

Screening and treatment of immigrants and refugees to Canada for tuberculosis: Implications of the experience of Canada and other industrialized countries

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OBJECTIVE: To assess the incidence of tuberculosis in immigrants and refugees in Canada and other industrialized countries; the effectiveness of the screening process; the incidence of drug resistance; recommendations for prophylaxis and therapy; and indications for and effectiveness of directly observed therapy.

DATA SOURCES: MEDLINE search of literature published from 1985 to 1995 with the key words 'tuberculosis', 'Canada', 'screening', 'drug resistance', 'drug resistance, multiple', 'immigration and emigration', and the title words 'directly observed therapy'.

STUDY SELECTION: All studies reporting data on incidence, the outcomes of screening, drug resistance, therapy and directly observed therapy were selected.

DATA SYNTHESIS AND CONCLUSIONS: Data synthesis led to the conclusions that immigrants and refugees to Canada have five times the nonimmigrant and non-Aboriginal rate of tuberculosis; that screening programs discover new cases of tuberculosis on and after arrival and that up to 20% of those scheduled to attend a tuberculosis clinic after arrival may never attend; that drug resistance is widespread in countries from which Canada receives immigrants; and that directly observed therapy for active cases can result in 100% conversion rates.

Key Words: *Directly observed therapy, Drug resistance, Immigration, Screening, Tuberculosis*

Dépistage et traitement de la tuberculose chez les immigrants et réfugiés qui arrivent au Canada : expérience du Canada et d'autres pays industrialisés

OBJECTIF : Évaluer les répercussions de la tuberculose chez les immigrants et les réfugiés qui arrivent au Canada et dans d'autres pays industrialisés. L'efficacité du processus de dépistage, l'incidence de la résistance aux médicaments, les recommandations quant à la prophylaxie et au traitement et les indications, ainsi que l'efficacité d'un traitement observé directement sont présentés ici.

SOURCES DES DONNÉES : Interrogation du réseau MEDLINE sur les articles publiés de 1985 à 1995, avec pour mots clés

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«tuberculose», «Canada», «dépistage», «résistance médicamenteuse», «résistance médicamenteuse multiple», «immigration et émigration», et les mots titres «traitement directement observé».

SÉLECTION DES ÉTUDES : Toutes les études faisant état de données sur l'incidence, les résultats de dépistage, la résistance médicamenteuse, le traitement et le traitement directement observé ont été retenues.

SYNTHÈSE DES DONNÉES ET CONCLUSION : La synthèse des données mène à la conclusion que les immigrants et les réfugiés qui arrivent au Canada souffrent cinq fois plus de tuberculose que les non-immigrants et les non-aborigènes; que les programmes de dépistage découvrent de nouveaux cas de tuberculose à l'arrivée et après, que jusqu'à 20 % des sujets attendus dans les cliniques de tuberculose après leur arrivée ne s'y présentent pas, que la résistance médicamenteuse est répandue dans les pays d'où arrivent les immigrants pour le Canada et que le traitement directement observé de cas actifs peut générer des taux de conversion de l'ordre de 100 %.

THE PURPOSES OF THIS PAPER ARE TO ASSESS, FIRST, THE INCIDENCE of exposure to tuberculosis and the presence of active tuberculosis in immigrants and refugees in Canada and, second, in other industrialized countries; third, the effectiveness of the screening process for tuberculosis in immigrants and refugees in Canada; fourth, the incidence of drug resistance in immigrants; fifth, recommendations for prophylaxis and therapy and the complications of therapy; and finally, indications for and effectiveness of directly observed therapy (DOT).

A MEDLINE literature search for 1985 to 1995 was conducted using 'tuberculosis' and the medical subject headings 'Canada' (54 titles); 'immigration and emigration' (162 titles); 'drug resistance' and 'drug resistance, multiple' (66 titles); and the title words 'directly observed therapy' (10 titles).

TUBERCULOSIS IN IMMIGRANTS AND REFUGEES IN CANADA

Forty-two per cent of tuberculosis patients in Canada from 1985 to 1987 were born outside Canada (1). Immigrants have rates of tuberculosis five times higher than those of Canadians who are neither immigrants nor Aboriginal. From 1970 to 1990, rates fell in immigrants of European origin but rose in those of Asian origin (2). In a study of 7028 immigrants in Montreal, 15% of those from countries with low rates of tuberculosis, 26% of those from intermediate countries, and 35% of those from countries with high rates were Mantoux-positive (defined as greater than 15 mm if they had been vaccinated with Bacille Calmette-Guérin, greater than 10 mm if not) (3).

