutol has been curative. This raises the question of whether such a treatment regimen might not be more widely applied following a needle aspirate to obtain material for mycobacterial culture.<sup>41</sup>

## Skin and soft tissue infections (bone and joint extension)

Skin and soft tissue NTM infections usually occur after injury, including injections, pedicures, acupuncture, surgery and some nonsurgical cosmetic procedures, in which foreign bodies or foreign material are involved. Since NTM are present in “sterilized” water and may grow in the presence of chlorine, benzalkonium chloride, glutaraldehyde and formaldehyde, they can cause postoperative infections. Most NTM can cause skin or soft tissue infection, but the most common causes are *M. marinum*<sup>13</sup> and the rapidly growing mycobacteria, including *M. fortuitum*, *M. abscessus*, *M. chelonae* and *M. ulcerans*. In the past decade *M. haemophilum* has become more common, usually associated with immunosuppression, and involving skin and joints.

*M. marinum*, a photochromogen, 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. These so-called fish tank or swimming pool granulomas may be treated with a combination of rifampin and ethambutol for 3 to 6 months. Clarithromycin in combination with ethambutol, doxycycline, minocycline or cotrimoxazole has also been used with success. Treatment may need to be continued for 12 months.

The *M. fortuitum* complex of rapidly growing mycobacteria includes *M. fortuitum*, *M. peregrinum*, *M. chelonae* and *M. abscessus*.<sup>40</sup> Speciation is clinically relevant, as there are some differences in clinical manifestations as well as in antibiotic susceptibilities.<sup>42</sup> About 60% to 75% of infections due to *M. fortuitum* complex are at cutaneous sites, and only 20% are pulmonary. Of cutaneous infections, approximately half follow surgery or trauma and may be associated with the presence of a foreign body. *M. fortuitum* and *M. abscessus* are the most frequent cutaneous pathogens. There is a strong association between *M. fortuitum* complex organisms and prosthetic devices such as breast implants or peritoneal dialysis catheters. Infections due to *M. chelonae* are strongly associated with corticosteroid therapy, and dissemination occurs most frequently with this species.

Treatment for *M. fortuitum* complex infection may require surgical excision and/or antibiotic therapy. Surgery is particularly successful for cutaneous infections associated with prosthetic devices. Debridement should include removal of the device. Antibiotic therapy should be guided by *in vitro* susceptibility testing. Most primary antituberculosis drugs are not active against *M. fortuitum* complex infections. The most active agents are clarithromycin and amikacin. A variable proportion of organisms are susceptible to cefoxitin, doxycycline, ciprofloxacin, sulphonamides and imipenem. In general, two active agents should be used.

*M. haemophilum* has been reported to cause skin and joint infections in normal and immunosuppressed hosts. Treatment with clarithromycin, rifampicin, ciprofloxacin and amikacin has been effective.

*M. ulcerans*, the third commonest cause of mycobacterial disease globally, is the etiologic agent implicated in “Buruli” skin ulcers in West Africa and Australia. It is not endemic to North America but is found in fish and aquatic snails<sup>43</sup> and can be seen after travel to Africa, Central and South America, Australia, New Guinea, Indonesia and Malaysia.<sup>44</sup> Diagnosis is challenged by the slow



growth of the organism (6-24 weeks) and is aided by PCR for IS2404. The lesions are debilitating painless ulcers, and the organism is believed to enter the skin through an abrasion. Early treatment may lessen long-term sequelae, such as contractures and the requirement for extensive debridement and plastic surgery.<sup>45</sup> Animal studies suggest that rifampin and amikacin are effective in the treatment of *M. ulcerans*,<sup>46,47</sup> and *in vitro* data indicate a role for clarithromycin in early disease.<sup>48</sup> Recent publications report that a combination of rifampin and streptomycin given for 8 weeks may supersede surgery in the initial treatment of Buruli ulcer.<sup>49,50</sup>

### Disseminated infection

In immunosuppressed patients, NTM infections may disseminate.<sup>51</sup> Dissemination is especially common in AIDS patients but has also been reported in patients with iatrogenic immunosuppression after solid organ transplantation or with chronic corticosteroid use, in a small number of patients with interferon-gamma receptor and interleukin 12 receptor abnormalities and, antedating AIDS, in hairy cell leukemia, a T-cell leukemia. MAC accounts for most AIDS mycobacterial bacteremia, generally occurring with CD4 lymphocyte counts below  $50 \times 10^6/L$ .<sup>52-54</sup> A variety of other NTMs can also cause disseminated infection in immunocompromised patients. These include *M. fortuitum* complex, *M. kansasii*, *M. goodii*, *M. simiae*, *M. haemophilum*, *M. szulgai*, *M. genovense* and *M. smegmatis*. Other infections have to be considered in the differential diagnosis of disseminated NTM disease, including TB and disseminated histoplasmosis.

Because of the high, 20% per year, incidence of MAC bacteremia, AIDS patients with CD4 counts under  $50 \times 10^6/L$  should be given mycobacterial prophylaxis.<sup>55</sup> The use of rifabutin 300 mg once daily achieves successful prophylaxis, but because of rifabutin's adverse effects clarithromycin 500 mg bid or azithromycin 1200 mg weekly is preferred.<sup>51,56</sup>

Patients with disseminated MAC may experience fever, sweats and weight loss. Gastrointestinal involvement is common and may be accompanied by nausea, vomiting, diarrhea and abdominal pain. Hepatosplenomegaly, lymphadenopathy, anemia, mycobacteremia and liver enzyme abnormalities may develop; elevation of alkaline phosphatase out of proportion to the elevation of transaminases is suggestive of disseminated MAC.

Lung disease may occur in patients with disseminated *M. kansasii* and MAC. Diffuse skin nodules may develop with disseminated disease due to *M. chelonae* or *M. kansasii*.

Most patients with disseminated MAC have AIDS and require concomitant antiretroviral therapy. It is important to choose a regimen that avoids a drug interaction. One of the macrolides, clarithromycin or azithromycin, should be given with ethambutol. The role of ethambutol is to prevent emergence of macrolide resistance. Rifampin interacts with most of the antiretroviral drugs, and rifabutin, which is less likely to cause drug interactions, is preferred if a rifamycin needs to be added to the regimen. Some antiretroviral drugs, including efavirenz, ritonavir and lopinavir, should be avoided since they affect

the metabolism of clarithromycin. Aminoglycosides and fluoroquinolones are possible alternatives in patients with macrolide-resistant MAC.

Treatment of disseminated *M kansasii* disease consists of rifampin, ethambutol and isoniazid. Rifabutin can be substituted if rifampin is contraindicated because of concomitant antiretroviral therapy. Other NTM can disseminate, and treatment regimens for these NTM are shown in Table 2.

In conclusion, it is important to note that the treatment of NTM disease at any site is rapidly evolving. Recent advice on management is provided by the British Thoracic Society Joint Tuberculosis Committee.<sup>57</sup> This committee reviewed the evidence on management of these infections and concluded that, on the whole, the evidence is not derived from controlled clinical trials, as very few have been reported. Where possible they graded the evidence according to the same criteria as are used in these *Canadian Tuberculosis Standards*.

### Summary Points:

#### Principles of Treatment of NTM Disease

1. Patients should be carefully evaluated to determine the significance of an NTM isolate. The presence of the organism in a sterile site or repeatedly from airway secretions in association with a compatible clinical and radiologic picture confirms the diagnosis.
2. Treatment of rapidly growing mycobacteria should be guided by *in vitro* susceptibilities. Other drug susceptibility testing is not standardized.
3. Treatment should usually combine at least two drugs of proven efficacy.
4. Contact follow-up is not necessary since NTM are not transmitted from person to person.
5. Duration of therapy has not been determined; in general, 6-12 months is required following negative cultures.
6. In soft tissue infections, because of rapidly growing mycobacteria, a combination of debridement and treatment with antimicrobials is recommended. For selection of antimicrobial agents, consultation with the laboratory should be undertaken regarding the reliability of *in vitro* testing.
7. Table 2 identifies usually useful agents.

Table 2 Treatment of Nontuberculous Mycobacterial Disease

Organism	Drugs	Duration
<i>M. avium</i> complex (MAC)	Clarithromycin 500 mg bid or azithromycin 250 mg daily Ethambutol 15 mg/kg (may use 25 mg/kg for initial 2 months) Rifampin or rifabutin ± aminoglycosides (streptomycin or amikacin) intermittently (occasionally a quinoline may be useful)	12 months after culture negative
<i>M. kansasii</i>	Rifampin plus ethambutol +/- isoniazid Clarithromycin or azithromycin ± aminoglycosides	12 months after culture negative
<i>M. xenopi</i>	Clarithromycin Ciprofloxacin Ethambutol	12 months after culture negative
<i>M. malmoense</i>	Rifampin Ethambutol Isoniazid +/-quinolones +/- macrolides	12 months after culture negative
Rapid growers ( <i>M. fortuitum</i> complex, <i>M. abscessus</i> , <i>M. chelonae</i> )	Based on <i>in vitro</i> sensitivity testing, the following: doxycycline, amikacin, imipenem, quinolones, sulfonamides, ceftazidime, clarithromycin	12 months after culture negative for lung disease; for soft tissue disease that is resectable concomitant antimicrobials for 3 months may suffice
<i>M. marinum</i>	Rifampin plus ethambutol ± minocycline or doxycycline ± trimethoprim/sulphamethoxazole ± amikacin ± clarithromycin	6-12 months
<i>M. haemophilum</i>	Ciprofloxacin Rifampin Amikacin Clarithromycin	Experience is limited; 12-18 months reported, but not in all cases
<i>M. genavense</i>	Clarithromycin Ethambutol Amikacin Rifabutin	Experience is limited; 12-18 months reported, but not in all cases
<i>M. ulcerans</i>	Rifampin Clarithromycin Ethambutol PAS*	Uncertain; surgical treatment is primary and may require skin grafting
Prophylaxis of disseminated <i>M. avium</i> complex disease in the HIV infected with CD4 < 50 x 10 <sup>6</sup> /L	Azithromycin 1200 mg weekly or Rifabutin 300 mg a day or Clarithromycin 500 mg bid	Life or control of HIV viremia with rise of CD4

\*paraaminosalicylic acid

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## International

Tuberculosis (TB) is a “maladie sans frontières”. There is no jurisdiction that illustrates this more clearly than Canada, where the majority of patients are foreign-born; among them, the clinical and mycobacterial patterns generally reflect the patterns of disease in their country of birth. TB control in Canada cannot, therefore, be divorced from the larger global or international context (see Chapter 18, Canada and International Tuberculosis Control).

### Global standards

Since 1991, there has been a global consensus, led by the World Health Organization (WHO), on what constitutes good practice in public health programs for TB. This is what has been termed the “DOTS Strategy” (directly observed treatment, short-course),<sup>1</sup> which is a combination of policies and strategies, as well as techniques to enhance TB control. At the level of policy, the first principle is the need for political commitment (i.e. declaration of public sector responsibility with a corresponding budget; appropriate management structure; published national guidelines; a sector-wide approach encompassing all existing cases, including those in the private sector; and policies to ensure that there is access to services). System-related elements include an uninterrupted supply of drugs, diagnosis and follow-up through a quality-assured system of bacteriology, a clearly defined monitoring process using international definitions and practices, and measures to protect against misuse of the medications, leading to drug resistance.

In March 2006, the Tuberculosis Coalition for Technical Assistance, in conjunction with the World Care Council, released the *International Standards for Tuberculosis Care*<sup>2</sup> and the *Patient’s Charter for Tuberculosis Care*.<sup>3</sup> The standards have been endorsed by many organizations involved in TB issues, including the WHO, the Stop TB Partnership and the International Union Against Tuberculosis and Lung Disease. The aim of the standards is to describe a widely accepted level of care for the management of persons who have, or are suspected of having, TB so as to facilitate public and private care providers in achieving this level of care for all of their patients (see Appendix H, International Standards for Tuberculosis Care).

### Compliance with international standards

Evaluating compliance with international standards necessitates a designated set of indicators and a designated set of individuals responsible for collecting and reporting the indicators. It also requires that those responsible for the immediate care of the patient share, in a timely and accurate manner, information necessary to evaluate adherence.

### International reporting

The existence of international standards necessitates a system, using internationally defined indicators, to monitor whether the standards are being achieved. The WHO has implemented a system to monitor the achievement of

global targets and has reported annually since 1999. For the latest global report, see <http://www.who.int/tb/en/>.<sup>4</sup>

## International cooperation and standard setting

As TB is a disease that knows no boundaries and is capable of creating and sustaining poverty (and is therefore a focus of poverty-reduction strategies of international development cooperation), industrialized countries should not only ensure that their clinical and public health practice is in line with international standards but they should also engage in standard-setting and in guiding and monitoring international development cooperation in this regard.

## Canada

TB control activities in Canada's provinces and territories are organized according to two models: a centralized control program that includes the provision of clinical services, and a program that has both centralized and decentralized public health elements but relies on community-based specialist and primary care physicians for the delivery of clinical services. The first model, which grew out of the sanatorium system, continues to exist in the provinces of British Columbia, Alberta, Saskatchewan and Manitoba, and the Yukon, Northwest and Nunavut territories, while the latter exists in Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador. The evolution from central to decentralized programs in eastern Canada occurred over many decades. In all models, there are three levels of government involved in public health in Canada: local or regional, provincial/territorial, and federal. In the description of the role of public health in this chapter, the management of the clinical aspects of TB control will not be addressed.

The public health role in TB can be divided into those aspects that are part of the infrastructure (structure) and those that are operational (function).

## Public health infrastructure for TB control<sup>5,6</sup>

### *Legislation to support surveillance and control*

Every province and territory in Canada has legislation that requires reporting of TB. The specific requirements in each jurisdiction specify who is required to make a report, to whom a report is made and the specific data elements required to be reported. Data elements typically include demographic data, risk factors for infection and disease, the sites and staging of disease, method of diagnosis, including results of laboratory tests, the treatment regimen and outcome of treatment (see Chapter 1, Epidemiology of Tuberculosis in Canada). Reporting at the local level is rolled up into the provincial/territorial database and then into the national reporting system. Confidentiality of the data is maintained throughout, as required by municipal, provincial/territorial and federal privacy protection legislation, unless disclosure is permitted by applicable legislation.

Public health legislation provides public health authorities with the powers to ensure that suspected or confirmed cases of active pulmonary TB receive timely diagnosis and treatment. While all reasonable measures are taken to obtain voluntary adherence to diagnosis and treatment, provincial/territorial legislation permits a variety of actions to be taken, including involuntary detention, if adherence cannot be obtained. Individuals deprived of their liberty through detention are entitled to due process and legal representation. Such authority is not often used, but TB is one of the communicable diseases for which it continues to be invoked.

In most jurisdictions, detention under public health legislation is only used until the patient is rendered non-infectious and thus is no longer an immediate risk to the health of the public. The expansion of existing TB legislation to encompass the concept of treating active TB until cure or treatment completion (see Appendix C, Definition of terms) has been proposed in the United States by the Advisory Council for the Elimination of Tuberculosis<sup>7</sup> and has been incorporated into state TB law in at least one jurisdiction.<sup>8</sup> Whether or not this should be included in Canadian provincial/territorial legislation must be carefully considered, engaging a broad-ranging debate among all stakeholders, not least the patients affected and population groups at highest risk.

Provincial/territorial governments should, as a matter of policy, periodically review TB-related public health legislation to establish consistency with current medical and public health practices.

### *Organized TB control program with a policy framework*

Public health TB control programs need dedicated and trained staff knowledgeable in specific aspects of TB. The required number and expertise of staff depend upon the local epidemiology of TB and the specific needs of the community. All TB control programs should have a designated program manager (whether at the local, regional or provincial/territorial level) to facilitate program planning, evaluation and coordination functions and should also have access to an epidemiologist to conduct evaluation and surveillance activities. Programs also require a defined mechanism for communication and coordination with local primary care and specialty physicians as well as community social support agencies and groups. For example, public health has an important role to play in encouraging and facilitating the involvement of specialty TB physicians or specialty TB clinics (if they exist in the community) in the management of TB patients. These relations will help to ensure prompt and complete reporting, effective case management and contact tracing, opportunities for continuing medical education, more effective outreach to high-risk groups, provision of culturally appropriate services and reduced psychosocial barriers to adherence, including the provision of directly observed therapy (DOT). Specific plans for coordination with HIV/AIDS programs are also needed because of the frequency of dual infection and the need to screen some contacts for HIV infection.

Unlike most other communicable diseases, TB has a long duration of case management that necessitates a unique set of policies and procedures. These include national standards (e.g. the *Canadian Tuberculosis Standards*) that are drafted in consultation with TB experts, updated periodically and revised as needed, and specific written procedures within provincial/territorial and local/regional jurisdictions that define the practice guidelines for TB treatment and prevention in the community. These procedures reflect differences in the epidemiology, administrative structures, legislation and resources available for TB control in each jurisdiction.

### *Laboratory diagnostic capability*

Public health laboratories serve an important primary diagnostic, reference and reporting function. Drug susceptibility testing is generally only available through the public health laboratory system, as are reference functions such as specialized isolate characterization for outbreak investigation. A central public health laboratory can also bank isolates to maintain a comprehensive database from the entire geographic area for subsequent testing as new methodologies evolve, and such centralization also assists in monitoring longer-term epidemiologic trends. For the decentralized diagnostic laboratory network, the public health laboratory has a leadership role in seeing that essential laboratory tests for TB control are available, accessible, standardized and reproducible, and have high sensitivity and specificity.<sup>6</sup>

### *Drugs and biologicals*

It is essential that public health TB control programs provide publicly funded drugs at no charge to the patient for the treatment of active disease and of latent TB infection (LTBI). TB is most common among those least able to pay for treatment. Provision of drugs at no charge improves adherence to treatment and establishes a role for public health in the monitoring of the treatment regimen against accepted standards. Public health programs provide tuberculin PPD (purified protein derivative) skin test solution, the current guidelines for testing and interpretation of results, and BCG vaccine for use in certain high-risk populations.

### *In-hospital care*

Some jurisdictions hospitalize persons with active TB, particularly for the initiation of therapy in those who are seriously ill, for infection control purposes, or for management of complications of the disease or treatment. Public health TB control programs should assess the level of access to in-hospital services and advocate for sufficient bed capacity and high-quality infection control standards. These considerations are especially relevant to the control of drug-resistant TB.

## Public health operational activities for TB control<sup>5,6</sup>

### *Setting of goals and objectives*

It is important that public health TB control programs set program priorities, goals, objectives and targets for achievement of program outcomes and processes. A defined set of indicators should be used and regularly reviewed to monitor progress and to identify areas requiring improvement. This process gives direction to program activities, establishes a framework for program planning and evaluation, empowers managers to improve efficiency and provides evidence to advocate for continued and enhanced funding for TB control programs to achieve programmatic goals and objectives. The strategy should also outline the roles and responsibilities of all partners in TB prevention and control.

### *Program planning, implementation and evaluation*

Program planning is based on the needs of the population and is therefore strongly influenced by the local epidemiology of TB, including that of high-risk populations. Program initiatives could include organized means of working with local community partners to reach high-risk populations for education about TB, to promote early detection of active disease, to identify those who would benefit from treatment of LTBI, to reduce stigma, to implement and evaluate DOT programs and to provide culturally appropriate services.

Evaluation is generally designed to measure the effectiveness and efficiency of programs and is particularly important for new initiatives. Program evaluation should lead to the modification of existing policies and practices, and to the development and implementation of new policies. It can also provide evidence to advocate for resource mobilization and research to support public health practice. Program evaluation should be carried out on a regular basis, and program inputs (material and human resources), processes and outcomes should be assessed against the program's goals and objectives. Performance is compared with appropriate set targets (see Chapter 6, Treatment of Tuberculosis Disease and Infection). The results of program evaluation should be communicated to funding authorities as well as to other TB control program managers to benefit others' programs.

### *Regular analysis of surveillance data and dissemination of results*

Public health departments at local/regional, provincial/territorial and the federal level receive and analyze data on reported cases of active TB. Each year, analyzed data on the previous year's incident cases and longer-term trends are published and presented to politicians, the public, the health care community and other key stakeholders (e.g. Citizenship and Immigration Canada, the WHO). This process allows the burden of TB and the control program to be scrutinized by the wider community, and permits comparison of the profile of TB in different jurisdictions. This latter function becomes

even more important as the rates of TB decline, because TB is increasingly a disease of high-risk populations such as Aboriginal Canadians and foreign-born persons from countries with a high TB incidence.

### *Case finding, case management, contact tracing and outbreak investigation*

The highest priority for TB control programs is the identification and treatment of persons who have active TB disease, especially those who are sputum smear positive. While the majority of cases of TB are diagnosed because medical attention is sought for symptoms, public health authorities carry out active case finding outside of the institutional setting under specific circumstances: screening of close contacts of infectious cases for evidence of disease activity, determining the source of infection for a pediatric case of TB, and case finding in well-delineated populations experiencing very high rates of TB, such as shelters for the homeless.

The treating physician and public health authorities share responsibility for case management during the prolonged period required for treatment. Public health staff educate patients and their family or household members about TB treatment and the potential for treatment-related side effects; monitor the occurrence of side effects; evaluate the potential for nonadherence to the prescribed drug regimen by identifying and reducing barriers to adherence (e.g. social, behavioural, social support, health belief, or other medical issues), including consideration of the use of incentives and enablers to promote adherence; and they may also supervise therapy. In many jurisdictions, DOT is routinely offered, whereas in others it is employed for part of the treatment or only to select persons (see Chapter 6, Treatment of Tuberculosis Disease and Infection).

The performance of contact investigations is the second highest priority for public health TB control programs. Public health staff ensure that all contacts of infectious cases are identified and tested according to current guidelines, assist in the administration and interpretation of TSTs, make recommendations regarding treatment of LTBI and emphasize the importance of such treatment. Another important function of public health staff of TB control programs is the investigation of TB outbreaks (see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control). Public health staff may also carry out ancillary surveillance activities, such as screening of high-risk populations for the prevalence of LTBI, if sufficient resources remain after case finding and contact investigation activities have been adequately funded.

### *Medical surveillance for inactive pulmonary TB*

This refers to medical follow-up of recently arrived immigrants, refugees and refugee claimants deemed to be at high risk of inactive pulmonary TB or LTBI progressing to active TB disease, usually on the basis of chest radiographic findings of prior TB (see Chapter 15, Immigration and Tuberculosis Control in Canada and Appendix I, Guidelines for the



Investigation and Follow-up of Individuals Under Medical Surveillance for Tuberculosis after Arrival in Canada (2007)).

### ***Entry into or departure from Canada of persons with suspected respiratory TB, untreated active respiratory TB or partially treated active respiratory TB***

Public health TB control programs potentially have a role to play in managing persons traveling into or out of Canada with suspected respiratory TB, untreated active respiratory TB or partially treated active respiratory TB, who may infect other persons if airborne isolation precautions are not followed. Failure to maintain continuity of treatment and clinical care increases the probability that drug-resistant TB will develop, and this may be more difficult and expensive to treat.

Guidelines for the management of such situations have been developed by the Canadian Tuberculosis Committee and the Public Health Agency of Canada. Please refer to <<http://www.publichealth.gc.ca/tuberculosis>>.<sup>9</sup>

### ***Training and education***

Public Health TB control programs should provide appropriate training for all program staff at the time of hire and at regular intervals to ensure that they continue to have accurate and current knowledge of TB and its management. Public health authorities also provide leadership in TB education so that community leaders, health care providers, policymakers, community agencies providing services to TB patients (e.g. staff of social services departments, correctional facilities, homeless shelters) and the general public are aware of and knowledgeable about TB. In particular, programs need to ensure that health care providers have an awareness of TB so as to facilitate the early identification of cases in the community. The plan of training, including the curriculum, the trainers responsible, the target groups and the calendar of training, should be explicitly outlined.

### ***Consultation***

Public health TB control programs, if called upon, serve as a source of information and consultation to the local community regarding appropriate infection control practices in different settings (e.g. hospitals, specialty clinics, long-term care facilities, correctional facilities, homeless shelters), the appropriate number of TB isolation rooms to meet community needs, the appropriate diagnostic tests to use in different circumstances for the diagnosis of active TB disease, and the screening modality that is most appropriate in a given setting.

## **Public health challenges in select settings**

While Canada has an overall low incidence rate of TB disease, rates within subpopulations vary widely, from rates comparable to those found in countries with high TB incidence to rates less than 1 per 100,000 population. Although

the fundamentals of TB prevention and control are similar in any jurisdiction, TB control programs in some settings face unique challenges.

### *Urban centres*

TB disproportionately affects the socially marginalized, emphasizing the social rather than medical aspect of this disease. Large urban centres face particular TB prevention and control challenges by virtue of the number of population subgroups at high risk of LTBI and progression to active disease, the number of high-risk settings for TB transmission and the multicultural nature of modern large urban centres.

### *Populations at high-risk of LTBI and active disease*

Populations of large urban centres, compared with the general Canadian population, comprise specific groups that are at high risk of LTBI (e.g. immigrants from countries with high TB incidence), of new or recurrent infection (e.g. injection drug users and homeless persons) and of progression to active TB disease once infected (e.g. persons with HIV/AIDS or those taking immunosuppressive treatments). Urban centres are also the location of many congregate settings (e.g. tertiary care hospitals, hospices, homeless shelters and correctional facilities) that house persons at high risk of active disease if infected with tubercle bacilli and where TB transmission can occur. Many of these populations are difficult to access using traditional TB control measures (see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control). The dramatic resurgence of TB in New York City in the early 1990s provides an illustration of what can happen when these factors are combined with a neglect of public health TB control infrastructure.<sup>10</sup>

### *Destination of recent immigrants from countries with high TB incidence*

The majority of immigrants arriving in Canada currently come from countries with high TB incidence and initially settle in major urban centres (see Chapter 1, Epidemiology of Tuberculosis in Canada). Immigrants cleared of having active disease but who are assessed to be at increased risk of progression of inactive pulmonary TB or LTBI to active TB disease are placed under immigration medical surveillance (see Chapter 15, Immigration and Tuberculosis Control in Canada, and Appendix I, Guidelines for the Investigation and Follow-up of Individuals Under Medical Surveillance for Tuberculosis after Arrival in Canada (2007)). The public health follow-up of these persons can constitute a significant workload for TB control programs in jurisdictions receiving a large number of immigrants. The diverse countries of birth of recent immigrants also challenge the ability of TB control programs to provide culturally and linguistically appropriate services and to overcome the stigma often related to TB in immigrants' country of birth. Foreign birth is also a significant predictor of drug-resistant TB,<sup>11</sup> which complicates the management of both the case and the contacts.

### *Areas of low TB incidence<sup>12</sup>*

Areas of low TB incidence have an ongoing potential for sporadic TB cases because of the likely extent of LTBI in certain population subgroups (e.g. older age groups and recent immigrants from countries with high TB incidence) and the acquisition of LTBI from travel to such countries. TB cases not detected in a timely manner have the potential to create prolonged and difficult-to-control outbreaks,<sup>13</sup> which pose immediate threats to the health of the community, expand the reservoir of LTBI, require significant diversion of already scarce public health resources and lead to avoidable complications and deaths in the patients affected.<sup>14</sup> Therefore, TB control programs in low-incidence areas need to maintain the capacity to find and treat sporadic cases, conduct contact investigations and prevent TB in those persons found to have LTBI and high risk of reactivation to TB disease.

Continued prevention and control of TB is the goal in low-incidence areas and is of national importance, since other jurisdictions in the country will be able to learn from and build upon their experience. A TB prevention and control plan should integrate local challenges to TB control and essential program elements into a strategy that takes into account the local or regional epidemiology of TB and provides interim objectives for assessing the implementation of the plan and its effectiveness.<sup>15</sup> Some of the components of the strategy will require additional resources for implementation and include the following.

**Sustaining tuberculosis control program resources:** The ultimate responsibility for TB control rests with the public sector. As TB case loads decrease there is the tendency to divert public health resources to other areas, potentially leading to the elimination of the TB control program rather than the disease itself and recreating the conditions that make a resurgence of TB likely.<sup>10</sup> Case counts alone should not be used as the basis for projecting resource needs since case numbers do not fully reflect the work involved in conducting contact investigations associated with each case, in investigating persons with suspected TB who do not, upon further investigation, turn out to have active disease, or in screening activities. Case counts also do not capture the work involved in management of a case who moves to another jurisdiction during treatment since, according to Canadian TB surveillance rules, the case is reported by the jurisdiction of usual residence at the time of diagnosis.

**Retaining dedicated staff:** In areas of low incidence, TB control resources and expertise may be decreased if the program is combined with other communicable disease control programs. A core TB control capacity with dedicated and accountable staff should be maintained with the ability to shift resources to TB control activities if needed. Access to an epidemiologist at the local or the provincial/territorial level is also essential to ensure that TB data are systematically and accurately captured and analyzed to help better characterize risk groups, leading to more effective, targeted interventions.

**Preventing the loss of TB expertise:** As TB case rates decrease there is a loss of practical experience with the disease and a decline in both public health and clinical expertise in the management of TB. Ongoing

investments are needed to retain experienced public health TB prevention and control staff and provide them with regular training so as to maintain accurate and current knowledge of TB and its management. Public health authorities also have a responsibility to ensure that local health care providers are aware of the currently recommended guidelines for the diagnosis and treatment of TB. If authority for TB control resides entirely at the local level, provincial/territorial TB control authorities should monitor local TB control programs for any lapses in program activities and for potential problems, such as protracted outbreaks. In jurisdictions where TB control authority is shared between localities and the province/territory, there may be the potential for TB experts to oversee and assist in control activities for several regions of the province/territory.

The providers and the arrangements for provision of public health services to First Nations populations vary among provinces/territories (see Chapter 14, Tuberculosis Control in First Nations and Inuit Populations). However, in all circumstances, TB prevention and control activities in First Nation communities are required to conform to the relevant provincial/territorial public health legislation where the community is located.

**Maintaining access to diagnostic capacity and specialized care facilities:** Jurisdictions with a low incidence of TB may not be able to maintain diagnostic proficiency or justify the expense of maintaining a TB laboratory. There also may not be a local facility with the experience and engineering features required for effective infection control to deal with TB patients who may occasionally require prolonged hospitalization or involuntary detention. Therefore, access to these services should be proactively secured at either the regional, provincial/territorial or interprovincial/territorial level and written policies and procedures used to facilitate the timely transportation of patients and/or specimens to these facilities.

**Shifting perspective from managing cases to preventing cases:** Although core control program capacities should be maintained, additional resources may be needed or some existing resources shifted to prevention activities, to achieve a more rapid decline in TB case rates. Raising the profile of prevention may prevent the loss of TB control program resources as case counts decline but will require the support of policymakers and the community. Garnering broad community support for public health TB prevention and control initiatives also has the capacity to improve the trust of public health authorities, improve the effective conduct of contact investigations and expand services for the targeted testing and treatment of LTBI in high-risk populations. TB prevention activities should be restricted to well-delineated projects with access to populations with a high incidence of LTBI and a high risk of progression to active disease if infected, methods to ensure that treatment of LTBI is completed, a feasible implementation plan and an evaluation component to assess whether resources are being used effectively.

### *Remote communities*

Although remote communities face some of the same challenges faced by TB control programs in areas of low disease incidence, these communities have some unique TB control challenges.

**Turnover of health care staff:** Health care professionals in remote communities have a limited number of colleagues with whom to share on-call duties or to consult on complex medical issues. There is often no health care infrastructure to support ongoing medical education and limited occupational, educational and socio-cultural opportunities for spouses/partners and families. As a consequence, remote communities often have a rapid turnover of health care providers, each with varying degrees of TB knowledge. The result may be diminished access to health care, fragmentation in patient care, delays in the diagnosis of active cases and a lack of thorough and timely contact investigations. Without a stable health care workforce there is also less opportunity to educate the local community about TB, which may result in a delay in accessing health care when a person develops symptoms consistent with active TB.

**Access to health care personnel and facilities:** Residents of remote communities may have to travel great distances to receive TB-related medical evaluation, advanced diagnostic procedures, consultations with specialists and hospitalization. As well, patient specimens will often need to be sent to distant diagnostic facilities for testing. The distances involved or the means of access to a community (e.g. road access alone during winter months when ice roads can be built) will often necessitate the use of air transportation, which can strain the budgets of TB control programs and impede the receipt of timely results. Adverse weather that grounds aircraft can also further delay the transport of patients, diagnostic specimens and medications. In jurisdictions with widely dispersed remote communities or with persons who spend prolonged periods of time “on the land” (e.g. some First Nations communities), the administration of DOT by health care workers may be impractical.

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## Introduction

The first priority of a tuberculosis (TB) control program is the early identification and curative treatment of all infectious cases. This reduces the bacterial burden and decreases the risk of infection being transmitted to others. The next priority is evaluation and follow-up of close contacts of active cases in order to identify secondary cases, source cases and those with recently acquired latent TB infection (LTBI).<sup>1-3</sup>

There is good evidence that close contacts of a case of infectious TB are at increased risk of active disease. During the contact investigation, 1% to 2% of close contacts are typically found to have active disease.<sup>4</sup> In addition, in 5% to 12% of contacts found to be infected active disease will develop within 2 years of exposure.<sup>5-7</sup>

## Definitions

**Index case:** the first case of active TB identified.

**Source case:** an active infectious case likely to have transmitted infection to others. The source case may or may not be the same as the index case.

**Contact:** a person identified as having come in contact with a case of active disease. The degree of contact is usually further defined on the basis of closeness. Contacts may be classified as close, casual, or community:

*Close household contacts* are those who live in the same household as the infectious case. Household contacts are considered by definition to share breathing space on a daily basis with the source case.

*Close nonhousehold contacts* are those who have regular, prolonged contact with the source case and share breathing space daily but do not live in the same household. These include regular sexual partners and close friends.

*Casual contacts* are those who spend time less frequently with the infectious case. These may include classmates, colleagues at work or members of a club or team.

*Community contacts* are those living in the same community or attending the same school or workplace.

## Principles of TB Transmission

The amount of contact necessary for TB infection to be transmitted is variable and depends on the infectiousness of the source case and the environment in which contact occurs. In general, laryngeal TB and pulmonary TB, particularly cavitary pulmonary TB, are considered the most infectious forms of the disease.<sup>8</sup> Sputum or other airway secretions are often culture positive and occasionally smear positive in patients with miliary TB.<sup>9</sup> 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.<sup>10</sup> Therefore, miliary and pleural TB should be considered as potentially contagious.

An important factor in determining infectiousness is whether or not acid-fast bacteria (AFB) are present on microscopic examination of sputum. It has been found that infectiousness is several times greater in smear-positive than in smear-negative cases.<sup>11</sup> Other factors that are associated with increased infectiousness include adolescence, adult age, coughing, sneezing and singing. It is important to consider all these factors together in evaluating the infectiousness of the case.<sup>1</sup>

The environment in which the contact occurs is also important in assessing infectiousness. 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*.<sup>12,13</sup> (see Chapter 3, Transmission and Pathogenesis of Tuberculosis).

## Objectives of Contact Investigation

Contact investigation has three main objectives:

- Identify and initiate treatment of secondary cases.
- Identify TB-infected contacts in order to offer treatment of LTBI.
- Identify the source case who infected the index case if the index case is a child, has primary TB or has nonrespiratory TB.

## Principles of Contact Investigation

### Prompt reporting of active cases

All province/territories legally require reporting of active TB. Prompt reporting to public health authorities allows the treating physician and TB control program staff to initiate the contact investigation quickly and carry it out in an organized, collaborative manner.

### Initiation of contact investigation as soon as possible

Although the interval between infection and disease can range from weeks to years, active TB is most likely to occur within 2 years after infection. Rapid evaluation of close contacts allows prompt identification of those who 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, public health authorities should ensure that all the necessary investigations to confirm the diagnosis and determine the degree of infectiousness have been initiated. All possible settings of transmission should be identified and efforts made to find contacts in those settings. If TB is strongly suspected, investigation of close contacts, especially children, HIV-infected contacts and others at high risk of disease progression if infected, should begin immediately while final confirmation of the diagnosis is awaited. Investigation of casual contacts should await confirmation of the diagnosis by culture or amplification testing.

## Contact investigation conducted in an organized and systematic manner

### *The infectiousness of the source case*

The extent of contact investigation is determined in large part by the degree of infectiousness of the source case. Smear-positive pulmonary cases are considered in general to be 6 to 10 times more contagious than smear-negative pulmonary cases, and cases of laryngeal TB are considered 4 to 5 times more contagious than smear-positive pulmonary cases.<sup>1,2</sup>

Children under age 10 are generally considered less infectious than adolescents and adults, and the investigation of household contacts of a pediatric index case is carried out primarily to find a source case. However, if children present with adult-type pulmonary TB (cough, cavitation on chest x-ray, smear-positive sputum) they may be infectious, and a contact investigation similar to that for smear-positive adults should be undertaken.

Cases of nonrespiratory TB are, with rare exception, considered non-infectious. Contact investigation surrounding such cases may be carried out with the aim of identifying a source case among close contacts. This is especially important if the case appears to have resulted from recent transmission, e.g. meningeal TB in a child.

### *The likely period of infectiousness*

Cases of pulmonary TB are generally considered to become infectious at the time of onset of cough. If no cough is reported or if the duration is difficult to determine, the time of 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.

