## *An Advisory Committee Statement (ACS)*

**Committee to Advise on Tropical Medicine and Travel (CATMAT)***

# THE RISK AND PREVENTION OF TUBERCULOSIS IN TRAVELLERS

### Introduction

*The annual risk of **Mycobacterium tuberculosis** infection may be as much as 300-fold higher in some tropical and developing countries than in western Europe and North America[1,2]. Infection with **M. tuberculosis** and active tuberculous (TB) disease can be a consequence of travel, but there are very few data from which to accurately estimate this risk. Available information suggests that individuals travelling or living overseas may have an exposure risk similar to that of the local population, depending on their activities and contact with local people[3,4].*

## 1. DETERMINANTS OF A TRAVELLER'S RISK OF TUBERCULOSIS EXPOSURE

Risk of exposure is likely to be influenced by local TB rates. World Health Organization (WHO) estimates of TB case rates per 100,000 population in 1995 are as follows: Southeast Asia 241, western Pacific 140, Africa 242, eastern Mediterranean 168, Americas (except United States and Canada) 123, Eastern Europe 47, and Western industrialized countries and Japan 23[5]. By contrast, the incidence of TB in non-Aboriginal people born in Canada was 1.9 per 100,000 in 1992[6].

Risk of exposure is likely to be related to duration of stay or travel in high-prevalence areas. The nature and circumstances of contact with local people are likely to be important determinants of risk of exposure. Work in a health-care setting in a high-prevalence country may be associated with a particularly high risk of exposure to TB.

## 2. THE RISK OF DEVELOPING ACTIVE TUBERCULOSIS FOLLOWING *M. TUBERCULOSIS* INFECTION

After infection with *M. tuberculosis*, indicated by tuberculin skin test (TST) conversion, an immunocompetent individual is estimated to have a 5% to 15% lifetime risk of progression to active TB. The annual risk is highest in the first 1 to 2 years after infection[7]. A number of factors, including diabetes mellitus, prolonged corticosteroid therapy, chronic renal failure, and malignant lymphoma may increase this risk. Co-infection with HIV is associated with the greatest risk of developing active TB, approximately 7% to 10% per year[8,9].

* **Members:** Dr. K. Kain (Chairperson); H. Birk; Ms. M. Bodie-Collins (Secretariat); Dr. S.E. Boraston; Dr. W. Bowie; Dr. H.O. Davies; Dr. J.S. Keystone; Dr. D.W. MacPherson; Dr. A. McCarthy (Executive Secretary); Dr. J.R. Salzman; Dr. D. Tessier.

**Ex-Officio Members:** Dr. E. Callary (HC); LCdr. D. Carpenter (DND); R. Dewart (CDC); Dr. E. Gadd (HC); Dr. C.W.L. Jeanes; Dr. H. Lobel (CDC).

## 3. MEASURES FOR REDUCING THE RISK OF TUBERCULOSIS

### 3.1 *Skin Testing and Chemoprophylaxis*

One strategy for prevention of TB is regular tuberculin skin testing with consideration of chemoprophylaxis if infection occurs. Chemoprophylaxis with isoniazid can reduce the risk of active TB by up to 90% in positive individuals when the infecting organism is sensitive to isoniazid and when compliance is high[10,11]. There is a small risk of hepatotoxicity with isoniazid use which increases with age, alcohol use, or underlying liver disease[12].

Several factors may limit the effectiveness of this strategy. Compliance with skin testing or chemoprophylaxis, or both, is often very poor in the general population and among health workers[13-17]. The optimal frequency of skin testing is uncertain; some cases of infection may progress to active TB in the intervals between TSTs. Isoniazid prophylaxis is likely to be ineffective if the infecting strain of *M. tuberculosis* is resistant or if the individual cannot tolerate the drug; experience with alternative chemoprophylactic regimens is limited.

### 3.2 *Bacille Calmette-Guérin Vaccination*

Bacille Calmette-Guérin (BCG) is a live vaccine developed in 1921 by repeated passage of *M. bovis* in culture. Several billion human doses of this vaccine have been administered. Two BCG products are approved in Canada for intradermal/intracutaneous use[18]. One-half the adult dose is recommended for children < 1 or < 2 years of age, depending on which product is used. Manufacturers' instructions list extensive skin disease and conditions associated with depressed cell-mediated immunity as contraindications. They recommend against concurrent administration with other vaccines, and advise caution with use in pregnancy although adverse effects on the fetus have not been demonstrated.

