# Treatment of latent tuberculosis in migrants to Victoria

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## Abstract

The proportion of eligible persons identified who are tested for latent tuberculosis (TB), offered treatment, and complete treatment are performance indicators in tuberculosis control. We report a retrospective database review of the Migrant Screening Clinic, Department of Respiratory and Sleep Disorders Medicine at Western Health Footscray Hospital during the years 1996–2006. Of 7,225 migrants aged less than 35 years, tuberculin skin testing (TST) was performed for 3,589 (49.7%), including 2,641 (65.6%) of 4,024 migrants under 35 years with an abnormal chest radiograph, and 2,297 (59.0%) of 3,893 migrants born in a high-burden country. Of 3,589 persons with both chest radiograph and TST results, 1,487 (41.4%) were referred for follow-up, including 81.3% of those with TST ≥10 mm. Outcome data were available for 1,047 persons considered for treatment of latent TB, of whom 12.5% did not attend an initial appointment, 21.6% attended and were not offered treatment, 65.9% attended and were offered treatment, and 41.7% completed treatment for latent TB. The Victorian program for treatment of latent TB in migrants has testing, treatment offer and treatment completions rates similar to other published studies. The impact on TB control is limited by the small proportion of migrants referred to this program. *Commun Dis Intell* 2015;39(4):E578–E583.

Keywords: screening; tuberculin; latent tuberculosis, treatment completion rate

## Introduction

The incidence of notified tuberculosis (TB) in Australia was 5.5 per 100,000 persons per year in 2013.[1] In Victoria, the incidence of notified TB was 6.7 per 100,000; and 88% of notified cases occurred in persons born overseas.[1] Notification of active TB in Victoria is mandatory under the *Public Health and Wellbeing Act 2008*.[2]

In 2009, Australia issued 186,421 permanent visas. Of 4.0 million temporary entry visas, 3.3 million were visitors and 320,368 were overseas students.[3] In the same year Victoria received 24.5% of all permanent visa applicants, 18.3% of all visitors and 33.1% of students.[3] The top 3 countries of birth for permanent additions to the Victorian population were India, Peoples' Republic of China, and the United Kingdom. Overseas students in Victoria increased from 13,500 in 1993 to 46,401 in 2004 and 117,711 in 2009.[3,4]

People who want to migrate permanently to Australia, or stay temporarily, must satisfy the health requirement specified in the Migration Regulations of the Australian Government.[5–8] Applicants for permanent entry are asked to undergo a medical examination, and chest radiograph if 11 or more years of age. Where x-rays show possible evidence of TB the applicant is asked to provide sputum for smear microscopy and culture, and may be asked to provide serial chest radiographs over 3–6 months. If active TB is found, Australian migration law does not allow a visa to be granted until the person has undergone treatment and been declared free of active TB. This is documented with repeat chest radiograph and sputum examination. Any required medical examinations and x-rays must be conducted by qualified doctors and radiologists nominated by the immigration department.[8] If a chest radiograph shows evidence of previous but now inactive TB the applicant may be asked to sign a Tuberculosis Health Undertaking (TBU) at the time of visa grant.[6] By signing the TBU, the applicant agrees to contact the Health Undertaking Service on a free call number on arrival in Australia. The applicant also agrees to report to a state or territory health authority for follow-up as directed by the Health Undertaking Service.[5,7] Applicants for temporary entry may be asked to undergo a chest x-ray, medical examination, and possibly further tests including sputum examination and repeat chest x-ray, depending on the length of intended stay in Australia, intended activity, and the TB risk rating of the applicant's country.[8] TBUs originate from visa applications lodged outside Australia (off-shore TBU), or inside Australia (on-shore TBU). Both off-shore and on-shore TBUs include permanent and temporary residency immigrants, refugees and other humanitarian entrants.[9]