Recent guidelines<sup>14</sup> published by the U.S. Centers for Disease Control and Prevention recommend that in the case of smear-positive or symptomatic disease the patient should be considered to have been infectious for a period of 3 months before symptom onset or before the first positive finding consistent with TB disease, (e.g. abnormal chest x-ray), whichever occurs first. 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. These guidelines are based on expert opinion rather than controlled trials. The decision about the period of contagiousness, then, will need to be determined for each case according to these guidelines and to the clinical situation. Priority should always be given to contact tracing during the period when the TB patient was symptomatic.

Please see Chapter 16, Tuberculosis Control Within Institutions, for a description of when airborne isolation may be discontinued with a suspected or confirmed TB case.

### *The degree of exposure to the source case*

The interview of an infectious TB patient to determine who the contacts are should ideally begin within 1 day of the case being notified. A follow-up interview 1-2 weeks later may be helpful in identifying additional contacts. Named contacts are then assigned priority on the basis of the likelihood of infection and the potential hazard to the individual contact if infected.<sup>14</sup>

- **AFB sputum smear-positive, cavitary pulmonary TB or laryngeal TB cases**

High-priority contacts include household contacts, contacts under age 5 years, those with risk factors for progression of LTBI to TB disease, (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Table 2), contacts exposed during bronchoscopy, sputum induction, autopsy and other high-risk medical procedures, and those exposed in congregate settings. However, it may not be feasible or necessary to assess all such contacts urgently. The extent and order of contact investigation is based on the extent of exposure to the case and the vulnerability of the contact.

The first circle of contacts includes those who live in the same household as the case, as well as close nonhousehold contacts (see earlier definitions). This circle usually does not include classmates or casual colleagues at work. It ideally includes at least 8 to 10 people who would not otherwise be expected to have a positive tuberculin skin test (TST) result. This can be difficult to evaluate when the background rate of positive TSTs is high (for example, people who immigrated to Canada from high-incidence countries or countries in which BCG vaccination was widely used in childhood). In these cases, TST results in Canadian-born children may be the most useful in assessing transmission. Thus, the first circle may have to be extended to include nonfamily contacts, such as close friends or workplace contacts who are not expected to be TST positive. If possible, testing of the first circle of contacts should begin within 7 working days of their being identified as contacts.

Transmission is considered to have occurred if a secondary case is identified in any contact, if there are TST converters, if the positive TST prevalence rate among contacts is higher (e.g. by at least 50%) than the rate of a similar population without recent exposure (see Table 1) or if a child under age 5 years is infected without another probable source. When transmission occurs, contact investigation should be extended first to other high-priority contacts who have not been assessed and then to a second circle, which may include classmates or colleagues at work, or those in recreational settings that are regularly frequented by the case. The results of the investigation of this group of contacts are then used to determine the need to expand the investigation yet further.

For laryngeal TB, contact investigation should include the second circle of regular contacts from the outset.

**Table 1**  
**Expected Prevalence of TST Result**  
**of  $\geq 10$  mm in Various Canadian Populations\***

Population	Expected Prevalence of TST $\geq 10$ mm
Canadian-born non-aboriginal children	< 3%
Canadian-born non-aboriginal adults, not BCG vaccinated	< 10%
Canadian-born non-aboriginal adults, BCG vaccinated	20%-25%
Aboriginal Canadian children	$\leq 5\%$ ; one study of Cree students in Quebec reported 15%
Aboriginal Canadian adults	20%-30%
Foreign-born children from high TB incidence countries <sup>†</sup>	15%-25%
Foreign-born adults who lived for 20 years or more in high TB incidence countries <sup>†</sup>	40%-50%; one study of Tibetan refugees reported > 90%
Health care workers	20%-40%
Residents $\geq$ age 65 in long-term care facilities	20%-30%
Residents in homeless shelters	40%
Correctional facility inmates	20%
Injection drug users	20%

\* Based on *Compendium of Latent Tuberculosis Infection (LTBI) Prevalence Rates in Canada*, Public Health Agency of Canada, 2007 (full report available at <http://www.publichealth.gc.ca/tuberculosis>).

<sup>†</sup> In Canada a "high TB incidence country" is defined as a country whose average WHO-estimated TB incidence rate over the most recent previous 3 years of reporting is  $\geq 15$  smear positive pulmonary TB cases per 100,000 population. International TB incidence rates may be viewed at <http://www.publichealth.gc.ca/tuberculosis>.

- **AFB sputum smear-negative respiratory TB cases**

High-priority contacts include children under age 5 years, contacts with risk factors for progression of LTBI to TB disease (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Table 2), other household contacts and contacts exposed during bronchoscopy, sputum induction, autopsy and other high-risk medical procedures. Other congregate setting contacts are of lower priority. However, each situation should be evaluated individually by public health authorities in collaboration with the treating physician.<sup>15-17</sup>

- **Other considerations**

The decision to expand a contact investigation can be difficult and should include consideration of the probability of finding infected individuals among more casual contacts. Contacts with less exposure have a positive TST prevalence rate that is usually four to six times less than that among household contacts.<sup>4,9,18-20</sup>

Although sometimes difficult to apply in practice, a systematic, organized approach to contact investigation is ideal for purposes of interpreting the results of TST testing. There is often pressure on a public health department or physician to initiate widespread contact investigation from the outset. When this is done, it is often impossible to interpret the results of a positive TST in individual patients. Contacts may then be mistakenly identified as recently infected and the undertaking expanded yet further. As well, this can lead to widespread concern among other contacts as to the infectiousness of the patient and the risk of transmission to casual contacts.

However, in some settings, it is far more practical and feasible to perform TSTs for an entire group (such as a class at school or coworkers in a work setting) than to attempt to identify the specific individuals who were most exposed. Factors such as the ability to reliably measure the degree of exposure of different individuals in the setting, the manner in which persons are grouped within the setting, and the capacity to be able to extend the investigation to a larger group if it becomes necessary<sup>21</sup> should be taken into account in deciding on the extent and number of persons 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 necessary to do widespread testing from the onset.

When there is a need to investigate a number of contacts in a single setting, such as school or workplace, it is often best to carry out the investigation on site. This usually leads to a higher number of contacts presenting for testing and for medical follow-up, and is a more effective and efficient way of carrying out the investigation and obtaining the necessary information.<sup>21</sup> However, this type of investigation requires very effective organization. Following certain principles will greatly facilitate the investigation:

- identify a single individual who will be responsible for organizational aspects of the screening;
- ensure that adequate human resources will be available throughout the screening process;
- adapt the screening session to the nature of the setting; ensure that screening is carried out at a time that is acceptable and in a manner that offers the best opportunity for contacts to come to the screening;
- ensure the collaboration of occupational health services, human resources or other administrative staff in the setting;
- carry out information sessions for as many people as possible before the screening sessions, including contacts as well as other individuals who are present in the setting;
- prepare a communication plan, and ideally identify one individual who is responsible for the media and communications to the general public;

- identify adequate medical and other personnel for timely follow-up evaluations;
- ensure that all contacts referred for medical evaluation will be managed in the same way and given the same information;
- ensure that the necessary results are transmitted promptly to public health/TB control;
- make all efforts to ensure that the confidentiality of the source case is maintained, unless required or permitted to disclose under applicable legislation, and avoid making any reference to any aspect of the clinical history of the source case.<sup>16,21</sup>

### Standard approach to the evaluation of contacts for the presence of active disease and evidence of recent infection

All close contacts should be interviewed systematically regarding the type and intensity of the contact, presence of symptoms, risk of progression to active TB if infected and history of treatment of TB or LTBI. If appropriate, further evaluation to exclude active TB must be carried out.\* Once active disease has been excluded, all exposed contacts should receive a TST unless there is a history of prior treatment of TB or a documented prior positive TST. The TST should be carried out and interpreted regardless of BCG vaccination status.

Special precautions must be exercised when investigating close contacts who are pregnant.\* Pregnancy does not constitute a contraindication to the TST. However, when a pregnant contact has a new positive TST or a TST conversion, or is symptomatic, she should undergo a single view (posterior-anterior) chest radiograph with double (front and back) shielding of the abdomen. If possible, and especially if the individual circumstances permit (for example, if the patient is asymptomatic and the period of chest radiograph deferral would be a matter of a few weeks), chest radiography should be avoided in the first trimester.

Contacts of patients who are HIV infected are more likely to be HIV infected themselves and should be investigated promptly.<sup>14,22</sup> Because of the high frequency and rapidity of progression from TB infection to TB disease in HIV-infected individuals, HIV counseling and testing should be offered to such contacts, as well as to any contacts found to have risk factors for HIV.

Conversion of the TST from negative to positive can take up to 8 weeks after infection. Therefore, if the initial skin test is performed within 8 weeks of the last exposure to the infectious case and is negative, a second skin test should be carried out at least 8 weeks after the contact was broken.

Investigation of casual contacts (those in the second circle or beyond) should not normally be initiated until the diagnosis has been confirmed in the source case. Although testing should not be unduly delayed, carrying out the tuberculin testing more than 8 weeks after the last contact with the infectious case ensures

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

that an adequate period for skin test conversion has occurred and obviates the need for further testing.

**There are almost no indications for a two-step TST in the setting of a contact investigation.** Skin test conversion can occur as early as 3 weeks after exposure,<sup>23,24</sup> and it will generally be impossible to differentiate between true TST conversion and a boosted reaction in the setting of a contact investigation. Therefore, any change in skin test reactivity should almost always be considered as a true conversion (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, for further information concerning the interpretation of the TST in contacts).

**Table 2**  
**Guidelines for Tuberculin Skin Testing in the Context**  
**of a Contact Investigation, According to Previous TST Results**

<p><b>No documented previous TST result</b></p> <p>In this case, a TST result of 5 mm or more on the first test or on the test at least 8 weeks after the last exposure is considered positive.</p>
<p><b>Documented previous TST result less than 5 mm</b></p> <p>In this case, the TST result of 10 mm or more on the first test or on the test at least 8 weeks after the last exposure is usually considered positive. However the circumstances of the contact must be taken into account. For example, if the source case is highly infectious, if there was close or prolonged contact, if the contact is under age 5 or if the contact has impaired immunity, then an increase of 6 mm from the previous TST result may be considered a conversion. Decisions in this regard need to be individualized.</p>
<p><b>Documented previous TST result between 5 and 9 mm, no history of treatment of TB disease or LTBI</b></p> <p>In this case, the TST should be repeated. An increase of at least 6 mm is considered a positive result, either on the initial TST or on the second test done at least 8 weeks after the last contact.</p>
<p><b>Documented previous TST result of 10 mm or greater or history of treatment for TB disease or LTBI</b></p> <p>Contacts who have a documented prior positive TST or history of treatment for active TB disease or LTBI should not undergo post-exposure TST. Evaluation of these contacts should include assessment for signs/symptoms of active TB disease and additional investigations (e.g. chest radiography, sputum examination) as deemed necessary. Clinical history and results of clinical investigations should guide treatment decisions.</p> <p>Very high-risk, severely immunocompromised persons (e.g. those who are HIV coinfecting) who are re-exposed to infectious TB after having already completed a satisfactory course of treatment for TB disease or LTBI in the past should be considered for a repeat course of treatment for LTBI.</p>



### Assurance that treatment of LTBI is initiated rapidly in those most susceptible

Once it has been determined that disease activity is unlikely (negative symptom inquiry, unremarkable or stable chest radiograph [posterior-anterior and lateral views for children], negative sputum or gastric aspirate smears), treatment of LTBI should be initiated immediately after the first TST, even if the result is < 5 mm induration, for the following persons:

- those with HIV infection and a high risk of TB infection (contact of infectious TB, from a high TB incidence country or high-risk lung scar on chest x-ray);
- contacts with other severe immunodeficiency and high risk of TB infection;
- children less than 5 years of age.

In the event that disease activity cannot be satisfactorily excluded until culture results are available, it is recommended that either a) treatment of LTBI be withheld until cultures are proven to be negative, or b) treatment for disease be started and revised to treatment of LTBI once cultures are proven to be negative.

Among children, the treatment may be stopped if the second TST, done at least 8 weeks after final contact with the infectious case, remains negative. If the child is very young (under 6 months of age) the treatment should be continued until the child is old enough ( $\geq 6$  months) to reliably respond to the TST. Chest radiography needs to be repeated if the child did not receive treatment of LTBI or if he or she has symptoms that suggest disease activity.

Contacts with HIV infection or other severe immunodeficiency should receive a full course of treatment of LTBI regardless of the TST results once active disease has been ruled out. This is because of the higher risk of a false-negative TST result and the high risk of disease if they are truly infected.

### Assurance that the contact investigation is coordinated and carried out by experienced personnel

Contact investigations may require considerable time, expertise and coordination, and are usually best managed by public health/TB control authorities in collaboration with the treating physician and other providers. TSTs need to be performed by those experienced in the administration of the test and the interpretation of the results (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, for a description of the method). Contact investigations carried out in work or school settings are often associated with high levels of anxiety and fear. Efforts to alleviate this type of response should be undertaken from the outset. Clear information needs to be provided, and plans should be made to carry out testing rapidly and in a well-organized manner. Communication to those in the setting from all personnel involved in the investigation must be clear and consistent, especially with regard to interpretation of the TST and decisions regarding treatment of LTBI.\*

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

## Evaluation of the contact investigation

Evaluation of the results of the investigation of each circle of contacts will allow determination of the risk of transmission, attack rates, etc. It is also important to know the number of contacts, particularly close contacts, who underwent a proper evaluation and, among those eligible for preventive therapy, the number who accepted and completed the same. Evaluation of the outcome of the contact investigation is essential for program evaluation in order to determine the appropriateness of the decisions made and future planning. Please see Chapter 6, Treatment of Tuberculosis Disease and Infection, for program performance standards for the treatment of LTBI.

### *Summary Points:*

#### Steps in Contact Investigation and Follow-Up

1. It is important that the treating physician and laboratory report all new or suspected cases of TB within 48 hours to appropriate public health authorities.
2. Public health authorities and the treating physician should collaborate to identify all household and other close contacts promptly.
3. Public health authorities and the treating physician should collaborate to interview close contacts regarding the circumstances and duration of contact, 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 close contacts with no previous history of TB or documented positive tests receive a TST.
5. Positive TST results in the context of contact investigation: see Table 2.
6. A history of BCG vaccination does not alter the interpretation of the skin test results. All such persons, as well as all children under age 5, all those who are symptomatic and all those who are HIV seropositive or severely immunocompromised (regardless of the results of the initial TST) should have a medical evaluation, including chest radiography.
7. Any close contacts with symptoms or radiographic abnormalities consistent with TB disease should have sputum or other specimens submitted promptly for culture for *M. tuberculosis*.
8. Treatment of LTBI should be recommended for contacts with the following:
  - positive TST (see above) or converter with a normal chest x-ray and no symptoms of active disease;

- TST < 5 mm if there is HIV infection and high risk of TB infection (contact of infectious TB, from high TB incidence country or abnormal chest x-ray);
  - TST < 5 mm if other severe immunodeficiency and high risk of TB infection;
  - TST < 5 mm in a child less than age 5 years until the repeat TST is negative at least 8 weeks after the last exposure and the child is at least 6 months old at the time of repeat testing.
9. The TST should be repeated at least 8 weeks after the last exposure for all close contacts who had an initial negative test
  10. Public health authorities should determine the need to extend the contact investigation according to the results of the investigation of close contacts, the contagiousness of the index case and the nature of the exposure of additional contacts
  11. Extended contact investigations must be carried out in a systematic and organized manner – public health/TB control should coordinate these investigations\*
  12. The results of the contact investigation should be evaluated

## Contact Investigations in Special Settings

Contact tracing can be particularly challenging under certain circumstances. Social and cultural factors, e.g. homelessness and illicit behavior, can set a group apart from society at large. Investigators need to be aware of these differences so that they do not become frustrated but, rather, prepare ahead of time by training staff and allocating adequate resources for these situations. The challenges include the following:

- difficulty identifying contacts
- many sites of potential exposure
- large numbers of contacts who are difficult to locate
- politically charged situations
- contacts with comorbidities, which complicate their assessment
- high prevalence of underlying TST positivity
- noncompliance with TB assessment among contacts
- access to care issues.

### Homeless and underhoused persons

Several studies have evaluated the outcome of TB contact investigations in the general population and have found a median of 4 (average 6) close contacts for each TB case.<sup>25,26</sup> Among marginalized populations, like homeless persons, fewer contacts are identified.<sup>25-27</sup> Many challenges exist when conducting

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

contact tracing in this population because their lifestyles, housing arrangements and social relationships are unconventional. Information that is easily collected from other individuals with TB can prove very difficult to gather from homeless cases. Questions about where contacts live can result in many locations being listed because cases are often highly mobile. Homeless cases often do not know the names of people they socialize with, so questions about contact names may prove fruitless.

Many homeless TB cases also suffer from comorbidities such as alcoholism, drug addiction or mental illness, which complicate the management of TB. They may have poor access to health services and be mistrustful of the health system, which would make them less likely to come forward for treatment. This leads to delays in TB diagnosis, worsening of the disease and prolonged periods of infectiousness resulting in 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 treatment of LTBI.<sup>28</sup>

Recent studies have suggested that the concentric circle approach (i.e. examining groups at lower risk of exposure only if higher risk groups have a high rate of infection) has its limitations.<sup>29-31</sup> Studies have demonstrated TB transmission occurring at times and places undetected by conventional contact investigation.<sup>30,31</sup>

### **Incorporating new approaches to contact tracing in special settings**

Newer approaches described in the literature are worthy of consideration, especially in nontraditional settings.

#### *DNA genotype fingerprinting*

DNA fingerprinting can be used to confirm or disprove suspected linkages between cases.<sup>32-34</sup> Genotyping also helps to identify case clusters that would otherwise not be recognized. The Massachusetts Department of Public Health evaluated the impact of DNA fingerprinting on their practice and reported that genotyping identified enough unexpected links and sites not considered by the concentric circle method to justify consideration of more casual contacts. Genotyping allows earlier recognition of clusters for timely investigation and institution of control measures, and has been found superior to routine contact investigation in identifying source cases for patients who are homeless.<sup>27,30</sup>

#### *Location-based contact investigation*

The role that social networks play in disease transmission has been extensively studied in sexually transmitted infections. This type of analysis examines relationships between cases and contacts to identify settings and behaviors that set the core group apart. Recently network analysis has been applied to the study of TB outbreaks.<sup>35</sup> Various authors have reported that epidemiologic links among cases were enhanced when inquiries about common locations were included in case interviews.

### *Testing casual contacts once at 8 weeks after last exposure*

Two studies have recently shown that a single TST performed 8 weeks after exposure is sufficient when evaluating casual and community contacts.<sup>36,37</sup> Testing once also avoids the misdiagnosis of TST conversion in populations that are prone to the boosting phenomenon from previous TB exposure.

### **Correctional facilities**

Residents of correctional facilities are known to have a higher prevalence of TB disease.<sup>38</sup> Facilities 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.

When an infectious case of TB is identified in a correctional facility, contacts that have spent time with the case during the infectious period need to be assessed. They can include fellow inmates and employees at the facility, transportation staff, visitors, individuals at other sites such as courthouses or other correctional institutions, and family or community members before incarceration. To assist in the identification of contacts, correctional facilities need to track inmate transfers, releases, and movement within a facility and within the system.

Correctional Service Canada guidelines are available for TB prevention and control in institutions that house inmates sentenced to 2 years or longer. To view the current guidelines, please see <http://www.publichealth.gc.ca/tuberculosis>.

### **Health care institutions**

When an unsuspected case of TB is found in a health care facility, often the appropriate infection control measures had not been in place to prevent transmission. This can result in a large number of contacts who need to be assessed: hospital staff (e.g. nurses, physicians, housekeeping staff, laboratory workers, radiology staff, physiotherapists, respiratory technologists), patients, family members, volunteers and visitors who were exposed to the case during the infectious period. If the case arrived from the community or was transferred from another facility, contacts outside the institution would also need to be considered.

It is important to approach contact identification in an organized fashion, systematically working out where the case had been during the infectious period. Some contacts are easier to identify than others. Staff assignment lists can be used to identify employees, but it is often difficult to identify other patients and visitors who may have shared the same air space as a case. In some circumstances, it may be necessary to post notices in the health care facility notifying individuals who were on site during a specific period about TB exposure and the need to follow up with their physician.

Staff who have been exposed are tested by the occupational health department of the facility. It is helpful to know their baseline TST result in order to identify

converters. Inpatients who were exposed are tested by the health care institution, but former patients, visitors, family members and other exposed persons should be advised in writing of the need to be assessed for LTBI. Notification may come from the hospital and/or public health authority and testing may be done by the hospital, public health authority or personal physician.<sup>39</sup>

### Immunosuppressed patients

Individuals who are immunosuppressed are at much higher risk of TB disease after infection with *M. tuberculosis*: among dialysis patients in British Columbia, the annual rate of TB was 25 times higher than among age-matched population controls.<sup>40</sup> Among HIV-infected persons, especially those with low CD4+ cell counts, up to 50% had TB in the first 2 years after infection with *M. tuberculosis*.<sup>41</sup>

Contact tracing among immunosuppressed patients is complicated by false-negative TST results due to anergy. However, routine anergy testing is not recommended (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus). Interferon-gamma release assays are being investigated as a possible replacement for the TST.

### Remote communities

Undertaking a contact investigation in a remote community may be especially challenging. In addition to the distances involved, there may be staffing and resource issues. In remote First Nations or Inuit communities there may also be language and cultural barriers to the successful completion of a contact tracing undertaking. Nowhere are organization, education and communication more important. A collaborative, nonjudgmental approach is encouraged by the provincial/territorial TB program, the local public health/TB control program, Health Canada's First Nations and Inuit Health Branch if it has responsibility for the community, local health care providers and the community working closely together to identify secondary cases and contacts and then to see that they are properly managed. Depending upon the circumstances, a mobile or portable radiography unit may need to be brought to the community. Otherwise, a special effort should be made to facilitate the timely transport of persons for investigation. Where possible, directly observed preventive therapy is the treatment of choice for newly infected contacts in First Nations and Inuit communities.<sup>42</sup>

### Contacts during air and other public transport travel

There is an international World Health Organization (WHO) protocol<sup>43</sup> for notifying certain contacts of a person with infectious TB who traveled on an international flight with a total duration of  $\geq 8$  hours (including ground delays after boarding, flying time and ground delays after landing) within the previous 3 months. The 8 hour duration is based on epidemiologic studies reviewed in the WHO guidelines.

In Canada, reports of the following TB cases who traveled by air should be made to the Public Health Agency of Canada (PHAC) through the provincial/territorial TB program using the reporting form available at <http://www.publichealth.gc.ca/tuberculosis>, (see Reporting Forms).

- infectious at the time of the flight, which means the case should have been in airborne isolation at the time of the flight as per the criteria in Chapter 16, Tuberculosis Control Within Institutions, Airborne Isolation of Patients with Suspect or Confirmed TB;
- flight occurred less than or more than 3 months previously; this is because the risk of someone being infected during the flight and developing disease does not cease after 3 months; also, some airlines are able to retrieve passenger records for flights more than 3 months previously;
- flight of any duration if the case has laryngeal TB (due to increased infectiousness), multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB (because of the more serious consequences of spread of infection);
- flight with a total duration of  $\geq 8$  hours (including ground delays after boarding, flying time and ground delays after landing) for other infectious TB cases.

The report should be made as soon as possible (e.g. smear positive, awaiting culture and antibiotic sensitivity results) as this speeds up the process of collecting the necessary passenger information from the airline.

Reporting of travel-related cases also applies to domestic Canadian flights. However, the 8-hour guideline for nonlaryngeal, non-MDR and non-XDR cases does not necessarily apply to small aircraft (if they do not have laminar airflow and high-efficiency air filters) or to trains, buses and other non-air transport because of their different ventilation characteristics. When in doubt as to whether transport contacts of an infectious TB case should be assessed, report the flight.

### **Possible contact with infectious TB cases during residence or travel in a country with high TB incidence**

Please refer to Chapter 13, Surveillance and Screening in Tuberculosis Control.

## **Management of a TB Outbreak**

### **Definition**

The definition of an outbreak of any disease is the occurrence of more cases than expected in a given time. In some instances, TB outbreaks will be identified only retrospectively, after cases have been found to be linked epidemiologically or by genetic analysis. In other cases, spatial or temporal associations may suggest

ongoing transmission and an outbreak. In low incidence settings, any such clustering should suggest an outbreak and prompt further investigation.

The following working definition of outbreak was recently proposed by the U.S. Centers for Disease Control and Prevention for planning investigations:<sup>14</sup>

- “During (and because of) a contact investigation, two or more contacts are identified as having active TB, regardless of their assigned (contact investigation) priority; or
- Any two or more cases occurring (within)  $\leq 1$  year of each other are discovered to be linked, and the linkage is established outside of a contact investigation (e.g. two patients who received a diagnosis of TB outside of a contact investigation are found to work in the same office, and only one or neither of the persons was listed as a contact to the other). The linkage between cases should be confirmed by genotyping results if isolates have been obtained.”

### Goals

The goals of the investigation and management of an outbreak of TB are

- 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 identify new cases of active TB and initiate treatment;
- to identify persons with recently acquired LTBI, so that preventive therapy can be given before active disease develops.

### Managing an outbreak

#### *Establish adequate staffing and resources*

It is essential from the onset of the outbreak that there be adequate staffing and resources for investigation and management:

- public health/TB control staff to register cases, define infectiousness, coordinate the investigation and provide consultation and communication with those in the field;
- field staff to collaborate with public health/TB control staff and in some cases to carry out the contact investigation and follow-up;
- medical consultants with expertise in TB to review chest films, evaluate patients for the presence of TB, hospitalize if necessary and manage suspected cases and contacts in a consistent manner and without delay;
- a clinical site in which chest radiography providing films of adequate quality may be conducted locally and promptly;



- hospital facilities that can offer airborne isolation, diagnostic examinations and treatment without delay;
- links to other laboratories and medical facilities to ensure that there is access to additional diagnostic and laboratory procedures as needed;
- adequate transportation of specimens, x-ray films and, if necessary, patients;
- staff who will be able to guarantee supervision of the complete course of drug treatment of all active cases (provision of at least 1 year's additional staffing after the outbreak is over may be required);
- communications personnel who will interact with the media and provide regular updates to the community on the status of the investigation;
- staff and resources to carry out the evaluation.

***Ensure that the roles and responsibilities of all those involved are clear***

It is also crucial, from the onset of the investigation, that the roles of all those involved in the investigation and management are clearly defined. Collaboration among all levels of health care needs to be established. There needs to be clear agreement regarding procedures to be followed in the investigation and management of suspected cases and contacts. There also needs to be regular feedback and communication among all levels and agencies involved in the investigation.

***Ensure that all staff are adequately trained***

All staff involved in the outbreak investigation and management need to receive training and education regarding TB and outbreak management.

***Prepare an initial description of the outbreak***

The extent of the outbreak should be estimated and defined for the purpose of the initial investigation.

***Identify source cases***

If not apparent, the source case or cases must be identified through aggressive investigation of all symptomatic individuals in the community.\*

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

### *Promptly isolate and treat cases of active disease*

All suspected infectious cases must be promptly isolated and investigated to confirm the diagnosis and the degree of infectiousness.\* Therapy must be initiated immediately. Therapy should also be started promptly for non-infectious cases.

Rapid diagnostic techniques, including sputum smears and rapid culture techniques, must be available without delay. In symptomatic individuals, respiratory secretions may be obtained spontaneously or using the sputum induction technique. In children and the elderly who are unable to raise secretions, gastric washings may be obtained. Hospitalization is indicated for those who are acutely ill, those whose diagnosis is uncertain and who require inpatient investigation, and those who require airborne isolation and cannot be adequately isolated outside the hospital setting.

### *Promptly initiate contact investigation*

Detailed information is necessary on the activities of the source case at home, (or in a shelter, correctional facility, etc.) at work and leisure, and the duration of symptoms, particularly the duration and productivity of the cough. Chest radiography must be carried out for all persons with a positive TST result (see Table 2), all those with a previous positive TST (regardless of the presence of symptoms), all children less than 5 years of age, all those who are severely immunocompromised and all those with symptoms (cough, fever, and/or weight loss).\*

In small communities or in certain settings it may be more efficient to screen the entire community or those in the setting at baseline, especially as it may be difficult to determine the exact level of contact in a small, close-knit community. In some settings, such as shelters, offering on-site screening (usually sputum and/or chest radiography) on an ongoing basis over a period of time may be the only way to ensure that most contacts are identified and screened.

### *Review history of TB in the 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.

### *Provide information*

It is crucial to provide information and results to the community or the setting involved as early as possible in the investigation of the outbreak, with regular updating. This will help reduce the level of anxiety in the community and will likely lead to greater cooperation and adherence to recommendations.

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\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

### *Evaluate both the process and outcome of the outbreak investigation*

An evaluation of the process and outcome of the outbreak investigation is crucial. DNA genotyping of isolates may be useful both in identifying the presence of an outbreak, mapping its extent and evaluating the results of the outbreak investigation and control.

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# Surveillance and Screening in Tuberculosis Control

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Key features of a tuberculosis (TB) control program include surveillance and screening activities.

## Surveillance – Definitions, Tools and Goals

**Surveillance** refers to an ongoing process of (a) systematic collection of pertinent 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.<sup>1</sup>

Surveillance should be done at all levels of the public health system. Data should be provided to those who set policy and implement programs. Specifically, 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.

### *Summary Point:*

- ▶ In the surveillance of TB, the ultimate goal is to reduce the incidence of disease and the spread of infection, which is achieved through early case detection and treatment, and to identify and treat persons with latent TB infection (LTBI) at high risk of active disease.

In the context of immigration, the term “medical surveillance” means the referral of immigrants with inactive TB or past TB to local public health authorities for examination and follow-up (see Chapter 15, Immigration and Tuberculosis Control in Canada).

## 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. The condition being screened for must be sufficiently prevalent for the screening procedure to be cost-effective, have agreed-upon diagnostic criteria, have a known natural history and be amenable to a definitive intervention.<sup>2</sup>

It is important that persons with conditions discovered through screening be able to access prompt and definitive medical attention, including counseling. In the case of TB, transmission of *Mycobacterium tuberculosis* should be interrupted or prevented from occurring.

Chest radiography is the primary screening tool when the focus is the identification of undiagnosed active cases of infectious pulmonary TB (in order to treat and render them noninfectious). Attempts at confirmation with sputum smear and culture are always required.\* In certain settings, the primary screening tool for active disease may be sputum smear and culture.<sup>3</sup>

\* A recommendation of the Canadian Thoracic Society’s Tuberculosis Committee

When the focus of screening is the detection of LTBI, the tuberculin skin test (TST) is used. Some persons with a positive TST may have active disease detected on further medical evaluation. New blood tests referred to as interferon-gamma release assays (IGRA) demonstrate significant promise as an alternative to the TST (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease).

TB screening activities focused on groups that are known to be at high risk of TB are referred to as targeted screening or testing. Screening activities may focus on the detection of prevalent active disease (e.g. active case-finding, such as in homeless persons or refugees arriving from an area of high TB incidence); on the presence of LTBI in persons at high risk of progression to active disease (e.g. close contacts of infectious TB or persons with severe immunocompromising conditions such as HIV); or on LTBI in groups with a high prevalence of infection and low risk of adverse events from the treatment of LTBI (e.g. school children born in countries of high TB incidence).

Targeted screening for LTBI is discouraged except for situations in which there are sufficient resources and a plan to complete a course of treatment for persons found to have LTBI. Screening of low-risk persons is also discouraged.

A number of factors may decrease the effectiveness of a screening program. These factors include application of the screening program to a group at low risk of LTBI or at low risk of progression to TB disease, groups that demonstrate a poor participation rate in screening, and those demonstrating limited adherence to the treatment of LTBI. These factors should be carefully considered (and interventions applied) in the design of any new screening program. Table 1 details the results of published screening evaluations in various targeted populations. Such results may be useful to “benchmark” an existing or planned screening program. The overall benefit of implementing a screening program for TB should be measured in terms of potential rewards and possible harm from the screening itself.<sup>61</sup>

Three basic strategies are critical to the prevention and control of TB, as follows (in order of priority):

1. Identification of persons with active TB and treatment completion
2. Investigation of contacts of infectious TB
3. Investigation of populations at risk of LTBI and progression to TB disease.

### Targeting Groups for Screening

High-risk groups for screening may change over time; therefore, periodic reassessment of the level of risk in these groups is necessary.

**The following is a list of groups that should be given a high priority for systematic screening, which in most instances is directed by public health authorities:**

- Close contacts of individuals with known or suspected active TB (see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control).



- Persons with HIV infection (see Chapter 9, Tuberculosis and Human Immunodeficiency Virus). Public health authorities, primary care providers and HIV/AIDS treatment providers have a shared responsibility to see that these persons are adequately screened and treated.
- Persons with a history of active TB or with chest radiographic findings suggestive of past TB who have not received adequate therapy.
- Foreign-born persons referred for medical surveillance by immigration authorities.
- Aboriginal communities with high rates of LTBI or TB disease.
- The poor, especially the urban homeless.
- Staff and residents of long-term care and correctional facilities (see Chapter 16, Tuberculosis Control Within Institutions).
- Those at risk of occupational exposure to TB, especially health care workers likely to be exposed to active cases of pulmonary TB (see Chapter 16, Tuberculosis Control Within Institutions).

**Other groups that should be considered for screening (usually delivered at the level of a primary care provider), depending on local epidemiology and resources, are as follows:**

- Persons of any age with risk factors for development of active TB (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Table 2, and Chapter 6, Treatment of Tuberculosis Disease and Infection, Table 6).
- Children under the age of 15 years who have lived in a country with high TB incidence and have immigrated within the past 2 years (see Chapter 8, Pediatric Tuberculosis). This includes adopted children from such countries.
- Persons aged 15 years and older who have lived in a country with high TB incidence, have immigrated within the past 2 years and have either been living with or in known contact with a TB case in the past or are at high risk for development of active TB.
- Persons at risk of active TB who are employed in settings where they may infect infants or persons who are immunosuppressed (e.g. child care facility or HIV care facility).
- Persons with a history of substance abuse.
- Persons who are traveling or residing in an area with a high incidence of TB and who have one or more of the following risks:
  - a high level of risk for development of active TB;

- plans to travel or reside for 3 months or longer (see below for specific recommendations based on length of stay and TB incidence rate in the area), particularly if the traveler is a child;
- intention to participate in a high-risk activity (e.g. health care work, refugee care, missionary or other work that may involve exposure to the resident population).

## Components of Screening

All screening programs should include the following:

- education and community outreach;
- informed consent;
- relevant history taking: history of BCG vaccination, contact with active TB, results of previous TSTs, and immunocompromising illness;
- referral for clinical evaluation of individuals who have a positive TST or are immunocompromised;
- complete and accurate record-keeping;
- compilation of summary data, including incidence of active TB in the group being screened, positive TSTs and LTBI treatment initiation and completion rates, to evaluate and assess the need for an ongoing screening program;
- ongoing staff training.

There are several factors to consider in establishing screening programs:<sup>2</sup>

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognized disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed-upon policy concerning whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of the diagnosed condition) should be economically balanced in relation to possible expenditure on medical care as a whole.

## Screening in Specific Situations

**HIV infection** (see also Chapter 9, Tuberculosis and Human Immunodeficiency Virus)

Persons with HIV infection and LTBI have an extremely high risk of progression to active TB disease. Immunosuppression interferes with the sensitivity of both

main screening tools: the TST and chest radiography. When possible, persons with HIV infection should be screened for LTBI with a TST *early* in the course of their HIV infection. The frequency of periodic retesting will be determined by the background risk of TB. Anergy screening is fraught with inconsistencies and is no longer routinely recommended.<sup>62</sup>

**Summary Point:**

- ▶ All persons with HIV infection should be screened and treated for LTBI.

### Persons with a history of active TB or high-risk chest X-ray

Persons with an abnormal chest X-ray consistent with TB (apical fibronodular changes) who have not received adequate therapy should be screened for active disease. Those found to have inactive disease and a positive TST result are good candidates for preventive therapy (see Chapter 6, Treatment of Tuberculosis Disease and Infection). Follow-up (i.e. annual medical evaluation) of persons with inactive TB is not recommended for those who have been adequately treated. Although regular follow-up can be considered for such persons not receiving adequate therapy, the cost-effectiveness of this strategy is questionable given that most persons with active disease may present with symptoms outside of the screening program.<sup>63</sup> Persons who are discharged should receive adequate education regarding the symptoms of disease and instructions for returning for medical evaluation. There should be no financial barriers for these persons to access such evaluation.

**Summary Point:**

- ▶ Periodic medical evaluation of persons with inactive TB that was previously untreated or inadequately treated can be considered. However, it is not uncommon for such persons to present with symptoms outside of the screening program.