Groups with significant tuberculosis rates other than immigrants are the aged (29% of cases are in those over 65 years of age), Aboriginals (17.5% of cases) and the urban indigent. Fifty per cent of pediatric tuberculosis cases in Canada are Aboriginal children (4).

There has been a steady decline in rates in the Inuit (from 580/100,000 population in 1970-72, to 80/100,000 in 1983-89) and Status Indian populations (from 150/100,000 in 1970-72, to 80/100,000 in 1983-89) (1). Census divisions with rates over 20/100,000 are all in northern Canada (80% of which are in the Aboriginal population), and those with rates of 10 to 19/100,000 are either in northern regions or in major metropolitan areas (with a disproportionate number of cases among the immigrant and Aboriginal populations).

In Canada, compared with the United States, there are relatively few patients who both have tuberculosis and are human immunodeficiency virus (HIV) positive. In British Colum-

bia it is estimated that since the HIV epidemic began fewer than 2% of the active cases of tuberculosis have HIV-positive status (5). However, the relative risk of tuberculosis in a person who is HIV-positive is 400 times greater than the risk in the general Canadian population, and thus HIV status constitutes the most important risk factor for tuberculosis (6).

TUBERCULOSIS IN IMMIGRANTS AND REFUGEES IN OTHER INDUSTRIALIZED COUNTRIES

In Canada, the United States, Australasia, Europe and Israel, immigrants have a considerable burden of latent tuberculosis with few clinical signs. The highest rates of clinical tuberculosis occur in immigrants from countries with high prevalence rates and in the first five years after immigration. However, higher rates persist even 20 to 40 years later in immigrants from countries with high prevalence rates (7,8).

Australia has an immigrant population of similar origin to that of Canada. In a study of 2290 inner city schoolchildren in Sydney, 27.5% of the foreign-born had a positive Mantoux compared with 2% of Australian-born children (9). If the overseas-born arrived in Australia after they were 10 years of age, they were twice as likely to have a positive tuberculin test than if they were younger than 10 years on arrival. Immigrants to Australia born in Vietnam, Cambodia and the Philippines had tuberculosis rates between 100 and 400/100,000 compared with 1.5/100,000 for those born in Australia (10). The incidence of tuberculosis in those with AIDS was 1579/100,000.

In New Zealand, tuberculosis rates were 10 times higher in Pacific Islanders, 15 times higher in other immigrant groups and five times higher in Maoris than in those of European origin (11). The age of the immigrants was a key risk factor: compared with those aged 0 to 14 years, the rates in those 15 to 24 years were four times higher; in those 25 to 44 years six times higher; in those 45 to 64 years 12 times higher; and in those over 65 years 16 times higher.

In Europe, tuberculosis notifications steadily declined until 1985, but since then have increased especially in drug-users, in HIV-positive patients and in recent immigrants from sub-Saharan Africa. In the Vaud canton of Switzerland 256 cases of tuberculosis were found by mass miniature x-ray testing among 50,784 immigrants: 1.4% of those from Africa, 1% from Turkey, 0.62% from the Middle East and 0.55% from Yugoslavia were diagnosed as needing prophylaxis (12). In a Belgian pediatric home care centre 80% of the tuberculosis re-

TABLE 1
Problems in screening for exposure to tuberculosis and case-finding in active tuberculosis

Screening for exposure to tuberculosis

Problem: Whom to screen

Solution: Pay meticulous attention in history-taking to risk factors (country of origin, exposed family member, alcoholism, HIV status, prior tuberculosis therapy), have a high suspicion for individuals with risk factors, take a careful history of past antituberculous medication, obtain a tuberculin test (and the two-step in nonreactors) and a chest x-ray in any individual with any risk factors

Case-finding of active tuberculosis

Problem: Where to direct case-finding activities

Solution: Have a high suspicion for any individual with any risk factor or symptom, remembering that:

- Infection at any period of life confers a 10% lifetime risk of tuberculosis
- Although 85% present as pulmonary tuberculosis, immigrants are more likely to present with nonpulmonary sites
- Although most infants and children present with classic respiratory symptoms, fever and weight loss, most cases in immigrants are found by contact tracing
- Although 80% present with the symptoms of an active infection (cough, fever, malaise), 20% are asymptomatic
- The tuberculin test may be falsely negative in 20%, especially in infants a few months of age, the elderly, those with advanced pulmonary disease, tuberculous serositis, those who are HIV-positive and other immunosuppressed patients
- The chest x-ray may be normal in 4%, and 20% are atypical (especially in the HIV-positive)
- The sputum culture may be negative in 15%

