Active approaches to latent tuberculosis: modelling public health strategies towards eliminating tuberculosis in Australia

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Declaration

This is to certify that:
(i) the thesis comprises only my original work towards the PhD except where indicated,
(ii) due acknowledgement has been made in the text to all other material used,
(iii) the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

.......................................................... Justin Timothy Denholm
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Soli deo gloria
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Abstract

The World Health Organisation has a stated aim of eradicating tuberculosis as a public health issue by 2050, defined as an incidence of less than one case of active tuberculosis per million people annually. Although a combination of factors, including a current global incidence of approximately 1,300 cases per million, suggests this outcome is unlikely to be achieved, such a target may be possible for appropriate low-prevalence areas. The central argument of this thesis is that Australia, with a current incidence of approximately 70 cases per million annually, is one country where consideration of eradication may be more realistic; this present work is devoted to exploring and evaluating the public health strategies that may contribute to reducing tuberculosis incidence in this setting, including evaluation of the potential for elimination of tuberculosis as a public health issue.

Currently, international strategies for reducing tuberculosis incidence emphasise early effective treatment of active infection and interruption of transmission. These are key strategies in high-transmission regions; however, in an Australian context the considerable bulk of new tuberculosis infections arise from reactivation of latent infection rather than local transmission. Accordingly, while maintenance of traditional public health approaches remains important, increased efforts along these lines are unlikely to lead to further reduction in tuberculosis incidence. Strategies focused on the prevention of disease following reactivation of latent infection have theoretic potential for greater impact, but their use in an Australian public health context requires specific evaluation.

This thesis reviews latent tuberculosis infection (LTBI) from clinical and epidemiological perspectives, in an attempt to consider whether its contribution to disease burden can be measured and whether ethical and effective public health strategies could enable Australia to achieve the goal of less than one new case per million population annually.

Following a general review of LTBI, four key limitations in current understanding of LTBI are elucidated, particularly a) uncertainty regarding assessment of population prevalence, b) lack of standardisation of Australian management approaches, c)
inadequate understanding of the epidemiology and optimal management of multidrug resistant LTBI and d) incomplete capacity for appropriate assessment for risk of reactivation to active infection. Chapters 2-5 will consider each of these limitations in turn and offer novel investigations to advance our understanding of these aspects of LTBI in an Australian context. These developments will then be incorporated into an assessment of potential public health strategies relating to LTBI screening and treatment. This evaluation (chapter 6) will use a mathematical modelling approach to consider effectiveness of LTBI-focused strategies for reducing TB incidence. An ethical evaluation of such strategies will also be offered in chapter 7, prior to a concluding assessment of the potential for adopting LTBI-focused public health strategies towards reducing tuberculosis incidence in Australia.
1. Latent tuberculosis: biology, management and population health

1.1 What is latent tuberculosis?

1.1.1 Biology
Following transmission of tuberculosis (TB) via inhalation of droplet-spread *M. tuberculosis* (MTB), several clinical outcomes are possible(1). Organisms may multiply and successfully evade host defences, which particularly consist of cellular immune responses(2, 3). Inadequately controlled organism replication results in acute tuberculosis infection, which may manifest in a variety of clinical presentations. While uncontrolled local infection produces primary pulmonary tuberculosis infection, spread of *M. tuberculosis* via lymphatic and haematologic routes may result in extra-pulmonary or disseminated disease(4, 5). Although treatable with combination antituberculous chemotherapy, active tuberculosis remains a disease associated with considerable morbidity and mortality(6).

In the majority of cases an effective immune response to inhaled tubercle bacilli prevents the occurrence of active primary infection. It remains unclear whether an effective immune response at the time of inhalation can eradicate *M. tuberculosis*, however, the predominant outcome appears to be the control of organism replication and spread through granuloma formation(7, 8). This condition is referred to as latent tuberculosis infection (LTBI). While *M. tuberculosis* has the ability to survive within these conditions for extended periods of time, during the time that effective immunologic control is exerted active disease is prevented(9, 10).

Once latent infection with *M. tuberculosis* has been established, viable bacilli may persist for decades in a non-replicating state, followed in some cases by reactivation(11). A lifelong risk of reactivation tuberculosis exists, with an especially heightened risk during the first few years after infection(12). It is commonly stated that an individual with latent tuberculosis infection has an approximately 10% lifetime risk of reactivation, however, as will be explored in this thesis, all such estimations contain significant uncertainty(13). Although the mechanisms that dictate

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1 Sections of this chapter have been published as Denholm JT, McBryde ES. The use of anti-tuberculosis therapy for latent TB infection. *Infection and Drug Resistance*, 2010; 3:1-10 (Appendix 1).
timing of reactivation are poorly understood, advanced age or the development of cellular immunodeficiency are associated with increased risk for reactivation of latent tuberculosis infection (14-16). This is particularly marked for deficiencies related to T-cell number or function, including anti-cancer chemotherapy, human immunodeficiency virus infection and use of anti-tumour necrosis factor antibody therapy (17-19). Other factors that may be important include nutrient deficiencies, particularly vitamin D (20).

1.1.2 Public health

The importance of LTBI is not limited to the individual, but is an important public health consideration also. Although tuberculous bacilli are not contagious in the latent setting, later reactivation may lead to active disease and further transmission. Given the significant public health impact and costs that are associated with active tuberculosis disease, steps to prevent the reactivation of LTBI may offer benefits that complement existing strategies relating to tuberculosis control.

In countries with a high prevalence of tuberculosis disease and transmission, it can be difficult to assess the relative contributions of reactivation of tuberculosis against new acquisition of infection. However in countries such as Australia, with low rates of active disease and transmission, the majority of active tuberculosis derives from previously latent infection. Accurate population assessment of the prevalence of LTBI and risk of future TB disease, then, is critical for public health planning and intervention in contexts such as Australia.

Where tuberculosis incidence has been reduced to very low levels, the relative importance of various public health interventions is correspondingly altered. Although active case finding and directly observed therapy (DOT) for active tuberculosis are important interventions in high incidence countries, for instance, the relative contribution that expansion of these strategies would have in Australia is limited by low levels of community transmission. For Australia, where highly effective therapy for active tuberculosis and effective public health responses are already well established, alternative strategies become more important. Given the conditions of TB infection in Australia, arguably the most valuable complementary strategies that could
be implemented involve detection of LTBI and interruption of reactivation. Active case finding for LTBI in high-risk populations and introduction of standardised approaches to its diagnosis and treatment may have greater impact on active TB prevalence and transmission than further scale-up of alternative strategies more appropriate for higher prevalence countries, such as case finding for active disease. However, the anticipated success of LTBI-focused strategies is critically dependent on factors such as the prevalence of latent infection in the population of interest.

Strategies targeting LTBI diagnosis and treatment in immigrant populations have been explored in a number of settings towards the aim of reducing subsequent reactivation of TB infections(21, 22). The cost-effectiveness of one such strategy was explored in a decision-analysis model, which considered the effect of screening and treatment for new immigrants into the United States(23). This study modelled the effect of TST screening and LTBI treatment for immigrants from 13 high-prevalence countries, with particular outcomes of interest being active tuberculosis infections, development of drug resistant strains of TB, morbidity, quality of life and death, as well as summary considerations of cost-effectiveness of LTBI-based strategies. The strategies involving detection and treatment of LTBI were found to be highly cost-saving and associated with significant gains in quality adjusted life years (QALY). Such screening programs have also been evaluated in clinical settings, including trials where both active and latent TB infection were screened for in immigration cohorts. One such study found that screening all immigrants to Canada was a cost-effective strategy, but that cohorts with higher probability of infection were significantly more cost-effective to screen(24, 25). These studies compared immigrants with close contacts of patients with active tuberculosis to reach these conclusions, however these findings are likely to apply to immigrants from countries of variable TB prevalence. Immigrant screening with TST versus IGRA has also been evaluated in Norway, with IGRA screening implemented after a positive cost-effectiveness analysis(26). However, some caution is required in adoption of such strategies. As will be considered in later sections of this thesis, considerable uncertainty exists regarding the accuracy of various tests for the diagnosis of LTBI, and the extent to which test characteristics can be assumed across a range of population prevalences, both of which may impact cost-effectiveness assessment considerably.
Robust evaluation of potential public health strategies incorporating LTBI is critically dependent on a number of key variables, particularly risk of reactivation in given populations. Some of these variables are only imperfectly understood. This thesis will explore a variety of local and more broadly generalisable factors in order to consider whether immigration related strategies targetting latent tuberculosis infection may be appropriate for development in an Australian context.