### Immigrants (see also Chapter 15, Immigration and Tuberculosis Control in Canada)

International migration imposes on host countries the responsibility to develop an understanding of migrant health care needs, among which TB prevention and treatment are prominent.<sup>61</sup> TB incidence rates vary widely among nations and regions.<sup>64</sup> Current immigration patterns to Canada are dominated by immigration of individuals from countries with high TB incidence.<sup>65</sup>

Persons emigrating from such countries may be at a several-fold increased relative risk of active TB when compared with individuals born in a low-incidence country.<sup>8,9,66-69</sup> There is great variability in the risk of active disease among migrants according to world region of origin, age at immigration, migrant type, time since immigration, referral for medical surveillance and socio-

economic status.<sup>69,70</sup> Immigrants to Canada represent the largest risk group for nonrespiratory TB disease in the country. While nonrespiratory cases are, with rare exception, noninfectious, contact tracing may be necessary to identify a source case among close contacts.<sup>71,72</sup>

The epidemiology of TB in foreign-born populations differs considerably, depending on the area of the world from which they emigrate. To tailor TB control efforts to local needs, epidemiologic profiles should be developed to identify groups of foreign-born persons in a jurisdiction who are at high risk of TB disease.<sup>69,73</sup>

#### *Summary Points:*

- ▶ Among immigrants to Canada, there is great variability in the risk of LTBI and TB disease.
- ▶ Epidemiologic profiles are a key component of targeted screening activities in this migrant population.

Persons who are referred for medical surveillance by Citizenship and Immigration Canada should be screened after arrival in Canada. Targeted testing of other immigrant groups should be determined by local epidemiologic profiles.

#### **The homeless and underhoused**

Homelessness is a risk factor for the acquisition of LTBI. Those who are infected may also be at increased risk of TB disease. Studies using DNA fingerprinting have shown that many cases in this population are due to recent infection.<sup>74-76</sup> In a San Francisco General Hospital study, 2,774 homeless persons were followed prospectively for 3.5 years. Among them, 32% were TST positive, and the incidence of new TB disease was 270 per 100,000 per year.<sup>40</sup>

The primary objective of screening in this population is interruption of transmission by finding active pulmonary TB cases. Computer models support strategies aimed at active case finding in this population.<sup>77</sup> Screening tools that have been used include symptom assessment, sputum culture and chest radiography. Acceptance of these methods has been variable among the homeless, but the use of incentives has been reported to increase participation.<sup>24,37</sup> A TST-based shelter screening program in Denver is likely to have reduced transmission among the homeless in that city through detection and treatment of active cases.<sup>78</sup>

Screening for LTBI is generally not recommended unless there is a way to ensure that treatment will be adhered to. Directly observed treatment for LTBI and the use of incentives have been shown to improve adherence, but this can be a costly endeavor.<sup>79,80</sup>

**Summary Point:**

- ▶ The primary goal of screening among the homeless is to find active cases.

In addition to the increased risk of LTBI resulting from disease burden and exposure to congregate settings such as shelters, homeless persons are likely to be at an elevated risk of infection with HIV, thus increasing the potential for large and difficult-to-control outbreaks.<sup>81</sup>

**Children and adolescents (see also Chapter 8, Pediatric Tuberculosis)**

A positive TST in a child usually indicates recent infection. In infected preschool children there is a high risk of progression to active disease and more severe, life-threatening forms of disease, such as meningitis or miliary disease. Infected adolescents may present with adult-type cavitary pulmonary TB. While active TB is uncommon among Canadian-born, non-Aboriginal children of Canadian-born parents, active disease among recently arrived foreign-born adolescents is relatively common. The place of infection is generally presumed to be a country of birth with a high TB incidence; however, transmission within Canada may also occur.

Children under the age of 15 years who have lived in a country with high TB incidence and have immigrated within the past 2 years (the period during which the risk of progression from LTBI to active disease is highest) should be screened for LTBI (see Chapter 8, Pediatric Tuberculosis). The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that such screening occur at first contact with the child.<sup>82</sup>

The benefits of treating LTBI in children are substantial. This is because of their young age, generally good physical health, long life expectancy and low risk of suffering from the complications of treatment. It is likely that the most impact on the future burden of TB in the population can be made with the optimization of contact tracing around infectious adults.<sup>83</sup>

Although it is estimated that approximately 75% of TB outbreaks occur in schools,<sup>84,85</sup> a number of factors conspire against the effectiveness of screening all students in a school (including postsecondary institutions) to prevent future cases of TB.<sup>83</sup> First, the rate of false-positive TST results among most Canadian-born, non-Aboriginal students is high because of their low LTBI prevalence rate. Second, the rate of LTBI treatment completion will probably be low without intensive efforts on the part of health care providers to maximize adherence. Third, such programs have a very low yield of diagnosing active cases of TB. Nevertheless, school-based screening may be cost-effective if 20% or more of the students have LTBI and at least 60% of those infected complete a course of treatment for LTBI.<sup>50</sup>

Targeted, school-based screening of high-risk groups, such as students who have lived in a high-incidence country and have immigrated to Canada within the past 2 years, may be useful if careful consideration is first given to the goals and outcomes of such programs.<sup>50,53,86</sup> These same principles apply to other

collective settings for children and youth, such as child care facilities and job training programs.<sup>55</sup> In the United States, the targeted testing of children, after administration of a risk assessment questionnaire, has been emphasized.<sup>58,59</sup>

Staff and volunteers in educational institutions do not require routine screening for LTBI upon hire or placement unless they are members of another targeted group for which screening is recommended (see above). Some jurisdictions screen recently immigrated child care workers for TB disease and LTBI even though they had not been referred for medical surveillance by Citizenship and Immigration Canada. The cost-effectiveness of such screening is not known.

#### *Summary Points:*

- ▶ Children under the age of 15 years who have lived in a country with high TB incidence and who immigrated within the previous 2 years should be screened for LTBI.
- ▶ Targeted screening for LTBI among children and youth in schools etc. may be cost-effective if 20% or more of persons screened have LTBI and at least 60% complete treatment for LTBI

#### **First Nations and Inuit communities** (see also Chapter 14, Tuberculosis Control in First Nations and Inuit Populations)

It is well documented that the TB incidence rate in many First Nations and Inuit populations is significantly higher than in the non-Aboriginal Canadian-born population. Rates are decreasing more slowly in most First Nations and Inuit populations. HIV infection rates may also be rising in this population. All Canadians have the right to good health without distinction of ethnicity, and much work needs to be done to reduce the burden of TB in those populations most affected.

Screening in Aboriginal communities can present several challenges, including but not limited to, language barriers, isolation and lack of access to health care staff with experience and education in TB.

Interpreters may be required to assess clients. Even those who can speak English or French may be more comfortable with their own language or dialect. Educational material and consent forms should be available in local languages and dialects.

Extreme isolation of some communities may lead to delays in diagnosis and treatment. Bacteriologic samples and x-ray films may have to be sent over long distances for processing and evaluation. Lack of community physicians and pharmacies may also contribute to delays in the initiation of appropriate therapy.

High staff turnover in more remote communities means that there is a need for a structured orientation program for nurses, physicians and other staff to increase awareness of TB and training in screening procedures. Aboriginal nurses, clerks, interpreters, community health representatives and other TB workers are among

the many individuals who require TB education. Such individuals are often the first contact with the health care system. They may be interpreting for unilingual clients and, as members of the community, are usually the most stable element in the program, since many health care workers who are non-Aboriginal are transient.

**Summary Point:**

- ▶ First Nations and Inuit peoples of Canada suffer from a relatively high burden of TB. TB control among these persons is hindered by poverty, cultural and linguistic differences, the remote nature of many communities and unstable medical care.

A recent statement from the National Advisory Committee on Immunization (NACI) highlights concerns of a higher risk of severe adverse events and death from BCG among First Nations peoples. The primary reason for this elevated risk is a high prevalence of severe combined immunodeficiency syndrome (SCIDS). The risk of SCIDS in different First Nations populations requires further investigation. NACI has recommended that BCG vaccination no longer be routinely offered to infants in First Nations and Inuit communities unless certain criteria are met (see Chapter 17, Bacille Calmette-Guérin Vaccination for details).<sup>87,88</sup> When a vaccination program is discontinued, it is important that a program of screening and treatment for LTBI be implemented. The optimal design of such screening programs is being investigated.

**Summary Point:**

- ▶ BCG vaccinations are no longer given in some First Nations communities with low TB incidence. The optimal approach to enhanced surveillance in these setting remains to be defined.

### Correctional facilities

The potential for very serious outbreaks in correctional facilities has been clearly demonstrated.<sup>89-91</sup> Factors that contribute to this high risk include high rates of LTBI and of HIV, and a high-risk environment for airborne transmission in older facilities. The potential for transmission of multidrug-resistant TB in this setting is particularly worrisome. Optimal TB control strategies will be determined by the characteristics of the correctional facility (see Chapter 16, Tuberculosis Control Within Institutions, for details).

### Travelers

The risk of developing LTBI during travel reflects the annual risk of infection (ARI) of the population in the country visited.<sup>92</sup> There is great variability in this ARI, estimates in 2002<sup>93</sup> ranging from 0.01% to 3% (Ellis E, Public Health Agency of Canada, personal communication, 2006). Preliminary results from

two Canadian studies suggest that, after 3 months of travel in a country with a high ARI, a post-travel TST with appropriate treatment of LTBI may be of comparable cost-effectiveness as the current estimated cost of treating a case of active TB in Canada.<sup>94,95</sup> Other screening options found to be less cost-effective included (1) two-step TST before travel, one-step TST after travel and LTBI treatment for converters, (2) LTBI treatment for TST-positive individuals before travel and (3) post-travel screening with chest radiography alone.

Risk of infection is a function of annual incidence of sputum smear-positive disease in the area, the ability of the local TB program to quickly diagnose and treat infectious cases, and the duration of stay in the area. International estimates of TB incidence rates may be viewed at <http://www.publichealth.gc.ca/tuberculosis>.

A post-travel, single-step TST is recommended for most persons, regardless of age, in regular contact with the general population of a country with an acid-fast bacilli (AFB) smear-positive pulmonary TB incidence rate of

- at least 200/100,000 for 3 months or longer;
- 100-199/100,000 for 6 months or longer;
- 50-99/100,000 for 12 months or longer.

Such testing is particularly important for persons at high or increased risk of progression from LTBI to active TB disease (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Table 2).

A pre-travel two-step TST and, if it is negative, a post-travel single-step TST is recommended for some persons:

- Individuals who are not candidates for treatment of LTBI unless recent conversion occurs (see Chapter 6, Treatment of Tuberculosis Disease and Infection, Table 6, for a list of those who should be treated). Examples include persons with pre-existing liver disease or older persons born in a country with high TB incidence, probably infected many years ago, often with a history of BCG vaccination. If such persons' TST result is converted during current travel, according to pre- and post-travel TST results, treatment for LTBI is indicated. But if only a post-travel TST is performed and is positive, it is difficult to know whether this represents recent or past conversion.
- Individuals who will be entering a serial TST screening program for occupational reasons (see below).

The post-travel TST should be done at least 8 weeks after the individual has left the country to allow time for postexposure skin test conversion to occur. There is no clinical utility in performing a TST for persons with a history of previous TB disease or a positive TST. For interpretation of the result, see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Table 1. For treatment of LTBI, see Chapter 6, Treatment of Tuberculosis Disease and Infection.

Travelers and all persons identified as having LTBI who decline treatment may be candidates for medical follow-up for symptoms and signs of TB disease. The



utility of such follow-up will be influenced by the individual risk of progression to active disease and would not be expected to extend beyond 2 years.

Travelers working in **specific settings** in which they may be exposed to exceptionally high rates of infectious TB cases, such as health care facilities, correctional facilities, refugee camps, inner city slums<sup>96</sup> and homeless shelters, should be screened after  $\geq 1$  month of work if their placement is short-term (as the ARI may reach 17%)<sup>14</sup> or annually if it is for a longer term. As is recommended for such work in Canada, a pre-work, two-step TST is recommended to reduce the chance of a false-positive TST conversion when the TST is repeated as part of a serial screening program.

#### **Summary Point:**

A post-travel, single-step TST is recommended for most persons in regular contact with the general population of a country with an AFB smear-positive pulmonary TB incidence rate of

- ▶ at least 200/100,000 for 3 months or longer;
- ▶ 100-199/100,000 for 6 months or longer;
- ▶ 50-99/100,000 for 12 months or longer.

#### **Other high-risk environments**

Workers and residents in certain environments, such as long-term care and other congregate settings, are at an increased risk of TB. They may have risk factors for active TB (e.g. HIV or other medical illnesses that increase the risk of progression from LTBI to active disease), and the environmental characteristics may be conducive to airborne transmission (e.g. crowding and poor ventilation). These and other settings (shelters and substance abuse treatment programs) may provide a good opportunity for screening for TB. See Chapter 16, Tuberculosis Control Within Institutions, for further details.

#### **Ethical Considerations for Surveillance and Screening**

The development of communicable disease policy, like all aspects of public health, raises ethical and legal dilemmas concerning the extent to which the rights of individuals can be limited by interventions aimed at the health of populations. The weight of these dilemmas depends on the extent to which the public health intervention affects the rights of individuals. For example, epidemiologic research that secures anonymity is minimally invasive, whereas mandatory treatment is maximally so. The HIV/AIDS pandemic has, of course, been the primary driver for bioethical and legal developments in public health. But in Canada, as well, the SARS (severe acute respiratory syndrome) outbreak in February to April 2003 set into motion a nation-wide rethinking of these issues,<sup>97</sup> culminating in Health Canada's extensive study *Learning from SARS*<sup>98</sup> Since that time new public health legislation has been considered at both the federal and provincial/territorial levels that could set out requirements for

both emergency and routine public health interventions. The developing law is complex and difficult to summarize. Yet, the fundamental ethical themes have remained constant.

In 2001, bioethicist Nancy Kass mapped out an ethical framework<sup>99</sup> that has proven to be useful for assessing public health programs and interventions. In part based on the United Nations 1984 Siracusa Principles<sup>100</sup> and in part reflecting basic bioethical principles,<sup>101</sup> the framework has the virtue of being far more concrete and practical than either set of principles. It is an analytical tool designed to help public health professionals consider the ethical implications of interventions, policy, research and programs. In the context of TB, for example, these concepts have been used in the United States to provide the justification for directly observed therapy, detention of nonadherent patients and court ordered punishment for failure to comply with a judicial order to be treated.<sup>102-104</sup>

Kass' framework applied to the public health surveillance and screening context may be summarized as follows:

Questions posed by Kass	Application to public health surveillance and screening
1. What are the public health goals of the proposed program?	1. Is the goal of surveillance or screening scientifically legitimate?
2. How effective is the program in achieving its stated goals?	2. Is there reasonable evidence that the surveillance or screening program will achieve these goals?
3. What are the known or potential burdens of the program?	3. Have burdens or harms of the program to individuals, such as loss of privacy and the confidentiality of results, been identified and minimized as much as possible?
4. Can burdens be minimized? Are there alternative approaches?	4. Is the program modified as necessary to minimize identified burdens without sacrificing effectiveness or scientific legitimacy?
5. Is the program implemented fairly?	5. Is there justification for disproportionate burdening of a subpopulation by the surveillance or screening program?
6. How can the benefits and burdens of a program be fairly balanced?	6. Are the benefits expected to outweigh the burdens incurred?

### Evaluation of TB Screening Programs

Periodic evaluation of screening programs should be carried out. As a minimum, the following parameters should be documented:

- screening and LTBI treatment practices;
- the impact of the screening practices on finding and preventing active TB cases;
- the relation and coordination of screening practices to/with other national and international TB prevention and control activities; and
- where possible, cost-effectiveness.

The results of the evaluation will be integral to the modification and optimization of the screening program. Table 1 summarizes the findings of various screening activities in at-risk populations. The studies represented here were obtained from a search of the English and French language literature (1980 to present) using the search terms “screening” and “tuberculosis”. Studies were included if they provided some outcome measures of the screening procedures and used either the TST or chest radiography as the screening tool.

**Table 1**  
**Summary of Published Screening Program Evaluations Among Migrants, the Homeless/Underhoused, Children and Adolescents**

Publication	Tool	Setting	N*	Yield	Outcome
<b>Migrants</b>					
Pitchenik 1982 <sup>4</sup>	Chest radiography	Haitian refugees, Florida 1980-81	15,544	101 (0.7%) active disease	Detection rate dependent on age
Enarson 1984 <sup>5</sup>	Chest radiography	Indochinese refugees, British Columbia 1979-81	8,692	21 (1.9%) active disease	Many with minimal pulmonary TB
Markey 1986 <sup>6</sup>	Chest radiography	Heathrow airport 1980-83	96,638	51 (0.1%) active disease	
Nolan 1988 <sup>7</sup>	Chest radiography	Southeast Asian refugees, Seattle 1980-81	9,328	78 (0.8%) active disease	Annual incidence decreased from 306/100,000 at time of immigration to 50/100,000 at 4-5 years after immigration
Orr 1990 <sup>8</sup>	Chest radiography and clinical exam	Immigrants referred for follow-up, Manitoba 1981-85	523	12 (3%) active disease	Response rate to initial examination: 82%; overall: 52%; those referred for follow-up contributed 20% of future cases of TB among immigrants
Wang 1991 <sup>9</sup>	Chest radiography and clinical exam	Immigrants referred for follow-up, British Columbia 1982-85	1,173	14 (1.5%) active disease	Response rate: initial examination 86%; those referred for follow-up contributed 20% of future cases of TB among immigrants
Bonvin 1992 <sup>10</sup>	Chest radiography	Migrants - Switzerland 1988-90	50,784	111 (0.2%) active disease	Detection rate dependent on world region of origin
Godue 1988 <sup>11</sup>	TST††	Refugee claimants	865	3 (0.1%) active disease, 329 (38%) positive TST	Response rate: 98%; positivity rate depended upon age of refugee claimant and country of origin
Blum 1993 <sup>12</sup>	Chest radiography and TST	Illegal aliens for adjustment of status, Denver 1987-88	4,840	4 (0.1%) active disease, 2,039 (42%) positive TST	Response rate: 74%; adherence with treatment, 70%
Binkin 1996 <sup>13</sup>	Chest radiography and clinical exam	U.S. immigrants and refugees classified as B1§ or B2	1,925 B1§ 3,195 B2	198 (10%) B1, 77 (2.4%) active disease	Response rate: initial examination 64%-99%
Norton 2000 <sup>14,15</sup>	TST	Foreign born college students at a U.S. college	171	59 (35%) positive TST	58% of those eligible started preventive therapy; adherence with treatment 46%
Callister 2002 <sup>16</sup>	Chest radiography	Asylum seekers screened on arrival in the UK 1995-1999	53,911	100 (0.24%) active disease, 209 (0.5%) referred for inactive disease	Detection rate dependent on world region of origin
van Burg 2003 <sup>17</sup>	Chest radiography	Asylum seekers, the Netherlands 1994-1997	46,424	103 active at entry (0.22%), an additional 51 cases presented in the next 10 months	Chest radiography at entry predicts future disease; age and country of origin contribute to risk
Levesque 2004 <sup>18</sup>	TST	Refugee claimants presenting for primary care, Montreal	227	49 (25%) positive TST	50% completion of treatment for LTBI
Carvalho 2005 <sup>19</sup>	TST	Undocumented immigrants, Italy	213	58% positive TST	Response rate 33%, 55/124 started treatment
Maloney 2006 <sup>20</sup>	Chest radiography	Visa applicants screened in Vietnam	14,098	1,179 abnormal x-ray, 183 (1.2%) active disease	Detection rate dependent on age, no history of tuberculosis or treatment, symptoms and cavitation/consolidation on x-ray
Brassard 2006 <sup>21</sup>	TST	Newly arrived immigrant children	2,524	542 (21%) positive TST	342 started treatment for LTBI, 316 with adequate adherence. Screening done in school
<b>Homeless and underhoused</b>					
Simon 1983 <sup>22</sup>	TST†	Domiciliary veterans	676	227 (33.6%) positive TST, 1 (0.1%) active disease	Response rate 92%; 6/227 (26%) started treatment for LTBI
Patel 1985 <sup>23</sup>	Chest radiography	Shelter dwellers	9,132	133 (1.46%) active disease	Response rate increased from 12% to 42% with incentives
Capewell 1986 <sup>24</sup>	Chest radiography	Shelter dwellers	4,687	42 (0.9%) cases active disease, 26 (0.6%) presented with symptoms	Response rate 26%-64%; 80% completed treatment
Barry 1986 <sup>25</sup>	Chest radiography and TST	Shelter dwellers	586	0.7% with active TB, 22% were TST positive	62% response rate for TST; 51% returned for reading

Publication	Tool	Setting	N*	Yield	Outcome
Friedman 1987 <sup>26</sup>	TST† and chest radiography	Welfare recipients with alcohol and drug abuse	970	314 (32.4%) positive TST, 9 (0.99%) active disease	Response rate 100%; 128/314 (41%) started treatment for LTBI
Alvarez 1987 <sup>27</sup>	TST	Domiciliary veterans	510	153 (30%) positive TST	Response rate 95%
Grzybowski 1987 <sup>28</sup>	Chest radiography, sputum, TST	Inner city	1,271	8 (0.6%) active disease, 397/902 (44%) positive TST	Response rate for all tests high (> 94%), 23% of TSTs not read, treatment for positive TST offered to 10 (2.5%); TSTs done "on the spot"
McAdam 1990 <sup>28</sup>	TST	Shelter-based clinic	1,853	6.0% active disease, 37% positive TST	36% completed treatment
Stevens 1992 <sup>29</sup>	Chest radiography	Shelter dwellers	547	No active disease	Response rate 44%; 42% follow up of abnormal x-rays
Paul 1993 <sup>30</sup>	TST	Shelter dwellers	161	79% positive TST	Response rate 27%; adherence with TST reading 81%
Zolopa 1994 <sup>31</sup>	TST	Shelter dwellers	1,226	32% positive TST	Response rate 82%, 8.5% HIV positive
Kumar 1995 <sup>32</sup>	Chest radiography	Temporary shelter	595	9 (1.5%) active disease	18% response rate, 5 (56%) completed treatment
Pilote 1996 <sup>33</sup>	TST	Homeless, San Francisco	1,257	293 (23%) positive TST, 3 (0.2%) active disease	Response rate 78%; increased adherence with first follow-up from 53% with monetary incentive and peer health adviser
Perlman 1997 <sup>34</sup>	TST	Needle exchange	476	2 (0.5%) active disease, 15% positive TST	Response rate 96.5%; 91.5% of TSTs read
Bock 1999 <sup>35</sup>	TST†	Inner city, Atlanta	4,701	809 (17%) positive TST	Response rate 65%, 84/409 (20%) completed treatment
Kimerling 1999 <sup>36</sup>	Sputum	Shelter dwellers	127	3.1% active disease	Response rate 95%
Southern 1999 <sup>37</sup>	Chest radiography	Hostels and day care centres, South London	2,000	0.5% active disease	Luncheon vouchers used as incentive
Fitzgerald 1999 <sup>38</sup>	TST	Needle exchange program, Vancouver	1,107	0.2% active disease	\$5 increased TST completion from 43% to 78%
Rusen 1999 <sup>39</sup>	TST‡	Needle exchange program, Toronto	171	31% positive TST	Self-selected group, 93% adherence with reading of TST
Moss 2000 <sup>40</sup>	TST	Homeless, San Francisco	2,774	0.36% active disease, 32% positive TST	Response rate 92%, 86% adherence with reading of TST
Salomon 2000 <sup>41</sup>	TST†	Needle exchange program, NYC	650	14% positive TST	Response rate 94%, 93% adherence with reading of TST
Solsona 2001 <sup>42</sup>	Chest radiography, TST‡	Homeless, Barcelona	447	1.1% active disease, 75% positive TST	
Brassard 2004 <sup>43</sup>	TST‡	IDU cohort	262	22% positive TST	94% adherence with reading of TST
<i>Children and adolescents</i>					
Cantin 1981 <sup>44</sup>	TST‡	Quebec born students (6-7, 11-12, and 16-17 years)	2,207	6-7 year olds: 8 (1%) TST at ≥ 5mm, 3 (0.4%) of whom had reactions ≥ 10mm. 11-12 year olds: 22 (3%) TST at ≥ 5mm, 12 (1%) of whom had reactions ≥ 10mm. 16-17 year olds: 22 (6%) TST at ≥ 5mm, of whom 12 (3%) had reactions ≥ 10mm.	Response rate: 86%. Results indicate that TST and BCG vaccination should be limited to select high-risk groups in metropolitan area of Montréal
Quillan 1990 <sup>45</sup>	TST‡	International college students	589	339 (58%) positive TST; no active cases discovered	158/290 (55%) of those eligible accepted treatment; 18 (5% of all infected and 11% of those starting) completed treatment
Michaud <sup>46</sup>	TST	Adolescents	1,796	42 (2.3%) LTBI	18 (43%) of eligible started treatment
Menzies 1992 <sup>47</sup>	TST†	Foreign-born students, young adults and health professional trainees	1,198	388 (32.4%) positive TST	Positive TST rate related to TB burden in country of birth, BCG and living in a poor neighborhood
Rothman 1993 <sup>48</sup>	TST‡	School children – outbreak	707	48 (68%) positive TST; 32/722 (4.4%) conversion	Response rate 100% (61% in non-outbreak school)

Publication	Tool	Setting	N*	Yield	Outcome
Rivest <sup>49</sup>	TST†	Secondary students	179	34 (19%) positive TST	
Mohle-Boetani 1995 <sup>50</sup>	TST†	School children		U.S. born: 0.6% kindergarten and 2.2% high school; born in high-endemic country: 18% kindergarten and 29% high school positive TST	Screening all children would save costs only when positive TSTs > 20%; targeted screening 5.7 times more efficient than screen-all strategy
Yuan 1995 <sup>51</sup>	TST†	High-risk school students	720	162 (22.5%) positive TST, 1 (0.1%) active disease	Response rate 41%; 56/162 (35%) started therapy; 52 (93%) completed; cost per case prevented \$13,493
Christy 1996 <sup>52</sup>	TST†	Urban pediatric clinic	401	4 (1%) positive TST	Response rate 64%; all positive TSTs in adolescents with risk factors
Henry 1996 <sup>53</sup>	TST†	Secondary school students	7,596	268 (3.5%) TST	Majority of those with positive TST had risk factors
Serwint 1997 <sup>54</sup>	TST†	Urban pediatric clinic	574	5 (0.8%) positive TST	Response rate 40%
Lifson 1999 <sup>55</sup>	TST†	Federally funded job training program	22,379	942 (4.2%) positive TST	LTBI rates highest among minorities, foreign born and older age; 85% with positive TST had a chest radiography and 69% started LTBI treatment
Scholten 1999 <sup>56</sup>	TST†	Elementary and secondary schools	298,506	2.1% positive TST	Positive TST rates related to place of birth and prior BCG
Doering 1999 <sup>57</sup>	TST†	Immigrant students	1,146	15% positive TST	89% eligible offered treatment; treatment completion 68%
Ozuah 2001 <sup>58</sup>	TST	Ambulatory clinic	2,920	1% positive TST	Questionnaire identified a group with higher infection rates
Froehlich 2001 <sup>59</sup>	TST†	Ambulatory clinic	31,926	1% positive TST	Questionnaire identified a group with higher infection rates
Gounder 2003 <sup>60</sup>	TST†	Primary and secondary school	788,283	1.2% positive TST in primary school and 9.7% in secondary school in 1998	Response rate 31%-77%, lower in secondary school; estimated cost per active case prevented in primary school \$123,152

\*Number completing screening, response rate = number completing screen/number eligible

†Positive =  $\geq 10$  mm induration

‡Positive =  $\geq 5$  mm induration

§B1 clinically active, not infectious; B2 not clinically active, not infectious

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# Tuberculosis Control in First Nations and Inuit Populations

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## 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 C, Definition of Terms). From 2004 population projections for the Aboriginal population based on the 2001 Canadian census, 1,126,819 persons identified their ethnic origin as Aboriginal: 756,099 as First Nations/North American Indian, 319,717 as Métis, and 51,003 as Inuit.<sup>1</sup> Of the First Nations (FN) population 748,371 persons are registered according to the terms of the *Indian Act* of 1876. These individuals are associated with 614 bands.<sup>2</sup> Fifty-three percent of registered FN individuals live on one of 2,796 reserves.<sup>2</sup>

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 FN and Inuit Populations

North and South American human remains dating from the time of pre-European contact show evidence of mycobacterial disease, although controversy exists about whether the findings in bone and mummified tissue represent infection with *Mycobacterium bovis*, *M. tuberculosis* or both.<sup>3</sup> However, epidemic TB in Canadian FN and Inuit populations occurred after European contact in the 19th and 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.<sup>4-8</sup>

The story of the TB epidemic in FN and Inuit populations speaks of transgenerational loss and suffering.<sup>4-8</sup> 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 TB control in the 21st century need to be aware of the existence of a “collective memory” of the suffering associated with the TB epidemic in these populations.

## Epidemiology of TB in FN and Inuit Populations

The epidemiology of TB in Canadian Aboriginal populations 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 Aboriginals 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.<sup>9</sup>
- While the incidence of TB in First Nations 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.<sup>9,10</sup>
- TB is proportionately more common among the very young in Aboriginal populations compared with Canadian-born non-Aboriginals, in whom a greater proportion of cases is seen in older age groups.<sup>9</sup>
- In western Canada, significantly greater clustering of TB cases has been noted in Aboriginal than in non-Aboriginal groups<sup>11</sup> as well as more advanced disease at presentation.<sup>12</sup>
- 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.<sup>13</sup>

### Responsibility for TB Control in First Nations and Inuit Populations

In the three territories of the Northwest Territories, Nunavut and Yukon, health care (including TB control) for First Nations and Inuit populations is delivered through the respective territorial departments of health. The territories have centralized TB programs directed by their respective chief medical officers of health. Contractual arrangements for consultative advice exist with selected provincial TB directors. Health Canada’s First Nations and Inuit Health Branch (FNIHB) does not have jurisdiction over the health care services of FN or Inuit persons who live in Canada’s territories.

For registered FN individuals who live in FN communities in one of the 10 Canadian provinces, the provision of public health services on-reserve is primarily the responsibility of FNIHB. TB control and other communicable disease control activities are usually shared responsibilities between FNIHB and provincial TB control services. Provincial departments (ministries) of health are responsible for insured health services provided to both registered and nonregistered FN, regardless of residence on or off reserve, and for Métis and non-Aboriginal Canadians. A variety of arrangements among levels of government for the delivery of public health services exist in the different provinces. In many instances, FNIHB and provincial departments of health have created systems to share and integrate aspects of health care delivery to their respective populations. FNIHB may also participate in contribution agreements, which allow FN to administer health programs themselves. Another means of providing health services is through Health Service Transfer Agreements, whereby authority and control of health resources rest with the community.



Hospital care for FN persons is provided, with few exceptions, in facilities that are off-reserve. Provision of care in these facilities is primarily the responsibility of the province/territory.

Public health legislation in each province and territory provides medical health officers (or equivalent) with powers to protect all persons, including FN individuals living on-reserve, from communicable diseases such as TB (see Chapter 11, The Role of Public Health in Tuberculosis Control).

## Determinants of 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.<sup>14</sup> Cytokine assays and studies of *in vivo* mouse models suggest that this strain is hypervirulent compared with other clinical isolates.<sup>15,16</sup>

### Host

#### *Comorbidities*

- Diabetes mellitus has been recognized as a risk factor for the development of active TB.<sup>17</sup> 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.<sup>18</sup> An increasing prevalence of diabetes has been noted among the Inuit.<sup>19</sup>
- End-stage renal disease is a risk factor for the development of active TB among persons with TB infection. 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.<sup>20</sup>
- Undernutrition is a risk factor for TB disease and occurs among subpopulations of Aboriginals.<sup>21-23</sup>
- Alcohol and drug abuse are associated with acquisition of infection and development of TB disease.<sup>24</sup> Marijuana and cocaine impair

macrophage function and cytokine production, suggesting a possible role in progression from infection to disease.<sup>25</sup> In the 1991 Aboriginal Peoples Survey, 73% of respondents on reserve thought that alcohol was a problem in their community.<sup>26</sup> 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.

- HIV – both ethnic origin and HIV status were recorded in only 2,793 of 14,022 TB cases reported to the Public Health Agency of Canada, 1997-2004. Of the 2,789 TB cases, 348 were HIV positive, of whom 25% (86/348) were Aboriginal, 27% (96/348) were Canadian-born non-Aboriginal, 47% (164/348) were foreign-born and 1% (4/348) were of unknown origin. HIV infection is increasing in incidence and prevalence in Aboriginal populations, and is a strong risk factor for development of disease in those with pre-existing latent TB infection or those who are subsequently infected with *M. tuberculosis*.<sup>9,27,28</sup>

### *Genetic factors*

- Linkage between susceptibility for 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 experiencing an epidemic of TB.<sup>29</sup>
- Although it has long been postulated that the immune response to *M. tuberculosis* is less vigorous among Aboriginal than non-Aboriginal Canadians, studies of other genetic loci associated with immune susceptibility are lacking.

### **Environment**

- Aboriginal communities have disproportionately high levels of overcrowded housing.<sup>30</sup> In communities experiencing new cases of infectious TB disease, an increased number of individuals will be exposed, leading to infection and disease. The Canadian Tuberculosis Committee has strongly recommended the provision of sufficient financial resources to enable Aboriginal communities to acquire and maintain housing that more closely approximates the Canadian National Occupancy Standard<sup>31</sup> and the average Canadian housing density as defined by Statistics Canada.<sup>32</sup>
- 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.<sup>30</sup> Diagnostic resources may be limited in isolated communities. Understaffing and high staff turnover rates are common in many remote communities (see Chapter 11, The Role of Public Health in Tuberculosis Control). Acute health care needs often claim the attention of overworked staff in preference to public

health programs, including TB control. Inclement weather may delay the transportation of patients and diagnostic specimens. Access to functioning radiologic equipment may be limited.

- Poverty is associated with an increased risk of TB. Poverty creates an “external” (e.g. crowded housing) and “internal” (e.g. undernutrition, unhealthy behavioural patterns) environment that promotes TB infection and disease. First Nations individuals with an annual income < \$10,000 are less likely than others to use health services.<sup>33</sup>

## Programmatic Issues in TB Control in Aboriginal Populations

In many provinces, FN populations are highly mobile in terms of travel between reserves and from reserve to urban areas. This presents challenges to contact investigation and case management, requiring communication and coordination between health jurisdictions.

A family history of congenital immune deficiency is a contraindication to childhood administration of BCG (see Chapter 17, Bacille Calmette-Guérin (BCG) Vaccination in Canada). An example is Severe Combined Immunodeficiency Syndrome (SCIDS), which has been noted among children born to an extended Canadian Cree family (M. Lem, First Nations Inuit Health Branch, personal communication, March 19, 2004). SCIDS has also been reported among the Navaho.<sup>34</sup> Interferon-gamma receptor deficiency has also been reported in a First Nations child who was inadvertently immunized with BCG.<sup>35</sup>

Partnership and collaboration with the community is important for TB control in Aboriginal as well as other minority populations. Health care workers should 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.<sup>36</sup>

Lack of knowledge about TB is strongly associated with negative attitudes about, and a worse experience of, the disease.<sup>37</sup> A proactive TB health education program that makes use of lay community resources – those who have recovered from the disease, their family members, elders and community health workers – is required in order to achieve a successful prevention and control program in Aboriginal communities.

## FNIHB Tuberculosis Sub-working Group (FTSG) Resolution of November 2005

At a 1997 National Consensus Conference on Tuberculosis, a recommendation was made that each province and territory in Canada should adopt an overall goal of tuberculosis elimination.<sup>38</sup> This goal was endorsed in a 1992 document entitled “National Tuberculosis Elimination Strategy for Aboriginal Peoples of Canada”.<sup>10</sup> However, in recent years, many experts have come to believe that elimination is not achievable in the foreseeable future and that setting an

unattainable goal is unhelpful for program planning. Thus, in 2005, FNIHB commissioned a report to determine whether TB elimination should continue to be the goal for FNIHB, or whether a new, evidence-based goal could be developed. In November 2005, after review of this report, the FTSG approved the following resolution:

“Recognizing the current global burden of TB and that no community exists in isolation, most Canadian experts agree that TB elimination is an unrealistic goal in the foreseeable future. FTSG endorses that an attainable goal should be used.

FTSG continues to advocate that TB elimination in Canadian Aboriginal populations be the ultimate vision for the program (as per WHO, STOP-TB and the International Organization for Migration).

In accordance with current scientific evidence, FTSG endorses the following long-term national goal: By 2015, reduce TB incidence to 3.6 per 100,000 among on-reserve First Nations and Inuit peoples across the 7 FNIHB regions in Canada. Such a goal is attainable by intensified efforts.

Regional long-term and short-term goals will be developed by each region and will be congruent with the national goal. Interim targets to be defined: % reduction in TB rates in 3 year and 5 year intervals. Indicators to monitor program strategies will need to be defined and finalized.”