HIV Human immunodeficiency virus. Adapted from reference 6

ferrals were immigrants; 48% of the children who were symptomatic had an identifiable adult source (13). Tuberculosis rates among immigrants to the United Kingdom in 1988 were 135/100,000 in Indians and 101/100,000 in Pakistanis and Bangladeshis compared with 4.7/100,000 in the population born in the United Kingdom (14). Hindu females who migrate to the United Kingdom have rates of tuberculosis 5.5 times higher than Muslim females, and Hindu males 3.7 higher than Muslim males. One hypothesis to explain this is that the Hindu vegetarian diet reduces immunity (15). Particular concentrations of HIV-positive patients with tuberculosis have been noted: 12% of tuberculosis patients in Paris and 18% in a neighbouring Département were HIV-positive; 10% of AIDS patients in Frankfurt and Italy and 37% in Spain had tuberculosis (16). During the 1980s HIV emerged as the most effective promoter of tuberculosis, with rates of reactivation of 8% per year (17).

In the United States, tuberculosis is 13 times more prevalent among the immigrant population than among the native-born (18). In a study of illegal Mexican immigrants in Denver, 42% had Mantoux tests greater than 10 mm, and 17% of the chest x-rays obtained showed old or current tuberculous infection (19). Immigrants to Seattle from Kampuchea and Laos had a 10-fold greater risk of having a positive sputum culture than other immigrants (20). Fifty-eight per cent of foreign-born students registering at the University of California at Los Angeles in 1988 had positive Mantoux reactions (21). The United States is a major reservoir of 10 to 15 million people with tuberculosis (22), with high concentrations among very disadvantaged groups: 50% of the homeless (23) and 18% of those living in shelters (24). These patients are a large high-risk group, but few can migrate to Canada from the United States, and immigrants from other parts of the world will therefore have a greater impact on Canada's tuberculosis rates.

Two per cent of Ethiopian immigrants to Israel had active tuberculosis (25).

Immigrants tend to have high rates of extrapulmonary disease (26). In one study in the United Kingdom 30% of Asian dialysis patients presented with extrapulmonary tuberculosis, although they had lived in the United Kingdom, on average, for 15 years without any clinical signs of tuberculosis. Asian dialysis patients now routinely receive tuberculosis prophylaxis (27).

THE EFFECTIVENESS OF THE SCREENING PROCESS FOR IMMIGRANTS AND REFUGEES

The World Health Organization (WHO) estimates that 1.7 billion persons worldwide are or have been infected with tuberculosis, with each year 8 million new cases of active tuberculosis and 2.9 million deaths (28), and 100 million with drug-resistant strains (29). There are 3.1 million people who have tuberculosis and are HIV-positive (30). Tuberculosis control in Third World countries receives only two cents of every 10 dollars spent on health (29).

Screening for exposure to tuberculosis and the finding of active cases in both immigrants and refugees and the rest of the population depend on both an excellently organized national program, and the persistent application of history-taking and clinical skills of individual physicians. The key element in detection is an appropriate level of suspicion that the patient could be asymptotically infected (Table 1).

The screening requirements of the Canadian immigration authorities include a full history, physical examination and laboratory investigations (Table 2). The Canadian Thoracic Society, the Canadian Lung Association, the Tuberculosis Directors of Canada and Health Canada suggest in addition a tuberculin test and cultures (Table 2).

Detailed evidence on how this surveillance and treatment system works is available for Manitoba, British Columbia and

TABLE 2
Screening of immigrants to Canada for tuberculosis

Section 11 of the Immigration Act* requires that every immigrant shall receive:

- a complete history and physical examination
- a urinalysis
- a VDRL (for those 15 years and over)
- a 36x43 cm chest x-ray (for those over 11 years). If the chest x-ray is abnormal, the person will be declared inactive only
 - if tuberculosis has been adequately treated
- or • there are two stable chest x-rays three months apart plus three negative sputum cultures taken more than 24 h apart (or one bronchial washing or one gastric lavage or one laryngeal swab)
- or • two stable chest x-rays more than six months apart

The Regulations approved by the Canadian Thoracic Society, the Canadian Lung Association, the Tuberculosis Directors of Canada and Health Canada†

Newly arrived individuals with a previous history of tuberculosis or an abnormal chest x-ray suspicious of inactive tuberculosis‡ should give:

- a complete history and physical examination
- a chest x-ray
- three sputum (or gastric lavage) specimens for smear and culture for *Mycobacterium tuberculosis*
- a tuberculin test

*Reference 84; †Reference 85; ‡In 1992 12,000 immigrants had such an x-ray. VDRL Venereal Disease Research Laboratory test

Quebec. Between 1982 and 1985, 21,959 immigrants entered British Columbia from Asia (31). Before they emigrated, 1173 (5.3%) had been judged to have inactive tuberculosis; on arrival in Canada 14 (1.5% of the 932 who were examined) were found to have active tuberculosis, and a further seven developed active tuberculosis over the next four years (0.33% per year, eight times the British Columbia rate). Ninety-four of the group examined in their country of origin and thought to have inactive tuberculosis either did not emigrate or landed in a province other than British Columbia, and 147 who landed did not comply with the mandatory screening program after arrival.