1.2 How is LTBI managed?

1.2.1 Diagnosis

Establishing whether latent tuberculosis infection is present in an individual is not straightforward, as no gold standard investigation exists. By definition, latent infection is asymptomatic and is not associated with pathognomic clinical findings(27). The most common investigations performed for the diagnosis of LTBI are radiological, particularly plain chest x-ray, and delayed sensitivity testing using purified tuberculosis protein derivatives (PPD)(14). Radiologic findings associated with risk of subsequent tuberculosis disease may include pulmonary scarring and granuloma, particularly in the upper lobes(28). Although those with radiologic changes are more likely to later develop reactivation disease, these changes may persist despite eradication of mycobacteria, and reactivation can occur despite normal radiologic investigations. PPD, typically injected into the subcuticular space according to the Mantoux method (tuberculin skin test, or TST), is used as an immunologic assessment of previous tuberculosis infection(29). Although commonly employed for more than a century, TST has a number of limitations in the diagnosis of LTBI. It is relatively non-specific for *M tuberculosis*, and positive reactions can be related to BCG vaccination or to non-tuberculous mycobacteria(30, 31). It may also remain positive life-long despite effective antituberculous therapy, or become negative due to immune dysfunction such as HIV infection. A more recent alternative to TST for immunologic diagnosis of LTBI is the use of interferon-gamma release assays (IGRA). IGRA tests for the presence of an effective T-cell response to *M tuberculosis*-specific proteins, indicating that circulating T-cells have previously been exposed to tuberculosis(32). In an appropriate clinical setting, the use of IGRA can overcome some of the limitations of TST, particularly related to reduced frequency of false-positive results(33). Several types of IGRA are in use worldwide, each of which
relies of detection of interferon-gamma after host cells are stimulated with *M tuberculosis* antigens(34). IGRA have been established as having increased specificity and predictive value than TST for LTBI however, for reasons that include increased cost and technological requirements, they are yet to be widely adopted for routine LTBI diagnosis in many parts of the world (35, 36).

Despite the difficulties in firmly establishing its diagnosis, LTBI is an entity with significant implications for infected individuals. Those with suggestive radiology or immunologic tests are at higher risk of reactivation of tuberculosis than those without these findings. Conversely, risk can be reduced through preventative chemotherapy to eradicate the tubercle bacilli, most commonly with isoniazid preventative therapy (IPT)(37). Given the increased risk associated with LTBI and the possibility of harm reduction through appropriate treatment, assessment and management of an individual’s risk of LTBI is important.

### 1.2.2 Individual treatment strategies

The antimicrobial agents used for the treatment of active tuberculosis are also those used and investigated for LTBI. However, not all medications effective against active tuberculosis are necessarily appropriate for the treatment of LTBI. Medications must be active against the latent phase of *M tuberculosis* and be sufficiently well-tolerated for treatment of an asymptomatic condition. Preferably, they should also require little regular monitoring, sterilize mycobacteria quickly and have a high threshold to the development of microbial resistance.

Treatment of LTBI at present requires extended courses of effective antituberculous therapy. Although strategies continue to be investigated to shorten the duration of these treatment regimens, it is expected that the long latent periods and slow replicative cycle of *M tuberculosis* will mean that treatment with existing agents will continue to be relatively lengthy for the foreseeable future. Accordingly, all regimens for the treatment of LTBI currently in use require months of anti-tuberculosis medications. Lengthy courses of therapy in asymptomatic patients are typically associated with high rates of poor adherence and loss to follow-up, with resultant decrease in efficacy of LTBI treatment programs(38, 39). Strategies to improve adherence with therapy have included educational programs, support from
pharmacists and other allied health care providers, medication alarms and reminder systems; however, the establishment of effective short-course regimens are ultimately likely to provide the most benefit in this setting (40-42).

In an attempt to improve compliance, intermittent dosing strategies for various LTBI regimens have been investigated, such as twice-weekly isoniazid instead of daily administration. These approaches will be reviewed in more detail below; however as a general principle, non-compliance is more likely to impact outcome if the regimen is intermittent rather than daily. Accordingly, it is recommended that all non-daily dosing schedules be administered by directly observed therapy (DOT) to ensure compliance.

Typically, antimicrobial agents for LTBI have been prescribed as monotherapy, most commonly with isoniazid or rifampicin (see below). In the setting of active tuberculosis, the use of single-medication therapy clearly leads to the development of antimicrobial resistance. For instance, when isoniazid alone was used for disease treatment, 71% of patients developed resistance after three months (43). Rather than being caused by the induction of resistance in individual organisms, this is believed to be due to the selection of small numbers of naturally resistant *M tuberculosis* organisms present at the time of treatment. However, the low number of bacilli present in latent tuberculosis infections means that the presence of any such naturally resistant organisms is uncommon (an estimated rate of 1 per $10^8$ organisms (44)), and monotherapy is generally effective. In situations where there is a high probability of drug-resistant organisms present, such a principle does not remain reliable, and alternative strategies may be required (see below).

As LTBI itself is an asymptomatic condition, treatment is given based on the risk of future reactivation. The decision to treat, therefore, involves a weighing of the risk of therapy against benefit from reduction in reactivation for the individual patient. Such decisions will necessarily be influenced by factors that either increase risk of reactivation (such as recent contact with active tuberculosis or the impending introduction of immunosuppressive medication) or risk of serious adverse effects of therapy (such as advanced age or pre-existing hepatotoxicity). In most settings, these factors are sufficiently varied that treatment decisions must be individually considered.
and made, rather than being applicable to broader populations outside of limited settings.

Overall, while the effectiveness of treatment for LTBI is clear from large studies such as those described here, it is important to recognise that there remains no test or method for determining whether treatment has been effective in the individual patient. Patients therefore should be counselled that treatment success cannot be guaranteed, and symptoms consistent with active tuberculosis should be investigated appropriately even following completion of LTBI treatment(45).

**LTBI in people with HIV**

Co-infection with HIV and tuberculosis is recognised as a significant issue worldwide. Although much of this awareness relates to the problems associated with active infection, the diagnosis and treatment of LTBI in people with HIV presents additional difficulties. Although HIV-positive people may be no more likely to be exposed to tuberculosis, once exposed they have considerably increased risk of progression to active disease, whether primary or secondary(46). Active tuberculosis is less likely to present in classic pulmonary forms in people co-infected with HIV, and it may be more difficult to exclude active infection than in those without HIV(47-49). This is problematic for the appropriate management of LTBI, as initiating therapy in the setting of unrecognised active infection may lead to treatment failure and the development of antituberculous drug resistance. For instance, one study of HIV-infected subjects in Cote d’Ivoire found that 1.9% of enrolled subjects had active tuberculosis at baseline, despite clinical screening intended to exclude such patients(50).

Interactions between anti-retroviral medications and treatment for LTBI may also be an important issue in both safety and effectiveness, and is dealt with in the relevant sections below.
1.2.3 Regimens for treatment of LTBI

*Isoniazid*

By far the most established and widely used medication for the treatment of LTBI is isoniazid. First identified in the early 1950’s, isoniazid has multiple effects on mycobacterial metabolism, including inhibition of mycolic acid synthesis (51, 52). Several dosing strategies are commonly employed, with evidence for both daily self-administered therapy and supervised administration (DOT) twice weekly in some settings.

Initial human trials of isoniazid preventative therapy established that prolonged therapy with isoniazid was effective in reducing subsequent active tuberculosis infections. In one of the earliest studies conducted, 800 Kenyan tuberculosis contacts were randomised to either receive 12 months of isoniazid or placebo (53). A 90% reduction in active TB diagnosis was observed in the isoniazid intervention arm, with 17 versus 2 patients developing active infections after 1 year. Studies investigating the use of longer courses found that no significant additive benefit accrued beyond 12 months of therapy (7). Subsequent studies investigated the potential of shorter courses of isoniazid therapy, such as the large International Union Against Tuberculosis (IUAT) trial (54). This international multicenter study randomised 28,000 subjects with fibrotic pulmonary lesions to receive 3, 6 or 12 months of isoniazid treatment (previously known as isoniazid preventive therapy, or IPT) or placebo, with follow-up continued for 5 years. While 12 months of isoniazid therapy prevented the largest number cases of active tuberculosis (75% reduction from placebo; cf 21% and 65% with 3 and 6 months respectively), it was also associated with a higher rate of serious hepatotoxicity. The study concluded that 6 months was the optimal duration, as it prevented the greatest number of tuberculosis infections per episode of hepatitis caused. Subsequently, a re-analysis of these results was performed and compared with other studies, particularly an Alaskan cohort, where it was suggested that amongst patients compliant with treatment, this reduction was 69% for 6 months of isoniazid and 93% for 12 months (55). This analysis also reviewed additional studies and recommended that the optimal duration of treatment was likely to be ‘9 or 10 months’, although no specific trial data was available for this duration of therapy.
Nonetheless this recommendation has become widely adopted, particularly in the United States where it forms the basis for national guidelines recommending this duration.

Isoniazid therapy in people with HIV

With widespread co-infection of HIV and TB, particularly in Sub-Saharan Africa, the effectiveness of isoniazid preventative therapy in various clinical settings with high HIV prevalence has also been explored. One placebo-controlled trial of 12 months of isoniazid in HIV-infected children has been conducted, in which HIV-infected infants in a high prevalence TB area were enrolled(56). Children were predominantly not receiving HAART. This study was stopped early after an interim report found a significant reduction in tuberculosis diagnosis and mortality in children receiving isoniazid (8% v 16% after a mean follow-up of 5.7 months). A follow up report on this study population suggested a very high compliance with prescribed therapy (>90%)(57). The long-term benefits of routine LTBI treatment in high prevalence settings are unknown, and further studies will be required to determine optimal strategies, including appropriate settings, duration of use and impact on drug-resistance in subsequent active tuberculosis infections. In HIV-infected adults with LTBI, meta-analysis of published studies has confirmed that isoniazid therapy is effective in preventing progression to active infection(58). This analysis of 7 studies, including 4529 subjects, suggested a relative risk of 0.4 (95% CI 0.24-0.65) in those with a positive TST, while a non-significant reduction (0.84, 95% CI 0.54-1.30) was found in those with negative baseline testing. However, other studies have shown that unselected HIV-positive populations may also benefit from LTBI therapy in areas with sufficiently high TB transmission(59). Current guidelines recommend that the HIV-positive people follow the same treatment protocols for therapy as HIV-negative people diagnosed with LTBI, with a 9-month course as optimal duration(38).