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# Immigration and Tuberculosis Control in Canada

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## Introduction

As the world becomes ever more globalized, travel and immigration ensure that national patterns of disease epidemiology are increasingly reflective of the international situation. This is very true for tuberculosis (TB): during the past four to five decades, the epidemiologic and demographic nature of the disease in many of the developed, primarily low-incidence regions of the world has been evolving as a consequence of migration and population mobility.<sup>1</sup>

The cultural, social and linguistic diversity of these new major risk groups poses challenges for programs initially designed from a domestic control perspective. Local control in nations with low TB incidence such as Canada, which maintains active immigration programs, may be more effectively attained in the future through international rather than domestic undertakings.<sup>2</sup>

As well as influencing broader aspects of TB control and elimination policies at a national level, immigration is important for those who deal with the disease clinically on a day-to-day basis. Understanding the nature of current immigration patterns and the rationale and practices related to the medical aspects of the Canadian immigration process can assist in the planning and delivery of TB control programs at the community level. Finally, it should be noted that the relation between immigration and the management of TB is a challenge commonly encountered by other low-incidence nations with large immigration programs.<sup>3</sup>

## An Overview of Immigration in Canada

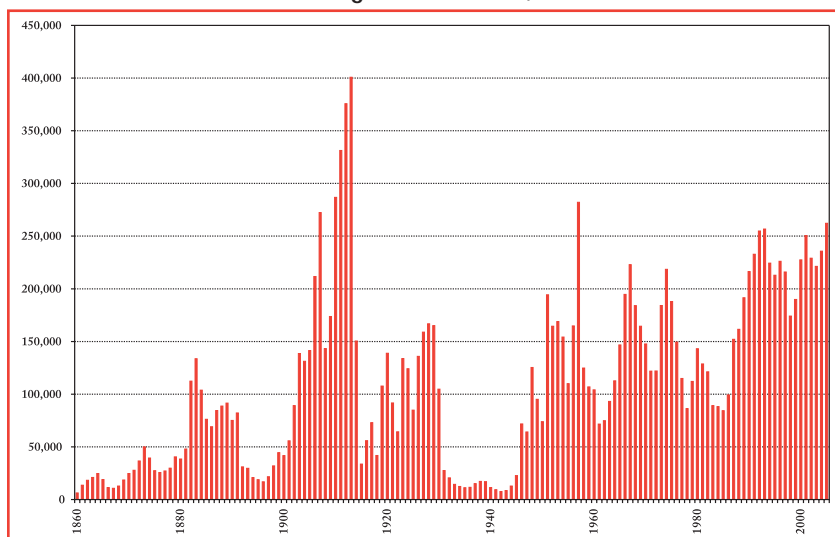
A country built as a result of immigration, Canada remains a nation with well-developed policies designed to attract and recruit arrivals from around the world. For the past decade, Canadian immigration levels have averaged approximately 225,000 individuals per year (Figure 1). This number includes all persons granted permanent residency, including refugees and immigrants (Table 1).

**Table 1**  
Permanent Residents by Immigration Category, 2004<sup>4</sup>

Immigration Class	Male	Female	Total
Economic class (including dependants)			
• Includes skilled workers, business immigrants, provincial/territorial nominees and live-in care givers	70,073	63,673	133,746
Family class			
• Includes spouses, partners, children, parents and grandparents	23,712	38,533	62,245
Protected persons			
• Includes government-assisted refugees, private refugee sponsorships and refugees recognized in Canada	16,978	15,708	32,686
Others			
• Includes humanitarian and compassionate admissions	3,392	3,754	7,146

In 2001, 18% of the total population of the nation was born out of Canada. This is the highest proportion of foreign-born people since 1931. Nearly 2 million people (6% of the total national population) in 2001 were individuals who had arrived in Canada during the previous decade.<sup>5</sup>

**Figure 1**  
Canadian Immigration Intake, 1860-2004<sup>4</sup>



The figures for those admitted permanently to Canada do not include individuals who are in Canada as temporary residents, such as visitors, students and workers, as well as the refugee claimants who have not completed the refugee determination process (Table 2).

**Table 2**  
Selected Temporary Residents and  
Refugee Claimants in Canada, 2004<sup>4</sup>

	Male	Female	Total	Percentage
Foreign workers	60,513	30,155	90,668	36.9
Foreign students	29,565	26,970	56,535	23.0
Humanitarian cases	13,424	10,277	23,701	9.6
Other	39,822	34,999	74,821	30.5
<b>Total</b>	<b>143,324</b>	<b>102,401</b>	<b>245,725</b>	<b>100.0</b>

Furthermore, international visitors number several million per year. All individuals applying for permanent residency in Canada and certain individuals applying for temporary residency are required to undergo an immigration medical examination (IME), which includes TB screening. However, most visitors do not require an IME.

Canada has a long history of accepting those affected by conflict, emergency and disaster. The selection of refugees is a formal component of the annual national immigration plan. Through that humanitarian process, populations already determined to be refugees under the United Nations Convention are selected in several international locations. These refugees may be assisted by the government or may be sponsored by organizations and individuals in Canada. They undergo a formal IME, including screening for pulmonary TB, before entering Canada.

International entrants who seek asylum in Canada (refugee claimants) have not been screened prior to their arrival. They are referred for an IME after making a refugee claim. The examination is to be undertaken shortly after arrival in Canada. Through this process, TB may be identified before the individual has completed the refugee determination process.

One characteristic of Canadian immigration is that large numbers of new immigrants now originate in regions of the world where local TB incidence and prevalence rates are several times greater than those observed in Canada (Figure 2). Rates in those populations tend to reflect the epidemiology of the disease in their country or region of origin.<sup>7</sup>

The second characteristic of Canadian immigration has been the location in which migrants settle in Canada after arrival. The majority of new immigrants and refugees to Canada settle in Ontario, Quebec, British Columbia and Alberta, mostly in urban areas such as Toronto, Montreal and Vancouver. To a significant extent, the national TB case load and the demand for TB control efforts mirror the settlement patterns of migrants in Canada (Figure 3).

**Figure 2**  
Proportion of Immigrants Born in Europe and Asia  
by Period of Immigration, Canada, 2001<sup>6</sup>

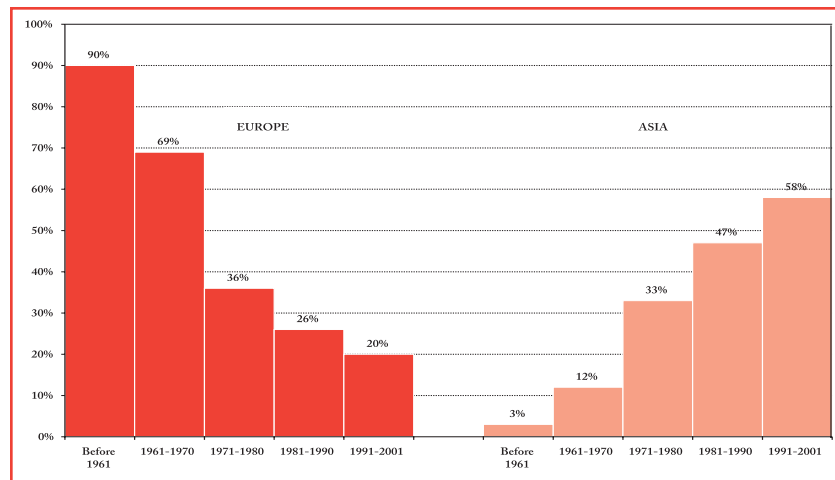
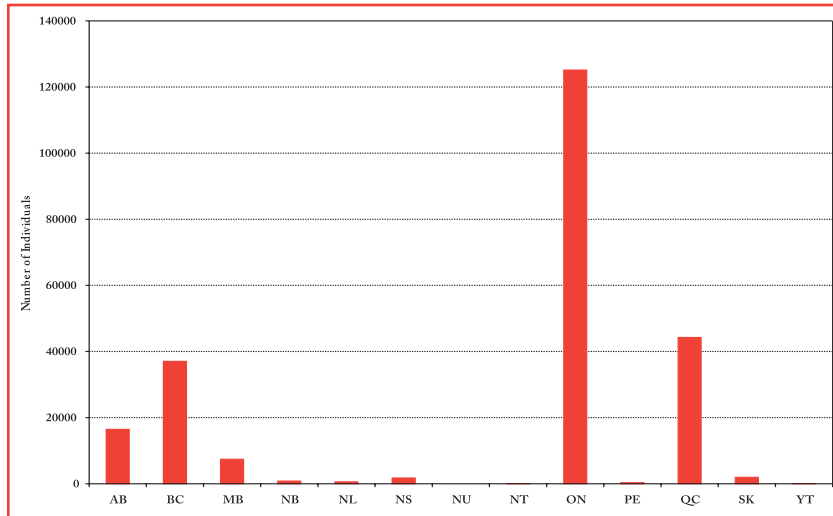


Figure 3  
Province of Destination of Newly Arrived Permanent Residents, 2004<sup>4</sup>



### Immigration Medical Screening

The present legislative authority for the medical aspects of Canadian immigration resides in the *Immigration and Refugee Protection Act (IRPA)* and Regulations, which became law in 2002. Protecting the health of Canadians is one of the key objectives of IRPA. Citizenship and Immigration Canada (CIC) is responsible for immigration processes, while CIC's Health Management Branch manages the health aspects of immigration. The Public Health Agency of Canada, based upon advice from the Canadian Tuberculosis Committee and its Immigration Subcommittee, provides technical advice on TB issues to CIC.

CIC has the mandate to assess applicants for permanent and temporary residency according to the three health grounds for inadmissibility under Section 38 (1) of IRPA, which are (1) danger to public health, (2) danger to public safety and (3) excessive demand on health or social services. Active pulmonary TB is considered to be a danger to public health. In balancing a foreign national's access to Canada and protection of the public health of Canadians, CIC has established a two-pronged strategy: immigration medical screening and a post-arrival medical surveillance program.

All applicants for permanent residency in Canada, refugee claimants and certain applicants for temporary residency are required to undergo an IME. Requirements for the examination are listed in Table 3.

Table 3  
Requirements for an Immigration Medical Examination

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 high TB incidence country/territory, 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 high TB incidence country/territory, as designated by the Public Health Agency of Canada. The occupational list is available at: < <a href="http://www.cic.gc.ca/english/information/medical/medexams-temp.asp">http://www.cic.gc.ca/english/information/medical/medexams-temp.asp</a> >.
Seriously ill foreign nationals	May be requested to undergo an IME if a CIC or Canada Border Services Agency officer has reasonable grounds to believe that the person is medically inadmissible in Canada, regardless of anticipated length of stay in Canada and country of origin.

A country/territory with a high incidence of TB is identified as a **designated country/territory** for the purpose of immigration. The designated country/territory list is provided and updated by the Public Health Agency of Canada. Basically, it represents countries/territories having a 3-year average incidence rate of smear-positive pulmonary TB of  $\geq 15/100,000$ . The list of designated countries is available at <http://www.cic.gc.ca/english/information/medical/dcl.asp>.

### Immigration Medical Examination and Assessment

The IME consists of the following components:

- review of past medical history;
- physical examination;
- mental examination;
- age-related routine tests
  - urinalysis, for applicants 5 years and above;
  - chest radiography, for applicants 11 years and above;
  - syphilis serology, for applicants 15 years and above;
  - human immunodeficiency virus (HIV) serology\*, for applicants 15 years and above, and for certain children

(\*routine HIV test introduced in January 2002)
- other tests as deemed necessary;
- medical assessment of records respecting the applicant.

Chest radiography has been the mainstay of the examination for TB. Other nations with organized national immigration screening programs, such as Australia and the United States, also use radiographic screening as a primary detection tool. Expanding immigration screening from the current radiographic

screening for pulmonary disease to routine screening for latent tuberculosis infection (LTBI) using the tuberculin skin test has been discussed and proposed.<sup>8,9</sup> This alternative screening method is not recommended as part of the IME, for epidemiologic, technical, cost and operational reasons.<sup>10</sup> Use of interferon- $\gamma$  release assays for LTBI as part of the IME is under consideration.

The medical examination is generally performed by designated medical practitioners (DMPs), who are physicians selected by Health Management Branch for this role. DMPs are supervised and trained by CIC Health Management Branch officers and perform the IMEs according to federal government standards. There are over 1,000 DMPs worldwide. The list of DMPs is available at: <http://www.cic.gc.ca/dmp-md/medical.aspx>. DMPs forward the results of IMEs, including x-rays, to one of the 10 regional medical offices (nine abroad and one at headquarters in Ottawa).

## Management of TB in the Immigration Context

Chest x-rays are examined for evidence of active or inactive TB disease by a local radiologist, and this is followed by an assessment done or supervised by a CIC Medical Officer. Chest x-rays are graded according to an 18-factor ascending scale of findings likely to be associated with prevalence of active TB disease and with the likelihood of progression to active pulmonary disease (Figure 4).

Applicants identified as having active TB are denied entry to Canada until proof of complete treatment: three negative sputum smears and cultures, and stable and/or improving chest x-rays taken over a minimum period of 3 months. The treatment should follow Canadian standards or, in some circumstances, follow the World Health Organization or the source country's national TB standards.

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 after arrival.

Inactive pulmonary TB is defined as follows:

- a) a history of 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.

Depending upon the history, the clinical status of the individual examined and chest x-ray findings, certain cases are considered to be inactive TB without any additional investigation.

## Figure 4 Radiological Scoring Form for the Canadian Immigration Medical Examination

Section E: page 2 of 2

### 4. Record of Special Findings Noted on the Applicant's Chest X-ray Film(s) Please review the list below and check all appropriate boxes

#### MINOR FINDINGS

- 1.1 Single fibrous streak / band / scar
- 1.2 Bony islets
- 2.1 Apical pleural **capping** with a **smooth inferior border** (< 1 cm. thick at all points)
- 2.2 Unilateral or bilateral costophrenic angle **blunting** (below the horizontal)
- 2.3 **Calcified nodule(s) in the hilum / mediastinum** with no pulmonary granulomas

#### MINOR FINDINGS (OCCASIONALLY ASSOCIATED WITH TB INFECTION)

- 3.1 **Solitary Granuloma** (< 1 cm. and of any lobe) with an **unremarkable hilum**
- 3.2 **Solitary Granuloma** (< 1 cm. and of any lobe) with **calcified / enlarged hilar lymph nodes**
- 3.3 Single / Multiple **calcified pulmonary nodules / micronodules with distinct borders**
- 3.4 **Calcified pleural lesions**
- 3.5 Costophrenic Angle **blunting** (either side **above the horizontal**)

#### FINDINGS SOMETIMES SEEN IN ACTIVE TB OR OTHER CONDITIONS

- 4.0 **Notable apical pleural capping** (rough or ragged inferior border and / or  $\geq$  1 cm. thick at any point)
- 4.1 **Apical fibronodular / fibrocalcific lesions** or apical **microcalcifications**
- 4.2 Multiple / single **pulmonary nodules / micronodules (noncalcified or poorly defined)**
- 4.3 Isolated **hilar or mediastinal mass/lymphadenopathy (noncalcified)**
- 4.4 **Single / multiple pulmonary nodules / masses  $\geq$  1 cm.**
- 4.5 Non-calcified **pleural fibrosis** and / or **effusion**
- 4.6 Interstitial fibrosis / parenchymal lung disease / acute pulmonary disease
- 4.7 **ANY cavitating lesion OR "Fluffy" or "Soft" lesions** felt likely to represent **active TB**.

**NONE OF THE ABOVE ARE PRESENT**

### 5. Certification by the Radiologist

**DECLARATION:** This is a true and correct record of my findings. IF THE X-RAY LIKELY REPRESENTS ACTIVE TB, THE REFERRING PHYSICIAN WILL BE NOTIFIED DIRECTLY.

Full name, writing address and telephone number (please print or stamp)

Signature

Date    Day    Month    Year

Location

IMM 5419 (08-1998) E  
OIC EXPLORÉ

## Medical Surveillance Program

The CIC Medical Surveillance Program notifies provincial/territorial public health authorities regarding applicants identified as having inactive pulmonary TB and thus subject to medical surveillance. For information on current details of the Program, please contact the following:

---

Citizenship and Immigration Canada  
Medical Surveillance Unit (MSU)  
Health Management Branch  
(613-941-7771)  
e-mail: nat-med-surveillance@cic.gc.ca

---

Such individuals receive a Medical Surveillance Undertaking Form (IMM 0535B) and an informational handout that provides instructions relating to contact with 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.

Since 2003, for individuals who apply for immigration within Canada, such as refugee claimants, the public health referral occurs at the end of the immigration medical assessment process rather than at the end of the complete immigration process. CIC's Health Management Branch forwards a notification form to public health or TB control authorities in the provinces/territories and provides an information and instruction letter to the applicant.

In February 2006, CIC implemented a new process for urgent referral of complex, inactive pulmonary TB cases at higher risk of reactivation to provincial/territorial public health authorities.

Over the past few years, the number of individuals identified as requiring surveillance has been reported to be approximately 2% of total annual immigration medical assessments (ranging from approximately 410,000 to 445,000).

Guidelines for the management of those placed under surveillance and referred to local public health/TB authorities have been prepared by the Canadian Tuberculosis Committee (Appendix I, Guidelines for the Investigation and Follow-up of Individuals Under Medical Surveillance for Tuberculosis after Arrival in Canada (2007)).

Since 2002, provincial/territorial public health authorities report the immigrant's compliance with the requirement for medical surveillance to the CIC Medical Surveillance Program. The definition of compliance is now defined throughout Canada as keeping the first appointment with the clinician or being assessed by a specialist designated by public health. Compliance reporting varies by province/territory, averaging 50% over the past few years.



For more information on CIC's operational guidelines regarding TB, please contact

---

Citizenship and Immigration Canada  
Director of Operations  
Health Management Branch  
e-mail: HMB-OPS@cic.gc.ca

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## Immigration Challenges Related to TB

The incidence of TB is high in many countries that are a source of immigrants to Canada. As well, many of these source countries do not have public health systems for TB diagnosis and treatment that are as developed as those found in Canada. Limitations of screening tools, quality of laboratories and x-rays, quality of reports provided by specialists in some areas of the world, and cultural and language barriers are issues affecting the evaluation and management of TB in individuals applying to come to Canada.

Specific operational factors and issues related to immigration (such as delay between the medical assessment and entry into Canada and deportation of individuals with TB) can also be very challenging.

## Health Care Coverage for Certain Groups of Migrants: the Interim Federal Health Program

Immigrants are expected to be 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 in Canada. CIC manages a health care coverage program, the Interim Federal Health Program (IFH), which was introduced for humanitarian reasons. The IFH program provides temporary emergency and essential health care coverage for certain immigrants in need of assistance during their settlement period in Canada. It is now almost exclusively limited to refugee claimants, Convention refugees and Canada Border Services Agency detainees. If an individual is deemed eligible for the IFH Program, health care coverage for necessary medical care and treatment for TB will be provided. Information on the IFH program is available at <http://www.fasadmin.com> and <http://www.cic.gc.ca/english/index.asp>.

Contact information for the IFH Program:

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Citizenship and Immigration Canada  
Interim Federal Health (IFH) Program  
Health Management Branch  
e-mail: CIC-IFH-program@cic.gc.ca

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## Conclusions

- The arrival of large numbers of immigrants from countries of the world with high incidence rates of TB during the past 40 to 50 years has altered the epidemiology of TB in Canada.
- Continued migration will cause the epidemiology of TB in Canada to mirror global TB patterns.
- Patterns of immigrant dispersal after arrival in Canada will continue to influence provincial/territorial and regional demands for TB control and prevention services.
- Current approaches to managing TB in new immigrants in Canada are based on chest radiographic screening of those applying for permanent residency or extended temporary stay (greater than 6 months and coming from a designated country/territory). Those noted to have active TB disease are denied entry to Canada until proof of complete, adequate treatment. Those noted to have inactive pulmonary TB are referred to provincial/territorial authorities for medical surveillance.
- Recent evaluation of available screening methods indicates that radiographic screening remains the most appropriate screening method for pulmonary TB.
- While there are common challenges in managing TB in Canadians and immigrants, some are specifically related to the immigration process and require CIC to work on an ongoing basis with its health partners to contribute towards protecting the health of Canadians and towards the global management of the disease.

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# Tuberculosis Control Within Institutions

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## Introduction and General Principles

The occupational risk of tuberculosis (TB) among health care workers was substantial and well recognized in the pre-antibiotic era.<sup>1</sup> As the incidence declined and effective therapy was developed to shorten or prevent hospital stay, hospitalization for TB in Canada declined rapidly. This resulted in relaxation of infection prevention and control measures, if not outright complacency about this problem. At present, patients with active TB are rarely admitted to most Canadian hospitals.<sup>2,3</sup> However, in health care facilities serving at-risk populations, such as Aboriginal Canadians, the urban poor or immigrants from high-incidence countries in Asia, Eastern Europe, Africa and Latin America, TB remains an important potential occupational hazard.<sup>3</sup>

The transmission of TB has been described in many institutional settings, including hospitals, long-term care facilities, shelters, rooming houses and prisons. A number of guidelines for health care facilities have been published, and although not directly applicable to other institutional settings the underlying concepts are certainly the same. While effective control measures for preventing transmission exist and are discussed below, most nosocomial transmission from infectious cases occurs before diagnosis. Accordingly, current guidelines for health care facilities emphasize the importance of early diagnosis through worker and client education programs.

These guidelines are based, as much as possible, on published evidence. However, there is very little evidence applicable to infection prevention and control that is based on randomized trials, generally considered the strongest level of evidence. This is for ethical and practical reasons — workers cannot be exposed to TB experimentally, nor can the interventions to reduce nosocomial transmission be randomly assigned to individual workers, since they are usually applied throughout entire institutions. Thus the majority of evidence comes from cohort and case-control studies, as well as analyses of outbreaks. Hence the ratings of levels of evidence are not given in this chapter, since almost all would be level II or III (according to the ratings described in the Preface). As well, in the interest of brevity, this chapter frequently cites the evidence base in several published extensive reviews<sup>1,3-5</sup> and in a detailed review with recommendations on this topic from the U.S. Centers for Disease Control and Prevention.<sup>6</sup> Interested readers are directed to these sources for additional detail.

### Determinants of TB transmission

TB is spread by the inhalation of airborne organisms. Infectious particles are generated when individuals with pulmonary or laryngeal TB cough, sneeze, sing, play wind instruments or, to a lesser extent, speak. Cough-inducing procedures such as bronchoscopy are associated with an increased generation of infectious, aerosolized particles. Aerosolization may also occur in laboratory and autopsy procedures or during activities such as the irrigation of TB-infected wounds. Once infectious particles have been aerosolized, they are spread throughout a room or building by air currents and can be inhaled by another individual. Inhalation of a single droplet nucleus containing less than three *Mycobacterium tuberculosis* bacteria can result in infection.<sup>7</sup> The probability of nosocomial transmission of TB will be affected by the following four groups of factors,

summarized in Table 1. In general, the greater the number of determinants present in any exposure the greater the likelihood of transmission.

**Table 1**  
**Factors Associated with Transmission of Tuberculosis**

Patient Factors	Diagnostic Factors	Treatment Factors	Environmental Factors
Number of infectious TB patients	Cough-inducing procedures, e.g. sputum induction or bronchoscopy	Delay in diagnosis	Inadequate germ-free ventilation
Respiratory secretions that are acid-fast bacteria (AFB) smear positive	Autopsy, preparation of pathology specimens, mycobacterial cultures	Inadequate or incorrect therapy	Overcrowding
Pulmonary or laryngeal disease		Administration of aerosolized therapies that induce coughing	Duration of exposure to infectious patient and proximity
Presence of cough		Wound irrigation	Absence of sunlight

*The number of infectious patients.* The number of infectious TB patients cared for, particularly those whose condition has not yet been diagnosed and who are not receiving therapy, is the most important determinant of risk of transmission. In Canadian institutions to which no patients with active TB are admitted each year, the risk to health care workers should be very low.

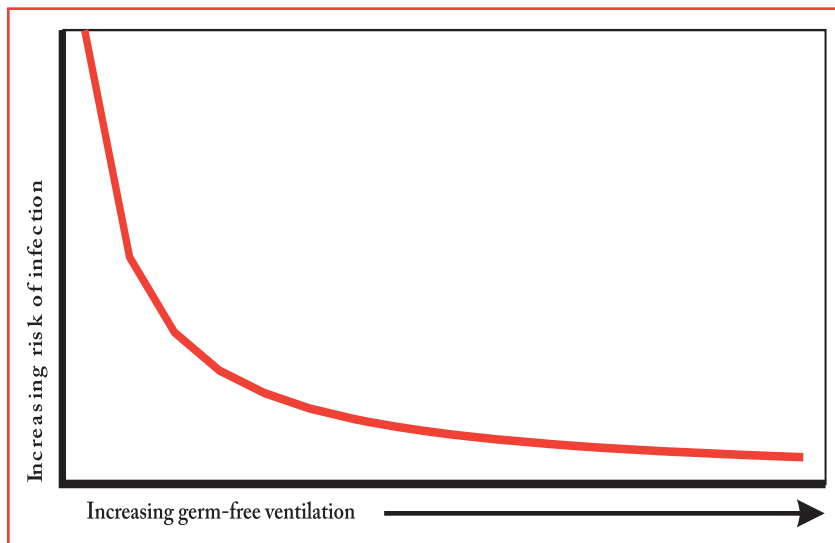
*Contagiousness of each patient.* This is difficult to quantify (see Chapter 3, Transmission and Pathogenesis of Tuberculosis), but delayed diagnosis or delayed recognition of drug resistance has been identified as a major contributing factor in almost all reports of hospital outbreaks of TB. Diagnosis may be delayed if manifestations are atypical, such as when TB occurs among elderly and/or immunocompromised persons, who now account for an increasing proportion of all cases. Delayed diagnosis occurs in almost half of all patients hospitalized for active TB, and this often results in significant exposure for health care workers and other patients.<sup>8</sup> Patients with laryngeal involvement may be particularly contagious.<sup>9</sup> Most patients with extrapulmonary disease alone are noncontagious, but it is very important to exclude concomitant pulmonary involvement: in one study, 50% of patients with proven pleural TB and no radiologic evidence of pulmonary disease had positive TB cultures from induced sputum.<sup>10</sup> Young children (< 10 years of age) are usually not contagious, although transmission has been documented rarely.<sup>11</sup> Adolescents may be as contagious as adults.

*Hours of exposure.* The risk of infection during **one hour** of exposure ranges from 1 in 4 during bronchoscopy of a patient with unrecognized smear-positive disease<sup>12</sup> and 1 in 60 during exposure to a patient with laryngeal TB<sup>8</sup> to 1 in 600 from treated active pulmonary TB patients on a 1950s TB ward with single rooms.<sup>12,13</sup> Even though the latter risk is low, if exposure is repeated often the cumulative risk can be high. For example, if workers had only one hour at that level of exposure each week, but every week had a similar exposure, their cumulative risk would be close to 100% after 10 years.

*Ventilation.* The exchange of indoor air with outdoor (“germ-free”) air will reduce the risk of infection by diluting the infectious particles. In buildings with sealed

windows and mechanical ventilation systems, a high percentage of recirculation can contribute to nosocomial transmission, unless the air being recirculated is treated to make it germ-free. This can be achieved by use of ultraviolet germicidal irradiation or high-efficiency particulate air (HEPA) filtration (see Environmental Engineering Controls). The effectiveness of ventilation in reducing risk of transmission in the institutional setting is unknown. However, it has been shown that ventilation levels in general patient (i.e. nonisolation) rooms is a key determinant of risk of TB infection.<sup>14</sup> As well, theoretically the risk of transmission should decrease exponentially with increasing fresh-air ventilation, as shown in Figure 1.

Figure 1  
Relationship between risk of tuberculosis transmission  
and germ-free ventilation



### Preventing spread of TB in Canadian health care facilities

A countrywide survey of Canadian acute care facilities revealed that 3,746 patients with pulmonary TB were treated in 191 health care facilities between 1989 and 1993.<sup>2,14,15</sup> The average number of patients with pulmonary TB treated each year in these health care facilities over this 5-year period varied from 0 to 102 (mean 4.1).

Reports from the United States documented several outbreaks of TB, including outbreaks of multidrug-resistant TB (MDR-TB) in health care facilities during the 1990s, largely because of failure by these health care facilities to implement appropriate TB control measures.<sup>3</sup> These findings heightened concern about the nosocomial transmission of TB and resulted in the formulation of recommendations for the prevention of nosocomial transmission of TB in health care institutions in Canada in 1996<sup>16</sup> and in the United States in 1994<sup>17</sup> and 2005.<sup>6</sup> Implementation of the recommendations has contributed to a reduction in nosocomial TB transmission.<sup>6</sup>



The recommendations called for a hierarchical approach to controls, including the following:

- *administrative* controls, such as more rapid isolation, diagnosis and treatment of patients suspected of active TB;
- *engineering* controls, such as improved ventilation in patient care areas; and
- *personal controls*, such as tuberculin skin testing of workers and use of more efficient particulate respirators (i.e. masks).

In health care institutions where many of these measures were implemented, there was a dramatic reduction in nosocomial transmission. In fact, over the past 10 years there have been no similar outbreaks reported in North America. Nevertheless, exposure to patients with unsuspected active TB and resultant transmission of TB infection continue to occur in Canadian health care institutions.<sup>14,18-20</sup> Given this situation, TB prevention and control programs remain essential within all Canadian health care facilities.

However, a significant concern with many previously published recommendations is the enormous cost they entail, especially for engineering controls. Some of these measures are not of proven efficacy or cost-effectiveness. Most of them are unnecessary in facilities where patients with active TB are only rarely admitted. These realities have been incorporated into the revised U.S. recommendations.<sup>6</sup>

### Risk classification: health care facilities

The risk categories presented here have been modified from previous classifications<sup>3,21</sup> based upon an extensive review of the available literature and expert opinion.<sup>6</sup> Although imprecise, they provide an accepted basis for recommendations. While the number of TB patients admitted is a key determinant, the likelihood of exposure to any one patient can vary considerably among institutions of different size. To account for this the classification is based on the number of active inpatient beds and number of TB cases of all forms, and sites.

#### Hospital with > 200 beds

- < 6 TB patients admitted annually = low risk
- ≥ 6 TB patients admitted annually = medium risk

#### Hospital with < 200 beds

- < 3 TB patients admitted annually = low risk
- ≥ 3 TB patients admitted annually = medium risk

#### Other facilities, such as long-term care

- < 3 TB patients admitted annually = low risk
- ≥ 3 TB patients admitted annually = medium risk

## Risk classification: health care workers

### *High-risk activities*

1. Cough-inducing procedures (sputum induction, pentamidine aerosol)
2. Autopsy
3. Morbid anatomy and pathology examination
4. Bronchoscopy
5. Designated mycobacteriology laboratory procedures, especially handling cultures of *M. tuberculosis*.

### *Intermediate-risk activities*

Work that entails regular direct patient contact (e.g. by nurses, nursing aids, respiratory technologists, social workers, physiotherapists) on units to which patients with active TB may be admitted. Members of housekeeping departments may be considered in this risk category if they are involved in cleaning patients' rooms.

### *Low-risk activities*

Minimal direct patient contact (in medical records, administration, maintenance); work on units where TB patients are unlikely to be admitted, such as obstetrics or gynaecology. However, classification of such units as low risk may be incorrect if the population they are serving (e.g. foreign-born patients from high TB incidence countries) has a high incidence of TB. Some of the longest delays in diagnosis may occur in such settings. Pediatric units are generally considered low-risk areas; however, TB transmission between two infants has been documented in a Canadian pediatric centre,<sup>11</sup> likely through contaminated respiratory equipment. Adolescents with TB are often as contagious as adults, and children aged 0-4 are highly susceptible. Furthermore, pediatric cases may well have acquired their disease from adult close family contacts who may expose staff and patients to TB while visiting. Hence pediatric centres should have TB infection prevention and control programs as strict as those of adult centres.

## Prevention of Transmission Within Institutions – Administrative Controls

### TB management program (all health care facilities)

It is essential that all health care facilities have a TB management program, supported at the highest administrative level.\* The general goal should be to prevent transmission of TB to staff and patients. On a practical level this means ensuring that measured indicators of transmission in this population are not different from those at community levels. Policies and procedures should clearly delineate the administrative responsibility for developing, implementing, reviewing and evaluating the various program components. Specific personnel with responsibility for the program within the health care facility should

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\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

be designated. This program should include policies and procedures for rapid identification, isolation and treatment of patients, reduction of nosocomial transmission through engineering controls and protection of staff through appropriate respirators (masks), education and tuberculin skin testing. An essential part of this program is annual review of indices of nosocomial transmission. Examples of such indices include (i) tuberculin skin test (TST) conversion among clinical personnel; (ii) the total number of TB patients admitted annually; (iii) the number of exposure episodes, i.e. TB patients admitted whose condition was initially undiagnosed, who are not treated and not in airborne isolation; and (iv) the number of patients whose TB was diagnosed only at autopsy.

In medium-risk hospitals a TB management committee is recommended, whose members should include persons with day-to-day responsibility for infection prevention and control and employee health, with representation from senior administration, laboratory, nursing, medicine, other health disciplines (e.g. respiratory technology) and public health. Additional members may be added from other employee groups (e.g. central supply, housekeeping, laundry, pharmacy, physical plant and maintenance).

In health care facilities where TB patients are rarely admitted, the management program may consist only of the capacity to diagnose patients with TB disease and an arrangement to transfer all such patients to another centre where the appropriate engineering and personal control measures have been implemented. In facilities with a transfer-out policy, there should be at least one area where patients can be kept in airborne isolation until they are transferred. In regions with few TB cases, the appropriate regional authorities should ensure that there are an adequate number of facilities with appropriate engineering and personal control measures to receive such patients with minimum delay.

It is strongly recommended that all facilities make available to their health care workers annual summary information on the clinical, epidemiologic and microbiologic features of patients whose TB is diagnosed within the hospital. This will help to increase awareness of TB in the patient population served by the hospital.

### **Risk assessment**

The first step of an institutional TB infection prevention and control program is an assessment of institutional risk and the risk for health care workers engaged in different activities. This assessment should include a retrospective review of all TB cases hospitalized in the institution, their diagnosis and outcomes over the preceding 5 years. It should also include a review of all results of tuberculin skin testing if available.

### **Training of health care workers**

A very important component of any infection prevention and control program is training of health care workers. This is certainly true for TB control within institutions. Health care workers should receive training in TB at the time of hiring and periodically thereafter. This should include awareness of epidemiologic and medical risk factors, signs and symptoms, mechanisms of transmission as

well as the importance of administrative, engineering and personal controls in the prevention of transmission.

### Early identification of patients with suspected TB (all health care facilities)

A high index of suspicion must be maintained.\* The presence of cough of more than 3 weeks' duration with or without weight loss and fever in a person belonging to one of the epidemiologic risk groups should prompt a thorough investigation to rule out TB (see Chapter 1, Epidemiology of Tuberculosis in Canada). Chest radiography should be carried out and sputum specimens tested for acid-fast bacteria (bacilli) (AFB) in suspect cases. Three sputum specimens should be collected (or gastric aspirates in children too young to produce sputum). These can be collected 8-24 hours apart (or longer if necessary). At least one should be collected in the early morning upon awakening. Collection of sputum samples must be performed in a safe environment (see below).

For all patients with suspected or confirmed infectious TB who are admitted to a health care facility, appropriate airborne isolation precautions should **immediately** be initiated. This means that patients whose respiratory secretions (e.g. sputum or bronchial alveolar lavage [BAL]) are AFB smear positive or who have a suspicious chest x-ray should be isolated. (This includes children of any age with AFB smear-positive respiratory secretions or gastric lavage, or strongly suspected active pulmonary TB.) Institutional policies should designate persons with the authority (usually the infection prevention and control personnel) to discontinue isolation precautions, monitor compliance with isolation procedures and manage breaches in isolation precautions. Some individuals with AFB-positive smears due to nontuberculous mycobacterial infection and many persons with "suspect" chest radiologic findings who are found later to have other pulmonary diseases will be placed under airborne isolation precautions. This is appropriate, as it is preferable to immediately isolate patients who later prove not to have active TB than to not implement appropriate isolation precautions for patients who later are proved to have contagious TB.

Empiric therapy should be considered for those cases in which TB is strongly suspected but for whom the diagnosis has not yet been confirmed by smear or culture. If the patient is at risk of drug resistance, the initial empiric therapy should be modified accordingly (see Chapter 7, Drug-resistant Tuberculosis).

### Airborne isolation in special situations

*Intensive care unit:* Patients with suspect or confirmed active TB should be placed in airborne isolation in an appropriately ventilated airborne isolation room within the intensive care unit. If such a room is not available arrangements should be made to transfer patients to facilities with such rooms as quickly as possible. In patients who require 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. When endotracheal suctioning is performed a closed suction apparatus should be used.

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

*Emergency department:* If the number of TB patients or TB suspects warrants it, the emergency department should be equipped with an airborne isolation room with appropriate ventilation. Such a room would also be useful for isolating patients with other airborne communicable diseases, such as varicella and rubeola. Whenever patients suspected of having active TB are seen they should be immediately triaged to this room. 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 TB has been excluded or confirmed.

*Surgery:* Surgery should be postponed or scheduled at the end of the day, as much as possible. Staff should wear appropriate masks, e.g. N95 respirators (see below) without valves, as these will protect the workers from inhalation of infectious particles while also protecting the operating field from contamination by the workers. Air supplied to the operating room should be exhausted and not exit the room to other patient care areas. This is usually the case, because of the presence of anaesthesia gases.