During 1979 to 1982, 8692 Indochinese refugees emigrated to British Columbia, and the immigration service was aware of 21 cases of active tuberculosis before the immigrants entered Canada (32). Seventy-five more cases were discovered after entry: 28 in the first three months, four in the next three months, 16 in months seven to 12, and 16 in months 12 to 24 of residence.

Of the immigrants admitted to Manitoba between 1981 and 1985, 523 (2.4%) were placed under surveillance for tuberculosis, and their subsequent incidence of tuberculosis was 4.5 times higher than in those not placed under surveillance (33). Of the 429 who were seen at least once in the tuberculosis clinic, eight had had a positive culture in their country of origin, a further nine had a negative culture in their homeland but a positive culture in Canada, and one was not tested at home but was positive in Canada, for a total of 19 cases (5%). Of the 483 immigrants scheduled to be seen in Winnipeg, 94 never attended, and 138 missed some clinic visits.

The experience of Manitoba and British Columbia shows that screening programs need to be able to locate and encourage cooperation in those who do not comply with screening after arrival, and to follow refugees for at least five years.

The detection of tuberculosis in immigrant children is es-

pecially important, because their rates are higher than those in the native-born, they are likely to be asymptomatic, and the high initial mobility of immigrant children results in a large number of potential contacts with the attendant costs of following up entire schools. Childhood exposure to an active case gives a lifetime risk of tuberculosis reactivation of 5 to 10% (34). In a study of two schools in Montreal, 9.4% of foreign-born children, but only 0.4% of Canadian-born children, had a positive Mantoux test (35). In British Columbia during 1979 to 1988 there were 233 cases of tuberculosis in children up to the age of 15 (36). Only 40% of the 197 cases of primary pulmonary tuberculosis presented with symptoms (mainly cough and fever) and only 48 were diagnosed because they presented with symptoms. The remaining 154 were diagnosed as a result of tracing (mostly adult) contacts. Bacteriological studies were obtained in 83%, and were positive in 22%. Chest x-rays were available for 94%, and lymphadenopathy was seen in 94% of these x-rays. The slowness of response to therapy and the diligence required in follow-up are demonstrated by the 125 patients with follow-up films: lymphadenopathy and consolidation worsened in 33% despite three months of therapy. After six months of therapy only two had clear chest x-rays, most cleared by two years, but 7% still had abnormal chest x-rays three years later.

The majority of immigrants settle in the 10 major cities, and health care workers in these cities need to be sensitized to the numbers expected to be infected with tuberculosis and the need for screening.

Within the first year each case of active tuberculosis is estimated to transmit tuberculosis to 2 to 4% of their household contacts (37), but 37% of HIV-positive patients will develop tuberculosis within five months of exposure in their household (38-40). Each case of untreated active tuberculosis over a lifetime is estimated to infect between seven and 77 other individuals.

The costs of screening 7573 illegal immigrants to Denver for tuberculosis were estimated at us\$209,000 (50% for personnel costs and 41% for x-rays), yielding a cost for each patient who completed isoniazid therapy of \$285 (19).

When sputum samples (which cost \$50 to 75) were also collected in a study of 249 immigrants in Seattle with findings on two chest x-rays consistent with pulmonary tuberculosis, only 5% of sputum cultures were found to be positive, and the cost per sputum-confirmed case of tuberculosis was us\$1,996 to 2,994 (20).

The costs of tracing the contacts of school children can be very high, partly because many students may be exposed to immigrants who tend to be mobile on first arrival in a new country. After a 10-year-old immigrant to Scarborough, Ontario, was noted to have active pulmonary tuberculosis, nine other family members were found to have markedly positive Mantoux reactions and chest x-ray changes compatible with tuberculosis, and were treated as having active tuberculosis. In the two schools involved, 722 children were screened with Mantoux tests: on first testing 7.1% (designated as 5 mm or greater if the child is in a class with an index case, or 10 mm or greater if not in such a class) and an additional 4.4% on second testing two to three months later had a positive Mantoux (35).

DRUG RESISTANCE IN IMMIGRANTS AND REFUGEES

Drug resistance can be systematically reduced if five requirements of appropriate therapy are achieved: prescribing an adequate regimen for the initial episode; testing for drug sensitivities; ensuring patient compliance; recognizing treatment failure (due mainly to resistance to isoniazid); and prescribing to overcome treatment failure (41).