Isoniazid treatment in children and adolescents

Isoniazid is regarded as safe in children, and is widely used for the treatment of LTBI from infancy. There is an increased rate of progression to active TB in children aged less than 5 years old, and LTBI therapy in this group is highly effective, perhaps more
so than in adults. In households with active tuberculosis infection, some studies have estimated that up to 30-40% children under 15 years may have LTBI (60, 61). Several large early trials have demonstrated that the risk of progression to active disease may be reduced by up to 90% with 12-month courses of therapy (62). Accordingly, WHO guidelines recommend that all TB-exposed children in whom active infection has been excluded receive a course of treatment for LTBI, however this is not routinely provided in many developing world settings (63, 64).

*Isoniazid treatment in pregnancy and lactation*

Isoniazid does not have teratogenic effects in humans, and has been widely used in regimens for the treatment of active infections in pregnancy (65, 66). Serious hepatotoxicity has been reported during isoniazid use in pregnancy, and one retrospective analysis of cases suggested a 2.5-fold (but not statistically significant) increase in hepatotoxicity in this setting (67, 68). Treatment for LTBI in pregnancy is sometimes deferred until after delivery for this reason, as pregnancy per se does not influence the risk of TB reactivation (69). However, an evaluation of various strategies has concluded that treating LTBI during pregnancy with isoniazid would be cost effective and improve overall outcomes, with increased hepatotoxicity more than offset by decreased tuberculosis infections (70). Guidelines generally support treatment of LTBI in pregnancy with isoniazid as the preferred option where there is high risk of reactivation, with close monitoring of liver function tests recommended (38).

Small amounts of active drug are present in breast milk when isoniazid is used in lactating women, in insufficient amounts for the treatment of LTBI in infants (38). No adverse effects on infants have been reported, however it is recommended that pyridoxine be given to breastfeeding infants when isoniazid is used in this setting (71, 72).

*Adverse effects and tolerability*

A number of large studies and reviews of isoniazid monotherapy have concluded that the incidence of serious hepatitis (ALT >5 upper limit of normal (ULN)) in young,
previously well patients is between 0.1-0.56%, a figure adopted by the American Thoracic Society for formulation of guidelines and recommendations(73-75). However, when routine liver function testing is performed throughout isoniazid therapy, discontinuation of medication occurs in around 4-10% of patients due to abnormal results(76-78). In a recent randomised trial, for instance, discontinuation due to serious hepatotoxicity was reported in 3.8%(78). Patients in this study included those at higher risk of side effects, including abnormal baseline LFT and those aged >35. The discordance between these liver function test results and clinical syndromes seen in various studies has led to recommendations against routine liver function testing during LTBI treatment in low risk patients, particularly those aged <35 with normal baseline liver function(79).

Peripheral neuropathy has been recognised in association with isoniazid preventive therapy since its inception(80). Isoniazid leads to neuropathy by competitively inhibiting the metabolic activity of pyridoxine, an activity that can be overcome in at-risk patients through the co-administration of pyridoxine supplementation. A genetic basis for this toxicity has been identified in variable acetylation of isoniazid between individuals, although malnutrition may also play a role in increasing neuropathy risk(81). Co-prescription of other neurotoxic agents such as stavudine (D4T) or didanosine should be avoided due to increased rates of peripheral neuropathy(82). Unlike the treatment of active tuberculosis, treatment regimens for LTBI are not usually supplemented by pyridoxine, but it may be considered in high-risk groups, including those with pre-existing neuropathy or additional risk factors for its development (eg HIV, diabetes, malnutrition or use of other neurotoxic medications)(38).

Isoniazid resistance

High prevalence tuberculosis regions worldwide have reported increasing rates of isoniazid resistance, with the resulting potential for decreasing effectiveness of isoniazid-based regimens for LTBI(83). South African serial surveys of antimicrobial sensitivity found an increase in isoniazid resistance from 6.9% to 12.4% in paediatric TB isolates between 1994-2005, a significant development in a treatment naïve cohort(84). In regions such as Uzbekistan and Azerbaijan, with a high proportion of
treatment failure and MDR-TB transmission, reported isoniazid-resistance is as high as 40-49% (85). Clearly in settings such as these, the effectiveness of isoniazid treatment will be considerably reduced, and alternative strategies for LTBI management are required.

**Rifampicin (Rifampin)**

Rifampicin acts by inhibiting bacterial DNA polymerase, and is currently recommended as second-line therapy for LTBI, or for use where the index case is known to be infected with isoniazid-resistant tuberculosis (38).

Rifampicin has been regarded as an attractive option for LTBI treatment due to the possibility of shortening duration of therapy, as was seen when the medication was introduced into treatment of active tuberculosis. The only randomised trial of rifampicin monotherapy for LTBI compared 3-months of rifampicin with 6 months of isoniazid therapy in patients with silicosis, and concluded that they were equivalent in effectiveness (86). A further retrospective study including 49 people exposed to isoniazid-resistant tuberculosis found that none progressed to active disease a mean 26 months after LTBI therapy with rifampicin monotherapy; however duration of therapy was non-standardised and often prolonged, with a mean duration of more than 6 months (87). In light of the probable increased effectiveness of 9-month courses of isoniazid over 6-month courses, subsequent adult studies have favoured treatment regimens longer than 3 months, usually 4-month courses of rifampicin (88). No study, however, has directly compared the effectiveness of 4 months of rifampicin against 9 months of isoniazid for the prevention of active tuberculosis; a key requirement if this regimen is to be used more widely in the future.

**Rifampicin therapy in people with HIV**

Rifampicin monotherapy for LTBI has not been studied in HIV-positive cohorts, with some authorities citing concerns about unrecognised active disease and the potential for development of rifampicin resistance (89). Rifampicin also interacts with a number of common antiretroviral medications such as efavirenz, and in particular rifampicin-
containing regimens should be avoided in patients being treated with protease inhibitors (PI), as enzyme induction may lead to sub-therapeutic levels of PI and increased rifampicin toxicity(90). Pharmacokinetic studies have suggested that PI boosted with ritonavir may still achieve acceptable serum levels however there has been no evaluation of LTBI therapy in this context, and rifampicin monotherapy is not recommended(91).

**Rifampicin in children and adolescents**

Rifampicin is recommended as an alternative to 9-months of isoniazid for children. Typically, 4-6 month durations are recommended, with no studies directly comparing the two regimens. In one series, 157 adolescent patients exposed to isoniazid-resistant index cases of tuberculosis were treated with a 6-month course of rifampicin, with no progression to active disease observed over a 2-year follow-up period(92).

**Rifampicin in pregnancy and lactation**

There are no controlled studies of rifampicin in pregnancy, and retrospective reviews are divided regarding any increased risk of congenital malformations(69). Use of rifampicin for latent tuberculosis is not recommended in pregnancy, although it has been used widely in the treatment of active tuberculosis in this context(38). Rifampicin is also present in breastmilk, at low concentrations that are considered safe for infants, but non-therapeutic(93).

**Adverse effects and tolerability**

The adverse effects of rifampicin have been compared with isoniazid in a recent international randomised trial(78). Patients diagnosed with LTBI (n=847) were randomised to receive either 4-month courses of rifampicin or 9 months of isoniazid, with early cessation of enrolment due to decreased serious adverse events in the rifampicin-receiving arm. Patients prescribed isoniazid were more likely to have serious adverse events overall (4.0% v 1.7%), with the bulk of adverse events relating to hepatotoxicity. Hepatotoxicity occurred in 0.7% of patients receiving rifampicin and in 3.8% of patients receiving isoniazid. Although the number of patients found to
have developed isoniazid hepatotoxicity in this study is high compared to previous investigations, this likely reflects a greater-risk patient group and represents a fair assessment of the relative toxicity of the two regimens.

**Rifampicin and pyrazinamide**

Initial studies of 2-month rifampicin and pyrazinamide (2RZ) regimens evaluated its effectiveness predominantly in settings with a high prevalence of both HIV/AIDS and tuberculosis (94). The first of these studies suggested that 2RZ moderately reduced the incidence of subsequent TB infection (RR 0.58 over 1 year; 95% CI 0.35-0.95) when compared with placebo; reduction somewhat less effective than a 6-month course of isoniazid. This effect waned quickly after treatment cessation, likely reflecting TB reinfection in a high prevalence setting. Subsequent studies performed in a variety of settings confirmed the effectiveness of this regimen, resulting to its adoption as an alternative recommendation for LTBI therapy(95, 96).

Between 2000-2002, a number of reports of increased frequency of side effects emerged, particularly hepatotoxicity requiring discontinuation of therapy(97-99). On the basis of these reports, a joint recommendation against the use of this regimen was issued in 2003 by the Centres for Disease Control and Prevention and the American Thoracic Society(100). A systematic review of LTBI treatment with 2-month rifampicin and pyrazinamide ultimately concluded that overall, drug discontinuation due to hepatotoxicity occurred in 2.0-17.6% of HIV-negative patients and 0-9.5% in patients with HIV co-infection(89). Accordingly, this regimen is no longer recommended in international guidelines.