### **Airborne isolation of patients with suspect or confirmed TB (all health care facilities except low-risk with a transfer-out policy)**

#### *General principles*

Infection prevention and control personnel should be notified of all patients with confirmed TB who are in the facility. They should also be notified of all patients who are placed in airborne isolation because of a high suspicion of TB. Patients should remain in an adequately ventilated airborne isolation room (see below). Visitors and staff entering the room should wear appropriate respirators (see below). Visits by children should be discouraged because of their increased susceptibility. TB patients leaving the room should wear a surgical mask or N95 respirator. (N95 respirators are not really necessary for patients, are more expensive, and may be less comfortable. However, some hospitals use an N95 respirator for patients to reduce the chances of personnel wearing a surgical/procedure mask, which would certainly be suboptimal.) If patients are going to other hospital departments, those departments should be notified. In general, however, movement outside of the room should be minimized.

#### *Discontinuation of airborne isolation in suspect TB cases*

Airborne isolation may be discontinued if three successive samples of sputum (spontaneous or induced) are negative on smear, unless TB is still strongly suspected, cultures are pending, and no other diagnosis has been made. The smears should be collected 8-24 hours apart, and at least one should be an early morning specimen. Isolation may usually be discontinued if another definitive diagnosis is made (e.g. cancer, pneumonia) and concomitant active TB is considered unlikely. It is important to note that a single negative AFB smear from BAL does NOT definitively exclude active TB and that three induced sputa have superior yield for the diagnosis of active TB than a single bronchoscopy.

#### *Discontinuation of airborne isolation in confirmed TB cases*

The degree and duration of contagiousness 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. Previous studies examining the duration of contagiousness after patients are started on therapy had seriously flawed study designs and limited power. As well, this issue has never been studied in a setting equivalent to that of a Canadian hospital, where most workers are TST negative and most patients have conditions that depress immunity.

A number of variables influence the length of time an individual remains infectious. These include the initial level of infectivity, the level of competence of the patient's immune response, the duration of and adherence to anti-TB therapy and the presence or absence of drug-resistant TB. Although most individuals experience bacteriologic improvement quickly when receiving appropriate therapy, transmission of multidrug-resistant TB has been reported in U.S. health care facilities from patients whose isolation precautions were discontinued after a fixed time interval of 2 weeks of therapy.<sup>3</sup> Therefore, criteria for discontinuation of isolation precautions should NEVER be based on a fixed interval of treatment (e.g. 2 weeks) but, rather, on evidence of clinical and bacteriologic improvement and evidence of the adequacy of the treatment regimes. In summary, isolation precautions should be continued until patients are highly likely to be noninfectious.

*Patients with smear-negative, culture-positive respiratory tuberculosis:* Airborne isolation may be discontinued after 2 weeks of appropriate multidrug therapy, as long as there is clinical evidence of improvement. The patient may go home earlier, but in hospital should be isolated for at least the first 2 weeks of therapy.<sup>22</sup>

*Patients with smear-positive TB:* These patients should remain in airborne isolation until three consecutive sputum smears are negative. These can be taken 8-24 hours apart, and at least one of them should be taken in the early morning. In addition, there should be clinical evidence of improvement and evidence of adherence to at least 2 weeks of multidrug therapy based on the known antibiotic sensitivity of the patient's organism.<sup>22</sup> In patients who are no longer able to spontaneously produce a sputum specimen, sputum induction would be useful and appropriate. More invasive testing, i.e. bronchoscopy, is not recommended for this purpose.

Initially smear-positive patients may be discharged home after 2 weeks of therapy, even if they are still smear positive. These patients are still potentially contagious. However, their household contacts were already heavily exposed and are often already receiving therapy for latent tuberculosis infection (LTBI). Thus, the risk of further transmission to these close contacts must be balanced by the social, mental and physical health benefits of the return home of the patient. However, contact with other non-household persons must be avoided. Hence the discharge may be made only if the following conditions have been met:\*

1. Directly observed therapy, if indicated, has been arranged.
2. Household air is not being recirculated to other housing units (e.g. apartment complex).

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

3. No infants or children under age 5 years or persons with immunocompromising conditions are present in the household, as they are at higher risk of progressing to TB disease if infected. An exception would be if they are already receiving treatment for TB disease or LTBI.
4. All immunocompetent household members have been previously exposed to the patient.
5. The patient is counselled NOT to return to work, school, or usual social activities, nor have visitors. Indeed they should refrain from going into any other indoor environment where TB transmission could take place. These precautions should be maintained until three consecutive sputum smears are negative. Smears can be taken 8-24 hours apart, and at least one of them should be taken in the early morning. Note that patients 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.
6. There should be clinical evidence of improvement and reasonable evidence of adherence to at least 2 weeks of multidrug therapy.
7. Until three negative AFB smears have been obtained, patients who attend out-patient follow-up should wear a mask while visiting the health facility. If home care or other personnel visit the patient at home they should wear appropriate masks, e.g. N95 or equivalent respirators.

In the event that a smear-positive, culture-negative condition develops during treatment, airborne isolation may be discontinued provided three consecutive sputum specimens are culture negative after 6 weeks of incubation.

*Patients with active MDR-TB:* Drug susceptibility test results are usually available within 2 weeks in a smear-negative culture-positive case and 3 weeks in a smear-positive case (see Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies) confirming, or not confirming, the effectiveness of therapy to date. Patients with MDR-TB must remain in airborne isolation for the duration of their hospital stay or until three consecutive sputum cultures are negative after 6 weeks of incubation.

*Patients with active XDR-TB:* Patients with active XDR-TB must remain in airborne isolation for the duration of their hospital stay or until three consecutive sputum cultures are negative after 6 weeks of incubation.

### ***Transfer of patients with suspected or known contagious TB***

During transport of patients from one facility to another or within a facility, patients should wear a surgical/procedure mask or N95 respirator (without an expiratory valve). If transport between facilities is required, patients should not use public transport. They should be transported in well-ventilated vehicles (i.e. with the windows open) as much as possible. Attendants should wear appropriate masks, e.g. N95 respirators.

## Environmental Engineering Controls

### Ventilation

Recent recommendations for reduction of the risk of nosocomial transmission of TB have included dramatic increases in ventilation. Increasing air changes per hour (ACH) from 1 to 6 will result in four to five times more rapid clearing of infectious particles from the air within a room. However, further increases above 6 ACH will have less and less effect, and increases above 12 ACH will be of very little added benefit.<sup>23</sup> There are considerable costs associated with increasing ventilation.<sup>24</sup> In general, as air exchanges are increased, so are the costs to build and maintain the system. Initial costs include installation of duct work for supply and return air systems. In older hospitals, this may involve significant demolition and remodelling. As well, ventilation systems need to be upgraded, with increased fan capacities as well as huge filtration systems. Recurring costs include the costs of heating or cooling the increased outdoor air required, as well as frequent inspection and maintenance of the fans, filters and duct work.

A number of authoritative groups or agencies have formulated recommendations regarding ventilation levels to reduce risk of nosocomial transmission of airborne pathogens, including not only TB but also measles (rubeola) and varicella. These agencies include the U.S. Centers for Disease Control and Prevention (CDC),<sup>6</sup> the Canadian Standards Association (CSA),<sup>25</sup> the American Society of Heating Refrigeration and Air-conditioning Engineers (ASHRAE),<sup>26</sup> and the U.S. Institute of Medicine.<sup>27</sup> These different bodies have published somewhat different ventilation standards for airborne isolation rooms and other patient care areas within hospitals, see Table 2. Differences among these recommendations are not based on consideration of different evidence but, rather, upon the risk-benefit acceptance level.

Table 2  
Ventilation Recommended for Selected Areas in Health Care Facilities

Area	No. of Mechanical ACH, by Recommending Agency				Direction of Air Movement (all agencies)*
	CTS	CDC	CSA	ASHRAE	
Autopsy suite	12	12	20	12	Inward
Bronchoscopy room	9-12	12	20	12	Inward
Emergency department and radiology waiting rooms	2	NS†	9	12	Inward
Operating room or surgical room	15	15	20	15	Outward
Airborne isolation rooms‡					
• Existing buildings	6	6	NS	NS	Inward
• New buildings	9	9	12	12	
General patient care, and nonisolation rooms	2	NS†	6	4¶	N/A

ACH = air changes per hour; CTS = Canadian Thoracic Society; CDC = Centers for Disease Control and Prevention; CSA = Canadian Standards Association; ASHRAE = American Society of Heating Refrigeration and Air-conditioning Engineers

\* Direction of airflow from hallway or corridor relative to space (inward means from hallway **into** room).

† Not stated, no recommendation made specific to these areas.

‡ Air-cleaning devices may be used to increase the equivalent ACH.

¶ Recommendation is for patient corridors.

### General hospital areas

It is important to ensure that there is adequate ventilation in general (i.e. nonisolation) inpatient rooms. This is because unsuspected TB cases are



placed in them, and these patients pose the greatest risk of transmission of TB infection to other patients and health care workers.<sup>14</sup> Yet substantial costs are associated with higher levels of ventilation in terms of initial installation, maintenance and energy costs. Unnecessary expenditures on ventilation may lead to underexpenditures in other areas that can also affect patient and health care worker safety. Recommendations should be based, as much as possible, on published evidence. Accordingly, the Canadian Thoracic Society's Tuberculosis Committee recommends a minimum of 2 ACH in these rooms, on the basis of the only published epidemiologic evidence.<sup>14</sup> In this study, conducted in Canadian hospitals, risk of transmission was very low in general patient care areas (including emergency departments) if ventilation levels exceeded 2 ACH. Recommendations of the Canadian Thoracic Society should be considered a minimum, given that the CSA recommends 6 ACH for in-patient rooms in acute-care hospitals;<sup>25</sup> 9 ACH for emergency departments; 9 ACH for clinic rooms, except family practice, gastroenterology and pediatrics, where 6 ACH is considered sufficient; and 3 ACH for corridors.<sup>25</sup> It is important to note that none of these CSA recommendations is supported by published evidence.

*Airborne isolation rooms (all hospitals except low risk with transfer-out policy)*

All agencies recommend that newly constructed isolation rooms should have 12 ACH. CDC recommends that pre-existing rooms should have at least 6 ACH.<sup>6</sup> Since the protective benefit of increasing air exchanges is marginal as the ACH are increased past 9, it is unclear whether achieving 12 air exchanges is an efficient use of hospital resources (see preceding discussion — increased expenditures for higher ventilation may result in reduced resources for other measures that could have greater benefit in protecting the health of patients or workers). Within existing facilities use of HEPA-filtered units that recirculate the air back into the same room or ultraviolet germicidal irradiation may be adjunctive methods to increase the effective germ-free ventilation. Air from the room should be exhausted to the outdoors, ideally exiting from the roof of the building. It is important that the exhausted air 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 must be passed through a HEPA filter before being exhausted.

- (i) The direction of air flow should be from the hall and into the room, and then exhausted outdoors. To achieve this, the ventilation system must be designed and must function so that the room is negative relative to the hallway outside. Past guidelines recommended very low pressure differentials, but subsequent studies have shown that the direction of air flow was not consistently from hallway into room with such low pressure differentials. Therefore, recent recommendations suggest a pressure differential of 2.5 pascals (equivalent to 0.25 mm or 0.01 inches of water).<sup>6</sup>
- (ii) Windows and doors should be kept closed at all times. Opening the window may cause reversal of direction of air flow, depending upon the prevailing wind direction and outdoor temperature.
- (iii) The air changes and direction of air flow should be verified at least every 6 months when the ventilation system is not being used. Direction of air

flow should be tested with smoke tubes at all four corners of the door daily when the room is occupied, unless the room is equipped with automatic pressure monitoring.

- (iv) The number of airborne isolation rooms required in medium-risk hospitals should be based on the number of patients admitted each year with suspected active TB who require airborne isolation. Airborne isolation rooms should be grouped together. This will make it easier technically to achieve the ventilation required and may reduce the risk of TB transmission to other patients, as well as facilitate care of these patients. In regions with very few TB admissions, the number of isolation rooms in the region should be decided by the regional authorities and appropriate resources made available to the hospital that will have such isolation rooms and receive all patients with active TB.

#### ***Sputum induction, or pentamidine aerosol (all hospitals)***

- (i) Ventilation should be at least 12 ACH.
- (ii) Direction of air flow should be inward (negative pressure).
- (iii) The air should be exhausted through a dedicated exhaust system or HEPA filtered.
- (iv) The smaller the room, the better and more practical. Ideally, specially constructed “booths”, which are commercially available, should be used.
- (v) Doors/windows should remain closed during and after the procedure long enough for air clearance in the room.

#### ***Bronchoscopy and autopsy (all hospitals)***

These areas tend to be much larger, so it is difficult to achieve consistently high levels of ventilation with inward direction of air flow. However, the increased risk of transmission associated with these activities warrants the significant expenditures required to achieve the following.

- (i) Ventilation should be at least 12 ACH.
- (ii) Direction of air flow should be inward (negative pressure).
- (iii) The air should be exhausted through a dedicated exhaust system or HEPA filtered.
- (iv) Doors/windows should remain closed during and after the procedure long enough for air clearance in the room.

#### ***TB and pathology laboratories (See Chapter 2, Mycobacteriology Laboratory Standards: Services and Policies)***

#### ***Entering rooms after generation of infectious aerosols has ended***

Staff often question when a room can safely be entered by personnel or used for another procedure, after generation of infectious aerosols has ceased. For

example, when can a bronchoscopy suite safely be used after completing the bronchoscopy of a patient suspected of having active TB? As shown in Table 3, this is dependent upon the level of ventilation expressed as ACH.

**Table 3**  
Time Needed to Remove Airborne Contaminants after Generation of Infectious Droplet Nuclei Has Ceased, by Number of Air Changes per Hour

Air Changes per Hour	Minutes Required for Removal at Two Levels of Efficiency	
	99%	99.9%
2	138	207
4	69	104
6	46	69
12	23	35
15	18	28
20	7	14
50	3	6

*ACH* = air changes per hour

\* This table was adapted from reference #6.

The values apply to a room in which the generation of aerosols has ceased, and they assume perfect mixing of the air in the room with a mixing factor of 1.0. If the mixing factor is known to be greater than 1.0, the minutes in the table should be multiplied by the mixing factor to determine the true room clearance time.

### Ultraviolet light

There is good evidence that ultraviolet germicidal irradiation (UVGI) has excellent germicidal 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.<sup>24</sup> Use of UVGI has been considered controversial because of potential skin cancer and eye complications. However, the risk of skin cancer with new, commercially available UVGI units is essentially nil. Possible eye complications can be avoided by proper installation of these units, which should be regularly inspected and maintained. There have been very few studies to evaluate the efficacy of UVGI, although this technology is being used with increasing frequency in some setting, such as homeless shelters, to improve germ-free ventilation without the cost of renovating the heating-ventilation-air conditioning (HVAC) system.

#### *Locations for safe and effective use of UVGI*

- (i) Above eye level (upper air irradiation) in occupied patient rooms, waiting rooms or corridors.
- (ii) Within ventilation air ducts that are exhausting air to the outside.
- (iii) Within ventilation air ducts that are treating recirculated air that is returned back into the same space.
- (iv) Within portable air cleaning units.

### *Situations where UVGI may be considered*

- (i) In bronchoscopy and autopsy areas, if ventilation is inadequate and cannot be upgraded to meet standards.
- (ii) Areas where exposure is unpredictable, such as the emergency department in medium-risk hospitals.

If upper air UVGI is used, the units should be installed above head height and should be constructed with baffles so that the room occupants cannot directly see the UVGI light. The units should be inspected every 6 months. It is also recommended to seek the help of someone with expertise in the use of UVGI prior to purchase and installation.

### **HEPA filtration**

HEPA filtration can be used to filter the exhaust from airborne isolation rooms or bronchoscopy suites. Small HEPA units (fixed or portable) may also be used to filter recirculated air in a room to increase the germ-free ventilation without the need for an increase in the amount of outdoor air supplied. The HEPA filters require careful monitoring and must be changed regularly, as clogged filters will result in a decrease in effective germ-free ventilation. For further information on HEPA filtration, please refer to the recent CDC guidelines.<sup>6</sup>

With both UVGI and HEPA filtration environmental controls, regular maintenance and documentation is necessary — it has been anecdotally observed that maintenance is often neglected, a situation that may render these controls essentially useless.

### **Personal Respiratory Protection: Respirators and Masks**

Standard surgical masks are effective in preventing larger exhaled droplets from health care workers from falling into wounds. However, they are less than 50% effective in filtering the much smaller droplet nuclei (1-5 microns) containing *M. tuberculosis* bacteria that may be inhaled and reach the alveolus. Therefore, current recommendations call for respirators (masks) that filter 95% of particles of 1 micron or larger and have less than 10% leak<sup>6,17</sup> to protect workers against airborne TB. The most widely used respirators for this purpose are NIOSH-designated N95 respirators, although there are other equivalent tight-fitting respirators with equivalent efficiency. These respirators should reduce the number of airborne particles inhaled by a worker by close to 90% because of their tight facial fit and a filter that effectively traps airborne TB organisms. Significant leakage can render a highly efficient respirator almost useless (for example, a 95% efficient respirator with 10% leak will result in better protection than a 99.9% efficient respirator with 20% leak).

### **Respiratory protection program**

Hospitals should develop a respiratory protection program, the first component of which is to select appropriate respirators (masks) for their workers. These should be certified by the manufacturer as meeting the criteria of filtering 95%

of particles of 1 micron size or greater. N95 respirators meet these criteria and are commonly used by health care workers in North America when caring for TB patients. In addition to these characteristics, it is important to select a respirator that will fit more than 90% of workers. It will be necessary to provide more than one respirator, as no one model will fit all workers' faces.

Another important component of a hospital respiratory protection program is education of health care workers regarding occupational risk of TB, the role of respiratory protection in reducing that risk and the importance of wearing the respirators properly, so that there is a tight facial seal. In some Canadian provinces/territories, formal respirator fit testing is required. However, there is no published evidence to date showing that a fit testing program results in reduction in the risk of nosocomial TB transmission or published evidence of other benefits for health care workers.<sup>27</sup> When TB patients are housed in negative pressure isolation rooms, the contribution of N95 respirators in preventing staff transmission is minimal.<sup>28</sup> Hence it is unlikely that formal respirator fit testing will have any significant impact in these settings. Furthermore, the reproducibility of fit-testing is poor.<sup>29,30</sup>

### Use of respiratory protection (respirators) (all hospitals)

In low-risk hospitals, including those with a TB case transfer-out policy, tight-fitting, high-efficiency particulate respirators must be available for staff whenever a patient is identified who is suspected of or confirmed to have active TB.\* They should be available for caregivers even while the patient awaits transfer to another facility that has adequate environmental and personal control measures. Appropriately worn respirators are particularly important in this setting, as such hospitals will often not have appropriately ventilated airborne isolation rooms in which to house patients while awaiting transfer.

These respirators should be worn by workers involved in the transport of patients suspected of or confirmed as having active TB, e.g. ambulance workers.

Surgical/procedure masks can be used by TB patients when they leave their rooms. This is because these masks are effective in trapping the large infectious particles expelled by TB patients (even though they are not effective in preventing inhalation of the much smaller airborne droplet nuclei). Some hospitals give N95 respirators (without exhaust valves) to patients when they leave their rooms. This has some potential advantages and potential disadvantages. The potential advantages are that only one type of respirator is used, which could reduce potential confusion. Second, the tight-fitting respirators may reduce escape of airborne droplets, particularly during coughing; this is a potential concern with loosely fitting surgical masks. The disadvantages are that the N95 respirators will be uncomfortable for patients, particularly those with limited respiratory reserve, if worn for a significant length of time. Furthermore, there is no information regarding their efficiency when worn in this way. There is no published evidence about the relative merits of surgical masks or N95 respirators for TB patients, hence there is no consensus on this point.

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

## Personal Controls: TST Screening and Treatment of Infection

The importance of proper baseline tuberculin skin testing for all potentially exposed health care workers in all health care settings cannot be overemphasized. At the time of employment, many workers may already be TST positive because of prior nonoccupational exposure, particularly foreign-born workers who could have been exposed before immigrating to Canada. In addition, many foreign-born workers and older Canadian-born workers in some provinces/territories may have received bacille Calmette-Guérin (BCG) vaccination. A summary of the provincial and territorial usage of BCG over time is provided in Appendix F, BCG Vaccine Usage in Canada — Current and Historical (for any updates, refer to <http://www.publichealth.gc.ca/tuberculosis>). In Canadian surveys between 10% and 20% of health care workers had positive TSTs at the time of hiring.<sup>31</sup> A compendium of LTBI prevalence rates among Canadian health care workers in general and other groups in Canada is available through the Public Health Agency of Canada at <http://www.publichealth.gc.ca/tuberculosis> and in Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control.

A second concern is the possibility of boosting, which has been documented in 3% to 10% of Canadian health care workers.<sup>31,32</sup> This is due to prior tuberculous exposure (e.g. foreign birth), BCG vaccination or nontuberculous mycobacterial infection (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease). These persons could be misdiagnosed later as having TST conversion if initial two-step testing is not done.

### Baseline tuberculin skin testing (all health care facilities)

At the time of hiring, all employees should have a two-step TST (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease) unless they have documented results of a prior two-step test. If prior results are used, these should be transcribed into the employee's health record.

Workers with a reaction of 10 mm induration or greater on the first or second test should be considered TST positive, referred for chest radiography and medical evaluation, and consideration of isoniazid treatment of LTBI (see Chapter 6, Treatment of Tuberculosis Disease and Infection). As they are now TST positive, no further TSTs should be performed on an annual screening basis or if in contact with an infectious TB case. Performing annual chest radiography of asymptomatic TST-positive staff is not recommended.

Workers with reactions of less than 10 mm to both tests should be considered TST negative for baseline screening purposes.

### Tuberculin skin testing following unprotected exposure (all health care facilities)

Any health care worker who has unprotected exposure to a patient who is ultimately confirmed to have active, contagious TB (termed an exposure

episode) must be considered at risk of infection.\* This includes situations in which the health care worker was not wearing a respirator and the patient's TB was undiagnosed, the patient was not in isolation and/or was not treated for a sufficient length of time.

For TST-negative workers, a TST should be done immediately and, if negative, repeated after 8 to 12 weeks. If TST conversion occurs, the worker should be referred for chest radiography and medical evaluation. As this is a contact investigation, see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for interpretation of the TST result and subsequent management.

If the worker was previously TST positive, there is no value in doing a TST now. The worker should be educated regarding the signs or symptoms of TB. If such symptoms develop, posterior-anterior and lateral chest radiography should be performed, and three sputum specimens should be tested for AFB.

### **Periodic tuberculin skin testing (clinical personnel in medium-risk hospitals or those performing high-risk activities in all hospitals)**

An annual TST is recommended for health care workers with negative baseline TST who are involved in moderate-risk activities in medium-risk hospitals and for workers involved in high-risk activities in all hospitals. See Chapter 4, Diagnosis of TB Infection and Disease, for the definition of skin test conversion and subsequent management of the worker.

Despite the importance of maintaining a TST program, anecdotal evidence suggests that compliance with these recommendations in Canadian health care facilities is less than ideal, as the onus for voluntary compliance with regular testing is on the health care worker. Institutions should take steps to educate staff on the utility of annual testing. Facilities are strongly encouraged to meet the minimum standard of baseline two-step and postexposure tuberculin skin testing. Workers who require further medical assessment should be seen by a physician experienced in the interpretation of TSTs and the treatment of LTBI.

### **Interferon-gamma release assays**

New interferon-gamma release assays have not been studied for use in serial testing. Therefore they are NOT recommended at this time for periodic or post-exposure testing of workers in health care facilities. (For further information on these new tests please see Chapter 4, Diagnosis of Tuberculosis Infection and Disease, Appendix D, Interferon-gamma Release Assays for Latent Tuberculosis Infection. An Advisory Committee Standard (ACS), the Canadian Tuberculosis Committee and updates at <http://www.publichealth.gc.ca/tuberculosis>.)

### **BCG vaccination**

BCG vaccination is a very controversial subject, because the efficacy of BCG vaccination has varied from zero to more than 80% in different randomized

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

controlled trials.<sup>33</sup> On the other hand, in several studies TST screening programs with provision of isoniazid to those with positive results have had overall efficacy of less than 20% because of poor compliance with screening and treatment recommendations.<sup>34-40</sup> BCG vaccination received in adult life will render subsequent TSTs uninterpretable. Therefore, hospital programs should either put considerable emphasis on proper performance of tuberculin skin testing with close follow-up to ensure that employees found to have TST conversion are evaluated and managed appropriately, or choose to go the route of BCG vaccination. A program cannot use BCG vaccination and also use periodic tuberculin skin testing for the same employees. This being said, we are unaware of any Canadian facility that routinely offers BCG vaccination, although this may be considered in TST-negative workers potentially exposed to multidrug-resistant TB (see Chapter 17, Bacille Calmette-Guérin Vaccination in Canada and the *Canadian Immunization Guide*).<sup>41</sup>

## Prevention of TB Transmission in Long-term Care Institutions

Long-term care institutions include homes for the aged, nursing homes, chronic care facilities, retirement homes or any other collective living centre.

At the time of hiring, all employees and regular volunteers should have a two-step TST (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease) unless they have documented results of prior two-step tests. If prior results are used, these should be transcribed into the employee's health record. A regular volunteer may be defined as one who expects to work 150 or more hours during the next year, meaning approximately a half day per week. Volunteers expecting to work less than 150 hours during the next year should be tested if they are from a population group with increased risk of active TB or LTBI (e.g. from a high TB incidence country or high TB incidence Canadian Aboriginal community), give a history of prior contact with a known or suspected TB case or are HIV seropositive. If they 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 3 weeks, unexplained weight loss, hemoptysis, loss of appetite, fevers or night sweats), then a TST should NOT be done, but these individuals should be referred for medical evaluation.

Annual screening of staff and regular volunteers depends upon the occurrence of TST conversion among the staff and volunteers. In general, it can be discontinued if the annual TST conversion rate is less than 0.5%. Whether serial screening is performed or not, employees known to be TST positive should be instructed to promptly report any symptoms suggesting TB, such as cough of more than 3 weeks' duration with or without fever, night sweats or weight loss.

Residents should undergo baseline posterior-anterior and lateral chest radiography on acceptance to the institution. If they have documented results of a prior TST, these should be transcribed into their record. However, if no prior TST results are available then the decision to perform routine baseline TST (including the two-step TST, Chapter 4, Diagnosis of Tuberculosis Infection and Disease) is controversial. The Canadian Thoracic Society's Tuberculosis Committee does not recommend a routine baseline TST, but it may be required



by public health authorities in some Canadian provinces/territories. The primary purpose of these TSTs is to establish a reliable baseline for comparison in the event that a resident is exposed to an infectious TB case. Thus the decision to routinely screen should be based on past incidence of active TB in the patient population served by the institution. In most long-term care institutions TB is rare, and two-step testing may be difficult to complete. In these settings a baseline TST is not recommended. If the population of residents is at increased risk of active TB (e.g. they are from a high TB incidence country or high incidence Canadian Aboriginal community, former urban poor or HIV infected), then baseline two-step TST is warranted. Serial (e.g. annual) TSTs are not necessary for residents.

## Prevention of TB Transmission in Homeless Shelters

The development of active TB and subsequent transmission in homeless persons is a well-described phenomenon. Reinfection has also been described in this population.

### Administrative controls

Recommendations for the use of TSTs and active case finding are given in Chapter 13, Surveillance and Screening in Tuberculosis Control. Screening for LTBI among the homeless can be labour intensive, while adherence to therapy of LTBI is often low. Furthermore, following up contacts of active cases can be extremely difficult and quite inaccurate as many contacts are invariably missed. Active case finding can also be challenging, as a large proportion of homeless persons may have chronic cough and other symptoms that can imitate the symptoms of TB. In centres where there is evidence of ongoing transmission, surveillance strategies will likely not be sufficient in controlling spread of the disease.

### Engineering controls

Given the difficulties in performing contact tracing and active case finding in the homeless population, primary prevention of TB through improving ventilation is perhaps the most important control strategy. Experimental evidence suggests that improving the fresh air ventilation can result in a dramatic decrease in TB transmission, especially in shelters with inadequate ventilation.

For areas frequented by clients it is recommended that shelters should provide fresh air ventilation of 6 ACH or 0.708 m<sup>3</sup> (25 cubic feet) per minute per person, whichever is higher. Shelters that cannot afford upgrades to their HVAC systems to provide 6 ACH should consider appropriately placed UVGI systems, as these can achieve equivalent air exchanges at a fraction of the cost.<sup>42</sup>

### Personal controls

Employees and regular volunteers of shelters have an increased risk of becoming infected with TB, because of frequent exposure to undiagnosed cases, inadequate ventilation in some settings and lack of appropriate respirators (masks) in

some settings. It is strongly recommended that these staff have a two-step TST (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease) before hire/placement unless they have documented results of a prior two-step test. If previous results are used, these should be transcribed into the person's health record. Those with a negative baseline TST should receive an annual TST. All TST conversions among shelter staff should be reported to the local public health authority, as this may be indicative of TB transmission within the facility. Staff with a positive TST at baseline or on annual screening should be assessed by a physician knowledgeable in the treatment of LTBI.

### Prevention of TB Transmission in Home Care

At the time of hiring, all staff should have a two-step TST (see Chapter 4, Diagnosis of Tuberculosis Infection and Disease), unless they have documented results of previous two-step tests. If prior results are used, these should be transcribed into the employee's health record. Persons with a reaction of 10 mm induration or greater on the first or second test should be considered TST positive, referred for chest radiography and medical evaluation, and considered for isoniazid treatment of LTBI (see Chapter 6, Treatment of Tuberculosis Disease and Infection). As they are now TST positive, no further TSTs should be performed on an annual screening basis or after contact with an infectious TB case. Persons with reactions of less than 10 mm to both tests should be considered TST negative for baseline screening purposes. Routine serial (e.g. annual) screening of staff is not necessary.

### Prevention of TB in Correctional Facilities

The following is based in part on Correctional Service Canada (CSC) guidelines for TB prevention and control in institutions in which inmates are sentenced to 2 years or longer.<sup>43</sup> To view the current CSC guidelines, see <http://www.publichealth.gc.ca/tuberculosis>. Recommendations have recently been published by the CDC<sup>44</sup> for the prevention and control of TB in U.S. correctional and detention facilities.

The risk of TB transmission is higher within correctional facilities because of several factors:

1. The prevalence of LTBI among inmates is higher than the Canadian average. This reflects the disproportionate numbers of Aboriginal Canadians, injection drug users, and homeless, all of whom have a higher prevalence of LTBI.
2. The risk of reactivation of LTBI to active TB is also higher because of the prevalence of HIV infection as well as alcohol and injection drug abuse in this population.
3. Diagnosis may be delayed because of lack, or poor use, of medical services.
4. Ventilation is often inadequate because of recirculation of air and a lack of open windows, especially in older prisons, which were built to achieve security, not airborne infection control.

5. The density of inmates may be high.
6. Transfer of inmates within and between facilities may be frequent.

## TB control program for correctional facilities

### *Administrative controls*

Institutional risk assessment is based on the baseline TB status of inmates and staff and an annual review of TB cases diagnosed among inmates (and, if any, among staff). Active case finding 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 diagnosis. 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 inadequate with an increased risk of relapse.

Inmates who are suspected of having active contagious TB should be placed immediately in an airborne infections isolation room until TB is ruled out or they have received sufficient treatment to render them no longer contagious. It is essential that inmates treated for active TB receive every dose under strict observation. If the inmate is discharged while still being treated for active TB, it is also essential that follow-up be arranged directly with local public health, so that directly observed treatment is not interrupted, even for a day.

Inmates and staff who are exposed to an infectious TB case should be investigated using the principles outlined in Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control. The investigation should be done in close collaboration with the local public health/TB control authorities.

### *Environmental controls*

General inmate areas (cells, dining and indoor recreation) should have germ-free fresh air ventilation of at least 2 ACH for purposes of TB control. Higher ACH may be necessary to comply with building codes for comfort and other reasons.

Airborne isolation rooms (cells) exist across Canada in CSC facilities with at least one per geographic/administrative region. The ventilation required for these rooms is a minimum of 6 ACH in existing prisons and 9 ACH in new facilities. The direction of air flow should be into the room, then exhausted outdoors. This should be verified with smoke tubes at four corners of the door when the room is occupied. Adjunctive use of HEPA filtration units and UVGI can be considered, especially in older correctional facilities where it is not practical or feasible to achieve the recommended levels of outdoor (fresh) air ventilation.

### *Personal controls - respirators*

N95 respirators (or equivalent tight-fitting, high-efficiency particulate masks) are recommended for staff in contact with an active or suspect TB case. Surgical/procedure masks are recommended for the TB case/suspect if not in an airborne isolation room. N95 masks can be used, if tolerated (see Use of Respiratory Protection (all hospitals)).

### *Tuberculin skin testing and treatment of LTBI for inmates and staff*

Inmates who will likely stay for 1 year or longer in any correctional facility should be screened for active disease and LTBI at admission using the two-step TST. Inmates with a positive TST, symptoms or signs of TB or a past history of TB should have chest radiography and medical evaluation. Past TB-related history should be ascertained carefully. This should include results of previous TSTs and chest radiography, as well as any prior treatment for LTBI or active disease. Incomplete treatment should prompt a thorough evaluation for possible active TB, including chest radiography, medical evaluation and sputum for AFB smears and cultures. To obtain an accurate past history in this population can be difficult but could be considerably simplified through access to a comprehensive electronic medical database. Long-term inmates should be re-assessed on an annual basis for symptoms or signs of TB and should receive a TST if the previous one was negative.

Inmates who will likely stay for less than 1 year in a provincial/territorial correctional facility should be assessed at admission for any symptoms or signs of TB, past history of TB diagnosis or treatment, and known immunosuppression, especially HIV infection. If any are present, chest radiography and medical evaluation are recommended.

All correctional facility staff should be assessed for symptoms or signs of TB on hire. It is strongly recommended that these individuals have a two-step TST at the same time, unless they have documented results of a prior two-step test. If previous results are used, these should be transcribed into the person's health record.

Treatment of LTBI is recommended for inmates and for staff with an increased risk of TB disease (see Chapter 6, Treatment of Tuberculosis Disease and Infection, Table 6).

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# Bacille Calmette-Guérin (BCG) Vaccination in Canada

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## Introduction

BCG is a live attenuated vaccine derived from *Mycobacterium bovis*. The original strain was developed at the Pasteur Institute in Paris in 1921. Subsequent strains have undergone further development through repeated subculturing in many laboratories around the world. These newer strains may differ, one from another, antigenically. It has been suggested that this variable antigenicity has resulted in variable immunogenicity.<sup>1</sup> Three parent strains, Glaxo, Tokyo and Pasteur, now account for more than 90% of the vaccines used, the Pasteur strain of BCG currently serving as the international reference strain of the vaccine. 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%.<sup>2</sup> In Canada there has been a longstanding interest in BCG.<sup>3</sup> Beginning in 1926 in Quebec<sup>4</sup> and 1933 in Saskatchewan,<sup>5</sup> 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.<sup>6</sup> However, in the wake of reports of disseminated BCG in children born with congenital immunodeficiencies<sup>7-9</sup> and questions about its indication,<sup>10,11</sup> BCG is also being discontinued 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.<sup>12,13</sup> However, data from interferon- $\gamma$  release assays have challenged that opinion, suggesting that BCG, while not preventing the establishment of infection in everyone, may prevent it in some.<sup>14</sup> 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%. Those trials that fulfilled more rigorous criteria and thus were arguably more scientifically valid showed high efficacy rates, from 75% to 80%. Further trials with greater statistical power showed higher efficacy, suggesting that the variation in the results had been a product of study design. A meta-analysis involving 10 case-controlled studies of BCG efficacy<sup>15</sup> indicated that a summary estimate of protection from BCG vaccination was at least 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.<sup>16</sup> 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.<sup>17</sup> A recent retrospective study found that BCG protective efficacy can persist for 50 to 60 years, indicating that a single dose might have a long-lasting effect.<sup>18</sup> The efficacy of BCG in adults is uncertain but is likely to be lower than that in children.

BCG vaccine does not provide absolute protection against TB, and the disease should be considered as a possible diagnosis in any vaccinee with a suggestive clinical presentation of TB, regardless of vaccination history.

## Administration

The only vaccine approved for use in Canada is BCG Vaccine (freeze-dried) (sanofi pasteur, Mississauga, Ontario). It is available as a culture of live bacilli and is given intradermally. The manufacturer's instructions regarding administration should be carefully followed. It 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 tuberculin test (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.<sup>19</sup> Interpretation of the TST results of BCG-vaccinated individuals is problematic, but certain parameters (See Chapter 4, Diagnosis of Tuberculosis Infection and Disease) will assist with the interpretation. Although most children develop a scar 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.<sup>20</sup>

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 the BCG over time is provided in Appendix F (for any updates, refer to <<http://www.publichealth.gc.ca/tuberculosis>>). 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 routine use of BCG vaccination in any Canadian population. However, it allows that, in some settings, consideration of local TB

\* A recommendation of the Canadian Thoracic Society's Tuberculosis Committee

epidemiology and access to diagnostic services may lead to the decision to offer BCG vaccination.<sup>21-22</sup> These considerations are the following:

1. In infants in First Nations and Inuit communities or groups of persons with an average annual rate of smear-positive pulmonary TB greater than 15/100,000 population (all ages) during the previous 3 years or with an annual risk of TB infection (ARI) greater than 0.1%, or if early identification and treatment of latent TB infection (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.