#### 3.2.1 Efficacy of Bacille Calmette-Guérin Vaccine

The results of a large number of studies of BCG efficacy have varied widely, from no demonstrable protection to more than 80% efficacy. The interpretation of these results remains controversial. A reappraisal of BCG studies has suggested that those with better methodology and with narrower confidence intervals around the estimate of efficacy tend to show greater protection[19]. A meta-analysis of 16 clinical trials and 11 case-control studies found an overall efficacy of 50% to 51%[20], and demonstrated a positive association between distance from the equator and vaccine efficacy[21]. Many BCG studies have been limited to children. Evidence for BCG efficacy is better established in children[22], and BCG may afford greater protection against severe forms of TB such as miliary TB and meningitis[23]. Limited information suggests that BCG confers some protection against TB in health-care workers[24]. Several studies have shown protection against leprosy[25,26].

Several hypotheses have been proposed to explain the considerable variation in efficacy among BCG studies. The most widely accepted explanation is an effect of exposure to environmental mycobacteria, which appears to either reduce or mask the protection conferred by BCG. Such exposure is more likely to occur in warmer climates, consistent with the meta-analysis finding of lower efficacy in populations closer to the equator[20,21].

#### 3.2.2 Safety and Adverse Effects of Bacille Calmette-Guérin Vaccination

Serious adverse events such as mycobacterial dissemination or death are very rare[27]. Local ulceration with a resultant scar is very common and regional lymphadenopathy may also occur. The risk of dissemination appears to be higher in immunocompromised vaccine recipients.

#### 3.2.3 Effect of Bacille Calmette-Guérin Vaccination on the Tuberculin Skin Test Reaction

A potential problem in the use of BCG is the effect on subsequent use of tuberculin skin testing. Estimates of the frequency with which BCG vaccination results in a positive TST vary widely[28], and may be affected by vaccine strain, age at vaccination, or other factors. BCG in infancy rarely explains the presence of a strong TST reaction years later[29,30]. Current recommendations suggest that the diameter of induration, the time elapsed since BCG administration, and the likelihood of exposure to TB be considered when interpreting a TST in an individual with a history of BCG vaccination[31,32]. The tuberculin response following BCG vaccination does not correlate with protection[33,34].

### 3.3 *Choice of Strategy for an Individual Traveller*

The advantages and disadvantages of both TB prevention strategies must be considered on an individual basis. A decision analysis, comparing BCG with TST or chemoprophylaxis for house staff in a "high-prevalence" American hospital, favoured BCG under most assumptions[35].

### Recommendations

Table 1 presents evidence-based medicine categories[36] for the strength and quality of evidence for each of the recom- mendations that follow.

1. All travellers to high-prevalence countries, particularly those travelling or living overseas with children, should be informed of the risk of TB (**B III**).
2. Travellers with significant immune compromise, such as HIV, should be informed of the serious risk associated with TB exposure and of the important limitations of either a BCG vaccination or periodic skin testing with chemoprophylaxis in the event of conversion (**A III**).
3. Travellers should be advised to avoid consumption of unpasteurized milk since it may contain *M. bovis* or other pathogenic organisms (**A III**).
4. Medical assessment of domestic workers or other host-country nationals who are in close contact with the traveller or the traveller's family particularly if a chronic cough is present, may reduce the risk of TB exposure as well as potentially benefiting the local person involved (**C III**).
5. Canadians working in health-care settings in developing countries should follow current infection control recommendations to the greatest degree possible to minimize the risk of exposure to TB[37-39] (**B III**).