**Isoniazid and rifampicin**

Three- or four-month courses of isoniazid and rifampicin were at least equivalent to 9 months of isoniazid alone in one randomised controlled trial in children < 15 years old(101). In this study, 926 children diagnosed with LTBI were randomised to either a short course or standard isoniazid regimen, and followed for a minimum of 3 years post-treatment. Greater compliance (78-89% v 65.5%) was seen in children prescribed short course regimens. Subjects who received short course therapy were also found to
have less radiologic change suggesting active disease during follow up (11% v 24%); however, no child from either group experienced a clinically and microbiologically diagnosed episode of active tuberculosis. 6% of children who received isoniazid therapy developed transient increases in liver enzymes, which was seen in 1.2% of short-course recipients. No patient from either group experienced severe hepatotoxicity or required treatment cessation for adverse effects.

**Isoniazid and rifapentine**

The combination of isoniazid and rifapentine has been of recent interest in the treatment of LTBI. Rifapentine is a long-acting rifamycin that has been used successfully as a weekly dose in the continuation phase of treatment for active TB, and has been shown in animal models to be effective against latent TB (102-104). Reviews of its use in the treatment of active tuberculosis suggest that it is generally well-tolerated in this setting, and associated with low rates of serious adverse effects (105).

Early studies compared weekly isoniazid (900mg) and rifapentine (900mg) for 12 weeks to daily rifampicin and pyrazinamide in household contacts of pulmonary TB (106). Contacts treated with weekly dosing were less likely to develop hepatotoxicity (1% vs 10%). However, this regimen may have been slightly less effective, with active TB infections occurring at a rate of 0.5 per 100 patient-years in the weekly dosing regimen versus 0.2 in the daily rifampicin and pyrazinamide group. This difference was not statistically significant, and both groups experienced substantially less active disease than expected from local background rates of 4% annually (107). Nonetheless, given the advantages associated with substantially shortened courses of therapy, a larger, prospective comparison with isoniazid was recently completed (108). A large cohort of approximately 8,000 subjects, predominantly household contacts of active TB cases, were randomised to receive 9 months of isoniazid or 12 doses of weekly isoniazid and rifapentine. Subjects randomised to shorter-course therapy were more likely to complete treatment (82.1% v 69%), while treatment-limiting adverse effects were somewhat more common (4.9% v 3.7%). Subsequent TB outcomes were shown to be non-inferior to isoniazid, with a trend towards significance favouring the new regimen. Following the release of this
study the United States Centers for Disease Control has released updated guidelines for the management of LTBI, recommending the combination of isoniazid and rifapentine as a preferred option for LTBI in many settings(109).

The combination of rifapentine and moxifloxacin has not been evaluated in humans, however it demonstrated equal efficacy with rifapentine and isoniazid in a mouse model of LTBI(110).

Overall, rifapentine appears to be an efficacious medication, with potential for shortening courses of LTBI therapy. It is now recommended for use in the United States, although at the time of writing not yet available in many countries including Australia. Further investigation is required into the potential for development of multidrug resistance during therapy.

**Treatment of suspected multidrug-resistant latent tuberculosis**

As reviewed above, the considerable bulk of therapies investigated for the treatment of latent TB infection are intended for infections with isolates sensitive to first-line tuberculosis medications. However, with an increasing global burden of multidrug-resistant tuberculosis (MDR TB), the presumption of infection caused by drug-sensitive TB isolates may not be justified in some clinical settings. Most commonly, this relates to people known to have been significantly exposed to a source of sputum smear-positive MDR TB. However, where patients are epidemiologically likely to have acquired LTBI in settings with very high prevalence of MDR TB it may also be questioned whether treatment of latent infection should include the possibility of multidrug-resistance de novo. It has been suggested that latent MDR TB may be less likely to reactivate than infection caused by drug-susceptible organisms, a finding supported by notification data in at least one national surveillance program(111, 112). It is presently difficult to quantify the likelihood of reactivation MDR TB, however, and the consequences of developing active infection are significant.

Evidence for treatment of LTBI in such settings is limited. A systematic review of this area identified two non-randomised studies considering the effectiveness of LTBI treatment in contacts of known MDR TB index cases(113). One prospective study
individualised medications included in the treatment regimen based on the sensitivity testing results from the household contact. Medications prescribed included high-dose isoniazid (15-20 mg/kg), ethambutol, ofloxacin and ethionamide. From 105 children with household contact, 41 received individualised therapy. During a 30-month follow-up period, 2 of 41 (5%) developed active TB infection, compared with 13 of the 64 (20%) who had not received chemoprophylaxis. A further study retrospectively evaluated the impact of high-dose isoniazid preventive therapy on close contacts of index patients with MDR TB(107). A six-month course of 400mg/day of isoniazid was initiated for 45 contacts of index patients with tuberculosis, with 2 contacts subsequently developing active TB. Both of the breakthrough contacts had MDR-TB, as did their index cases. More recently, individualised regimens for treating LTBI have also been used by the US Centers for Disease Control in the setting of MDR-TB outbreaks in Micronesia, although little data has yet been reported regarding effectiveness(114). By contrast, on the basis of limited available evidence, the WHO does not recommend the use of second-line agents for treating LTBI(63).

Even in settings where rates of active MDR TB are extremely high, such as countries of the former Soviet Union, it is unlikely that the routine use of second-line antituberculous medications for LTBI will be justifiable given the risks of subsequent reinfection and the possibility of contributing to further drug resistance. However, individualised treatment regimens may be considered in patients based on sensitivity testing in contact isolates and personal risk/benefit considerations.

Cost-effectiveness

The relative cost-effectiveness of various regimens for treatment of LTBI has been evaluated in several recent studies. Ziakas and Mylonakis(115) compared nine months of daily isoniazid with four months of daily rifampicin using meta-analysis of 3586 published patients in four head-to-head trials. They conclude that rifampicin therapy is associated with significantly decreased discontinuation rates (RR 0.53; 95% CI 0.44-0.63), hepatotoxicity (RR 0.12; 95% CI 0.05-0.3) and decreased cost (USD 972.20 vs 1062.50) than 9 months of isoniazid. However, the difference in cost in this analysis was heavily influenced by the use of laboratory testing, which assumed monthly testing of liver function and complete blood counts in all patients. Such
testing is arguably unnecessary in low risk patients with normal baseline investigation, and may result in unwarranted discontinuation of therapy due to mild abnormalities (116). Due to higher cost of rifampicin medication, cost-effectiveness comparison would favour isoniazid if monthly testing were not performed. Nonetheless, frequent laboratory testing is performed in many countries, and this analysis suggests the superior cost-effectiveness of rifampicin under such conditions. A second analysis of cost-effectiveness used a mathematical model that included broader societal and healthcare costs in the analysis, and also suggested that rifampicin was more cost-effective than isoniazid-based regimens (117). These authors have also performed a separate analysis incorporating the newer long-acting rifamycins, concluding that these therapies would also be cost-effective (118).

All studies highlight the benefits associated with shorter-courses of effective LTBI therapy, and suggest that improved completion rates are likely to offset the higher medication cost of rifamycins.

**Novel and emerging therapies**

Currently, a number of novel pharmacologic agents with activity against *M tuberculosis* are in various phases of development (105). Several of these medications have begun preliminary assessment in animal models of LTBI, including moxifloxacin and PA-824 (110). Although most novel agents have not been directly assessed in the treatment of LTBI, a larger spectrum of available agents will provide greater options for antituberculous therapy and may yield new possibilities for LTBI treatment. Ultimately, it would be advantageous if LTBI could be treated with a different class of drug from those used for active tuberculosis, reducing concerns regarding the uncertainty of drug resistance patterns in patients with LTBI, as well as limiting the possibility of resistant active TB following failed therapy.

**Non-pharmacological therapies**

Finally, the future potential for non-drug treatments for eradication of LTBI, particularly vaccines and other immunotherapies, remains to be fully explored. Vaccines against tuberculosis have been most often conceived as tools for preventing
establishment of latent infection or the subsequent emergence of active disease. However more recently there has been interest in the development of ‘therapeutic’ vaccines that augment eradication of LTBI or alleviate the natural history of reactivation in relevant ways(119, 120). The existing BCG vaccine has a moderate capacity for reducing active infection rates, but no role in post-exposure management of LTBI(121-123). Several novel DNA and subunit vaccines have demonstrated some promise in animal models. One study in a murine LTBI model found that therapeutic DNA vaccination had no effect on reactivation, but when used in conjunction with moxifloxacin treatment augmented its bactericidal effects(110). An alternative therapeutic vaccine, RUTI, involving liposomally delivered fragmented *M. tuberculosis* cells, has also been shown to enhance the effect of short-course chemotherapy in animal models, with ongoing clinical trials continuing(124, 125). Effective vaccines against the latent phase of tuberculosis infection would be a welcome adjunct to LTBI management but remain distant from clinical use at present.

Non-vaccine immunotherapy has perhaps been considered more frequently in non-tuberculous mycobacterial (NTM) infections, however may be of benefit in TB also, particularly in the setting of extensively drug-resistant infection(126). Investigations into intravenous immunoglobulin (IVIG) and 16α-bromoepiandrosterone (HE2000) have shown anti-tuberculosis effect, while adjunctive therapy with thalidomide analogue CC-3052 has been shown to enhance mycobacterial clearance(126-129). One small study suggested that adjunctive IL-2 may reduce the duration of smear-positivity during treatment of pulmonary TB, however a subsequent RCT did not confirm this finding(129, 130). GM-CSF increases phagocytosis of non-tuberculous mycobacteria, and has also been shown to reduce mycobacterial persistence in a murine lung model (131, 132). Overall, trials of immunotherapy have so far largely concentrated on animal models of active infection however they may have a future role in shortening LTBI treatment regimens when used as adjunctive therapy.