This rate of smear-positive pulmonary TB, 15/100,000, is the same rate as that determined by the Canadian Tuberculosis Committee and the Public Health Agency of Canada to represent a high incidence of infectious TB in designated geographic areas outside Canada. For information on international smear-positive pulmonary TB incidence rates, refer to <<http://www.publichealth.gc.ca/tuberculosis>>.

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.<sup>11</sup> 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 8, Pediatric Tuberculosis).

2. Individuals, including health care workers and laboratory workers, repeatedly exposed to persons with untreated, inadequately treated or drug-resistant active TB or tuberculosis bacteria in conditions under which protective measures against infection are not feasible (although primary treatment of the source, removal from the source or treatment to prevent disease in the exposed person is generally preferred). Consultation with a TB and/or infectious disease expert is recommended. Again, the efficacy of BCG in adults is uncertain.
3. 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, particularly multidrug-resistant (MDR) TB, is high. Please see Chapter 13, Surveillance and Screening in Tuberculosis Control, regarding use of the TST for pre-travel and post-travel diagnosis of LTBI. Factors that would favour the BCG option might include poorer access to repeat skin testing, personal preference against taking isoniazid (INH), contraindications to taking INH, such as liver disease or previous intolerance to INH, and the limited number of treatment options if infected with an MDR strain. Travellers with medical conditions, particularly HIV infection, that may be associated with an increased risk of progression of LTBI to active disease should carefully weigh the risk of travel to a high incidence area with their physician in determining the most appropriate means of prevention.

BCG vaccination of First Nations infants has now been discontinued in the Atlantic provinces and British Columbia. In Alberta, the rationale for continued use of the BCG has been challenged,<sup>10</sup> and a process of systematic withdrawal has begun.<sup>23</sup> 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.

### Administration With Other Vaccines

BCG vaccine should not be given until at least 4 weeks after administration of any live vaccine, because such vaccines may suppress the immune response, resulting in lowered immunogenicity.<sup>22</sup> Live vaccines (e.g. measles-mumps-rubella) may be given simultaneously with BCG, administered at a different site. Simultaneous administration of the inactivated vaccines against diphtheria, pertussis, tetanus and polio does not interfere with the immune response to BCG vaccination.<sup>24</sup> Therefore these vaccines may be given at the same time but at a different site.

### Adverse Reactions

Adverse events following BCG vaccination are notifiable only in some provinces/territories, and thus their frequency may be underestimated. In order to provide accurate surveillance, reporting of adverse events to the Public Health Agency of Canada is strongly recommended irrespective of local legislation. For a copy of the “Adverse Events Following Immunization” reporting form, refer to <[http://www.phac-aspc.gc.ca/im/ae-fi-form\\_e.html](http://www.phac-aspc.gc.ca/im/ae-fi-form_e.html)> or the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association).

Following 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.<sup>25</sup>

### *Local reactions*

The majority of local reactions occur within 5 months of vaccination and consist of prolonged skin ulceration, suppurative adenitis and localized abscess. *M. bovis* BCG can be cultured from approximately 5% of lymph nodes.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup> It appears that systemic treatment with anti-TB drugs is ineffective.<sup>29</sup>

### *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. Less common reactions include fever, conjunctivitis, iritis and erythema multiforme. The most serious complication of BCG is disseminated BCG. It usually occurs within 6 months of vaccination, although long latent periods have been reported,<sup>30</sup> and is usually fatal. In a study conducted by the IUATLD, disseminated BCG occurred in 3/1,000,000 recipients.<sup>26</sup> In studies conducted in Canada, a different rate of occurrence of disseminated BCG is being reported.<sup>7-9</sup> Between 1993 and 2002, 21 BCG vaccine-related adverse events were reported. Fifteen of these 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, 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.<sup>9</sup> 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.<sup>31</sup> 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 Society. 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 lymphotropic 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. Vaccination of pregnant women should preferably be deferred until after delivery, although harmful effects in the fetus have not been observed. The vaccine should not be administered to individuals receiving drugs with anti-TB activity, since these agents may be active 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.<sup>32</sup> It occurs in immunocompetent patients and responds to conventional anti-TB therapy, with the caveat that the organism is always resistant to pyrazinamide.

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# Canada and International Tuberculosis Control

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## Introduction

Recently an Ottawa taxi driver of Lebanese origin, speaking of House of Commons wrangling, said “Canadians don’t know how lucky they are. They should appreciate it and share it.” The comment seems relevant to this discussion of the global tuberculosis (TB) burden in the context of trying to eliminate TB in Canada. The latter will not be achieved unless we attend to the former!

## 2005 Global TB Rates

In 2005, the global estimated incidence of new TB cases was 136/100,000, whereas the reported rate was 74/100,000.<sup>1</sup> The provisional Canadian reported rate was 5/100,000 in 2005.<sup>2</sup> While the industrialized world contemplated TB elimination, the incidence rate per 100,000 population had just stabilized or was in decline in all six World Health Organization (WHO) regions. However, the total number of new cases continued to rise slowly, primarily due to case-load growth in the African, Eastern Mediterranean and South-East Asia regions.<sup>1</sup> Of the world’s 6.5 billion people, one-third is estimated to be infected by *Mycobacterium tuberculosis*. In 2005, from this infected pool, there were an estimated 8.8 million new cases of TB disease, of which 3.9 million were smear positive. The actual number of cases reported in 2005 was 4.8 million, with 1.6 million deaths due to TB, including 195,000 deaths of people coinfecting with HIV.

Although diagnosis is simple, only 60% of new sputum smear-positive cases in 2005 were detected and reported to have access to treatment under the directly observed treatment short-course (DOTS) strategy (see definition in the next section). Treatment is eminently affordable.<sup>3</sup> In the 22 countries with the highest number of new TB cases, which together account for approximately 80% of all new TB cases globally, the 2007 median TB control cost per patient was US\$259, including US\$26 for first-line drugs.<sup>1</sup>

## History of Global TB Control

Historically, the first international public health effort to control the disease began with the Paris International Conference for Internal Medicine 1867,<sup>4</sup> which acknowledged that one-quarter of European adults died of TB. Although the rates were falling from about 1830 onward, the toll from TB was devastating, and coordinated action was necessary.

In 1882 the announcement by Robert Koch of his discovery of the TB bacillus, for which he was later awarded the Nobel Prize, was followed by efforts to develop tuberculin as a means of treatment. The annual TB congresses<sup>4</sup> of the first decade of the 20<sup>th</sup> century considered treatments, the significance of *Mycobacterium bovis* in animals and humans, risk of transmission through milk, vaccine development, and control of TB through the creation of an international anti-TB bureau. As the world recovered from World War I in 1920, delegates of 33 nations assembled at the Sorbonne in Paris, pledged themselves to cooperate in the fight against TB and declared the need for an organization that would coordinate the findings of all investigations – the International Union against

Tuberculosis (The Union), which later became the International Union against Tuberculosis and Lung Disease.<sup>4</sup>

The second world war created a huge increase in TB cases. In response, the International Tuberculosis Campaign (1946-52) was mounted and saw the expansion of BCG vaccination to cover the global population, the development of screening and active case finding, and the expansion of inpatient facilities (sanatoria). At the first meeting of The Union after the second World War, in 1946, it was proposed to the new WHO that TB control be made a priority. As its first disease-specific activity, WHO established its Tuberculosis Division in 1947. The introduction of drug treatment immediately after World War II was greeted with short-lived euphoria as it became clear that treatment with individual drugs rapidly induced drug resistance and failure. The claim from Edinburgh,<sup>5</sup> based on work in that centre starting in the early 1950s, that combination drug treatment could cure patients was revolutionary and initially rejected, but the results of a large multi-centred international trial, coordinated by The Union, confirmed that TB could indeed be cured with combination drug treatment.<sup>6</sup>

The American Tuberculosis Association called a national conference at Arden House in 1960, which set out the elements of a public health program for TB that remains the basis of all subsequent strategies.<sup>7</sup> Expert committees of the WHO, building on the Arden House Conference, developed a series of technical reports outlining a global strategy. A major focus of the strategy was case finding, as this was thought to be the key challenge.

By the end of the 1960s, TB case rates had dramatically and steadily declined throughout the industrialized world, but disease remained a challenge in developing countries. In consequence, a Mutual Assistance Program was proposed by Canadian Eddie O'Brien at the 1962 annual meeting of The Union in Toronto. This consisted of two components: a "travelling seminar", funded primarily by the Netherlands and focused on Africa, and a program to develop national associations, funded by Canada and focused primarily on Asia.<sup>8</sup>

By the early 1970s, with the addition of rifampicin, the TB community quickly recognized the possibility of rapid cure. However, Stefan Grzybowski<sup>9</sup> published data from national prevalence surveys in Korea and Taiwan demonstrating that the current efforts at TB control, far from diminishing the problem, actually enhanced it by neglecting high-quality treatment and adequate outcomes in their focus on case finding. This led international experts to suggest strengthening primary health care as a means of ensuring treatment delivery.<sup>9</sup>

In 1978, the Minister of Health of the United Republic of Tanzania invited international experts to propose a strategy for a national program to address both TB and leprosy, hitherto left for mission hospitals to deal with. The proposal developed by Karel Styblo put an emphasis on quality of treatment and on documentation of the outcome within the public health system.<sup>3</sup> This approach was applied in Benin, Kenya, Malawi, Mali, Mozambique, Nicaragua, Senegal and Yemen as national tuberculosis control programs.

In the late 1980s, the World Bank undertook a Health Sector Priorities Review 1989-1993 to look at health services from the point of view of investment

in development. In this review, Styblo's work with The Union was assessed as demonstrating that TB control was among the most cost-effective of any investment in health in low-income countries. The five key elements of this investment became the DOTS strategy: government commitment to making TB control a priority, sputum smear microscopy to detect cases in persons with symptoms of TB, standardized short-course chemotherapy under proper case-management conditions, uninterrupted supply of high-quality, standardized drug regimens, and a reporting and recording system that tracks every case to final outcome to ensure that program quality is maintained.<sup>10</sup>

In 1993, TB was declared a global public health emergency by the WHO in recognition of the growing burden of disease allied with failing public health infrastructure and co-infection with HIV.<sup>11</sup> Despite this declaration, DOTS expansion was slow. What was needed was a global effort to mobilize civil society.<sup>12</sup> The response was the STOP-TB Partnership, with seven working groups: one on DOTS expansion, the second on DOTS Plus for multidrug-resistant (MDR) TB, the third on HIV-TB, the fourth on new diagnostics, the fifth on new drugs, the sixth on vaccine development and the seventh on advocacy, communications and social mobilization to engage communities in building support from the grass roots for DOTS programs and to encourage donor countries to finance work in high TB incidence countries.

The partnership was led by Jacob Kumaresan from 1999 to 2003 and Marcos Espinal beginning in 2004. Countries with a high TB burden committed themselves to the target of finding 70% of smear-positive pulmonary cases and successfully treating 85% of such cases by 2005. Remarkably, 50% of the estimated cost of reaching the target was found by these countries themselves. Although rich countries participated in the STOP-TB Partnership, funding was slow to materialize and was one of the impediments to reaching the 2005 target.

### Are We Making Progress?

There is a growing global recognition that TB, as one of the diseases of poverty, must be controlled to reach the Millennium Development Goals.<sup>13</sup> All 191 United Nations member states have pledged themselves to the following targets for 2015: reducing extreme poverty by 50%; educating all to sixth grade; cutting deaths in children under age 5 by 67%; reducing maternal mortality by 75%; addressing gender equity; reversing the rise of HIV, malaria and other diseases, including TB; ensuring a sustainable environment; and building a global partnership to achieve these goals. This is a tall order and one that challenges all nations and all peoples. The estimated cost is US\$760 billion, just a little less than the world's military spending in 2005 (US\$900 billion).<sup>14</sup>

The TB targets for 2005 within the Millennium Development Goals were to detect 70% of new smear-positive cases and successfully treat 85% of these cases. The actual results were 60% case-detection rate and 84% treatment success rate for new smear-positive cases.<sup>1</sup> Some of the greatest improvements in DOTS coverage and case detection have been seen in the high-burden countries of Bangladesh, India, Indonesia, Myanmar and the Philippines.

The Global Plan to Stop TB 2006-2015<sup>15</sup> aims to halt and reverse TB incidence and to halve the disease prevalence and death rates compared with 1990. By 2005, the prevalence and death rates were down to 217/100,000 and 24/100,000 respectively,<sup>1</sup> the goals being 150/100,000 and 15/100,000 by 2015.<sup>16</sup> This goal would prevent 14 million deaths by treating 50 million persons with the DOTS strategy and would include the treatment of 800,000 MDR-TB cases (56% of all MDR-TB cases rather than the present 2%) plus 3 million cases coinfecting with HIV. In order to reach these targets the plan expects a new, rapid diagnostic test for smear-negative TB by 2008 and a rapid test for detecting drug susceptibility by 2010, available at peripheral laboratories. There is similarly a goal to introduce a new drug or combination of drugs by 2010 that reduces treatment duration to 3-4 months with clinical trials for a 1-month treatment regimen by 2015. The vision is to have regimens that are effective against MDR-TB, are compatible with antiretroviral therapy and are effective against latent TB infection. The target date for a new, safe, effective vaccine is 2015. This second global plan is couched as a commitment to meaningful involvement of patients and community with assurance that TB is on the global development agenda, strengthened by the STOP TB Partnership. Ultimately the goal is that by 2050, TB will cease to be a global public health problem with less than one new case per million population annually.<sup>15</sup> There is a lot to do!

The STOP-TB Partnership is committed to more than expanding DOTS. It is determined to link TB to HIV for purposes of voluntary testing and counselling, and referral for antiretroviral treatment, especially in Africa where the rates of coinfection in some countries are over 50%. It has also addressed the problem of MDR-TB. Having completed the third global surveillance for MDR-TB based on reports from 77 countries or settings, WHO reports that the median percentage of MDR-TB was 1.1% among new cases, 7% among previously treated cases and 1.7% among all cases combined. Areas with more than 10% MDR-TB included parts of the former USSR, Israel (primarily among immigrants from the former USSR) and parts of China (Liaoning and Henan).<sup>17</sup> A few regions are able to examine trends, but it is too early to see the impact of DOTS Plus programs, which use second-line drugs for MDR-TB.

### Successes and Obstacles

One of the measurable successes has been the Global Drug Facility (GDF), which created access to high-quality drugs at costs as low as US\$11 per patient for countries that faced funding shortages but had made a commitment to a control program.<sup>18</sup> The Green Light Committee has rationalized the management of MDR-TB regimens by requiring approval for use of second-line regimens and has merged with the GDF.<sup>19</sup> The HIV-TB committee of the STOP-TB Partnership has created a focus on testing and counselling followed by access to antiretroviral treatment for HIV-positive TB patients. Funding and infrastructure have increased dramatically for the new vaccines, diagnostic tests and drug treatments that will be necessary to eliminate TB globally. For current information on the successes and plans of the STOP-TB Partnership, please visit its Web site at <http://www.stoptb.org>.

Another success is the publication in 2006 of the *International Standards for Tuberculosis Care (ISTC)*,<sup>20</sup> which describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, or are suspected of having, TB. They will be particularly helpful for non-government TB program providers. Please see Appendix H for further details.

The obstacles to reaching targets remain shortage of trained staff, lack of political commitment, poor laboratory facilities and inadequate management of MDR-TB cases and of HIV-infected individuals with TB.

## Role for Canada in Global TB Control

At the National Consensus Conference on Tuberculosis in 1997, it was recommended that each province and territory adopt an overall goal of TB elimination (defined as less than 1 case per 100,000 population) through an interim goal of a 5% reduction in the number of new and relapsed cases each year, with a focus on high-risk groups.<sup>21</sup> The overall average rate of decline in new cases from 1992 to 2002 was 2.4%. At this rate, it will be 2070 before the Canadian TB rate is 1/100,000.<sup>22</sup> To try to achieve a rate of 1 case per million population (which the Global Plan to Stop TB 2006-2015 has defined as elimination) will, of course, take even longer.<sup>15</sup> Thus it seems worth considering alternative strategies.

In the past two decades the proportion of TB cases in Canada that are foreign-born has increased from 38% to 67% in 2004.<sup>2</sup> This trend is also found in other high-income countries, where economic disparity has resulted in increasing numbers of migrants from countries with high TB incidence. The response of many countries to this reality has been the recommendation for more stringent screening measures for active TB and latent TB infection.

Recent Canadian-led research shows that investment in DOTS scale-up in Mexico, Dominican Republic and Haiti would not only save lives and prevent spread of disease but would also reduce health care costs in those countries and have a very substantial impact in reducing health care costs in the United States, a country receiving large numbers of immigrants from these three countries.<sup>23</sup> This modelling of DOTS scale-up in immigrant-source countries is strong evidence in support of investment in global TB control on the part of high-income nations.

The government of Canada, through the Canadian International Development Agency (CIDA), has provided support for global TB control to the FIDELIS (Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB) projects at the International Union against Tuberculosis and Lung Disease, finding additional TB cases in 60 countries, to the WHO for the Global Drug Facility, to DOTS program support and antiretroviral HIV treatment, to the Global Fund to Fight HIV/AIDS, TB and Malaria, and to other country-specific TB programs.

What remains to complete a happy picture of reduced rates of TB is to ensure that political will is strong enough to fund universal application of DOTS.<sup>24</sup> This will require a grass roots movement not just in countries with high TB

incidence but also in donor countries like Canada. To become involved in advocacy for global TB control, contact STOP-TB Canada at <http://www.stoptb.ca>. There is no doubt that an investment abroad reaps benefit at home and has the additional humanitarian impact of reducing diseases and saving lives and dollars where it is applied.

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## Canadian Tuberculosis Surveillance Systems

### The Canadian Tuberculosis Reporting System (CTBRS)

Provincial and territorial tuberculosis control programs participate in this national surveillance system by reporting to Tuberculosis Prevention and Control, Public Health Agency of Canada, all new and re-treatment cases of active tuberculosis that meet the Canadian case definition. (NOTE; Prior to 2008 in Canada, re-treatment cases were known 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* 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. a) Documented evidence or adequate history of previously active TB which was declared cured or treatment completed by current standards, and
  - b) At least 6 months have passed since the last day of previous treatment\*, and
  - c) Diagnosed with a subsequent episode of TB which meets the active TB case definition.

OR

2. a) Documented evidence or adequate history of previously active TB which cannot be declared cured or treatment completed by current standards, and
  - b) Inactive<sup>†</sup> for 6 months or longer after the last day of previous treatment,\* and
  - c) Diagnosed with a subsequent episode of TB which 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 among the following groups: Canadian citizens, permanent residents, refugees, refugee claimants, and protected persons.

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 where treatment starts is to report the case.

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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 "Treatment Outcome of New Active or Re-treatment Tuberculosis Case" form at the end of treatment.

## Data submission

Data are submitted in either paper or electronic format and 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.publichealth.gc.ca/tuberculosis>.

From the data collected by the CTBRS, the Public Health Agency of Canada publishes an annual report on the epidemiology of tuberculosis called *Tuberculosis in Canada*, first published in 1995, following the transfer of responsibility for this national surveillance system from Statistics Canada. Data are reported according to province/territory, type of tuberculosis, bacterial status, age, sex and origin/birthplace. 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 (CTBLSS)

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 annual data on drug susceptibility test results for all TB isolates to Tuberculosis Prevention and Control, Public Health Agency of Canada. Data are reported in both paper and electronic format and comprise the information found on the *M. tuberculosis Complex Antimicrobial Susceptibility Reporting Form*.

The Public Health Agency of Canada publishes an annual report using the data collected by the CTBLSS 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:

Tuberculosis Prevention and Control  
Public Health Agency of Canada  
100 Eglantine Driveway, AL 0603B  
Ottawa, ON K1A 0K9

Telephone: (613) 941-0238  
Fax: (613) 946-3902  
TB\_1@phac-aspc.gc.ca



Active Tuberculosis Case Report Form –  
New and Re-treatment Cases

EFFECTIVE JANUARY 2008

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WHEN COMPLETED

**Province/Territory/Patient ID**

1. Reporting province/territory:   2. Register case number: \_\_\_\_\_ 3. Unique identifier: \_\_\_\_\_ 4. Date of birth: Year: \_\_\_\_\_ Month: \_\_\_\_\_ Day: \_\_\_\_\_ 5. Sex: Male  Female

6. Usual residence: City/Town/Village: \_\_\_\_\_ Postal code: \_\_\_\_\_  
County and Health Unit: \_\_\_\_\_  
Lives on First Nation's reserve most of the time? 1  Yes 2  No 8  N/A 9  Unknown

**Origin**

7. Canadian born?  **II** 6  Foreign-born Country of birth: \_\_\_\_\_  Origin Unknown  
1  Status Indian (Registered) 2  Métis  
3  Inuit 4  Other Aboriginal (specify): \_\_\_\_\_  
5  Canadian born non-Aboriginal Country of birth of mother: \_\_\_\_\_  
Country of birth of father: \_\_\_\_\_  
Under age 15?

Year of arrival in Canada: \_\_\_\_\_ Year: \_\_\_\_\_  
Immigration status at the time of diagnosis: 1  Canadian citizen/Permanent resident 2  Refugee  Convention refugee  Refugee claimant  
Temporary resident: 5  Work 6  Student 7  Visitor 8  Immigration status – Other (if other, specify): \_\_\_\_\_

**Diagnosis**

8. Date of diagnosis: Year: \_\_\_\_\_ Month: \_\_\_\_\_ Day: \_\_\_\_\_ ICD 9: \_\_\_\_\_ ICD 10: \_\_\_\_\_

9. Chest X-Ray: 1  Normal 2  Abnormal 3  Not done 9  Unknown If abnormal: 1  Cavitory 2  Non-cavitory

**Bacterial Status**

10. Microscopy: Sputum, Bronchial Wash, GI Wash, Node Biopsy, Urine, CSF, Other  
Negative, Positive, Not done, Unknown

11. Culture: Sputum, Bronchial Wash, GI Wash, Node Biopsy, Urine, CSF, Other  
Negative, Positive, Not done, Unknown

12. Case Criteria: 1  Culture positive 2  Clinical diagnosis

13. If initial positive culture – Antibiotic resistance?  Other (specify): \_\_\_\_\_  
 Unknown

DRUG	Result				DRUG	Result				DRUG	Result			
	Susceptible	Resistant	Not done	Unknown		Susceptible	Resistant	Not done	Unknown		Susceptible	Resistant	Not done	Unknown
INH	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Streptomycin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Ethionamide	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EMB	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Kanamycin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
RMP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Capreomycin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Rifabutin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PZA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Ofloxacin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					

14. Genotyping results? 1  Yes 2  No 9  Unknown MIRU: \_\_\_\_\_ RFLP: 1  Yes 2  No

**Treatment Details**

15. Date treatment started: Year: \_\_\_\_\_ Month: \_\_\_\_\_ Day: \_\_\_\_\_

16. Initial drugs prescribed (check all that apply)  No drugs prescribed  Other (specify): \_\_\_\_\_  
 INH  RMP  Streptomycin  Ofloxacin  Rifabutin  
 EMB  PZA  Kanamycin  Ethionamide  PAS  
 Capreomycin  PAS  Unknown

17. Death before or during treatment? 1  Yes 2  No 9  Unknown If yes, date of death: Year: \_\_\_\_\_ Month: \_\_\_\_\_ Day: \_\_\_\_\_  
1  TB was the cause of death  
2  TB contributed but was not the cause of death  
3  TB did not contribute to death

**TB History/Case Finding/Risk Factors**

18. First episode of TB disease? 1  Yes 2  No If no: Year of previous diagnosis: \_\_\_\_\_  
Previous diagnosis occurred in: 1  Canada 2  Other country: \_\_\_\_\_  
Previous treatment completed or cured: 1  Yes 2  No 9  Unknown  
If yes, last date of previous treatment: Year: \_\_\_\_\_ Month: \_\_\_\_\_ Day: \_\_\_\_\_  
Previous treatment with (check all antibiotics used):  INH  EMB  RMP  PZA  
 Streptomycin  Ofloxacin  Rifabutin  
 Kanamycin  Ethionamide  
 Capreomycin  PAS  
 Other (specify): \_\_\_\_\_  
 Unknown

19. Case finding: 1  Symptoms compatible with site of disease 2  Incidental finding  
3  Post-mortem 4  Contact investigation  
5  Immigration medical surveillance 7  Occupational screening  
1  Initial immigration medical exam done outside Canada 8  Other screening  
2  Initial immigration medical exam done inside Canada 9  Other (specify): \_\_\_\_\_  
10  Unknown

20. Risk factors/Markers: HIV 1  Positive 2  Negative If positive, year of 1st positive test: \_\_\_\_\_  
If negative, year of most recent test: \_\_\_\_\_  
3  Test refused 4  Test not offered 5  Unknown

Contact with person with active TB in past 2 years: 1  Yes 2  No 9  Unknown  
Diabetes mellitus type 1 or 2: 1  Yes 2  No 9  Unknown  
End-stage renal disease: 1  Yes 2  No 9  Unknown  
Homeless (at diagnosis or within the previous 12 months): 1  Yes 2  No 9  Unknown  
Lives in correctional setting at time of diagnosis: 1  Yes 2  No 9  Unknown  
Long-term (≥ 1 month) corticosteroid use (prednisone ≥ 15 mg/day or equivalent): 1  Yes 2  No 9  Unknown  
Previous abnormal chest x-ray (fibronodular disease): 1  Yes 2  No 9  Unknown  
Substance abuse (known or suspected): 1  Yes 2  No 9  Unknown  
Transplant related immunosuppression: 1  Yes 2  No 9  Unknown  
Travel to high incidence TB country in last 2 years (if yes, how long in weeks): 1  Yes 2  No 9  Unknown  
Other (specify): \_\_\_\_\_ 1  Yes 2  No 9  Unknown





Treatment Outcome of a New Active or Re-treatment Tuberculosis Case

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WHEN COMPLETED

EFFECTIVE JANUARY 2008

1. Reporting province/ territory		2. Register case number		3. Unique identifier		4. Date of birth Year Month Day		5. Sex Male Female 1 2	
6. If transfer from diagnosing province/territory, please state treating province/territory				7. Register case number (if different from 2 above)		8. Unique identifier (if different from 3 above)			
9. Date of diagnosis Year Month Day			10. Date treatment started Year Month Day			11. Last day of treatment Year Month Day			
12. Initial drugs prescribed (list all that apply)									
<input type="checkbox"/> INH <input type="checkbox"/> EMB <input type="checkbox"/> RMP <input type="checkbox"/> PZA				<input type="checkbox"/> Streptomycin <input type="checkbox"/> Capreomycin <input type="checkbox"/> Ethionamide <input type="checkbox"/> Rifabutin <input type="checkbox"/> Kanamycin <input type="checkbox"/> Ofloxacin <input type="checkbox"/> PAS					
<input type="checkbox"/> No drugs prescribed <input type="checkbox"/> Other (specify) _____				<input type="checkbox"/> Unknown					
13. Did resistance develop during treatment? 1 <input type="checkbox"/> Yes   2 <input type="checkbox"/> No   3 <input type="checkbox"/> Not tested  ↓ If yes, please check drug(s) (check all that apply)					14. What was the treatment outcome? (Check one only)				
<input type="checkbox"/> INH <input type="checkbox"/> EMB <input type="checkbox"/> RMP <input type="checkbox"/> PZA					1 <input type="checkbox"/> Cure – negative culture at completion of treatment* 2 <input type="checkbox"/> Treatment completed – without culture at end of treatment* 3 <input type="checkbox"/> Death before or during treatment				
<input type="checkbox"/> Streptomycin <input type="checkbox"/> Ofloxacin <input type="checkbox"/> Rifabutin <input type="checkbox"/> Kanamycin <input type="checkbox"/> Ethionamide <input type="checkbox"/> Capreomycin <input type="checkbox"/> PAS <input type="checkbox"/> Other (specify) _____ <input type="checkbox"/> Unknown					Date of death Year Month Day 1 <input type="checkbox"/> TB was the cause of death 2 <input type="checkbox"/> TB contributed to death but was not the underlying cause 3 <input type="checkbox"/> TB did not contribute to death				
<input type="checkbox"/> Other (specify) _____ <input type="checkbox"/> Unknown					4 <input type="checkbox"/> Transferred to new country – outcome of treatment unknown (specify new country) _____ 5 <input type="checkbox"/> Failure – continued or recurrent positive cultures after 4 or more months of treatment 6 <input type="checkbox"/> Absconded (lost to follow-up before completion of 80% of doses) 7 <input type="checkbox"/> Treatment ongoing 8 <input type="checkbox"/> Other (specify) _____   9 <input type="checkbox"/> Unknown * if MDR-TB please see guidelines for definitions				
15. Treatment regimen (for drugs taken > 1 month) (check all that apply)					16. Major mode of treatment:				
<input type="checkbox"/> INH <input type="checkbox"/> EMB <input type="checkbox"/> RMP <input type="checkbox"/> PZA					1 <input type="checkbox"/> Modified 2 <input type="checkbox"/> Standard 3 <input type="checkbox"/> Enhanced				
<input type="checkbox"/> Streptomycin <input type="checkbox"/> Ofloxacin <input type="checkbox"/> Rifabutin <input type="checkbox"/> Kanamycin <input type="checkbox"/> Ethionamide <input type="checkbox"/> Capreomycin <input type="checkbox"/> PAS <input type="checkbox"/> No drugs prescribed <input type="checkbox"/> Unknown <input type="checkbox"/> Other (specify) _____					1 <input type="checkbox"/> DOT (Directly Observed Therapy) 2 <input type="checkbox"/> Daily, self-administered 3 <input type="checkbox"/> Other (specify) _____ 8 <input type="checkbox"/> Other (specify) _____ 9 <input type="checkbox"/> Unknown				
					17. Adherence estimate (% of medication received)				
					1 <input type="checkbox"/> 80%+   2 <input type="checkbox"/> 50-79% 3 <input type="checkbox"/> < 50%   9 <input type="checkbox"/> Unknown				



The Canadian Tuberculosis Laboratory Surveillance System  
M. TUBERCULOSIS COMPLEX ANTIMICROBIAL  
SUSCEPTIBILITY REPORTING FORM

Système de surveillance des laboratoires de tuberculose au Canada  
RAPPORT SUR LA SENSIBILITÉ DES SOUCHES DU COMPLEXE  
M. TUBERCULOSIS AUX ANTIMICROBIENS

FOR INTERNAL USE ONLY - POUR USAGE INTERNE SEULEMENT		Unique Source Laboratory ID No. - Identificateur unique du laboratoire déclarant:			
Date Rec'd at TBPC: Date de réception au LATB:		_____			
TBPC Number: Numéro du LATB:		Date specimen / culture received at laboratory: Date de réception échantillon / culture au laboratoire:			
_____		_____			
<b>Specie:</b> <input type="checkbox"/> M. tuberculosis complex (species known)* <b>Espèce:</b> <input type="checkbox"/> Complexe M. tuberculosis (espèce connue)* <input type="checkbox"/> M. bovis <input type="checkbox"/> M. bovis BCG <input type="checkbox"/> MTB Complex (species unknown) <input type="checkbox"/> Complexe MTB (espèce inconnue)					
<b>Have susceptibility test results been previously reported for this patient? - Des résultats d'antibiogramme ont-ils déjà été fournis pour ce patient?</b> <input type="checkbox"/> No / <input type="checkbox"/> Oui → What is the previous Unique Source Laboratory ID No.? Identificateur antérieur? _____ → What is the previous Form No. (if known)? N° de formulaire antérieur? (Si connu) _____					
<b>Note: Only DRUG TESTING RESULTS OF ONE ISOLATE are to be reported.</b> No subsequent drug testing results for the same patient are to be reported unless the sensitivity pattern changes.		<b>Note: Ne fournir que les RÉSULTATS POUR UN SEUL ISOLAT par patient à moins d'un changement du profil de sensibilité.</b>			
1	Province / territory from which this report originates: Province / territoire qui soumet ce rapport:	_____ (see code list) _____ (voir liste de codes)	<b>PROV / TERR CODES PROV / TERR</b> 10 = N.L. / T.N.-L. 46 = Man. 11 = P.E.I. / Î.-P.-É. 47 = Sask. 12 = N.S. / N.-É. 48 = Alta. / Alb. 13 = N.B. / N.-B. 59 = B.C. / C.-B. 24 = Que. / Qc 60 = Y.T. / Yn. 35 = Ont. 61 = N.W.T. / T.N.-O. 62 = Nvt. / Nt.		
2	Province / territory from which specimen originates: Province / territoire d'où provient l'échantillon:	_____ (see code list) _____ (voir liste de codes)			
3	Patient's date of birth: Date de naissance du patient:	_____ (CCYYMM/DD) _____ (SSAAMM/JJ)	<input type="checkbox"/> Unknown / Inconnu		
4	Patient's gender: Sexe du patient:	<input type="checkbox"/> Male / Masculin <input type="checkbox"/> Female / Féminin <input type="checkbox"/> Unknown / Inconnu			
5	<b>LABORATORY RESULTS</b> <b>RÉSULTATS DE LABORATOIRE</b>	<b>Concentration</b> (if different from on file) <b>Concentration</b> (si autre que spécifiée)	<b>Results</b> (check appropriate box for every drug) <b>Résultats</b> (cocher la case pertinente pour chaque antibiotique)		
	<b>Antituberculous Drugs</b> <b>Antituberculeux</b>		Sensitive Sensible	Resistant Résistant	Other (specify) Autre (préciser)
	<b>SM</b> (Streptomycin) (Streptomycine)	mg / L	<input type="checkbox"/>	<input type="checkbox"/>	
	<b>INH</b> (isoniazid) (isoniazide)	mg / L	<input type="checkbox"/>	<input type="checkbox"/>	
	<b>RMP</b> (Rifampin) (Rifampicine)	mg / L	<input type="checkbox"/>	<input type="checkbox"/>	
	<b>EMB</b> (Ethambutol) (Éthambutol)	mg / L	<input type="checkbox"/>	<input type="checkbox"/>	
	<b>PZA</b> (Pyrazinamide)	mg / L	<input type="checkbox"/>	<input type="checkbox"/>	
	<b>2nd line drugs (specify)</b> <b>Antituberculeux mineurs (préciser)</b>	<b>Concentration</b>	Sensitive Sensible	Resistant Résistant	Other (specify) Autre (préciser)
1.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
2.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
3.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
4.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
5.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
6.	mg / L	<input type="checkbox"/>	<input type="checkbox"/>		
6	<b>Comments - Commentaires</b>				

\* include/inclus: M. tuberculosis, M. africanum, M. canetti, M. caprae, M. microti, M. pinnipediti.

## Definition of terms

- 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** In the context of tuberculosis treatment, a patient who was lost to follow-up before completion of 80% of recommended doses.
- 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 disease** This denotes the presence of current active tuberculosis, most often on the basis of positive bacteriology but in approximately 15%-25% of cases on the basis of appropriate clinical and/or radiological and/or pathological presentation as well as treatment response.
- Adherence** A term that is often used interchangeably with **compliance** and refers to the patient's and health care provider's ability to follow management guidelines appropriately. It most often refers to the strict adherence by the patient to the prescribed regimen of anti-tuberculosis drug treatment or preventive therapy.

- Aerosol** Small droplets of moisture that are exhaled or coughed up. In a patient with **pulmonary tuberculosis** they may contain *Mycobacterium tuberculosis* bacteria that are suspended in the air and lead to the spread of infection. Generation of infectious aerosols is greatest with laryngeal and **cavitary** pulmonary disease.
- 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 the room volume.
- Airborne isolation** The conditions into which a patient with suspected or proven **active** tuberculosis may be placed for purposes of preventing transmission to other persons. In most institutional settings airborne isolation is provided by a combination of increased ventilation, (e.g. in the room occupied by the patient) and the use, by staff or visitors, of personal protective wear (respirators that filter 95% of particles of 1 micron or larger and have less than 10% leak).
- Anergy** A condition wherein a person has diminished ability to exhibit delayed T-cell hypersensitivity reaction to antigens because of a condition or situation resulting in altered immune function. When referring to an inability to react to a skin test, the correct term is “cutaneous anergy”.
- Bacillary (bacterial)-positive** This denotes a specimen that is **acid-fast** smear and/ or **culture-positive**, with *Mycobacterium tuberculosis* complex being the species isolated on culture.
- Bacille Calmette-Guérin (BCG)** A live attenuated vaccine derived from *Mycobacterium bovis* used to prevent or moderate tuberculosis disease.
- BACTEC** A commercially available broth-based laboratory technique using radiometric methods in which rapid growth and drug susceptibility results are available usually within a few weeks.