Although HIV-positive patients are 20 times more likely to have other HIV-positive persons in their households, and HIV-positive patients have an 8% annual acquisition of tuberculosis, there does not yet appear to be an excess of drug resistance in such patients studied in Haiti, Zaire or the United States (42).

Short-course therapies of six months have become an important form of treatment. It is therefore of major concern that these therapies can have high rates of failure if offered to patients infected with *Mycobacterium tuberculosis* resistant to isoniazid and to rifampin (43). For example, only half of the patients in Denver with pulmonary tuberculosis resistant to both isoniazid and rifampin eventually had negative sputum cultures, even after prolonged individually tailored DOT with multidrug regimens, and 46% of those with treatment failure or relapse died (44).

In Manitoba from 1980 to 1989, 1478 cases of active tuberculosis were diagnosed, specimens were cultured for 1392, and 78% of these were positive (45). Seven per cent of these culture-positive cases were drug resistant. For immigrants in whom tuberculosis developed in their first year in Canada, the odds ratio of being resistant was 9.9 compared with other Canadians with tuberculosis. Ninety-one per cent of the drug resistance was to first line drugs (isoniazid and streptomycin).

Treaty Indians in Manitoba, however, had the same risk of resistance as the other patients born in Canada. In Manitoba 15% of culture-positive immigrants were resistant to one or more drugs compared with 4% of other patients (45).

In New York City during April 1991, 41% of patients with positive tuberculosis cultures were HIV-positive, and prior anti-tuberculosis therapy was the strongest factor predicting drug resistance to one or more drugs (odds ratio 2.7) or to isoniazid plus rifampin (odds ratio 5.3) (46). In patients who had not previously been treated, from 1955 to 1991 resistance to isoniazid increased from 3% to 15% and to streptomycin from 1% to 9%; from 1978 to 1991 resistance to rifampin increased from 1% to 9% (46). By 1991, 25% of the patients could transmit isoniazid-resistant organisms, and 20% could transmit organisms resistant to both isoniazid and rifampin. In a survey during 1991-92 of patients reported to the New York City Department of Health as having tuberculosis, 14% of both immigrant and American-born patients were reported as showing combined resistance to isoniazid and rifampin (47). In Santa Clara, California, 41% of immigrants were resistant to one or more drugs (48).

In Israel 37% of immigrants from Russia, 16% from Ethiopia and 12% of other patients were resistant to at least one drug (49).

There is considerable resistance to antituberculous drugs in countries from which Canada draws immigrants (Table 3). Among untreated patients there was resistance to at least one drug in 12% in Malawi (50), 15% in Korea (51), 17% in a sample of 10 Latin American countries (52), 20% in both Gujarat, India (53) and Haiti (54), 27% in Ghana (55) and 35% in Turkey (56). Among treated patients 32% were resistant to at least one drug in Lahore, Pakistan (57), 41% in Haiti (54) and 47% in Korea (51), and 56% were resistant to isoniazid in Gujarat (53). In a small study of gene mutations in *M tuberculosis* at the Pitié-Salpêtrière Hospital in Paris, of the 11 untreated non-European immigrants 55% were resistant to rifampin, 64% to streptomycin and 100% to isoniazid, all by known gene mutations (58), but at Mount Sinai Hospital in New York City immigrants from the Third World were less likely to be multiple-drug resistant than other patients (59). In Rio de Janeiro 8% of the contacts of multiple-drug resistant patients contracted tuberculosis within a two-year period, with 50% acquiring tuberculosis with the same multiple resistance pattern, 10% a different multiple-drug resistant pattern, and 40% with susceptible organisms, showing that tuberculosis can be acquired from multiple sources, even in those living with an index case (60).

Particularly troubling is the finding that resistance in some developing countries is higher among young people (who are more likely to migrate). In Korea initial drug resistance was found in 32% of patients with tuberculosis under 30 years of age and 14% in those over 59 (51). Similarly in the United States, 22% of children under 15 and 9% of patients over 65 with tuberculosis were resistant (61).