Under arrangements with the Department of Health Victoria, the Department of Respiratory and Sleep Disorders Medicine at Western Health Footscray Hospital has provided post-migration screening for TB in Victoria since 1996. Migrants who have been issued an off-shore TBU or have an abnormal chest radiograph at the time of an on-shore visa application are referred to the Migrant

Screening Clinic (MSC). In this clinic the prevalence of active TB at entry is 505 per 100,000.[10] Migrants are offered a tuberculin skin test (TST) if under 35 years of age and the chest radiograph is abnormal, or if under 35 years of age and a refugee,[12] or if under 35 years of age and born in one of the high burden countries whose migrants have the highest TB incidence in Victoria.[13,14] The age of 35 years was chosen based on Australian guidelines current during the period under study.[11,15] The frequency and severity of isoniazid-associated hepatitis increase with age.[16]

The MSC is a screening service, seeing each person once, and referring persons who need further assessment to other health services. Persons with symptoms suggestive of TB, or with one or more chest radiographs suggestive of active TB, are defined as suspected active TB and referred to other specialist clinics. The Victorian Government TB program is advised of non-attendees with a chest radiograph suggestive of active TB; TB program nurses are asked to contact the person, and may make a home visit. Those without such features, but with a history of TB diagnosis, a positive TST, or one or more chest x-rays thought likely to represent previous TB, are defined as inactive TB. Migrants with a positive TST[17] are referred to specialist respiratory or infectious disease clinics for treatment.

The objective of this study was to determine from a retrospective review of the Migrant Screening database the proportion of eligible persons identified in the MSC during the years 1996–2006 who were tested for latent TB, offered treatment, and completed treatment.[18]

## Methods

### Study population

All persons under 35 years of age with TST and chest radiograph performed in the MSC during the period November 1996 to June 2006 were identified from a search of the Migrant Screening database. The information extracted included whether the chest radiograph was normal or abnormal, the result of the TST, and the outcome of referral to specialist clinics for treatment of latent TB. Persons notified to the Department of Health with active TB were excluded from the study population, as they were not eligible for treatment of latent infection. Descriptive summary statistics were used to report findings.

### Ethics approval

The study was approved by the Human Research Ethics Committee of the Department of Health Victoria, and by the Human Research Ethics Committee of the Royal Melbourne Hospital Research Foundation.

## Results

Between November 1996 and June 2006, 18,359 persons were given an appointment at the MSC, of whom 15,352 (83.6%) attended. Of the 7,225 attendees aged less than 35 years, 6,949 (96%) had a chest radiograph result recorded. TST results were available for 3,589 (49.7%) attendees including 2,641 (65.6%) of 4,024 migrants under 35 years with an abnormal chest radiograph, and 2,297 (59.0%) of 3,893 migrants under 35 years born in a high-burden country. Of 3,589 persons with both chest radiograph and TST results, 1,487 (41%) were referred for follow-up, including 81.3% of those with TST of 10 mm or more, and 93.9% of those with TST of 15 mm or more (Table 1).

**Table 1: Percentage of persons tested who are referred for follow-up, by tuberculin skin test diameter**

| TST | Tested | Referred | |
|---|---|---|---|
| mm | n | n | % |
| 0–4 | 1,490 | 70 | 4.7 |
| 5–9 | 415 | 48 | 11.6 |
| 10–14 | 431 | 192 | 44.5 |
| ≥15 | 1,253 | 1,177 | 93.9 |
| Total | 3,589 | 1,487 | 41.4 |

TST Tuberculin skin test.

Of those referred to specialist clinics, 36 were found to have active TB. Of the remaining 1,451 persons referred, 1,334 had TST ≥10 mm, of whom 1,047 (78.5%) had an outcome recorded for the referral. These 1,047 persons eligible for the treatment of latent TB comprised 576 males (55.0%), mean age of 26.4 years, a mean TST of 20.8 mm in diameter, and 77.6% had an abnormal chest x-ray. Most of these people (84.8%) were born in a country with a high TB incidence.[14] The top 5 countries of birth were China 19.4%, Vietnam 15.7%, India 11.8%, Indonesia 5.2% and the Philippines 3.7%. The outcome of referral is shown in Table 2. Of 1,047 persons referred, 916 attended an initial appointment, 690 were offered, 546 commenced, and 437 completed treatment.