- Booster phenomenon** The presence of an initially negative **tuberculin skin test (TST)** response followed by a positive response when the test is repeated at any time from 1 week to 1 year later. The phenomenon often occurs many years after infection, most notably in the elderly. The initial negative response is based on the subject's initial failure to "recall", immunologically, prior infection. To avoid inadvertent labelling of a positive response as due to TST conversion, especially when serial skin testing is planned, initial **two-step skin testing** may be recommended.
- Canadian Tuberculosis Committee** A federal/provincial/territorial/non-governmental health organization committee that provides scientifically based advice to the Public Health Agency of Canada on tuberculosis prevention and control strategies and priorities for Canada, and provides a forum to address issues of common concern related to provincial/territorial tuberculosis prevention and control programs. For further information, see <http://www.publichealth.gc.ca/tuberculosis>.
- Case holding** This term refers to all aspects of the diagnosis and initiation of therapy of an **active** case of tuberculosis, including the completion of an adequate course of therapy.
- Cavitary disease** This is a radiologic-pathologic label referring to evidence of lung destruction, i.e. evidence on chest x-ray or pathology of 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.
- Chemotherapy** The provision of drug therapy to treat **active disease**.
- Chronic case** A patient in whom it has been impossible to eradicate the organism completely and who continues to chronically excrete organisms. It often occurs in **drug-resistant** disease, especially in subjects with an intact immune system.

<b>Cluster</b>	Two or more isolates found to share an identical genotype (“fingerprint”) using a method such as Mycobacteria Interspersed Repetitive Unit (MIRU) testing, insertion sequence 6110 (IS6110) based restriction fragment length polymorphism (RFLP) testing or spoligotyping.
<b>Compliance</b>	See <b>adherence</b> .
<b>Contact</b>	A person identified as having come in contact with an <b>active</b> case of disease. The degree of contact is usually further defined as close household, close non-household, casual and community contacts. The level and duration of contact usually suggests the risk of becoming infected.
<b>Conversion</b>	<p>A change in the result of a test for <i>Mycobacterium tuberculosis</i> infection that is interpreted to indicate a change from being uninfected to infected. With the <b>tuberculin skin test</b> (TST), a 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:</p> <ol style="list-style-type: none"><li>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.</li><li>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.</li></ol>
<b>Culture-positive disease</b>	The isolation of <i>Mycobacterium tuberculosis</i> complex (excluding BCG strain) from sputum, body secretions, or tissue.
<b>Cure (active tuberculosis)</b>	Culture-negative at the completion of treatment; for <b>multidrug-resistant TB</b> (resistant to at least isoniazid and rifampin), a patient who has been consistently culture negative (with at least five results) for the final 12 months of treatment. If there was only one positive culture with no clinical evidence of deterioration, a patient may be considered cured provided that the positive culture is followed by at least three consecutive negative cultures taken at least 30 days apart.

<b>Delayed-type hypersensitivity (DTH)</b>	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. Cell-mediated reactions are contrasted with an antibody (or humoral) response. DTH typically peaks 48-72 hours after exposure to the antigen.
<b>Designated country/territory</b>	As per s.30(1)(c) of the <i>Immigration and Refugee Protection Regulations</i> , if an individual is seeking entry to Canada for a period of greater than 6 months and has resided or sojourned, at any time during the 1 year period immediately preceding the date of seeking entry, for 6 consecutive months in a designated country/territory, then he/she is required to undergo an immigration medical examination. The designation of a country/territory is based primarily upon international tuberculosis incidence rates published by the Public Health Agency of Canada, (see <a href="http://www.publichealth.gc.ca/tuberculosis">http://www.publichealth.gc.ca/tuberculosis</a> ).
<b>Defaulter</b>	A patient whose treatment was interrupted for 2 or more consecutive months
<b>Directly observed prophylaxis (DOP)</b>	The process whereby a health care worker or pill dispenser watches the patient swallow each dose of medication for <b>latent tuberculosis infection</b> , helping to ensure higher treatment completion rates. DOP is also known as directly observed preventive therapy (DOPT).
<b>Directly observed therapy (DOT)</b>	The process whereby a health care worker or pill dispenser watches the patient swallow each dose of medication, helping to ensure that higher treatment completion rates are achieved. It may be subclassified as modified, standard or enhanced. Modified DOT refers to DOT for only part of the treatment period, typically during the initial phase, followed by self-administered therapy during the continuation phase. Standard DOT refers to DOT throughout the initial phase and the continuation phase. Enhanced DOT also refers to DOT throughout both phases but also includes <b>incentives</b> and <b>enablers</b> .
<b>DNA probe</b>	A molecular diagnostic technique whereby the organism grown on culture can be rapidly speciated within a matter of hours.

- Drug resistance** A strain of *Mycobacterium tuberculosis* resistant to one or more of the four **first-line drugs**: isoniazid, rifampin, pyrazinamide or ethambutol. Streptomycin was once but is no longer considered a first-line drug in Canada.
- Elimination** The elimination of tuberculosis as a global public health problem, defined by the Stop TB Partnership (see <http://www.stoptb.org/globalplan/>) as an incidence of tuberculosis disease of less than 1 per million population.
- Enabler** A practical item given to a patient to make **adherence** (e.g. to treatment or to clinic appointments) easier.
- Extensively drug resistant tuberculosis (XDR-TB)** Tuberculosis due to bacteria resistant to at least isoniazid and rifampin from among the **first-line** anti-tuberculosis drugs, plus resistance to any fluoroquinolone and to at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).
- First-line anti-tuberculosis drug** First line antibiotics for the treatment of **active tuberculosis disease**, including isoniazid, rifampin, ethambutol and pyrazinamide. Streptomycin was once but 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*.
- High tuberculosis incidence countries** Having a rate of sputum smear-positive pulmonary tuberculosis (3 year average), as estimated by the World Health Organization, of 15 per 100,000 or greater. The 3-year moving average is used to adjust for unstable rates in some jurisdictions. Estimated **sputum smear-positive pulmonary tuberculosis incidence** rates are used rather than the country reported **incidence** rates, as they adjust for under-reporting of cases and are 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>.



<b>Incentive</b>	A gift given to patients to encourage or acknowledge their <b>adherence</b> to treatment.
<b>Incidence</b>	The number of new occurrences of a given disease during a specified period of time.
<b>Index case</b>	The first or initial active case from which the process of contact investigation begins.
<b>Induration</b>	The soft tissue swelling that is measured when determining the <b>tuberculin skin test</b> response to <b>purified protein derivative (PPD) tuberculin</b> . It is to be distinguished from <i>erythema</i> , which is not measured, i.e. does not constitute a measurable reaction to the antigen.
<b>Infectious</b>	The condition whereby the patient can transmit infection to others by virtue of the production of infectious <b>aerosols</b> . Those with smear-positive <b>cavitary</b> and laryngeal disease are usually the most infectious.
<b>Interferon gamma release assay (IGRA)</b>	In-vitro T-cell based assays that measure interferon- $\gamma$ (IFN- $\gamma$ ) production and that have been developed for the diagnosis of <b>latent tuberculosis infection</b> (LTBI). These assays operate on the basis that T-cells previously sensitized to tuberculosis antigens produce high levels of IFN- $\gamma$ when re-exposed to the same mycobacterial antigens. At the present time, two different types of IGRAs are registered for use in Canada and present possible alternatives to <b>tuberculin skin testing</b> (TST). These are the Quantiferon <sup>®</sup> -TB Gold In-Tube (Cellistis Limited, Carnegie, Victoria, Australia) and the T-SPOT. <i>TB</i> <sup>®</sup> (Oxford Immunotec, Oxford, UK) assays.
<b>Intermittent therapy</b>	Therapy administered 2 or 3 times a week. This therapy should always be administered in a fully supervised, <b>directly observed</b> fashion and is usually reserved for the period after the initial intensive daily portion of therapy.
<b>Intradermal</b>	The method of injecting either <b>PPD</b> skin test antigen using the <b>Mantoux</b> technique or vaccinating with <b>BCG vaccine</b> .

<b>Inuit</b>	An <b>Aboriginal</b> people in Northern Canada, who live primarily in Nunavut, Northwest Territories, northern Quebec and northern Labrador. The word means “people” in the Inuit language – Inuktitut.
<b>Latent tuberculosis infection (LTBI)</b>	The presence of latent or dormant infection with <i>Mycobacterium tuberculosis</i> with no evidence of clinically <b>active disease</b> . The immunocompetent host generally has a lifetime risk of infection progressing to active disease ( <b>reactivation</b> ) in the range of 10%. Subjects deemed to have LTBI are by definition non-infectious. Depending on their contact history, age, chest radiographic findings, and associated medical conditions, they may be candidates for <b>treatment of latent tuberculosis infection</b> .
<b>Mantoux technique</b>	The technical term to describe the intradermal injection of 5 tuberculin units of <b>PPD</b> into the forearm. This is the recommended technique to administer <b>tuberculin skin testing</b> .
<b>Métis</b>	People of mixed Aboriginal and European ancestry who identify themselves as Métis and are distinct from <b>First Nations people, Inuit</b> or non-Aboriginal people.
<b>MGIT</b>	Mycobacteria growth indicator tube; a non-radiometric broth-based culture system. Detection of growth is due to the development of measurable fluorescence as a result of oxygen consumption.
<b>Multidrug-resistant tuberculosis (MDR-TB)</b>	Tuberculosis due to bacteria resistant to isoniazid and rifampin with or without resistance to other first- or second-line anti-tuberculosis drugs.
<b>NAA</b>	Nucleic acid amplification tests. New molecular diagnostic tests aimed at increasing sensitivity so that very small numbers of organisms can be detected by either increasing the amount of their nucleic acid or by increasing the signal of the probe. Although these tests are highly specific, at this time they have not obtained a sensitivity that would allow them to replace <b>culture</b> .

<b>New active case of tuberculosis disease</b>	An incident case of active tuberculosis with no documented evidence or adequate history of previously <b>active</b> tuberculosis.
<b>Non-nominal reporting</b>	A reporting system in which no identifying information or names are provided to public health officials when tuberculosis data are reported.
<b>Nontuberculous mycobacteria (NTM)</b>	All mycobacterial species except those that cause tuberculosis ( <i>Mycobacterium tuberculosis</i> [including subspecies <i>M. canetti</i> ], <i>M. bovis</i> , <i>M. africanum</i> , <i>M. caprae</i> , <i>M. microti</i> and <i>M. pinnipedii</i> ) and those that cause leprosy ( <i>M. leprae</i> ).
<b>Outbreak</b>	The following working definition of outbreak has been proposed by the U.S. Centers for Disease Control and Prevention for planning investigations: <ul style="list-style-type: none"> <li>• During (and because of) a contact investigation, two or more contacts are identified as having active TB, regardless of their assigned (contact investigation) priority; or</li> <li>• Any two or more cases occurring (within) <math>\leq 1</math> year of each other are discovered to be linked, and the linkage is established outside of a contact investigation (e.g. two patients who received a diagnosis of TB outside of a contact investigation are found to work in the same office, and only one or neither of the persons was listed as a contact to the other). The linkage between cases should be confirmed by genotyping results if isolates have been obtained.</li> </ul>
<b>Polymerase chain reaction (PCR)</b>	The process whereby genetic material is amplified and subsequently evaluated for the presence of DNA material to identify various mycobacterial species.
<b>Prevalence</b>	The number of people with the disease that are alive during a specified period of time.
<b>Preventive therapy</b>	See <b>treatment of LTBI</b> .
<b>Primary tuberculosis</b>	This includes <b>primary respiratory tuberculosis</b> and <b>tuberculous pleurisy in primary progressive tuberculosis</b> , (ICD-9 codes 010-010.9; ICD-10 codes A15.7 and 16.7).

**Primary respiratory tuberculosis**

This occurs usually, but not always, in a child, and is due to infection within the preceding 24 months with *Mycobacterium tuberculosis* complex. It includes **pulmonary** (lung parenchyma) tuberculosis, as well as tuberculosis of the intrathoracic lymph nodes, larynx, trachea, bronchus, or nasopharyngeal sinuses (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).

**Pulmonary tuberculosis**

In Canada, pulmonary tuberculosis includes tuberculosis of the lungs and conducting airways, which includes tuberculous fibrosis of the lung, tuberculous bronchiectasis, tuberculous pneumonia, tuberculous pneumothorax, isolated tracheal or bronchial tuberculosis and tuberculous laryngitis (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 tuberculin standardized in the past. The usual tuberculin test uses 0.1 mL of PPD standardized to 5 tuberculin units (TU).

**Reactivation**

The development of **active disease** after a period of **latent tuberculosis infection**.

**Registry**

The systematic collection of data pertaining to all active cases of tuberculosis in a given jurisdiction, to allow for effective case holding and the collection of epidemiologic information.

**Relapsed case of tuberculosis**

Prior to 2008 in Canada: documented evidence or adequate history of previously active tuberculosis that became inactive but now meets the active tuberculosis case definition.

Effective 2008 in Canada: **re-treatment case of tuberculosis** that is understood to be due to the inability to eradicate the previous episode of disease.

**Respiratory isolation**

See airborne isolation.

**Respiratory tuberculosis**

This consists of **primary tuberculosis** (which includes **primary respiratory tuberculosis** and **tuberculous pleurisy** in primary progressive tuberculosis), **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 except 010.1; ICD-10 codes A15-16 except 15.7 and 16.7).

**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.

**Re-treatment case of tuberculosis**

1. a) Documented evidence or adequate history of previously active TB which was declared cured or treatment completed by current standards, and
  - b) At least 6 months have passed since the last day of previous treatment\*, and
  - c) Diagnosed with a subsequent episode of TB which meets the active TB case definition.

OR

2. a) Documented evidence or adequate history of previously active TB which cannot be declared cured or treatment completed by current standards, and
  - b) Inactive† for 6 months or longer after the last day of previous treatment,\* and
  - c) Diagnosed with a subsequent episode of TB which meets the active TB case definition.

\* 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 “Treatment Outcome of New Active or Re-treatment Tuberculosis Case” form at the end of treatment.

† Inactivity for a respiratory tuberculosis case is defined as 3 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. Inactivity for a non-respiratory 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 other than **first-line** drugs, (isoniazid, rifampin, ethambutol and pyrazinamide) and other than those with unclear efficacy. 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 ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin and sparfloxacin, (5) rifamycins, other than rifampin, such as rifabutin, (6) salicylic acid–anti folates, 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. The results for sputum **acid-fast bacteria** (AFB) smears typically are reported as numbers of AFB per high-powered microscopy field, or else as a graded result from no AFB to 4+ AFB. The quantity of stained organisms is associated with the degree of **infectiousness**.
- 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**.
- Sputum smear positive** Cases of 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 to new country—outcome of treatment unknown** A patient who has been transferred to a recording and reporting unit outside of Canada 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.

<b>Treatment failure (active tuberculosis)</b>	Positive <b>sputum</b> cultures after 4 or more months of treatment or two positive <b>sputum</b> cultures in different months during the last 3 months of treatment, even if the final culture is negative.  For <b>MDR-TB</b> (resistance to at least isoniazid and rifampin), treatment is considered to have failed if <ul style="list-style-type: none"> <li>• two or more of five <b>cultures</b> recorded in the final 12 months are positive; or</li> <li>• any one of the final three cultures is positive; or</li> <li>• if a clinical decision has been made to terminate treatment early because of poor response or adverse events.</li> </ul>
<b>Treatment of latent tuberculosis infection (LTBI)</b>	The provision of <b>preventive therapy</b> , usually in the form of isoniazid, to individuals infected with <i>M. tuberculosis</i> but without <b>active disease</b> . This is also known as chemoprophylaxis.
<b>Tuberculin skin test (TST)</b>	Skin test to identify whether a person has <b>delayed-type hypersensitivity</b> reaction to tuberculin antigens.
<b>Tuberculosis case</b>	A case of disease defined in Canada as caused by <i>Mycobacterium tuberculosis</i> complex (i.e. <i>M. tuberculosis</i> [including subspecies <i>M. canettii</i> ], <i>M. bovis</i> [excluding BCG strain], <i>M. africanum</i> , <i>M. caprae</i> , <i>M. microti</i> or <i>M. pinnipedii</i> ).
<b>Tuberculous pleurisy in primary progressive tuberculosis</b>	This disease state is characterized by pleuritis and pleural effusion, usually in an adolescent or young adult, but possibly in any age group, due to recent (within the preceding 24 months) infection with <i>Mycobacterium tuberculosis</i> 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 or disseminated/miliary disease, is believed to have occurred 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.

# APPENDIX D

## Interferon-Gamma Release Assays for Latent Tuberculosis Infection

An Advisory Committee Statement (ACS)  
The Canadian Tuberculosis Committee\*†

### Preamble

*The Canadian Tuberculosis Committee provides the Public Health Agency of Canada (PHAC) with ongoing, timely and scientifically based advice on national strategies and priorities with respect to tuberculosis prevention and control in Canada. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best currently available scientific knowledge and medical practice. It is disseminating this document for information purposes to the medical and public health communities involved in tuberculosis prevention and control activities.*

*Persons administering or using drugs, vaccines, or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.*

\* **Members:** Dr. R. Long (Chair); Dr. H. Akwar, Dr. A. Al-Azem, Ms. C. Case, Dr. E. Ellis (Executive Secretary), Dr. K. Elwood, Dr. B. Graham, Ms. C. Hemsley, Dr. V. Hoepfner, Dr. A. Kabani, Dr. M. Lem, Ms. J. Marshall, Dr. P. Orr, Ms. E. Randell, Dr. P. Rivest, Ms. S. Sarkesh, Dr. L. Scott, Dr. F. Stratton, Dr. L. Sweet, Dr. W. Wobeser, and Ms. J. Wolfe.

† This statement was prepared by Drs. M. Gardam, D. Kunimoto, R. Long, D. Menzies and M. Pai (with secretariat support provided by Dr. R. Stirling). It has been approved by the Canadian Tuberculosis Committee.



The following recommendations are based in general upon a review of the literature and expert opinion as of October 2006. With more interferon-gamma release assay-related research being published all the time, the field is quickly evolving. As a result, this Advisory Committee Statement will be periodically updated as warranted. The updated Statements, along with a list of referenced studies grouped by category, will appear on the Public Health Agency of Canada website at <<http://www.publichealth.gc.ca/tuberculosis>>.

## Introduction

Recently, in-vitro T-cell based assays that measure interferon- $\gamma$  (IFN- $\gamma$ ) production have been developed for the diagnosis of latent tuberculosis infection (LTBI). These assays operate on the basis that T-cells previously sensitized to tuberculosis antigens produce high levels of IFN- $\gamma$  when re-exposed to the same mycobacterial antigens.<sup>1</sup> At the present time, two different types of IFN- $\gamma$  release assays (IGRAs) are registered for use in Canada and present possible alternatives to tuberculin skin testing (TST). These are the QuantiFERON<sup>®</sup>-TB Gold In-Tube (Cellestis Limited, Carnegie, Victoria, Australia) and the T-SPOT.TB<sup>®</sup> (Oxford Immunotec, Oxford, UK) assays.

The first commercial IGRA was the QuantiFERON-TB assay, and this assay used purified protein derivative (PPD) as the stimulating antigen. This assay was replaced by the QuantiFERON-TB Gold (QFT-G) assay that uses TB-specific antigens. The T-SPOT.TB test, the first IGRA registered in Canada, is also currently CE marked, a requirement to market a product in the European Union (EU) that indicates the product meets the applicable requirements of the EU directives. As of January 2007, the T-SPOT.TB test has not been FDA approved. Because of the rapid evolution of these assays and the variations in cut-points and technical methods used, it is important to note that this statement is based on published literature on QFT-G and QFT-G In-Tube, and research and commercial versions of the T-SPOT.TB assay.

The newer IGRA assays use *M. tuberculosis* specific proteins encoded by genes located within the region of difference 1 (RD-1) segment of the *M. tuberculosis* genome. These antigens are not found in Bacille Calmette-Guérin (BCG) vaccine and many non-tuberculous mycobacterial (NTM) species.<sup>1</sup> The immunogenic antigens encoded within the RD-1 of *M. tuberculosis* are found in *M. leprae*, wild type *M. bovis*, and certain of the NTM (including *M. kansasii*, *M. marinum*, *M. szulgai*, and *M. flavescens*). Theoretically, the presence in the host of these species could cause a false positive IGRA. While *M. leprae* and *M. bovis* are uncommon species in Canada, and are therefore unlikely to cause cross reactions, the NTM, *M. kansasii*, *M. marinum*, *M. szulgai*, and *M. flavescens* (listed in approximate order of their frequency in Canada) are not uncommon. Cumulatively, as many as 1 or 2 isolates of these species are grown for every 10 isolates of *M. tuberculosis* (National Microbiology Laboratory, Public Health Agency of Canada).

In 2005, the US Centers for Disease Control and Prevention (CDC) recommended that the FDA-approved version of QFT-G assay may be used in

place of the TST for all indications, including contact investigations, evaluation of immigrants, and serial testing of health care workers.<sup>2</sup> In 2006, the UK National Institute for Health and Clinical Excellence (NICE) TB guidelines recommended a hybrid, two-step approach for LTBI diagnosis: initial screen with TST, and subsequent IGRA testing, if available, of those who are TST positive (or in whom TST may be unreliable), to confirm TST results.<sup>3</sup>

## Test Descriptions

### QuantiFERON-TB Gold In-Tube

The QFT-G assay is available in two formats, a 24-well culture plate format (approved by the US Food and Drug Administration [FDA], and currently used in the US), and a newer, simplified In-Tube format (not FDA approved as yet; but available in countries other than the US). In Canada only the QFT-G In-Tube test is available. The QFT-G In-Tube assay uses peptides from early secreted antigenic target 6 (ESAT-6), culture filtrate protein 10 (CFP-10), and a portion of TB7.7. In this assay, one millilitre (mL) of blood is drawn into each of three tubes: a negative control, a positive mitogen control, and a tube that contains the *M. tuberculosis* specific RD-1 antigens CFP-10, ESAT 6 and TB7.7. The tubes are incubated as soon as possible but within 16 hours at 37°C for 16-24 hours and then centrifuged. Plasma is removed and assayed for IFN- $\gamma$  by enzyme linked immunosorbent assay (ELISA). The plasma is stable for up to 4 weeks at 4°C or can be frozen at -20°C for 3 months. Using the software provided with the commercial kit, the ELISA read-out is used to calculate the amount of IFN- $\gamma$  as IU/mL. After correcting for the negative control, an IFN- $\gamma$  value of  $\geq 0.35$  IU/mL is considered positive.

### T-SPOT. TB

The T-SPOT. TB test is an in-vitro diagnostic assay that measures IFN- $\gamma$  release following T-cell exposure to ESAT-6 and CFP-10. The T-SPOT. TB test is available in two formats – a 96 well plate (T-SPOT. TB 96) or eight well strips (T-SPOT. TB 8). In this assay, 8 mL of blood is collected into sodium citrate cell preparation tubes. Following isolation and washing of the peripheral blood mononuclear cells (PBMC),  $2.5 \times 10^5$  viable cells are added to each of four microtitre plate wells: a negative (nil) control, a positive control and two patient test wells (containing ESAT-6 and CFP-10 respectively). The T-SPOT. TB assay incubates PBMCs with *M. tuberculosis* antigens, and measures the number of T-cells producing IFN- $\gamma$  using an enzyme linked immunospot (ELISPOT) assay. The results of the test are interpreted by comparing the number of spots produced in the patient test wells compared to the number in the corresponding negative and positive control wells. What constitutes a positive result depends upon the number of spots produced in the negative control well. The product insert or the manufacturer's website should be consulted for further information on the interpretation of the test.

## Uses of interferon-gamma release assays in various population groups

The precise indications for use and interpretation of the results of IGRAs remain uncertain at this time. The following sections are meant to give guidance on the use and interpretation of these assays in various population groups and in various clinical settings.

### 1. Serial testing

There are very few published studies of results of serial testing with IGRA. Several small studies have examined results of repeated IGRA in patients who were receiving treatment for active TB<sup>4-9</sup> or LTBI.<sup>10,11</sup> Results from these studies have been contradictory – in some studies IGRA responses increased,<sup>5,6</sup> in others they decreased,<sup>4,7,8</sup> while in others no change<sup>10,11</sup> was seen following treatment. Thus no clear conclusions can be made from these longitudinal studies. As well, the effect of treatment could not be distinguished from random and biologic variability in these studies. The only published study of serial IGRA testing in untreated but exposed persons was conducted among health care workers in India.<sup>12</sup> In this study conversions, reversions, and non-specific variations occurred with serial testing with QuantiFERON-TB Gold In-Tube, as they do with TST. To meaningfully interpret repeat IGRA results, further studies are needed to determine the optimal thresholds to distinguish new infections (i.e., conversions) from non-specific variations.

#### *Recommendation:*

- ▶ There is insufficient published evidence to recommend serial IGRA testing in populations exposed to tuberculosis such as health care workers or prison staff and inmates. Serial screening for LTBI should continue to be done using the TST, as recommended by the *Canadian Tuberculosis Standards*.<sup>13</sup>

### 2. Diagnosis of LTBI in children

Evaluation of new tests for diagnosis of LTBI in children is particularly difficult because of the lack of a gold standard, even in patients with active disease. As well almost all of those identified with LTBI are treated because of their increased risk of disease development. Studies to date in pediatric populations have involved subjects with different clinical conditions who underwent different tuberculin and IGRA tests.<sup>14-21</sup> In two studies, from high incidence countries, an equal proportion of subjects were TST and IGRA positive,<sup>14,17</sup> while in two studies, IGRAs were more frequently positive.<sup>20,21</sup> In one study the proportion positive was not reported,<sup>18</sup> and TST was more often positive in three studies – a difference that was not explained in two,<sup>16,19</sup> but was related to BCG in the third.<sup>15</sup> In four studies, QFT results were indeterminate in 32%,<sup>18</sup> 17%<sup>16</sup> and none of the subjects,<sup>17,19</sup> these differences in test performance are also unexplained. Given these

heterogeneous methods, and findings, no meaningful inferences can be drawn. It cannot even be stated whether IGRAs are equivalent, better, or worse than TST in this population. Hence, at this time the most prudent action is to await further published evaluations of IGRA in this population, as this a very active area of investigation.

**Recommendation:**

- ▶ Use of IGRA is not recommended in children, until published evidence is available consistently demonstrating the utility and accuracy of these tests in pediatric populations.

### 3. Immigrant screening

In previously published statements, the Canadian Thoracic Society has not recommended routine or mass screening of new immigrants for LTBI using the TST.<sup>22</sup> The vast majority of persons identified to have LTBI are at low risk of subsequent disease, making this TB prevention strategy much less cost effective than other strategies, such as contact investigation.<sup>23</sup> In addition, in published reports from large scale screening programs the overall impact has been low because of substantial non-adherence, by patients and providers, with recommendations for screening, follow-up and LTBI treatment.<sup>23-28</sup> The limited published experience using these tests under routine program conditions suggests that using new IGRA will not significantly improve programmatic efficiency.<sup>29</sup>

On the other hand foreign born persons, because they have a higher prevalence of LTBI, **SHOULD** be targeted for LTBI screening if they have clinical conditions that increase the risk for reactivation of LTBI.<sup>30,31</sup> These clinical conditions include the following:<sup>13</sup>

- HIV infection
- transplantation (related to immunosuppressant therapy)
- silicosis
- chronic renal failure requiring hemodialysis
- carcinoma of head and neck
- recent TB infection ( $\leq 2$  years)
- abnormal chest x-ray – fibronodular disease or granuloma
- treatment with glucocorticoids
- treatment with tumor necrosis factor (TNF)-alpha inhibitors
- diabetes mellitus (all types)
- underweight (for TB purposes, this is a body mass index  $< 20$  for most persons)
- cigarette smoker
- children under the age of 15 years who have lived in a country with high TB incidence and have immigrated within the past 2 years
- persons aged 15 years and older who have lived in a country with high TB incidence, have immigrated within the past 2 years and have either

been living with or in known contact with a TB case in the past or are at high risk for development of active TB

*Note: A country is considered to have a high TB incidence if its World Health Organization estimated sputum smear positive pulmonary TB incidence rate is 15/100,000 or higher (3 year average). To view current rates, please see <http://www.publichealth.gc.ca/tuberculosis>.*

**Recommendation:**

- ▶ Routine or mass screening for LTBI for all immigrants with either TST or IGRA is NOT recommended. However, targeted screening for LTBI after arrival in Canada is recommended among foreign born with clinical conditions that increase their risk of reactivation of LTBI. For these persons, the TST should be used.

#### 4. Contacts of a case of active infectious tuberculosis

There are seven published reports comparing IGRAs with TST in the context of contact investigation.<sup>32-38</sup> Two studies evaluated QFT-G versus TST of  $\geq 10$  mm as a positive result in contacts of TB cases.<sup>33,35</sup> These two studies suggest that QFT-G results were similar to TST in non-BCG vaccinated contacts, but correlated with exposure better than TST in BCG vaccinated contacts. There were five studies using ELISPOT based assays versus TST in contacts.<sup>32,34,36-38</sup> One used the Heaf test,<sup>33</sup> the other four studies used the Mantoux test, with two using  $\geq 5$  mm<sup>36,37</sup> and two using  $\geq 10$  mm<sup>34,38</sup> as constituting a positive result. Overall the T-SPOT.TB was similar to TST in contacts, with better performance in BCG vaccinated persons. In the absence of BCG, the IGRAs appeared have similar rates of positivity as the TST, although there were discordant results. In the presence of BCG, there were significantly fewer positive results in the low exposure groups with the IGRAs than with the TST. This is consistent with numerous studies demonstrating that the IGRAs have better specificity.

Given that several studies have found significant discordance between TST and IGRA results (both TST+/IGRA- and the reverse, TST-/IGRA+) and because the biological basis of this discordance is uncertain, the reliance on IGRA should depend on the clinical context. Where the pretest probability of infection is high – as in a close contact of an active, infectious case – it is important not to miss identifying recently infected persons. In such circumstances, a TST (or both TST and IGRA) should be used, and if either is positive, the contact should be considered to have LTBI. However, in contacts who are felt to have a low pretest probability of having acquired LTBI, and who have no other significant risk factors for progression to active disease if infected (please refer to the ‘Immigrant screening’ section for a discussion of these risk factors), IGRA testing may be used in conjunction with the TST to improve the specificity of the TST. In such contacts with a known reason for a falsely positive TST (e.g., a prior history of BCG vaccination after infancy), the result of the IGRA

can be used to reduce the likelihood of administering treatment for LTBI to persons with falsely positive TSTs.

***Note about timing of simultaneous TST and IGRA***

When TST and IGRA are to be performed simultaneously, it is important to consider the issue of timing. Although one human study has shown that previous TST does not affect a subsequent ELISPOT result,<sup>39</sup> there are animal studies that suggest that TST might boost subsequent measurements of IFN- $\gamma$ .<sup>40,41</sup> Given the paucity of data on this issue, it is recommended that, when possible, blood be drawn for IGRA prior to or on the same day as placing the TST. This will avoid any potential effect of PPD sensitization on subsequent IFN- $\gamma$  measurements.

***Recommendations:***

1. IGRAs may be **used as a confirmatory test for a positive TST** in contacts who, based upon an assessment of the duration and degree of contact with an active infectious case, are felt to have a low pretest probability of having recently acquired LTBI and who have no other high or increased risk factors for progression to active disease if infected.<sup>13</sup>
2. For close contacts or those contacts who have high or increased risk for progression to active disease if infected, a TST (or both TST and IGRA) should be used, and if either is positive, the contact should be considered to have LTBI.
3. If both TST and IGRA testing will be used, it is recommended that blood be drawn for IGRA prior to or on the same day as placing the TST.

## 5 Immunocompromised persons

Published data on the use of IGRAs in immunocompromised populations are limited. Two studies have examined the sensitivity of the T-SPOT.*TB* test in this population.<sup>42,43</sup> In one study, the T-SPOT.*TB* test had high sensitivity for detecting active tuberculosis in HIV-infected and uninfected Zambian adults.<sup>42</sup> The results of the T-SPOT.*TB* test, when compared to the TST, also suggested that it had greater sensitivity than the TST in the HIV-positive population. In a recent study comparing the performance of the T-SPOT.*TB* versus TST versus expert physician panel diagnosis (which included a TB epidemiologic survey, chest radiograph and two-step TST in end stage renal disease patients receiving hemodialysis), the T-SPOT.*TB* test was more closely correlated with known tuberculosis risk factors such as prior active disease and an abnormal chest film, than the TST.<sup>43</sup>

In a study in 590 HIV-positive persons, QFT-G In-Tube was used to assess for LTBI<sup>44</sup> with no TST comparison performed. Overall, 4.6% of HIV-positive persons were found to have a positive IGRA result, 78%

had risk factors for LTBI. Only 20 (3.4%) of the study population had indeterminate results, with higher rates in those with CD<sub>4</sub> counts <100. In a second study,<sup>45</sup> 318 hospitalized patients were tested with both QFT-G and TST. The concordance between QFT-G and TST was significantly lower in BCG vaccinated individuals. Of particular concern was the fact that the QFT-G gave an indeterminate result in 68 (21.4%) persons.

#### *Recommendations:*

1. In an immunocompromised person, the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI.
2. However, in light of the known problem with false-negative TST results in immunocompromised populations, a clinician still concerned about the possibility of LTBI in an immunocompromised person with a negative initial TST result may perform an IGRA test. If the IGRA result is positive, the person might be considered to have LTBI. If the IGRA result is indeterminate, the test should be repeated to rule out laboratory error. If the repeat test is also indeterminate, the clinician should suspect anergy and rely on the person's history, clinical features, and any other laboratory results to make a decision as to the likelihood that the person has LTBI. The approach of accepting either test result (TST or IGRA) as positive will improve the sensitivity of detecting LTBI in immunocompromised populations, which would appear a desirable goal. However, in a meta-analysis of five randomized trials, all conducted in TB high incidence countries, isoniazid was of no benefit in TST negative HIV infected adults. Thus the clinician must weigh the potential benefit of detecting more persons with positive test results against the lack of evidence for the benefit of isoniazid treatment in such persons.

## 6 'Low risk' persons with a positive TST result

TST positive immunocompetent adults (persons > 14 years of age) at relatively low risk of being infected with TB, and of progressing to active disease if infected, may be referred to TB control physicians or clinics for consideration of treatment of LTBI. These would include (i) persons found to be TST positive on employment or post-secondary school screening, but having no history of TB contact, no clinical condition that increases the risk of reactivation, and a normal chest x-ray, and (ii) TST positive immigrants from high TB incidence countries (see the 'Immigrant screening' section above for a definition of high TB incidence countries) having no clinical condition that increases the risk of reactivation and a normal chest x-ray. Their TSTs could be falsely positive on account of BCG vaccination or exposure to non-tuberculous mycobacteria. To improve the specificity of

diagnosing LTBI and reduce the likelihood of administering treatment of LTBI to persons with false positive TSTs, an IGRA may be performed.

**Recommendation:**

- IGRA may be performed in TST positive, immunocompetent adults who are at relatively low risk of being infected with TB and of progressing to active disease if infected. Persons with a positive IGRA result may be considered for treatment of LTBI.

## 7. The diagnosis of active TB disease

There are two reasons for evaluating IGRAs among patients with active TB: 1) to use active TB as a surrogate reference standard for LTBI (most studies would fit in this category); and 2) to determine if IGRAs will be helpful in diagnosing active TB *per se*. Both approaches have limitations. The first reason is based on the logic that anyone with active TB must have TB infection – albeit not latent. From an immunological perspective, active TB occurs when the host immune response is unable to contain the latent infection, thus it is possible that the sensitivity of IGRAs in active disease may not reflect their sensitivity in LTBI. The second reason to perform the test is based on the assumption that evidence of TB infection (i.e. a positive IGRA result) is useful to diagnose active disease. This is problematic because IGRAs, like the TST, are incapable of distinguishing between LTBI and active disease, and most cases of TB disease occur in populations with high prevalence of LTBI.

It has been suggested that IGRAs have the potential to serve as useful tests to rule out active TB in selected populations (e.g. children, immunocompromised) where microbiologic diagnosis is hard to establish. In other words, while a positive IGRA may not always indicate active disease, a negative IGRA may indicate lack of TB infection and, therefore, disease. For IGRAs to be useful in excluding active disease, they must be highly sensitive in patients with active TB. As reviewed previously,<sup>46,47</sup> the sensitivity of IGRA in active TB is comparable to the sensitivity of TST, and by extension, both tests have sub-optimal sensitivity in patients with active TB. This reflects the well known diminished immune response in patients with active TB at the time of diagnosis, particularly with more advanced disease, malnutrition, or older age.<sup>48,49</sup> Thus, a negative IGRA or TST cannot be used alone to exclude the diagnosis of active TB.<sup>2</sup>



**Recommendation:**

- IGRAs are not recommended for the diagnosis of active TB. Clinicians who manage patients with suspected TB disease should align their practice with the *Canadian TB Standards*,<sup>13</sup> and the International Standards for TB Care,<sup>50</sup> and use sputum smear microscopy and culture to investigate patients with suspected active TB.