From the 1960s to the 1980s rates of resistance worldwide were highest in those Asian countries with intermediate development levels sufficient to permit medications to be readily

TABLE 3
Percentage resistance to antituberculous drugs in selected countries of emigration to Canada

Location	No prior therapy										Prior therapy										
	Number of drugs					Specific drugs					Number of drugs					Specific drugs					
	≥1	1	2	3	4	TO	INH	RI	ST	ET	≥1	1	2	3	4	TO	INH	RI	ST	ET	
Pakistan											32	19	9	4	0		15	5	18	9	
India	20	14	5	1			14	0	7	4							56	37	27		
Ghana							27	0	23	0											
Malawi	12						5	4	1	4	0										
Kenya							5	4		0.5											
Haiti	20							19	1	5	2	41									
Latin America	17	12	3	1			17	7	1	12	0.4										
Korea	15			5				13		7	2	47		13			42	15	19	11	
	% Initially resistant to										% Acquired resistance to										
Turkey	35	16	8	1	1	27	5	11	21	4	53	19	19	10	6	53	30	36			

ET Ethambutol; INH Isoniazid; RI Rifampin; ST Streptomycin; TO Total. Pakistan (reference 57; 256 culture + patients, Mayo Hospital and Lahore General Hospital, Lahore); India (reference 53; 570 samples from KJ Mehta Tuberculosis Hospital, Armagadh, 1983-86); Ghana (reference 55; 99 patients, Agogo Hospital, 1985-87); Malawi (reference 50; 373 patients, Karonga Lepa Evaluation Project, 1986-93); Kenya (reference 86; 374 adults presenting with first case of suspected tuberculosis to Infectious Diseases Hospital or Ngaira Avenue Chest Clinic, Nairobi. Resistance in HIV-positive cases was 7.5% for INH, 1% for ST); Haiti (reference 54; 268 patients, Hôpital Albert Schweitzer, Deschapelles, 1988); Latin America (reference 52; 30 clusters each of 35 smear-positive patients detected in tuberculosis control programs during "the second half of the 1980s to the early 1990s" in Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Haiti, Mexico, Paraguay and Peru); Korea (reference 51; 127 new and 62 previously treated cases in the 1990 nationwide tuberculosis prevalence survey); Turkey (reference 56; 785 patients, Sureyyapasa Center, Istanbul, 1992)

available but without health care systems well financed enough to ensure regularly supervised administration (62). However, a poor country such as Tanzania, through an excellent national program, has maintained initial rifampin resistance below 1% for the past 15 years, despite the HIV epidemic; Korea and Algeria also have well-run national control programs (61).

RECOMMENDATIONS FOR PROPHYLAXIS AND THERAPY, AND COMPLICATIONS OF THERAPY

The effectiveness of isoniazid prophylaxis has been confirmed by randomized controlled trials, with maximum benefit occurring after 12 months, although compliance is better with six months' prophylaxis (6). Patients with only an abnormal tuberculin test should be given prophylaxis for six months, those with a stable abnormal radiograph consistent with previous tuberculosis for 12 months, and those with HIV for 24 months (63). Nine months' prophylaxis is recommended for children (64).

After reviewing the world literature on drug resistance from the 1960s onwards, Iseman and Sbarbaro (62) concluded that, for a patient without apparent risk factors for resistance, a three-drug regimen of isoniazid, rifampin and ethambutol is indicated, and for patients from an area with a high prevalence of resistance, a four-drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol is indicated. For patients with a history of prior chemotherapy or who are epidemiologically at risk for resistance, a five-drug regimen including three drugs to which the patient had not previously been exposed should be used.

The Centers for Disease Control and Prevention in Atlanta, Georgia (65), based on experience with drug resistance in the United States (Tables 4,5), recommends a four-drug regimen (isoniazid, rifampin, pyrazinamide, and streptomycin

or ethambutol) for the first two months, until drug susceptibilities are known. This would ensure that 95% of patients would be treated with a regimen that includes two drugs to which they are sensitive. Sputum conversion is also accomplished faster than with a three-drug regimen. A patient who defaults on the four-drug regimen is also more likely to be cured and not relapse when treated for the same duration as a patient receiving three-drug therapy.

Careful discussion of potential side effects and the benefits of therapy is essential to avoid discontinuance of therapy.

THE EFFECTIVENESS OF AND INDICATIONS FOR DOT

Studies using DOT with a patient-centred approach, training of the health team to be sensitive to patients' needs, social service assistance and thorough case management of therapy have been shown to be 100% effective in treating tuberculosis, and all other methods are ineffective compared with this gold standard (66).

A study in California that did not use DOT did use several patient-centred approaches: the educators spoke Korean and Spanish; the taking of medications was linked with other activities; and ways to remember medications and future appointments and test results were recorded in a booklet (67). At each visit questions were answered, misunderstandings were explained, and tailored education messages based on the initial interview and subsequent assessments, educational reinforcement about tuberculosis, enlistment of support from family and friends, and contracting were used. Among patients with active tuberculosis adherence to the medication regimen improved from 57% with usual care to 71%, and for patients receiving prophylactic treatment adherence improved from 14% with usual care to 42%, but these results are not as good as in studies that used DOT.