Finally, while much emphasis is placed on the development of new technological approaches to preventing tuberculosis reactivation, it must also be pointed out that a variety of non-specific social and health interventions are clearly associated with reduced risk of LTBI progressing to disease(133). Factors such as smoking cessation and improved nutrition may have incompletely understood mechanisms, however are
associated with substantial reduction in risk and should be incorporated in individual and public health strategies alongside whatever technological advancements are possible.

Summary

The current evidence for LTBI therapy shows that there are a number of effective options for substantially reducing the risk of subsequent active TB disease. On an individual level, effectiveness may be limited by poor adherence and side effects. At a population level, strategies for treating latent tuberculosis may be potentially threatened in many areas by rising rates of drug resistance. The recent establishment of isoniazid and rifapentine-based shorter course therapy provide advantages to current regimens based on isoniazid alone. A variety of additional improvements in aspects of LTBI therapy may be possible in the future and need to be explored. Overall, however, it appears that LTBI therapy is already sufficiently effective, safe and cost-effective for use in selected individuals and potentially on a wider scale than occurs currently. The evidence for a number of the described alternative regimens is accruing, providing sufficient information and impetus for evaluating their use in public health strategies in Australian contexts through incorporating into mathematical models, to which this thesis will later return.

1.3 Population-based strategies relating to LTBI

1.3.1 Theoretic value and examples of use

In regions where tuberculosis prevalence is high, there is ongoing opportunity for uninfected people to be exposed to tuberculosis. Strategies for reducing tuberculosis in such communities tends to appropriately focus on the control of active infection, through early case diagnosis, effective and available treatment of detected cases and, in some settings, isolation of people with tuberculosis during the infective period. These approaches are necessary and important for reducing tuberculosis spread in high-prevalence areas, and indeed, in any region with active cases. In countries where the prevalence of active tuberculosis is low, however, it is relatively unusual for person-to-person spread to occur. In these settings, particularly when coupled with migration from higher prevalence countries, it is more common for cases of active
tuberculosis to represent reactivation from previously latent infection. In this context, the relative importance of LTBI is increased, and while strategies targeting active infection remain valuable it is arguable that LTBI-focused approaches will also be required.

Public health strategies directed towards LTBI could take a variety of context-specific forms. Where subgroups of a population are at higher risk of reactivation it may be appropriate to develop targeted campaigns for testing and treatment. For example, children under the age of 5 having close contact with infectious cases of tuberculosis disease and those living with HIV are known to have higher rates of tuberculosis reactivation, and in some countries these may be sensible target populations. Intensified case finding and treatment of LTBI amongst high risk contacts of people with active tuberculosis has been shown to reduce active disease and mortality (64). Where the rate of TB infection is sufficiently high, such as in sub-Saharan Africa, it has been recommended that HIV positive people universally receive treatment for LTBI after active infection is excluded, although in many countries these recommendations are not carried out (134). Alternatively, in countries with high immigration rates, testing and treatment for LTBI may be incorporated as part of pre- or post-migration screening programs or community outreach programs(135). The aim of such programs would be to allow treatment for LTBI to be offered, reducing the subsequent development of active disease. In Switzerland, a voluntary immigrant screening program for LTBI was found to be feasible, however was limited by poor adherence and loss to follow-up (136). In the United States, TST was re-introduced to immigration screening in 2007, with IGRA now also accepted for this purpose (137). A diagnosis of LTBI during immigration screening is not considered a barrier to travel, however initiates a post-migration referral for consideration of treatment and/or other appropriate management. In Australia, no specific screening for LTBI is required (138). CXR is required for active TB screening, and abnormal findings may prompt further investigation leading to LTBI diagnosis and consideration of treatment. There is currently, however, no systematic policy of LTBI identification or treatment in Australia. The potential impact and implications of introducing such policies will be explored later in this thesis.
1.3.2 Limitations in development and assessment of public health strategies

International introduction of LTBI based approaches to public health control of tuberculosis has been slow, and highly variable in different regions. Partly this is likely to reflect the cultural difficulties associated with TB control in regions where it is a low prevalence disease, and so perhaps perceived as less important. One additional reason, however, arises from the difficulty of designing such programs and rigorously assessing their impact and effectiveness. As will be considered below, key elements of LTBI epidemiology, particularly accurate assessment of population prevalence and likelihood of reactivation, remain uncertain. Without substantial improvement in this understanding, it will remain difficult to justify the introduction of LTBI-based approaches to public health, despite a growing international acceptance of their importance. The following sections, then, will critically review the current approaches to these two aspects of LTBI epidemiology before proceeding to investigate strategies for improvement.

1.4 Estimating population prevalence of LTBI

Tuberculosis has been proposed to be contagious since the time of Avicenna (c 1000AD), however the identification of Mycobacterium tuberculosis as the causative agent of ‘consumption’ did not occur until Robert Koch in 1882. Despite the eventual broad acceptance of the infectious agent and human-to-human transmission, the concept of latency was not appreciated until some decades later. In many countries around the 1900-1930’s, the idea of the ‘at-risk child’ was popular, leading to undernourished or ‘sickly’ children, especially those from families with active TB infections, being moved into rural locations where it was felt they were less likely to come into contact with the infection(139). Eventually, the idea of long latency periods was accepted, with correspondingly different strategies for identifying and protecting vulnerable people through isolation from active cases.

TST has been used since the 1890’s as evidence of contact with tuberculosis, with a parallel recognition of its utility in identifying people who may currently have had LTBI. Prior to this time, epidemiology of tuberculosis was confined entirely to that of active infections and their complications, with death rates being the most consistently recorded outcome in most settings.
1.4.1 Population surveys

Large population prevalence studies of tuberculosis infection have been performed in a variety of countries and settings. In these prevalence surveys, a variety of diagnostic algorithms may be applied, typically involving some or all of interview, clinical assessment, chest x-ray, tuberculin skin testing and sputum microscopy and culture. In most studies, the primary aims include a broad assessment of tuberculosis infections within a community, with particular emphasis on active tuberculosis infections. Although information specifically regarding latent tuberculosis infection is often less emphasised, the information collected in many surveys allows estimation of latent tuberculosis infection prevalence, most commonly by proportions of various populations with TST reactivity in the absence of evidence of active tuberculosis disease.

Theoretically, the incidence of latent tuberculosis infection could be measured by use of serial TST assessments and measurement of rates of conversion to positivity in previously TST negative people. Apart from the logistic difficulties of performing serial large-scale assessments of this type, there are additional problems with this approach. Repeated tuberculin exposure through TST may enhance reactivity, a phenomenon known as ‘boosting’. Some people who were previously TST reactive may become negative on repeat testing, and the significance of this change is unknown. In some settings historically, TST negative people have been vaccinated with BCG, further confounding serial surveys, although the effect of BCG vaccination on TST reactivity diminishes over time(140). Additionally, in some populations the interpretation of serial testing results may be hampered by concurrent immunosuppression, particularly in settings where HIV infection is common. For these reasons, serial testing, although sometimes performed, is problematic and alternative approaches have been pursued. Although potentially more difficult to interpret, many studies are based on cohorts where a single TST is performed to assess rates of infection in particular age cohorts. Many studies have confirmed steadily rising rates of TST positivity with age; a phenomenon most readily explained by the exposure to active tuberculosis. In a setting where the background risk of tuberculosis acquisition is constant, the annual risk of tuberculosis infection can be
established by considering the proportion of people in each age group who are TST positive.

As mentioned above, TST-based surveys have a number of limitations in accurately assessing the population prevalence of latent tuberculosis infection\(^{(31, 141)}\). Countries with high tuberculosis prevalence typically have high rates of BCG vaccination, which has the potential to increase the rate of TST positivity found in surveys. High rates of endemic non-tuberculosis mycobacteria may also artificially inflate the results of such studies. Finally, the need to have a follow-up reading of the size of induration means that subjects have an opportunity to be lost to follow-up, or to be included after recording induration at inappropriate timing. Nonetheless, regional and national tuberculosis surveys have been performed in a variety of settings, and considerable expertise has been developed in overcoming these limitations. Surveys typically assume that a positive TST reaction (\(\geq 10\)mm) is equivalent to tuberculosis infection, although some efforts are made in many studies to correct for factors such as BCG vaccination rate.

Crude population prevalence of tuberculosis infection is initially calculated by dividing the number of positive TST by the total sample population:

\[
\text{Point prevalence} = \frac{\text{Cases}}{\text{population}}
\]

Or, using TST alone as a diagnostic test,

\[
\text{Prevalence of tuberculosis} = \frac{\text{Number of subjects with reactive TST}}{\text{total number of subjects}}
\]

Where studies, particularly nationwide prevalence surveys, are conducted to consider active and latent infection, diagnosed active cases may first be removed from the total cases before calculating the prevalence of inactive disease.

\[
\text{Inactive tuberculosis prevalence} = \frac{(\text{Total cases} – \text{active cases})}{\text{population}}
\]

These crude prevalence figures may then be adjusted to derive more accurate estimation of the entire population from the sample. For instance, subjects from rural
areas typically have higher rates of TST positivity than urban dwellers. If people living in rural areas comprise 50% of a nation’s total population but only 30% of the subjects in a prevalence survey, the prevalence may be adjusted to account for this discrepancy.