**Table 2: Outcomes of referral for treatment of latent tuberculosis**

| Outcome | n | % |
|---|---|---|
| Did not attend initial appointment | 131 | 12.5 |
| Attended initial appointment but treatment for latent TB not offered | 226 | 21.6 |
| Treatment of latent TB offered but patient refused | 144 | 13.8 |
| Started but failed to complete treatment for latent TB | 109 | 10.4 |
| Completed 6 months isoniazid | 224 | 21.4 |
| Completed 9 months isoniazid | 205 | 19.6 |
| Completed 2 months rifampicin + pyrazinamide or other treatment of latent TB | 8 | 0.8 |
| Total | 1,047 | 100.0 |

## Discussion

The National Tuberculosis Advisory Committee includes the screening of high risk groups for latent TB as a key activity in TB control.[19] In the United States of America the proportion of eligible persons identified who are tested for latent TB, offered treatment, and complete treatment are recommended performance indicators in tuberculosis control.[18]

This study found that the proportion of the target groups tested for latent TB was 65.6% in those with an abnormal chest radiograph, and 59.0% in those born in a high-burden country. At the MSC, migrants are advised that tuberculin skin testing is not required for immigration assessment and many decline the offer of TST.

Although 93.9% of persons with a TST ≥ 15 mm were referred for follow-up, only 44.5% of those with TST in the 10–14 mm range were referred. This likely relates to former Australian guidelines that in the presence of a history of previous bacille Calmette-Guérin (BCG) vaccination, tuberculin reactions of 15 mm or more may be regarded as an indication of possible super-infection with tuberculosis.[11] However, Marks and others found that the risk of TB in tuberculin positive refugees increases linearly with TST reaction size above 10 mm; the risk, and the relation of risk to TST reaction size, were unrelated to BCG scar status.[20] More recent Victorian guidelines[15] state that a single BCG vaccination in early childhood (before 5 years of age) is likely to be followed by a negative TST response when testing is performed after 10 years or more. Any reaction of 10 mm or greater in this setting is significant, and should not necessarily be attributed to BCG.[15]

A limitation of this study is that we did not perform interferon-gamma response assays (IGRA). One study of contact tracing has shown that an IGRA had a higher positive predictive value than TST.[21] Another study which included recently exposed immigrant close contacts found that the positive predictive value of IGRA for subsequent development of TB disease was comparable to that of the TST, irrespective of the TST cutoff (10 or 15 mm).[22]

Among persons referred for follow-up, 12.5% did not attend an initial appointment, 21.6% attended and were not offered treatment, 65.9% attended and were offered treatment, and 41.7% completed treatment for latent TB. Of the 916 persons attending a specialist clinic, 690 (75%) were offered treatment. This is consistent with large scale studies in which physicians did not recommend treatment to 20%–30% of patients who appeared eligible.[23] Many factors may have influenced these outcomes. Hart found that physicians' reasons for not offering treatment of latent infection to Victorian migrants with TST > 15 mm included previous adequate treatment, reactivation thought unlikely, and TST likely due to prior BCG.[24] Anibarro et al.[25] found that recent immigration (<5 years residence) and social risk factors including unemployment were independently associated with a lower rate of treatment completion. They considered that preventive measures may not constitute a major priority for newly arrived immigrants; furthermore, communication with health care providers is not always easy due to language barriers and socio-cultural reasons that make it difficult to convince otherwise healthy people of the importance of treatment; and that precarious employment situations also complicate regular attendance at follow-up visits.[25] Overseas visitors who hold temporary visas are

generally not eligible for Medicare to cover their medical and hospital expenses, and may not hold overseas visitor health cover.[26]