TABLE 4
Initial treatment regimen options for children and adults

Option 1	Isoniazid, rifampin, pyrazinamide, ethambutol or streptomycin daily for eight weeks. Stop ethambutol or streptomycin when sensitivity to isoniazid and rifampin is demonstrated Then isoniazid plus rifampin daily (or two to three per week by DOT) for 16 weeks in areas where isoniazid resistance not documented $\leq 4\%$ Total treatment duration should be six months AND three months beyond culture conversion to negative*
Option 2	DOT of isoniazid, rifampin, pyrazinamide, ethambutol or streptomycin daily for two weeks, then twice a week for six weeks Then isoniazid plus rifampin twice a week for 16 weeks by DOT
Option 3	DOT of isoniazid, rifampin, pyrazinamide, ethambutol or streptomycin for six months [†]

HIV-positive status: Options 1, 2 or 3 can be used, but should be continued for nine months AND at least six months beyond culture conversion to negative

Pregnancy: Neither streptomycin (may cause congenital deafness) nor pyrazinamide (absence of teratogenicity has not been demonstrated) should be used. The regimen is for nine months, and until drug susceptibilities are known, the preferred initial regimen is isoniazid, rifampin and ethambutol

Lactation: Isoniazid, rifampin and ethambutol are safe because the concentrations passed into breast milk are very low. Conversely, breast feeding while taking these drugs confers no protection on the baby

If the patient is clinically, smear- or culture-positive after three months: a tuberculosis medical expert should be consulted

*DOT Directly observed therapy; HIV Human immunodeficiency virus. *The American Academy of Pediatrics (reference 64) recommends option 1, and in the case of bone, joint, miliary or meningitic tuberculosis, 10 months of isoniazid and rifampin; †The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full six months. There is weaker evidence that streptomycin can be discontinued after four months if the isolate is susceptible to all drugs. The evidence for stopping pyrazinamide before the end of six months is equivocal for the thrice/week regimen, and there is no evidence of the effectiveness of this regimen with ethambutol for less than the full six months. Data from reference 65*

The Korean National Tuberculosis Program in 1989 without using DOT achieved 96% efficacy (conversion in those completing isoniazid/rifampin/ethambutol) and 80% efficiency (conversion in those starting isoniazid/ rifampin/ethambutol) through excellent organization, careful monitoring of resistance and shorter treatment regimens (51).

A study of illegal aliens in Denver who had been screened for tuberculosis linked adherence to medications with subsequent acquisition of legal immigrant status, and obtained 70% adherence to therapy (19).

Studies that used small financial incentives (68) or telephone reminders with personal contact after a failed appointment showed minimal effects (69).

The effects of introducing DOT were assessed in a retrospective review of all patients with positive *M tuberculosis* cultures in Tarrant County Health Department, Texas (70). A period of six years of unsupervised therapy was followed by a period of six years of DOT with isoniazid, rifampin and pyrazinamide (plus ethambutol or streptomycin or capreomycin until isolates were confirmed to be fully sensitive to the first three drugs). There was a dramatic reduction in primary resistance from 13.0% to 0%, in acquired resistance from 10.3% to 0%, in multidrug resistance from 6.1% to 0% and in relapse from 20.9% to 0%. During DOT, medications were administered under observation Monday through Friday for the first two to four weeks of therapy, and then twice weekly for the next six months. About 30% of the patients in both treatment periods had a history of alcohol abuse.

In Denver in another population with a high (57%) incidence of alcohol abuse, DOT was given with isoniazid, rifampin, pyrazinamide and streptomycin given daily for two weeks, then in high doses twice weekly for another six weeks followed by isoniazid and rifampin twice weekly for another 18

weeks (71). Thirteen of the 160 patients were lost to follow-up (mostly because they moved out of Denver) and four died. In the remainder there were no treatment failures and only two relapses (both of them alcoholics who became culture-negative after four weeks of therapy but then missed some appointments). In patients with pulmonary tuberculosis, sputum cultures became negative after a median of 4.6 weeks, and 100% by 20 weeks.

Studies of intermittent DOT (thrice-weekly therapy for the entire treatment period) in Hong Kong (72), (thrice-weekly therapy for three months followed by twice-weekly therapy for three months) in Madras (73), and in Romania (74) are as effective as programs that begin with daily observed therapy for the first two to four weeks.

In contrast, in a self-administered regimen planned to last six months, 39% of the patients dropped out of the study, and in a nine-month regimen 49% dropped out (75). The cost of the six-month regimen was us\$327 per patient, whereas the Denver DOT regimen cost us\$397 per patient but could be reduced to us\$283 if two chest x-rays and two cultures were deleted, by relying on the greater efficacy of DOT (76). In New York City only 11% of the tuberculosis patients discharged from one hospital followed up in clinic (77), but therapy completion rates of up to 98% are experienced when DOT is used (78).