## Interpretation in persons with both TST and IGRA test results

While the current recommendations for use of IGRA tests are limited (see above), there may be situations where IGRA testing has been performed outside of the above recommendations. If both IGRA and TST results are available and the clinician is unsure how to interpret the results, the following is recommended:

### Risk of developing disease if infected with *M. tuberculosis*

	High			Low		
	IGRA positive	IGRA negative	IGRA indeterminate	IGRA positive	IGRA negative	IGRA indeterminate
<b>TST positive</b>	Consider treatment for LTBI			Consider treatment for LTBI	Treatment for LTBI is not necessary	Repeat IGRA test or base interpretation on TST result
<b>TST negative</b>	Consider treatment for LTBI	Treatment for LTBI is not necessary if immuno-competent	Repeat IGRA test or base interpretation on TST result	Consult TB specialist	Treatment for LTBI is not necessary	

*Disclaimer: this table is offered in the context of this Statement and is NOT meant to be a comprehensive guide to the management of LTBI. For comprehensive guidance on the management of LTBI, the reader is referred to chapters 4 and 6 of the Canadian Tuberculosis Standards.<sup>13</sup>*

## The cost-effectiveness of interferon- $\gamma$ release assays

At present there are few published studies comparing the cost-effectiveness of IGRA with TST.<sup>51-53</sup> Available analyses have demonstrated that if the unit costs for the new IGRA are substantially higher than those of TST, then these new tests will be cost-effective only in situations where their specificity is substantially higher. The manufacturers' retail prices for QFT-G In-Tube and for T-SPOT.TB will vary by clinical setting and the volume ordered. To this must be added \$22.00 for ancillary costs per QFT-G In-Tube test for drawing blood, transport of specimens to the laboratory, and technician time for performing and reporting the test – based on a recently published programmatic experience.<sup>29</sup> As the technician time for performing the T-SPOT.TB test is greater than for the QFT-G In-Tube, the ancillary costs associated with T-SPOT.TB test are slightly higher. By contrast the total cost of TST is only \$14 in public

health settings,<sup>31,51,54,55</sup> although may be higher in primary care settings if not covered by provincial/territorial health insurance. Hence QFT-G In-Tube and T-SPOT.TB will be cost-effective, compared to the TST, only in populations where a high proportion were BCG vaccinated after infancy.<sup>56</sup>

#### *Recommendation:*

- ▶ Given their higher unit and labour costs, new IGRAs will be less cost-effective than TST in most clinical situations and populations. In low risk populations who were BCG vaccinated after infancy, the most cost-effective strategy is initial TST followed by QFT-G In-Tube for those who are TST positive.

## Conclusions

In the diagnosis of LTBI, IGRAs have a number of potential advantages over the TST. Current commercially available assays that are based on combinations of RD-1 antigens such as ESAT-6 and CFP-10, have excellent specificity, with minimal false-positive test results due to vaccination with BCG, and sensitization by certain NTM. Other benefits of these tests are that they require only a single visit by the patient and pose no risk of serious skin reactions.

A major advantage of the TST is that results have been validated through follow-up of large cohorts to determine subsequent incidence of active TB. Based on these studies, risk of disease in an individual with certain risk factors and a given TST reaction can be predicted with some accuracy. However, to date, none of the IGRAs have been validated prospectively in this way.

The initial material and ancillary costs of IGRAs are greater than those of the TST, and cost-benefit analyses have demonstrated that this means these tests will be less cost-effective in most populations. The occurrence of many reactions that are discordant with TST reactions is of concern, because this phenomenon of discordance remains largely unexplained. Therefore individuals who are IGRA positive and TST negative will be difficult to manage appropriately.

It is important to note that, like the TST, IGRAs are not recommended for the diagnosis of active TB. The precise indications for use and interpretation of results, particularly with regard to future risk of active TB disease, remain uncertain at this time. Future research is needed to define the ability of these assays to predict the development of active disease, their reproducibility, and to assess the health and economic implications of their use. Further studies, particularly prospective studies with simultaneous performance of TST and IGRAs, would be of great interest.

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## Tuberculosis education and training resources

Tuberculosis (TB) education and training are fundamentally important to TB prevention and control. The aim of this appendix is to provide information that may be useful to organizations and individuals with regard to the many excellent TB education and training sources and resources that exist within Canada and internationally. Where gaps in resources are found, it is hoped that collaborative partnerships among those seeking them will develop, and that coordination of effort to create and disseminate new resources will occur.

TB education and training materials are available in a variety of formats: text-based, Web-based, video, and CD/DVD. There are also a number of TB courses, workshops and TB-related conferences that may be attended in person or via videoconferencing.

Health care providers, community agencies, the general public and patients each have specific needs with regard to TB education and/or training. Although some of these needs will be similar, others will be unique and specific to that particular target audience. The resource listing has been divided into sections accordingly.

The following resource listing is provided as a public service. It is the responsibility of the user to evaluate any materials, tools and programs they access from these sources prior to use.

### TB Resources for Health Care Providers, Patients and the General Public

#### Canadian sources

- Canadian Health Network  
[www.canadian-health-network.ca](http://www.canadian-health-network.ca)

Canadian-specific contributions to the Network are encouraged!

- Canadian Lung Association  
[www.lung.ca](http://www.lung.ca)
- Public Health Agency of Canada  
[www.phac-aspc.gc.ca](http://www.phac-aspc.gc.ca) (general)  
[www.publichealth.gc.ca/tuberculosis](http://www.publichealth.gc.ca/tuberculosis)
- TB Canada  
This secure Website, part of the Canadian Network for Public Health Intelligence, is for persons involved in TB prevention and control in a service, education or research capacity. It provides a forum for discussion and makes it easier to request technical advice/assistance from others. To register, visit [www.cnphi-rcrsp.ca](http://www.cnphi-rcrsp.ca). Click on your language of choice and then on “Apply for a new account”. Complete all the fields in the application and type in the words “TB Canada” in the comments box under the words at the bottom of the application and submit.

**U.S. sources** (Note that U.S. recommendations may differ from those found in the *Canadian Tuberculosis Standards* because of different TB epidemiology, public health practice and clinical practice in the U.S.)

- American Thoracic Society  
[www.thoracic.org](http://www.thoracic.org)
- Tuberculosis Education and Training Network  
[www.cdc.gov/tb/TBETN/default.htm](http://www.cdc.gov/tb/TBETN/default.htm)
- TB Education and Training Resource Guide  
[www.cdc.gov/tb/pubs/TB\\_Edu\\_Train\\_Resources.htm](http://www.cdc.gov/tb/pubs/TB_Edu_Train_Resources.htm)
- Tuberculosis Education and Training Resources  
[www.findtbresources.org/scripts/index.cfm](http://www.findtbresources.org/scripts/index.cfm)
- U.S. Regional Training and Medical Consultation Centers  
[www.cdc.gov/tb/rtmcc.htm](http://www.cdc.gov/tb/rtmcc.htm)

While each centre serves a geographic part of the U.S., they all list various resources on their Websites that may be useful for TB prevention and control activities outside the U.S.

### Tuberculin Skin Test (TST) Resources

- The U.S. Centers for Disease Control and Prevention video entitled “Mantoux Tuberculin Skin Test” (Cat. No. 00-5457, English only) provides a clear, detailed demonstration of the steps involved in administering and reading the test. It may be ordered free of charge by completing an order form available on-line at [www2.cdc.gov/nchstp\\_od/piweb/tborderform.asp](http://www2.cdc.gov/nchstp_od/piweb/tborderform.asp).
- TST practice may be done by intradermal injection of water into a hot dog. There are also a number of sources from which mannequin “arms” may be purchased on which to practise injections and/or reading of TST

reactions. Some of these sources can be found at [www.findtbresources.org/scripts/index.cfm](http://www.findtbresources.org/scripts/index.cfm).

- A Web-based interactive algorithm is available to assist in TST interpretation at [www.meakins.mcgill.ca/respepi/homeE.htm](http://www.meakins.mcgill.ca/respepi/homeE.htm).

### **Other Organizations that Provide Information/Resources about TB**

- Global Alliance for TB Drug Development  
[www.tballiance.org](http://www.tballiance.org)
- International Union Against TB and Lung Disease (IUALTD)  
[www.iuatld.org](http://www.iuatld.org)
- Stop TB Canada  
[www.stoptb.ca/index.shtml](http://www.stoptb.ca/index.shtml)
- Stop TB Partnership/World Health Organization (WHO) Stop TB Development  
[www.stoptb.org](http://www.stoptb.org)

# APPENDIX F

## BCG vaccine usage in Canada – current and historical (October 2007)

The following information was kindly provided by provinces/territories and Health Canada's First Nations and Inuit Health Branch.

Please report any errors or omissions to Tuberculosis Prevention and Control, Public Health Agency of Canada, 100 Eglantine Driveway, AL 0603B, Ottawa, Ontario K1A 0K9 or by e-mail to TB\_1@phac-aspc.gc.ca

Province/Territory	BCG Usage (except First Nations Communities)	BCG Usage* (First Nations Communities)
Alberta	Discontinued in the early 1970s (was being used for health care workers)	Discontinued in 41 of 44 communities as of 2007
British Columbia	Discontinued in the 1970s for health care workers	Discontinued in all communities in 2003
Manitoba	Discontinued in the 1970s for health care workers	Offered to infants in most communities
New Brunswick	Routine use for nursing students began in 1949; discontinued in the 1970s	Discontinued in the 1970s
Newfoundland and Labrador	Routine use for school students began in 1948; discontinued in 1975	Discontinued for aboriginal persons in Labrador in 1979
Northwest Territories	Routine use of the BCG vaccine began in 1954. Routine vaccination of Inuit infants living in communities where TB is endemic. Also offered to immigrant infants whose families are from TB endemic countries	Routine vaccination of First Nations infants living in communities where TB is endemic. Endemic TB is defined as greater than 10% infectivity (active TB and latent TB infection) or total burden of latent TB infection
Nova Scotia	Discontinued in 1979 (was being used for health care workers)	Discontinued in the 1970s
Nunavut	Vaccine offered to all newborns	

Province/Territory	BCG Usage (except First Nations Communities)	BCG Usage* (First Nations Communities)
Ontario	Used for some health workers prior to the 1970s	Offered to infants in North Western Ontario, Thunder Bay and Sioux Lookout Zones
Prince Edward Island	Discontinued in 1966 for school students and in 1976 for health care workers	Discontinued in the 1970s
Quebec	Clinical use began in Montreal in 1925 with routine use for school students beginning in 1948; discontinued in the mid-late 1970s for school students and more recently for health care students	Discontinued in all communities in 2005
Saskatchewan	Clinical use began in 1933; discontinued in 1987	Offered to infants in 24 of 65 communities plus the Northern Inter-Tribal Health Authority (NITHA)
Yukon	Discontinued in the early 1990s	

\* Routine use began in the late 1940s; current use varies by province/territory.

# APPENDIX G

## Recommendations for the screening and prevention of tuberculosis in patients with human immunodeficiency virus (HIV) and the screening for HIV in tuberculosis patients and their contacts

An Advisory Committee Statement (ACS)\*  
The Canadian Tuberculosis Committee†‡

### Preamble

*The Canadian Tuberculosis Committee (CTC) provides Health Canada with ongoing, timely and scientifically based advice on national strategies and priorities with respect to tuberculosis prevention and control in Canada. Health Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practice.*

*It is disseminating this document for information purposes to the medical community involved in the care of individuals with tuberculosis and/or HIV/AIDS.*

\* **Source:** *Canada Communicable Disease Report* 2002;28(ACS-7). URL: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/02vol28/28sup/acs7.html>

† **Members:** Dr. V. Hoepfner (Chair); Dr. M. Baikie; Dr. C. Balram; Ms. P. Bleackley; Ms. C. Case; Dr. E. Ellis (Executive Secretary); R. K. Elwood (Past Chair); Ms. P. Gaba; Dr. B. Graham; Dr. B. Gushulak; Ms. C. Hemsley; Dr. E. S. Hershfield; Ms. R. Hickey; Dr. A. Kabani; Dr. B. Kawa; Dr. R. Long; Dr. F. Stratton; Ms. N. Sutton; Dr. L. Sweet; Dr. T. N. Tannenbaum.

‡ This statement was prepared by Dr. R. Long, Dr. S. Houston, and Dr. E. S. Hershfield. It has been approved by the Canadian Tuberculosis Committee, Canadian Thoracic Society of the Canadian Lung Association, Canadian Infectious Disease Society, and Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, Health Canada.

## Screening and Prevention of Tuberculosis in Patients with HIV

The HIV epidemic has had a dramatic impact on tuberculosis (TB) rates and tuberculosis control in populations in which both infections are prevalent<sup>(1)</sup>. HIV, in particular advanced HIV (AIDS), is the most potent risk factor ever identified for the progression to disease of recent or remotely acquired infection with *Mycobacterium tuberculosis*<sup>(2)</sup>. It operates by destroying the two types of immune cell most important to the containment of tubercle bacilli (macrophages and CD4 receptor bearing lymphocytes)<sup>(3)</sup>. Among people infected with *M. tuberculosis* who are not receiving highly active antiretroviral therapy (HAART), the estimated risk of active tuberculosis relative to patients with no known risk factor is 170.0 for AIDS and 113.0 for HIV infection without AIDS<sup>(2)</sup>. Cases of TB thus produced increase the risk of transmission of *M. tuberculosis* within the community, thereby constituting a second, indirect mechanism by which HIV increases TB morbidity<sup>(4)</sup>.

In Canada, dormant or latent tuberculosis infection (LTBI) is most commonly found in four groups: those born in countries where TB is endemic, Aboriginal people, the inner city poor and homeless, and elderly people<sup>(5)</sup>. Co-infection with HIV is not uncommon among inner city people with a history of injection drug use<sup>(6)</sup>.

Recent data suggest that the incidence of HIV/AIDS is increasing among Aboriginal people<sup>(6-8)</sup> and those born in tuberculosis endemic countries<sup>(9)</sup>. Treatment of LTBI has been shown to reduce the risk of progression to active disease in HIV-TB co-infected individuals<sup>(10,11)</sup>. The following recommendations are made:

1. Every patient with newly diagnosed HIV infection should be assessed for the presence of active TB at the time of diagnosis of HIV. An inquiry about symptoms that would suggest active TB (cough, especially if productive or associated with hemoptysis, fever, night sweats, weight loss) should be made and any history of TB or known/likely exposure to it ascertained. For patients who report that they have received treatment of active TB or LTBI in the past, the adequacy of that treatment must be assessed. As well, a physical examination that includes examination of extrapulmonary sites of disease, such as lymph nodes<sup>(12)</sup>, and chest radiography should be performed, and features of current or past TB sought. The examiner should be aware that the clinical presentation of TB may be altered in the presence of HIV infection and that radiographic features may be altered or absent in approximate proportion to the individual's degree of immunosuppression<sup>(3)</sup>. People with suspected active TB should have sputum or other appropriate specimens submitted for acid-fast bacilli (AFB) smear and culture.
2. Health care workers caring for patients with HIV infection should maintain a high level of suspicion for TB.
3. Except in those with a history of active TB or a well documented previous, positive tuberculin skin test (TST), every HIV-infected person should be given a TST with intermediate strength (5-TU) purified protein derivative

by the Mantoux method, which should be read 48 to 72 hours later by a health care worker experienced in reading TSTs.

4. TB screening with TST should be performed as soon as possible after HIV infection is diagnosed, because the reliability of the TST can diminish as the CD4 lymphocyte count declines.
5. For those in whom annual testing is felt to be justified by high infection rates, a baseline two step TST should be considered<sup>(2)</sup>.
6. Induration of  $\geq 5$  mm on the TST should be considered indicative of TB infection<sup>(2,3)</sup>.
7. Routine anergy testing is not recommended<sup>(13,14)</sup>. Administration of TB preventive therapy to anergic, HIV-infected individuals has not been found to be useful or cost-effective if none of the other indications is present (see below)<sup>(15-17)</sup>.
8. TST negative patients with evidence of old, healed TB on the chest radiograph, especially those with a history of TB exposure, should be considered for TB preventive therapy once active tuberculosis has been excluded. Repeat TST may be considered after institution of antiretroviral therapy and evidence of immune reconstitution<sup>(3)</sup>.
9. Unless specifically contraindicated, HIV-positive patients who a) have a positive TST ( $\geq 5$  mm of induration), b) have not already been treated for TB infection, and c) have test results excluding active TB should be strongly encouraged to take preventive therapy<sup>(1,18-20)</sup>. This preventive therapy is indicated even if the date of TST conversion cannot be determined. Because of the very high risk of development of active TB in HIV-TB co-infected individuals, creative means of enhancing adherence, such as directly observed preventive therapy, should be considered, particularly if there are concerns about the patient's adherence. Preventive therapy regimens and monitoring are outlined in the 5th edition of the *Canadian Tuberculosis Standards*, Web site: <[http://www.lung.ca/tb/TBStandards\\_Eng.pdf](http://www.lung.ca/tb/TBStandards_Eng.pdf)>.
10. HIV-infected close contacts of patients with infectious TB should receive treatment for presumptive LTBI, even when repeat TST after contact is not indicative of latent infection<sup>(20)</sup>. Because re-infection can occur, this may, at times, imply re-treatment of a person who has already undergone treatment in the past.
11. Preventive therapy is recommended during pregnancy for HIV-infected patients who have either a positive TST or a recent history of exposure to active TB, after active tuberculosis has been excluded.
12. HIV-infected people who are candidates for, but who do not receive, TB preventive therapy should be assessed periodically for symptoms of active TB as part of their ongoing management of HIV infection. Clinicians should educate them about the symptoms of TB and advise them to seek medical attention promptly should such symptoms develop.



13. The administration of BCG vaccine to HIV-infected patients is contraindicated because of its potential to cause disseminated disease.
14. HIV-infected patients should be advised that certain activities and occupations may increase the likelihood of exposure to TB. These include volunteer work or employment in health care facilities, correctional institutions, and shelters for the homeless, as well as travel to TB endemic countries.

TB disease in an HIV-infected person is an AIDS defining illness. Both TB and AIDS should be reported to the Public Health Department<sup>(21)</sup>.

### Screening for HIV in TB Patients and Their Contacts

Patients with TB constitute an important “sentinel” population for HIV screening. In some African countries with high TB prevalence, HIV prevalence exceeds 50% among TB patients<sup>(22)</sup>. Between 1985 and 1992, TB patients in the United States were 204-fold more likely to have AIDS than the general population<sup>(23)</sup>. The benefits of identifying previously unrecognized HIV infection are substantial in terms of both the opportunities for preventing future HIV transmission and the large potential benefits to the patient of antiretroviral therapy<sup>(3)</sup>. Knowledge of the HIV serostatus of TB patients may also influence the treatment of their TB<sup>(17)</sup>. Even in those not receiving antiretroviral drugs there may be an increased risk of adverse reactions from antituberculosis drugs<sup>(24)</sup>. Because HIV-infected people are at risk of peripheral neuropathy, co-administration of pyridoxine with isoniazid may be prudent. For some HIV-infected TB patients malabsorption of their anti-tuberculosis drugs has been reported, so that measurement of serum drug levels may be necessary if there is a poor response to treatment<sup>(3)</sup>. The following recommendations are made:

1. All patients with newly diagnosed TB should be strongly encouraged to undergo HIV serologic testing according to established guidelines<sup>(25,26)</sup>.
2. HIV-testing of contacts of infectious TB cases should be considered if they are at risk for HIV<sup>(27,28)</sup>.
3. Additional information resources concerning HIV should be available to patients for whom HIV testing is recommended as well as to other patients seen by TB programs.

Health care providers, administrators, and TB controllers should strive to promote coordinated care for patients with TB and HIV, and to improve information sharing between TB control programs and HIV/AIDS programs.

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# APPENDIX H

## International Standards for Tuberculosis Care

The Public Health Agency of Canada (PHAC), the Canadian Thoracic Society and the Canadian Tuberculosis Committee endorse the *International Standards for Tuberculosis Care (ISTC)* and the *Patients' Charter for Tuberculosis Care*. The documents are available at <http://www.nationaltbcenter.edu/international/> and <http://www.who.int/tb/publications/2006/istc/en/index.html>. A concise version of the *ISTC* was published in the *Lancet Infectious Diseases* (2006;6:710-25).

The following is the summary from the *ISTC*. In the list of standards below, italicized notes refer to Canadian specific recommendations based on the *Canadian Tuberculosis Standards*.

The purpose of the *International Standards for Tuberculosis Care (ISTC)*<sup>1,2</sup> is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have or are suspected of having tuberculosis (TB). The *Standards* are intended to facilitate the effective engagement of all care providers in delivering high-quality care for patients of all ages, including those with sputum smear-positive, sputum smear-negative and extrapulmonary TB; TB caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms; and TB combined with human immunodeficiency virus (HIV) infection.

The basic principles of care for persons who have or are suspected of having TB are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out. Prompt, accurate diagnosis and effective treatment are not only essential for good patient care, they are also the key elements in the public health response to TB and the cornerstone of TB control. Thus, all providers who undertake evaluation and treatment of patients with TB must recognize that as well as delivering care to an individual they are assuming an important public health function that entails a high level of responsibility to both the community and the individual patient.

Although government TB program providers are not exempt from adherence to the *Standards*, non-program providers are the main target audience. It should be emphasized, however, that national and local TB control programs may need to develop policies and procedures that enable non-program providers to adhere to the *Standards*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations.

In addition to health care providers and government TB programs, both patients and communities are part of the intended audience. Patients are increasingly aware of health care issues and expect that their care will measure up to a high standard, as described in the *Patients' Charter for Tuberculosis Care*.<sup>3</sup> Having generally agreed-upon standards will empower patients to evaluate the quality of care that is being provided to them. Good care for individuals with TB is also in the best interest of the community.

The *Standards* are intended to be complementary to local and national TB control policies that are consistent with World Health Organization (WHO) recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice. They focus on the contribution that good clinical care of individual patients who have or are suspected of having TB makes to population-based TB control. A balanced approach emphasizing both individual patient care and public health principles of disease control is essential to reduce the suffering and economic losses from TB.

The *Standards* should be viewed as a living document that will be revised as technology, resources and circumstances change. As written, the *Standards* are presented within a context of what is generally considered to be feasible now or in the near future.

The *Standards* are also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care*, developed in tandem with the *Standards*. The *Charter* specifies patients' rights and responsibilities and will serve as a set of standards from the point of view of the patient, defining what he or she should expect from the provider and what the provider should expect from the patient.

## Standards for Diagnosis

- Standard 1** All persons with otherwise unexplained productive cough lasting 2-3 weeks or more should be evaluated for tuberculosis.
- Standard 2** All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two, and preferably three, sputum specimens obtained for microscopic examination. When possible, at least one early morning specimen should be obtained.
- Standard 3** For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.

**Standard 4** All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

*NOTE: In Canada, spontaneously expectorated sputum, induced sputum, bronchial washings and lavage, post-bronchoscopy sputum or gastric aspirate are acceptable.*

**Standard 5** The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (NOTE: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

**Standard 6** The diagnosis of intrathoracic (i.e. pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection (positive tuberculin skin test or interferon-gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

*NOTE: In Canada, interferon-gamma release assays are not currently recommended in children.*

## Standards for Treatment

**Standard 7** Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.

*NOTE: In Canada, treatment of TB should be undertaken collaboratively with the public health department.*

**Standard 8** All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol. The preferred continuation phase consists of isoniazid and rifampicin given for 4 months. Isoniazid and ethambutol given for 6 months is an alternative continuation phase regimen that may be used when adherence cannot be assessed, but it is associated with a higher rate of failure and relapse, especially in patients with HIV infection.

The doses of antituberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

*NOTE: In Canada, the combination of isoniazid and ethambutol for 6 months in the continuation phase of treatment is not recommended.*

**Standard 9** To foster and assess adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed therapy—DOT) by a treatment supporter who is acceptable and accountable to the patient and to the health system.

**Standard 10** All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (2 months), at 5 months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately, see Standards 14 and 15. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.

*NOTE: In Canada, patients with respiratory TB are recommended to submit sputum for both microscopy and culture at 2 months, 4 months (if treatment failure is suspected) and at the end of treatment.*

**Standard 11** A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

**Standard 12** In areas with a high prevalence of HIV infection in the general population and where tuberculosis and HIV infection are likely to co-exist, HIV counseling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counseling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

*NOTE: In Canada, all incident cases of TB are recommended to undergo HIV testing.*

**Standard 13** All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

*NOTE: In Canada, patients with CD4 cell counts less than 200 cells  $\times 10^6/L$  should receive prophylaxis for other infections (see MMWR, 2002;51(RR-8) for details).*

**Standard 14** An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be performed promptly.

*NOTE: In Canada, all initial isolates of M. tuberculosis should be tested for INH, rifampin, ethambutol and pyrazinamide drug susceptibility as a minimum.*



**Standard 15** Patients with tuberculosis caused by drug-resistant (especially multiple-drug resistant [MDR]) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient-centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

## Standards for Public Health Responsibilities

**Standard 16** All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

**Standard 17** All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

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# APPENDIX I

## Guidelines for the Investigation and Follow-up of Individuals under Medical Surveillance for Tuberculosis after Arrival in Canada (2007)

*These guidelines were prepared by the Immigration Subcommittee of the Canadian Tuberculosis Committee. They have been approved by the Canadian Tuberculosis Committee and the Canadian Thoracic Society and replace all previous versions, including the most recent one published in 2001<sup>1</sup> and summarized in 2003.<sup>2</sup> Information on the epidemiology of tuberculosis (TB) and on the immigration medical examination (IME) provided in section 1 and 2 of the last guidelines is now provided in the Canadian Tuberculosis Standards, 6<sup>th</sup> edition (see Chapter 1, Epidemiology of Tuberculosis in Canada, and Chapter 15, Immigration and Tuberculosis Control in Canada). Future revisions of these guidelines will be posted at <<http://www.publichealth.gc.ca/tuberculosis>>.*

### Purpose of the Medical Surveillance Requirement

In order of priority:

1. to assess for the presence of prevalent active TB;
2. to assess the individual's candidacy for treatment of latent TB infection; and
3. to assess the individual's need for continued TB follow-up.

### Individuals Referred by Citizenship and Immigration Canada (CIC) for Medical Surveillance for TB

Individuals newly arrived in Canada may have been referred by CIC for either urgent or regular medical surveillance for TB as a condition of entry into Canada, or because of a previous history of TB or an abnormal chest radiograph suggestive of inactive TB.<sup>3-9</sup>

1. Urgent medical referrals are to be assessed within 7 days of arrival in Canada by a Canadian public health authority because of complex inactive pulmonary TB (PTI) and/or other complex, noninfectious TB.

2. Regular medical referrals are to report to or be contacted by a public health authority within 30 days of arrival in Canada.

The CIC Health Management Branch standard criteria for the stability of PTI are three negative TB 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. Chest radiographs are scored according to a hierarchical system in which the highest scores are given to abnormalities suggestive of prevalent active TB (see Table 1, adapted from Figure 4, Chapter 15, Immigration and Tuberculosis Control in Canada, in the *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition).

The criteria to determine an urgent medical referral are the following:

1. A medical condition placing the applicant at high risk of progression from latent TB infection to active disease with a chest radiograph graded 4.1 to 4.7. These conditions are
  - a) HIV/AIDS
  - b) transplantation with immunosuppressive therapy
  - c) end-stage renal disease (chronic renal failure/hemodialysis).
2. Any case of nonrespiratory TB (see Chapter 5, Nonrespiratory Tuberculosis, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition) under treatment.
3. Any other significant factors that can make the management of the contacts in Canada more difficult if latent TB infection progresses to active disease (such as suspected multidrug-resistant TB [MDR-TB] or extensively drug-resistant TB [XDR-TB] because of previous contact with MDR-TB or XDR-TB cases).
4. A chest radiograph graded as follows:
  - a) 4.5: non-calcified pleural fibrosis and/or effusion likely related to TB
  - b) 4.6: parenchymal lung disease likely related to TB
  - c) 4.6: acute pulmonary disease likely related to TB.
5. A chest radiograph graded 4.7 (any cavitating lesion or “fluffy” or “soft” lesions likely related to TB) or with extensive, significant anomalies that render the determination of radiological stability difficult and/or doubtful.
6. A known case of treated MDR-TB or XDR-TB.
7. Any individual who is understood to have received treatment for two or more independent episodes of TB in the past (respiratory or nonrespiratory).
8. Any individual with a past history of TB that received particularly unusual/unconventional treatment, as determined by a CIC Medical Officer after consultation with a Canadian TB specialist.

**Table 1**  
**Citizenship and Immigration Canada Chest**  
**Radiograph Report, IMM 5419 (08-1998) E**

3.4	Calcified pleural lesions
3.5	Costophrenic angle blunting (either side above the horizontal)
4.0	Notable apical pleural capping (rough or ragged inferior border and/or $\geq 1$ cm thick at any point)
4.1	Apical fibronodular/fibrocalcific lesions or apical microcalcifications
4.2	Multiple/single pulmonary nodules/micronodules (noncalcified or poorly defined)
4.3	Isolated hilar or mediastinal mass/lymphadenopathy (noncalcified)
4.4	Single/multiple pulmonary nodules/masses $\geq 1$ cm
4.5	Noncalcified pleural fibrosis and/or effusion
4.6	Parenchymal lung disease/acute pulmonary disease likely related to TB
4.7	Any cavitating lesion or “fluffy” or “soft” lesions felt likely to represent active TB

The criteria to determine a regular medical referral are the following:

1. A chest radiograph graded 3.5 and over unless there is formal evidence that the abnormality seen is not related to TB (e.g. lung tumour) or the individual has already been identified as requiring urgent referral.
2. Adequate and complete treatment for active respiratory TB diagnosed during the IME with stability of chest radiographs and negative sputum smears and cultures following treatment.
3. History of previous respiratory or nonrespiratory TB.

### **Compliance with a CIC Medical Surveillance Requirement for TB**

Compliance is defined as keeping the first appointment with the clinician or being assessed by a public health designated specialist. Compliance with the undertaking is important for the immigrant as future eligibility for Canadian citizenship depends in part on how well the conditions of entry were met.

### **Management of Other Newcomers to Canada Identified as Having Certain Medical Conditions**

Some newcomers are identified as having medical conditions that do not correspond to the criteria for medical surveillance as defined by CIC.

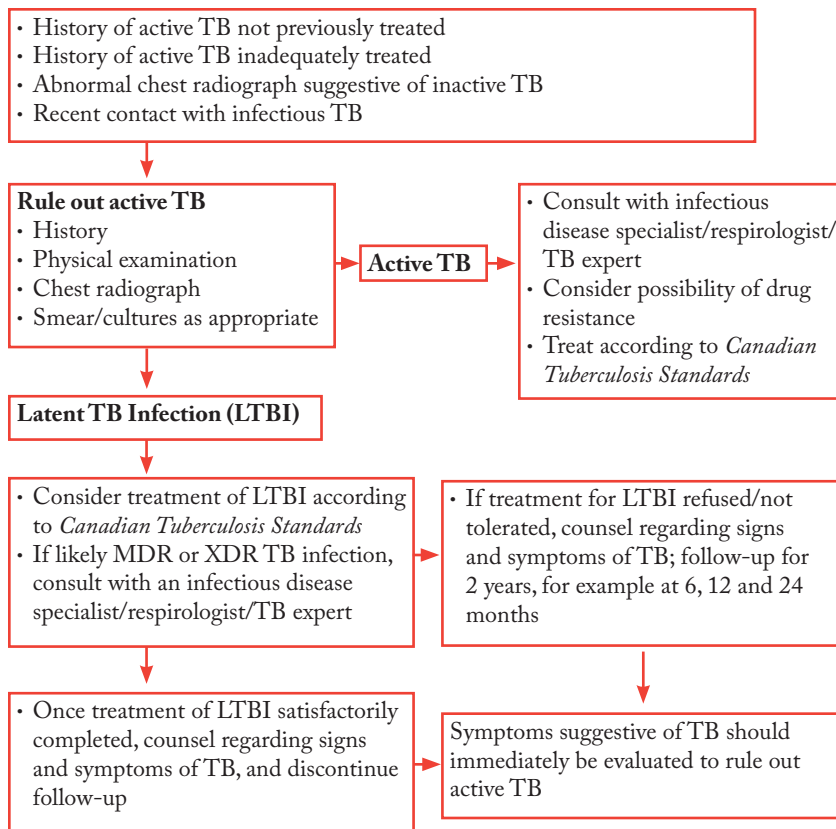
However, these medical conditions are considered to be risk factors for the development of active TB only in the context of a previous infection of *Mycobacterium tuberculosis* (see Table 2, adapted from Chapter 4, Diagnosis of Tuberculosis Infection and Disease, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition).

As part of their routine medical care, it is recommended that such newcomers undergo a medical evaluation for TB as outlined in these guidelines.

**Table 2**  
**Risk Factors for the Development of Active TB among Persons Infected with *Mycobacterium tuberculosis***

Risk Factor	Estimated Risk of TB Relative to Persons with No Known Risk Factor
<b>HIGH RISK</b>	
Acquired immunodeficiency syndrome (AIDS)	110-170
Human immunodeficiency virus (HIV) infection	50-110
Transplantation (related to immunosuppressant therapy)	20-74
Silicosis	30
Chronic renal failure requiring hemodialysis	10-25
Carcinoma of head and neck	16
Recent TB infection ( $\leq 2$ years)	15

**Figure 1**  
**Assessment of individuals for tuberculosis**



## Medical Assessment of CIC Referrals

All individuals referred for medical surveillance should undergo at least one complete medical evaluation by, or in consultation with, a physician experienced in the diagnosis and management of TB (see Figure 1). Documents and radiographs pertaining to the IME, accessible through CIC (see Chapter 15, Immigration and Tuberculosis Control in Canada, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition), may inform the evaluation and establish the reason for referral. The important components of this initial medical evaluation include the following:

1. A comprehensive history:
  - a. reason for medical surveillance referral;
  - b. demographic information (e.g. date of birth, sex, country of birth, country of last residence);
  - c. past history of TB and treatment of past TB disease or LTBI;
  - d. family history of TB and/or recent contact with respiratory TB;
  - e. personal medical history with a TB-specific symptom inquiry (e.g. cough, weight loss, fatigue, fever, night sweats, hemoptysis), record of comorbidity, including immunodeficiency states, currently prescribed medications, and history of BCG vaccination(s).
2. Targeted physical examination, guided by the history and available laboratory data.
3. Other investigations as considered relevant:
  - a. chest radiograph, other radiological studies as indicated by the history and physical examination results;
  - b. sputum for mycobacterial smear and culture (in asymptomatic patients with PTI an induced sputum is preferred<sup>10</sup>);
  - c. tuberculin skin test (TST) if no documented result;
  - d. interferon-gamma release assay: see Appendix D, Interferon-gamma Release Assays for Latent Tuberculosis Infections, Canadian Tuberculosis Committee Advisory Committee Statement, in the *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition.

### In the event of a diagnosis of active TB...

If a diagnosis of active TB is established, the public health department must be notified and treatment with an appropriate regimen of anti-TB drugs instituted (see Chapter 6, Treatment of Tuberculosis Disease and Infection, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition). The treatment regimen should take into account the possibility of drug-resistant TB, given that this condition is not uncommon in parts of the world from which many patients are emigrating

(see Chapter 7, Drug-resistant Tuberculosis, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition).

### **In the event of a diagnosis of latent TB infection or of healed TB not previously treated or inadequately treated ...**

Treatment is recommended as per Chapter 6, Treatment of Tuberculosis Disease and Infection, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition.

The elimination of TB in Canada will depend upon the identification of infected individuals and treatment of their LTBI to arrest the progression to active disease. Therefore, it is critical that those involved in the investigation and follow-up of individuals referred for medical surveillance for TB be committed to identifying and treating infected individuals who are at increased risk of active TB disease. This includes monitoring of their adherence to the prescribed treatment of LTBI. Adherence to prescribed treatment may be problematic for those under medical surveillance,<sup>11</sup> and nonadherence has been associated with the development of TB disease in refugees.<sup>12</sup> Cultural and community factors may influence patient adherence.<sup>13</sup> Strategies to improve adherence should be utilized as appropriate. Consultation with local public health authorities and/or TB clinics as well as the *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition, may provide direction.

Young persons (particularly those < 5 years of age) with LTBI who have been identified through investigation of their parent(s) or guardian(s) may be at increased risk of progression to active TB and are likely to tolerate treatment of LTBI without complication.

### **In the event of a need for further follow-up...**

1. If a diagnosis of inactive TB is made and the individual has had treatment, then follow-up should be individualized (see Chapter 6, Treatment of Tuberculosis Disease and Infection, and Chapter 7, Drug-resistant Tuberculosis, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition). Consultation with a TB expert is required if infection with MDR-TB or XDR-TB is known or suspected (see Chapter 7, Drug-resistant Tuberculosis, *Canadian Tuberculosis Standards*, 6<sup>th</sup> edition).
2. The duration of follow-up may typically last up to 2 years, for example at 6, 12 and 24 months. However, closer or longer follow-up may be judged prudent by the examining physician. Follow-up examinations should include, as a minimum, a symptom inquiry, chest radiograph and, if the patient is symptomatic, specimens for AFB (acid-fast bacteria) smear and culture. Follow-up may vary depending upon the risk of relapse or reactivation, especially with a drug-resistant strain of TB. It is not uncommon for persons who are under routine medical surveillance to present with symptoms of active TB disease outside of the scheduled review appointment.<sup>14</sup> Therefore, it is important to ensure that barriers to accessing medical care, should symptoms develop, are minimized.

3. The risk of TB disease in immigrants may persist for 10 years or more after arrival.<sup>15</sup> Persons who are discharged from follow-up should be advised to seek medical attention promptly if they experience symptoms that suggest disease activity and to advise their medical providers of their history of having been under immigration medical surveillance for TB.

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