The completion rate in our study, expressed as the number completing treatment over those initiating treatment, was 437/546 (80%), which is in the upper range for treatment completion in foreign born persons and similar to other data from Australia.[27,28] Completion rates for the treatment of latent TB in Europe are considered unsatisfactory.[29] Rennie et al. found that offering patients a choice of treatment (6 months isoniazid or 3 months isoniazid and rifampicin) improved completion rates, with most patients preferring the shorter regimen.[30] Shorter regimens may have higher completion rates.[31] Supervised, clinic-based administration of treatment for latent TB may significantly reduce adherence.[32] Monthly house calls may increase completions rates.[33] Younger patients are less likely to complete treatment of latent infection.[34] A shorter treatment regimen may result in better adherence.[35]

Data from this and other studies can be used to estimate the contribution of treatment of latent infection in migrants on a TBU to tuberculosis control. The current study is of a highly selected group of recently arrived migrants: those who have been issued a TBU for an abnormal chest x-ray at the time of visa application. The incidence of TB in this group is 160 per 100,000,[10] which is much higher than the incidence in all overseas-born Victorians of 21.9 per 100,000.[36] During the 10 years 1996 to 2006, 18,359 migrants on a TBU were referred to the MSC. This was only a small fraction of the total number of migrants entering Victoria – approximately 46,000 permanent visa applicants in 2009.[3] It is not surprising that MacIntyre found only 25 of 218 (11.5%) notified cases in 1991 had been on a previous TBU.[37]

Active TB among contacts contributes relatively little to the burden of TB in Victoria. In the years 2005–2010, 4.1% of cases were linked to another notified case.[36] Among 783 contacts of 231 cases of active TB in 1991 there were 8 incident cases of active TB in the following 2 years.[38] Isoniazid prophylaxis did not significantly predict risk of disease; however, only a low number of individuals received prophylaxis.[38] Thus the potential benefit of treatment of latent infection in Victoria is mainly to the individual being treated, with little effect on future transmission.

Denholm et al.[39] argued that since the considerable majority of new diagnoses of active tuberculosis in Australia arise from reactivation of previously latent infection in those born in high-prevalence regions, the potential exists to reduce tuberculosis incidence through new public health policy aimed at the detection and treatment of latent infection in immigrants, thereby preventing reactivation. However, modelling by Denholm and McBryde[40] suggests that while broad immigration-related strategies targeting latent infection would be effective for reducing TB incidence, they are likely to be too inefficient for introduction as an across the board public health measure. They suggested strategies targeting immigrants from high-prevalence regions may be an effective and efficient public health intervention, which could be considered for TB incidence reduction in Australia. The MSC has conducted a program of targeted testing and referral for latent TB since 1996. The current study shows it has had a modest rate of treatment completion.

Any plan to extend testing of immigrants for latent TB would need to consider cost-effectiveness, resources and a number of ethical issues.[39,41,42] Denholm and McBryde reported significant variation in clinical practice relating to the diagnosis, treatment and management of latent TB.[43] This includes the likelihood of recommending and commencing therapy and the practices relating to clinical management during treatment. A chest radiograph with features suggestive of previous TB is a risk factor for subsequent active TB, and an indication not only to exclude currently active TB, but also to consider the place of treatment of latent infection in that individual.[17]

Denholm and McBryde argue that in order for treatment of latent TB infection to be an effective public health strategy, the development of, and regular updating of guidelines that are relevant, consistent and most importantly acceptable, across a broad range of stakeholders is an important step.[43] It is encouraging that 75% of the targeted group who were referred by the MSC and who attended specialist clinics for consideration of treatment of latent TB were offered treatment, but consensus on who should be offered treatment is essential before testing for latent TB is expanded in this population.

The Victorian program for preventive treatment of latent TB in migrants has testing, treatment offer and treatment completions rates similar to other published studies. Even if all migrants on a TBU were offered testing and treatment for latent infection, the reduction in active TB cases would be small, principally because only a small fraction of migrants entering Victoria have an abnormal chest radiograph and are placed on a TBU.

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