Noncompliance can be expected to occur in patients with psychiatric illness, alcoholism, drug addiction or who are homeless (66), but cannot be predicted on the basis of age, sex, socioeconomic status or estimates by health personnel (79). Interviews with intravenous drug users in Brooklyn, New York showed that DOT is appropriate because many of them had little knowledge about tuberculosis or their own tuberculosis status, and were afraid of detention for tuberculosis and

TABLE 5
Dosage recommendations for the initial treatment of tuberculosis in children and adults

Drug	Dosage*			
	Daily		2-3 times/week	
	Children [†]	Adults	Children	Adults
Isoniazid (mg/kg)	10-20	5	20-40	15
Maximum (mg)	300	300	900	900
Rifampin (mg/kg)	10-20	10	10-20	10
Maximum (mg)	600	600	600	600
Pyrazinamide (mg/kg)	15-30	15-30	50-70	50-70
Maximum (g)	2	2	3 g if 3/week 4 g if 2/week	
Ethambutol [‡] (mg/kg)	15-25	5-25		
If 2/week			50	50
If 3/week			25-30	25-30
Maximum (g)	2.5	2.5	2.5	2.5
Streptomycin (mg/kg)	20-30	15	25-30	25-30
Maximum (g)	1	1		
Maximum if 2/week			1.5	1.5
Maximum if 3/week			1	1

*The Canadian Thoracic Society 1994, Table 2 (reference 6) has the following differences: (i) the upper daily limit for streptomycin for children is 40 mg/kg; (ii) a 'usual daily dose' of isoniazid 300 mg, rifampin 600 mg, pyrazinamide 1500 mg, ethambutol 800 to 1200 mg and streptomycin 1000 mg is specified, rather than the 'maximum dose' of the American authority; (iii) the doses for 'twice-weekly therapy' for isoniazid are 900 to 1200 mg, pyrazinamide 2500 mg, ethambutol 2400 mg and streptomycin 1000 mg. The Canadian Pediatric Society, Table 1 (reference 87) has the following differences: (i) the upper daily dose for isoniazid is 15 mg/kg and for streptomycin is 40 mg/kg, and the range for pyrazinamide is 20 to 40 mg/kg; (ii) the dosage for streptomycin for twice-weekly therapy is 20 to 40 mg/kg. The American Academy of Pediatrics (reference 64) has the following differences: (i) the upper daily dose for isoniazid is 15 mg/kg; (ii) the daily dosage for pyrazinamide is 20 to 40 mg/kg; (iii) the upper daily dosage for streptomycin is 40 mg/kg. [†]Children 12 years old or younger; [‡]Ethambutol is not recommended for children whose visual acuity cannot be measured (usually six years old or younger), but should be considered for children with organisms resistant to all other drugs, when susceptibility to ethambutol has been demonstrated or is likely. Data from reference 65

therefore stopped treatment (80). Completion rates for therapy in one study of homeless patients in the United States improved from 44% to 89% when the provision of shelter and food vouchers was added to DOT (81). (There has been no research on reactivation rates if free housing is discontinued once the patient has completed treatment.)

The four essential aspects of DOT are that therapy should be highly patient-centred (the patient should experience no barriers to receiving therapy), resistance should be carefully monitored and treated, a monitoring and information system should be meticulously maintained, and therapy cannot be delegated by the DOT worker to a family member because that person may connive with the patient or be under pressure from the patient not to complete the therapy (eg, a child repeatedly spits out the tuberculosis medications) (82).

Options for control other than DOT are treatment of all known active tuberculosis cases in the home country for six months before immigration (the current Australian policy); a payment on completion of therapy to new arrivals who need prophylaxis (on the model of the \$1,000 payment in France for completion of antenatal care); or requiring new arrivals to post a bond, which would be repaid plus interest on completion of therapy, but these are less likely to ensure completion of therapy.

CONCLUSIONS

Exposure to tuberculosis is widespread among immigrants to Canada. Active tuberculosis is most likely to develop in immigrants from countries with a high prevalence

and during the first five years in Canada, but risks remain higher over the following 40 years than they do for the population born in Canada.

Canada is not optimally organized to detect and follow patients who are at risk for developing tuberculosis because Canada has no national reference centre to track movement between provinces, and there is separation of the responsibility for surveillance (Laboratory Centre for Disease Control) from that for treatment (physicians and public health departments).

DOT should be instituted for each active case of tuberculosis, and the name of each patient continuing or completing therapy should be circulated at the beginning of each month to treating physicians and public health departments, permitting prompt reinstitution of DOT by public health departments in those patients who discontinue therapy (83).

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