Once population prevalence has been calculated, an estimation of the annual risk of tuberculosis infection (ARTI) is commonly offered. The formula used by the World Health Organisation for calculating annual risk of infection assumes that the point prevalence of LTBI in the population of interest remains stable over time(142). In this formula R = annual risk of infection, p= probability of LTBI and a=mean age of population. It should be noted that this formulation is based on the risk of not having LTBI (1-p), with the annual risk, R, being calculated from (1 – risk of not having LTBI). A variation sometimes employed substitutes (1/a+ 0.5) for (1/a), if age data collected in the survey was recorded based on full years at last birthday(30).

\[ R = 1 - (1-p)^{1/a} \]

For example, in a population of 100,000 schoolchildren, 5000 are found to be positive with TST. The cohort has a mean age of 8. So, using the above formulas, the population prevalence of LTBI is 5% (0.05), and the ARTI would then be calculated as:

\[
\begin{align*}
R &= 1 - (1 - 0.05)^{1/8} \\
R &= 1 - (0.95)^{1/8} \\
R &= 1 - 0.994 \\
R &= 0.006
\end{align*}
\]

Therefore, the annual risk of infection in this population would be 0.006 (0.6%) per year.

Where assessment of TST reactivity prevalence is made in multiple age cohorts of the same population, the results of ARTI calculations can also be compared, to consider how risk of TB infection is changing over time. These comparisons may provide useful supporting evidence for changing prevalence over time, for instance following
the introduction of public health interventions or other factors influencing risk of TB infection.

To review this process and interpretation of TST surveys, we will examine two previously published tuberculosis prevalence studies, conducted in Korea and Nepal.

In 1995, Korea conducted its seventh nationwide tuberculosis prevalence survey (143). Over six previous surveys, public health research in Korea has demonstrated a steady reduction in tuberculosis, including both latent infection and active disease. In this study, clusters including 64,713 people were screened with TST, CXR and sputum bacteriology. From this sample, children aged between 5 and 9 were selected for assessment of latent tuberculosis prevalence and calculation of the annual risk of infection (see below). From the 5,412 included, the majority (4,555) had received BCG vaccination in infancy. As is standard for unselected populations, a TST induration of ≥10mm was considered positive. 3.4% of children aged 5-9 (mean age 7.5 years) had positive TST reactions. Using the above formula, the ARTI in this cohort was calculated to be 0.46% per year (reported in text as 0.5%). This figure can be compared with the calculated ARTI in subjects aged less than 30 in the same study. 15.5% of subjects aged less than 30 were positive on TST, which correlates with an ARTI of 0.006 (0.6%) per year. Overall, this study suggested that both active infection (data not shown here) and LTBI rates were falling in comparison with the previously conducted studies.

In 2006, Nepal conducted the country’s first nationwide TST survey (144). This study targetted children aged between 5 and 7 years old. 17,260 children were included, of whom 79.7% had evidence of previous BCG vaccination. Reaction size cut-off was selected retrospectively by examination of the distribution of TST reaction sizes amongst the children without previous BCG vaccination. A second mode was observed amongst this group at 16mm, and prevalence calculated using the mirror method, which assumes that the cut-off represents the median value of those who truly TB infection (30).

The following formulas were used for prevalence and ARTI calculation:
Prevalence = \[\frac{(\text{number of subjects with TST 16mm}) + 2(\text{number of subjects with TST >16mm})}{\text{total number of subjects}}\]

\[\text{ARTI} = 1 - (1-\text{prevalence})^{1/\alpha+0.5}\]

Using this method, the Nepalese survey suggested a prevalence of 7.0%, with a corresponding ARTI of 0.86% (0.0086). If a standard TST cut-off of 10mm had been adopted, the prevalence would have been 10.0%, with an ARTI of 1.24% (0.0124).

1.4.2 Improving estimates of LTBI with alternative study methods

The inherent limitations of TST as a primary tool for the diagnosis of latent tuberculosis infection have been discussed above. Alternative tests with higher sensitivity and (particularly) specificity would be valuable for improving the accuracy of population-based surveys of LTBI. One such approach would be to conduct large-scale population surveys along the lines of existing TST surveillance, using IGRA as the diagnostic test. Such surveys would be likely to have significant advantages, including decreased rates of false-positive reactions. This would be particularly valuable given that the bulk of TB screening programs are conducted in areas of high tuberculosis prevalence, where rates of BCG vaccination tend to be correspondingly high. However, there are substantial logistic implications for such a program, such as the requirement for laboratory processing facilities, trained operators, the need for blood sampling and the cost associated with both of the available IGRA tests. Despite the potential advantages, to date no nation-wide screening program has adopted IGRA in conjunction or replacement of TST.

Several large IGRA trials have been conducted and may provide assistance in preparing for the logistic challenges of a nation-wide survey. For instance, Paul Vinton and colleagues screened 481 hospital staff members with both an IGRA (Quantiferon-TB Gold In-Tube test) and TST to consider concordance and strength of association with risk factors for TB acquisition(35). Although they found poor concordance between the tests (κ=0.16), IGRA positivity had a significantly better correlation with TB-associated risk factors. Conversely, TST positivity was strongly associated with a history of BCG vaccination, an effect particularly marked in discordant test results (TST+/IGRA-).
Although the majority of IGRA studies for LTBI detection have been conducted in developed countries, screening has also been performed in countries such as India, Vietnam and Peru. These studies highlight that difficulties related to the use of IGRA can be overcome, and perhaps signal that large-scale prevalence studies may be conducted in the future.

1.4.3 Mathematical approaches to improving experimentally-derived LTBI prevalence

Both of the studies previously discussed demonstrate some attempts to correct crude TST positivity rates in order to estimate latent tuberculosis infection prevalence. In the Korean study, TST positivity was first corrected for active tuberculosis infections and then adjusted according to demographic variation. In the Nepalese study, no data relating to active infections was collected however the mirror method was used to adjust TST results in order to increase specificity in a context with high rates of BCG vaccination. This approach, and the assumptions that facilitate its use, is outlined below.

One of the underlying concepts allowing the mathematical adjustments mentioned is the concept of the ‘mixture model’. A mixture model refers to a study (in this case, of TST reactivity) where two distinct sub-populations are present within the population being observed. In the context of tuberculin reactivity, one straightforward example is that some subjects would be positive due to BCG vaccination, while other positive results represent true tuberculosis infection. When TST reaction sizes of all subjects from a tuberculin survey with positive reaction are displayed in a frequency histogram (figure 1.4.1) a bimodal distribution is commonly observed. In this example, subjects who have a history of BCG vaccination are clustered with a mean induration of less than 5 mm, while those with a history of exposure to active tuberculosis have a mean induration of 16 mm. In this example, two known populations have been combined however in a population-wide tuberculin survey both groups would be included in data collection without previous knowledge of these categories. If this total population had been sampled without awareness of the two underlying groups, a distribution as seen in figure 1.4.2 would have been obtained.
1.4.1 TST induration size distribution in a simulated cohort containing BCG vaccinated and LTBI individuals

1.4.2 TST induration size distribution in a simulated cohort with cause of reactivity suppressed
Although in reality the situation is often complicated by additional factors such as exposure to non-tuberculous mycobacteria, the underlying concept of multiple populations being sampled remains important. Various attempts have been made to reliably separate out different groups found within one sample population, with one of the most common being the ‘mirror method’. The mirror method assumes that each group is normally distributed around a mean TST induration size. First, the two (or more) modes in the total population are identified. In the above example, these would be at 1 and 16 mm. The larger mode is assumed to be related to true latent tuberculosis infection, while lesser modes are deemed secondary to BCG vaccination and/or non-tuberculous mycobacterial infections. To calculate the number of people with true LTBI, the number of subjects with TST induration of greater than the second mode (in this case, 16 mm) is multiplied by two to account for those with true infection whose induration was less than the mode. This is then added to the number who recorded induration of 16 mm in order to calculate the total number of subjects considered to have true LTBI. A similar process can be followed for each mode observed.

1.4.4 Theoretical mathematical approaches

In 1985, a widely influential article by Karel Styblo compared the risk of smear positive tuberculosis with rates of tuberculin skin test positivity found in related populations(145). The data for this study were drawn from 16 countries, predominantly prior to the introduction of effective anti-tuberculosis therapy, and used measured rates of tuberculin skin test positivity, smear positive infections and mortality to consider whether a fixed ratio could be used to describe the relationship between these various aspects of tuberculosis epidemiology. Styblo’s method assumed a constant mortality with smear positive infection (50% case fatality) and duration of infection (2 years), and estimated that for every 1% of a population that became TST + (incidence of latent tuberculosis infection), a mean of 50 people/100,000/year would develop smear positive tuberculosis (incidence of smear positive active infection).

When Styblo wrote, information regarding active tuberculosis was difficult to collect. For the purposes of planning national and international strategies for tuberculosis
control, this parameter was considered important from attempting to estimate rates of active disease from experimental tuberculin positivity rates. Latterly, WHO and IUAT-driven country-wide tuberculosis surveillance have provided more accurate information regarding rates of smear positive disease and mortality, and such calculations would potentially be most valuable in reverse; allowing the estimation of LTBI prevalence from known mortality and smear positive disease data.