Table 1
Strength and quality of evidence – summary sheet

**Categories for strength of each recommendation**

| CATEGORY | DEFINITION |
|---|---|
| A | Good evidence to support a recommendation for use. |
| B | Moderate evidence to support a recommendation for use. |
| C | Poor evidence to support a recommendation for or against use. |
| D | Moderate evidence to support a recommendation against use. |
| E | Good evidence to support a recommendation against use. |

**Categories for quality of evidence on which recommendations are made**

| GRADE | DEFINITION |
|---|---|
| I | Evidence from at least one properly randomized, controlled trial. |
| II | Evidence from at lest one-well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. |
| III | Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees. |

6. Travellers going to high-prevalence countries for extended periods (e.g. 3 months; less, if risk is expected to be high) or working in a health-care setting in a developing country for any period of time should be offered a TST with five tuberculin units of purified protein derivative (including two-step testing where indicated) unless there is a past history of tuberculosis or a well-documented previous positive TST[40] (**B III**).
7. If the initial TST is found to be positive (≥ 10 mm induration in healthy immunocompetent travellers), current management guidelines should be followed[32] (**B III**).
8. If the TST is negative, the individual should be informed about practical means of avoiding TB exposure. Persons should be advised to choose either BCG vaccination or a TST at least every 2 years, but preferably annually, as well as 3 to 6 months after leaving the high-prevalence area (**B III**). If a TST becomes positive, the traveller should be assessed by someone with expertise in TB to consider the use of chemoprophylaxis and to determine the chemoprophylactic regimen (**A I**).
9. In making the choice between BCG vaccination or periodic skin testing with prophylaxis in the event of conversion, the following factors should be considered:
   - anticipated feasibility of, and compliance with, repeated skin testing and chemoprophylaxis
   - likelihood of isoniazid intolerance (age, liver disease, excess alcohol use)
   - likelihood that an infecting strain of *M. tuberculosis* may be isoniazid-resistant (depends on local rates of primary resistance)
   - individual preference
   - age – the role of BCG vaccination may be particularly important in children especially those < 1 year of age (**B III**).
10. Where possible, BCG should be administered at least 4 weeks before the anticipated exposure to tuberculosis (**B III**).
11. A "baseline" measurement of the tuberculin reaction 3 months after BCG vaccination may be considered to aid in the interpretation of any subsequent TSTs[31] (**C III**).
12. Regardless of the duration of travel or the preventive measures employed, TB must be considered in the differential diagnosis of illness in Canadians returning from high-prevalence countries as well as in immigrants from those countries (**A III**).

## References


1. Murray CJ, Styblo K, Rouillon A. *Tuberculosis in developing countries: burden, intervention and cost*. Bull Int Union Tuberc Lung Dis 1990;65:6-24.
2. Styblo K. *Overview and epidemiologic assessment of the current global tuberculosis situation with an emphasis on control in developing countries*. Rev Infect Dis 1989;11(Suppl 2):S339-S46.
3. McCarthy OR. *Asian immigrant tuberculosis – the effect of visiting Asia*. Br J Dis Chest 1984;78:248-53.
4. Hynes N, ed. *The 1994 annual volunteer health status report.* In: *The health of the volunteer: quarterly and annual review*. Washington, DC: U.S. Peace Corps, 1995. Appendix A.
5. CDC. *Global estimates of future tuberculosis morbidity and mortality*. MMWR 1993;42:961-64.
6. Wilkins K. *Tuberculosis incidence in Canada in 1992*. Health Rep 1994;6:301-09.
7. Styblo K. *Recent advances in epidemiological research in tuberculosis*. Adv Tuberc Res 1980;20:1-63.
8. Selwyn PA, Hartel D, Lewis VA et al. *A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection.* N Engl J Med 1989;320:545-50.
9. Braun MM, Badi N, Ryder RW et al. *A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire*. Am Rev Respir Dis 1991;143:501-04.
10. Ferebee SH. *Controlled chemoprophylaxis trials in tuberculosis: a general review*. Adv Tuberc Res 1970;17:28-106.