Styblo’s rule became established in WHO methodology for tuberculosis epidemiology. Its assumptions, however, were acknowledged to be problematic and likely to be altered by varying conditions, particularly social changes related to in-country economic and social development and the introduction of effective antituberculous therapy. Treatment was considered likely to reduce mortality and decrease duration of infection, while HIV infection would reduce the proportion of smear positive cases in a population. Despite these concerns, it has not been until recent years that experimental evidence to directly challenge Styblo’s rule has been established. In 2008, the Styblo rule was reassessed using serial national prevalence studies in the Republic of Korea, China and the Philippines (146). In each country, the results of TST surveys were used to calculate annual rates of tuberculosis infection (ARTI) and compared with prevalence of smear-positive active tuberculosis. ARTI was calculated at the mean time between the birth year and the survey year for the cohort sampled, and smear-positive cases of pulmonary tuberculosis were recorded from adjusted national reporting data in that year. Styblo’s rule would predict that the ratio between annual risk of tuberculosis infection and prevalence of smear-positive pulmonary tuberculosis should be in the order of 1\%: 100 per 100,000 population, or alternatively, that the ratio between incident smear positive infections and latent infection incidence should be 1:20. However, no such consistent mathematical ratio could be identified in the new data. The in most recent available surveys, while the ratio of ARTI to smear-positive tuberculosis in the Republic of Korea was 1:3.2, the ratio in China and the Philippine was 1:5.8 and 1:4.4 respectively. Furthermore, as trends in all three countries were considered over serial surveys, no consistent relationship could be found between ARTI and the prevalence or the incidence of smear positive tuberculosis infection.
Although these studies contradict Styblo’s rule, they have not established an alternative method for calculating rates of latent tuberculosis infection from active disease epidemiology, or vice versa(147). Each of the countries surveyed did, however, demonstrate that the ratio between active and latent infection was consistently smaller than predicted by Styblo. This is to be expected based on changes in practice that affect Styblo’s assumptions, particularly the reduction in duration of tuberculosis infectivity with modern antituberculous chemotherapy. However, the extent of this reduction does not appear to be either constant or predictable, leading to the suggestion from some authors that an underlying connection may not reliably exist(146). Although there must clearly be some relationship between active disease and latent infection, the factors governing the relationship between the two are likely to be complex, and may not be readily generalisable between populations, due to greatly varying local conditions in critical factors such as delay to time diagnosis or housing density.

1.4.5 Need for improved methods

In summary, currently there exists no established mathematical connection between epidemiologic data related to active tuberculosis infections and the underlying burden of latent infection in a population. Attempts to discover a simple mathematical relationship between rates of active tuberculosis and latent infection suggest that such a relationship appears unlikely, and alternative approaches to estimating population burden of latent tuberculosis are required. These methods may include improvements in large-scale testing of individuals or generation of novel mathematical models, however it is likely that effective and generalisable solutions will require a combination of both strategies to be employed.

1.5 Estimating reactivation rates

1.5.1 Basis for current estimates

It is widely quoted that people with latent tuberculosis have an approximately 10% lifetime risk of reactivation, with the greatest risk during the first 5 years after infection(89, 148, 149). One of the largest studies to consider reactivation followed more than 80,000 Puerto Rican children for a mean of 19 years(150). Children were enrolled between 1949-1951; selected from a larger cohort of school children on the
basis of a positive TST. Overall, an active TB case rate of 90.2/100000/year was observed, with marked differences depending on the age at the time of positive TST. Children aged below 6 were twice as likely to reactivate as those older, with higher rates also noted amongst those whose TST was more strongly positive. A TST induration of 6-10mm (<5 being considered negative) was associated with reactivation rates between 40-59/100000/year depending on age, while those with TST >16mm had rates between 123-238/100000/year. The authors of this study appear to have contributed to the now widely-adopted ‘10% lifetime risk’ estimate although it was an extrapolation in the context of young children with strongly positive TST reactions.

More sophisticated approaches have used mathematical modelling to address some of the limitations associated with the long latent periods possible with TB. Vynnycky and Fine developed a model based on British TB data which suggests that calendar year of acquisition, as well as age, is relevant when considering long-term TB trends(151). Their analysis suggests that summary lifetime rates of LTBI reactivation have been in the order of 12-14% for some decades, with significantly higher rates prior to the 1930’s (figure 1.5.1).
1.5.1 Predicted lifetime risks for developing all forms of pulmonary tuberculosis (top) and infectious pulmonary tuberculosis (bottom) for persons infected during 1900-1990 in England and Wales, by age at infection. Reproduced from Vynnycky (143).

One explanation for varying rates of reactivation is that they are reflective of underlying immunological states. For instance, alteration of immune responses with age may be a primary determinant of likelihood of reactivation, and larger TST responses could reflect less efficient immune containment or greater burden of infection. However, there may also be significant confounders present in this analysis. As we have seen, TST is an imperfect test for LTBI, and it may be that a number of children in this cohort were not actually infected. Young children with a positive TST,
for instance, may be more likely to reactivate because they are behaviorally less likely to have been exposed to environmental mycobacteria than adults. If this were the case, positive TST in younger children would be more likely to reflect a true result, and the proportion of true positives may be higher than in older age groups. The same argument could be mounted against the significance of larger TST results, suggesting that this is not about risk stratification amongst people with LTBI but about groups biased in containing different proportions of truly infected people. Both possibilities have been acknowledged, however, in the absence of improved methods for accurately diagnosing individual infection or estimating population prevalence, are difficult to resolve.

1.5.2 Limitations in current understanding and possibilities for improvement

While reactivation is clearly a genuine issue, as can be seen by TB infections in those emigrating from high-prevalence regions, estimation of absolute risks can be problematic due to inaccuracy in diagnosis and risk of re-exposure(149). Accurate assessment of individual or population risk, however, is critical for determining cost-benefit of LTBI management strategies.

As the previous section has reviewed, there are a variety of experimental and mathematical approaches to improving estimates of LTBI prevalence. Success with these methods is likely to be the most important factor in allowing improved estimates of reactivation rates and absolute risks/benefits. Once these methods have been perfected, it may be possible to re-analyse older data to improve analysis. For some study questions, these new methods may also be used to develop more appropriate samples or cohorts in which to measure reactivation rates.

While there remains uncertainty regarding the rates of reactivation following LTBI, there are at least significant areas of understanding regarding the relative risks of reactivation. This includes risk based on age of acquisition and recognised defects of immunity, allowing risk stratification between individuals and groups of infected people. It also includes quantification of relative risk reduction associated with LTBI therapy. Improved ability to assess or estimate LTBI infection will provide more accurate evaluation of absolute risk of reactivation TB, and corresponding
improvements in cost-benefit analysis and impact of LTBI-based approaches to TB control.

1.6 Summary of the limits of current understanding of LTBI and implications for evaluation of public health strategies

As has been surveyed in this chapter, current understanding of LTBI is lacking in several important ways. On an individual level, all available diagnostic tests are suboptimal, with no gold standard test for establishing the presence of LTBI. Although effective therapies for the eradication of LTBI exist, no post-treatment test of cure is available, which introduces a further conceptual barrier to treatment uptake added to the prolonged duration and potential for side effects. When extended into population-based attempts to model the effectiveness of public health strategies related to LTBI, these issues may be magnified further, and need to be considered appropriately in the design of any model to evaluate policies. As the aim of this thesis is to develop a model for the evaluation of public health strategies relating to LTBI, these issues raised need to be addressed in order to allow robust and helpful evaluation to be conducted. An outline of the planned approach follows.

Improved estimation of LTBI prevalence and rates of reactivation are clearly needed, as existing methods surveyed above are inadequate. A variety of important aspects of public health management of tuberculosis rely on accurate assessment of these basic features of LTBI epidemiology. Estimates of the likelihood of TB reactivation in specific populations, the effectiveness of isoniazid preventative therapy and the value of screening and control strategies are critically dependent on a solid understanding of both aspects. However, as surveyed above, to date reliable estimation of both prevalence and risk of reactivation has been lacking. Chapter 2 will explore existing and novel methods for estimating the prevalence and risk of reactivation of latent tuberculosis infection in a population, using both survey data and mathematical modelling approaches. These methods will be particularly applied to estimating risk of tuberculosis in immigration cohorts to Australia.

Given the range of potential approaches to management of LTBI identified in this chapter, Chapter 3 will consider actual practice amongst Australian clinicians through
review of existing guidelines and a recent practice survey. This will provide an improved understanding of the ‘real-world’ context for the introduction of new public health strategies, and a more realistic comparator for subsequent advances.

Another area of deficiency highlighted by this review relates to MDR TB. Public health strategies which included treatment of LTBI with current preventative therapies would be ineffective in individuals with MDR LTBI. Currently, our understanding of the outcomes of such a treatment failure, including risk of MDR reactivation and secondary transmission, are limited, particularly in low-prevalence environments such as Australia. Chapter 4 presents a novel investigation into MDR TB transmission and MDR LTBI reactivation in Victoria, Australia, which provides local data to address this deficiency and will allow relevant modelling of MDR TB impact to be conducted.

Approaches that permitted individual level risk-stratification of those with LTBI would be of benefit, by identifying those most likely to reactivate. This would allow improved assessment of risk-benefit balance for individuals considering treatment and support the development of more cost-effective public health strategies. Approaches to risk stratification will be considered in Chapter 5, with a particular emphasis on identifying risk factors of sufficient magnitude and frequency to warrant incorporation into a mathematical model of TB in Australia.