11. International Union Against Tuberculosis Committee on Prophylaxis. *Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial*. Bull Int Union Tuberc Lung Dis 1982;60:555-64.
12. Kopanoff DE, Snider DE, Caras GJ. *Isoniazid-related hepatitis*. Am Rev Respir Dis 1978;117:991-1001.
13. Chan JC, Tabak JI. *Risk of tuberculosis infection among house staff in an urban teaching hospital*. South Med J 1985;78:1061-64.
14. Barrett-Connor E. *The epidemiology of tuberculosis in physicians*. JAMA 1979;241:33-8.
15. Geiseler PJ, Nelson KE, Crispin RG. *Tuberculosis in physicians: compliance with preventive measures*. Am Rev Respir Dis 1987;135:3-9.
16. Wobeser W, To T, Hoeppner VH. *The outcome of chemoprophylaxis on tuberculosis prevention in the Canadian Plains Indian*. Clin Invest Med 1989;12:149-53.
17. Yuan L, Richardson E, Kendall PRW. *Evaluation of a tuberculosis screening program for high-risk students in Toronto schools*. Can Med Assoc J 1995;153:925-32.
18. National Advisory Committee on Immunization. *Canadian immunization guide*. 4th ed. Ottawa, ON: Health Canada, 1993:29-34. (Supply and Services Canada, Cat. No. H49-8/1993E).
19. Clemens JD, Jackie JH, Chuong JH et al. *The BCG controversy: a methodological and statistical reappraisal*. JAMA 1982;249:2362-69.
20. Colditz GA, Brewer TF, Berkey CS et al. *Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature*. JAMA 1994;271:698-702.
21. Wilson ME, Fineberg HV, Colditz GA. *Geographic latitude and the efficacy of Bacillus Calmette-Guérin vaccine*. Clin Infect Dis 1995;20:982-91.
22. Colditz GA, Berkey CS, Mosteller F et al. *The efficacy of Bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature*. Pediatrics 1995;96:29-35.
23. Rodriques LC, Diwan VK, Wheeler JG. *Protective effect of BCG against tuberculosis meningitis and miliary tuberculosis: a meta-analysis*. Int J Epidemiol 1993;22:1154-58.
24. Brewer TF, Colditz GA. *Bacille Calmette-Guérin vaccination for the prevention of tuberculosis in health-care workers*. Clin Infect Dis 1995;20:136-42.
25. Ponnighaus JM, Fine PEM, Sterne JAC et al. *Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi*. Lancet 1992;339:636-39.
26. Stanley SJ, Howland C, Stone MM et al. *BCG vaccination of children against leprosy in Uganda: final results*. J Hyg (Camb) 1981;87:223-48.
27. Lotte A, ten Dam HG, Henderson R. *Second IUATLD study on complications induced by intradermal BCG vaccination*. Bull Int Union Tuberc 1988;63:47-83.
28. Snider DE. *Bacille Calmette-Guérin vaccinations and tuberculin skin tests*. JAMA 1985;253:3438-39.
29. Menzies R, Vissandjee B. *Effect of Bacille Calmette-Guérin vaccination on tuberculin reactivity*. Am Rev Respir Dis 1992;145:621-25.
30. Young TK, Mirdad S. *Determinants of tuberculin sensitivity in a child population covered by mass BCG vaccination*. Tuberc Lung Dis 1992;73:94-100.
31. CDC. *The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by the Advisory Committee for the Elimination of Tuberculosis (ACET)*. MMWR 1996;45:(RR-4):1-18.
32. Canadian Thoracic Society, Tuberculosis Committee. *Essentials of tuberculosis control for the practising physician*. Can Med Assoc J 1994;150:1561-71.
33. Hart PD, Sutherland I, Thomas J. *The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in tuberculin sensitivity and to technical variations in the vaccines*. Tubercle 1967;48:201-10.
34. Comstock GW. *Identification of an effective vaccine against tuberculosis*. Am Rev Respir Dis 1988;138:479-80.
35. Greenberg PD, Lax KG, Schechter CB. *Tuberculosis in house staff: a decision analysis comparing the tuberculin screening strategy with the BCG vaccination*. Am Rev Respir Dis 1991;143:490-95.
36. MacPherson DW. *Evidence-based medicine*. CCDR 1994;20:145-47.
37. International Union Against Tuberculosis and Lung Disease and World Health Organization. *Control of tuberculosis transmission in health-care settings*. Tuberc Lung Dis 1994; 75:94-5.
38. CDC. *Guidelines for preventing the transmission of* ***Mycobacterium tuberculosis*** *in health-care facilities, 1994*. MMWR 1994;43 (RR-13):1-131.
39. LCDC. *Guidelines for preventing the transmission of tuberculosis in Canadian health-care facilities and other institutional settings*. CCDR 1996;22S1:1-50.
40. Committee to Advise on Tropical Medicine and Travel. *Tuberculosis screening and the international traveller*. CCDR 1996;22:149-55.