Once these issues have been addressed, a method of evaluation of public health strategies will be offered in two ways. First, a mathematical model of Australian tuberculosis will be developed, and a variety of potential public health strategies focusing on LTBI screening and treatment in the setting of immigration will be evaluated. This model and its findings are presented in Chapter 6. Secondly, the potential introduction of new public health strategies also brings with it a range of ethical issues, which will be considered in Chapter 7 with a proposed framework for prospective consideration.
2. Estimating latent TB prevalence and TB risk in immigrant cohorts

Given the high relative importance of LTBI in a low tuberculosis transmission region such as Australia, a robust understanding of the risk of future reactivation is critical for modelling the effectiveness of proposed public health strategies. Such an appreciation would most naturally come from an accurate estimation of the number and proportion of people infected in a given population, combined with a clear understanding of the natural history of LTBI, particularly accurate estimates of reactivation risk following infection. As has been reviewed in the previous chapter, all such estimates are problematic both because of intrinsic limitations in existing tests for latent infection, and also because such investigations are not uniformly performed in an Australian setting. Nonetheless, any improvements in accurate estimation of future risk of tuberculosis disease in relevant cohorts would provide significant assistance in strengthening both theoretical understanding of the natural history of tuberculosis infection, and pragmatic evaluation of the likely effectiveness of a variety of public health interventions targeting LTBI. In particular, since the considerable majority of active cases of tuberculosis arise in Australian residents born overseas, improving estimates of either LTBI prevalence or future tuberculosis risk in immigrant cohorts would be of particular interest.

Although no systematic screening of migrants for LTBI is currently performed in Australia, internationally large-scale TST surveys have been performed in a variety of relevant countries and regions of origin. Additionally, data on immigration cohorts to Australia is collected routinely, and records of tuberculosis disease following arrival is also available locally. This raises several possibilities for the use of these existing data sources to improve estimates of LTBI prevalence and/or subsequent risk of tuberculosis disease in immigration cohorts. These estimates could then provide an improved foundation for the rational assessment of public health strategies in these communities.

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2 Sections of this chapter have been published as McBryde ES, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting. *Medical Journal of Australia*, 2012;197(8):458-461. (Appendix 2)
This chapter will explore three potential strategies for resolving uncertainty regarding estimates of LTBI prevalence and future risk of tuberculosis disease in Australian migrant populations, each using existing data sources, in order that subsequent models of TBI may be developed. Section 2.1 will use Chinese national TST survey data and Australian immigration records to directly estimate the prevalence of TST-reactivity in Chinese migrant cohorts. This method allows estimation of TST reactivity in migrant cohorts, but its utility is limited by the implicit assumption that a positive TST is equivalent to latent TB infection, or at least directly proportional to risk of future tuberculosis disease. Section 2.2 will then attempt to address this limitation by extending these estimates through adjustment using a previously published random-effect, latent class method. This method improves the potential usefulness of TST survey data by relaxing the assumption of perfect TST test performance inherent in the earlier method, however is demonstrated to be significantly limited by the restricted proportion of TST reactivity permitted in a given cohort. Finally, section 2.3 will consider a novel potential approach for bypassing the modelling reliance on LTBI prevalence altogether through the use of immigration data and subsequent Victorian tuberculosis diagnoses. This method does not require knowledge of an individual’s LTBI status, or surrogates such as population prevalence of TST reactivity, to estimate future risk of active TB. This method is then explored with the intention of providing a basis for tuberculosis disease risk estimates in a subsequent mathematical model (Chapter 6).

2.1 Estimating tuberculin test reactivity in Chinese immigrants

2.1.1 Background

Over the last two decades, between 20 to 35 thousand new migrants have arrived in Victoria annually(152). Although the largest number of new arrivals originates from countries with low prevalence of TB disease such as New Zealand and the United Kingdom, approximately one-third arrive from Asian countries with moderate to high tuberculosis prevalence. Amongst arrivals from Asian countries, China and India are most strongly represented, with migrants from these countries constituting a combined 21% of all new arrivals in 2007. The prevalence of LTBI is likely to be substantially higher in new arrivals from these countries than in lower-prevalence
countries, and correspondingly, these cohorts are likely to contribute disproportionately to LTBI prevalence in annual immigration cohorts overall.

Formulating robust models involving LTBI importation requires both global and country-specific estimates of prevalence. However, accuracy of estimation will be most important in these countries which both contribute large number of new arrivals and where baseline prevalence is expected to be highest. Accordingly, this first phase of improving estimation of LTBI prevalence will concentrate on immigrant cohorts from the People’s Republic of China. These cohorts will be used to establish a method for estimating LTBI prevalence, which, if successful, could be expanded to apply the method to all immigrant cohorts to Australia.

Since 1979, periodic nationwide surveys of tuberculosis epidemiology have been conducted in the People’s Republic of China (153-157). These surveys have been large-scale, random studies, typically involving greater than one million subjects tested for tuberculosis infection. Although a primary emphasis of these studies has been to identify active tuberculosis disease, tuberculin skin tests were also performed in a number of cohorts, and estimates of the annual risk of tuberculosis infection generated. These studies were performed at 5 year intervals between 1979 and 1996, and allow an appreciation of dynamic tuberculosis incidence and prevalence of TST reactivity in a representative Chinese population over this period of time. While TST reactivity is unlikely to correlate precisely with LTBI, section 2.2 will subsequently consider the possibility of adjustment of TST reactivity rates to better reflect LTBI population prevalence (figure 2.1.1).
For a variety of reasons, this cohort is useful for the purposes at hand. First, immigrants from the People’s Republic of China is a relatively large group, with approximately 20,000 Chinese citizens arriving for long-term stay in Australia each year. Second, Australia’s status as a low-risk country for tuberculosis acquisition greatly reduces the confounding factor of acquired infection in residents who develop active infections subsequent to arrival. Third, as outlined above, Chinese nation-wide tuberculin skin test surveys have been conducted periodically over this period to allow calculation of crude annual risk of tuberculosis infection. Fourth, the bulk of Australian cases of active tuberculosis infections are diagnosed in immigrants from high prevalence countries such as China, and accurate assessment of LTBI burden in immigration cohorts is needed to predict epidemiologic trends in active infections. Finally, identifying LTBI prevalence in immigration cohorts provides information to allow rational assessment of screening and intervention strategies and calculation of their efficiency and effectiveness.
2.1.2 Aim

To estimate the prevalence of TST reactivity amongst Chinese immigrants to Victoria between 1979 and 1996.

2.1.3 Methods

Chinese national TB survey data was available for 1979, 1985, 1990 and 1996. In addition to data collected regarding active tuberculosis infection, these surveys included TST evaluation of representative cohorts of children. Rates of TST reactivity in various age groups were then used to generate an annual risk of tuberculosis infection (ARTI); that is, to determine the rate at which children became TST reactive over time. ARTI were taken from each of the survey years and linear extrapolation was performed to assign ARTI to intra-survey years.

Figures obtained from the Australian Bureau of Statistics were then used to identify the ages of all Chinese immigrants to Victoria from 1980 to 1997. Immigration data from this source was available by 5 year cohort (ie 0-4, 5-9 etc), and individuals were assigned the mean age of their cohort for the purpose of calculations.

For each year in the period 1979-1996, the ARTI calculated above was used with the immigration cohort for the following year in order to estimate the number of migrants who were TST reactive. Prevalence estimates were produced by the formula: 1-(1-ARTI)\(^{\text{mean age}}\). For the purposes of this initial analysis, TST reactivity was considered diagnostic of LTBI.

All data used in this analysis is from published literature and publically available sources, and relates to non-identifiable information. According to the rules of our institutions, no application for Human Research Ethics Committee consideration was necessary.

2.1.4 Results

The ARTI from national surveys was found to be 0.64, 0.59, 0.64 and 0.7% in the respective survey years. Table 2.1 shows the measured and extrapolated ARTI along with integer number of estimated LTBI amongst Chinese migrants arriving in Victoria in each year. The estimated population prevalence ranged from 19.8 to 25.7%,
representing a total of between 58 and 613 individuals emigrating with latent tuberculosis infection.
<table>
<thead>
<tr>
<th>Year</th>
<th>ARTI</th>
<th>Number of Chinese migrants</th>
<th>Mean age of migrants (years)</th>
<th>Population prevalence estimate (%)</th>
<th>Predicted LTBI cases#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>0.64%</td>
<td>289</td>
<td>39.3</td>
<td>22.3</td>
<td>64</td>
</tr>
<tr>
<td>1980</td>
<td>0.632%</td>
<td>292</td>
<td>41</td>
<td>22.8</td>
<td>67</td>
</tr>
<tr>
<td>1981</td>
<td>0.623%</td>
<td>256</td>
<td>41.5</td>
<td>22.7</td>
<td>58</td>
</tr>
<tr>
<td>1982</td>
<td>0.615%</td>
<td>261</td>
<td>47.8</td>
<td>25.7</td>
<td>67</td>
</tr>
<tr>
<td>1983</td>
<td>0.607%</td>
<td>447</td>
<td>47.6</td>
<td>25.3</td>
<td>113</td>
</tr>
<tr>
<td>1984</td>
<td>0.598%</td>
<td>862</td>
<td>42.6</td>
<td>22.6</td>
<td>195</td>
</tr>
<tr>
<td>1985</td>
<td>0.59%</td>
<td>937</td>
<td>37.3</td>
<td>19.8</td>
<td>185</td>
</tr>
<tr>
<td>1986</td>
<td>0.60%</td>
<td>665</td>
<td>41.0</td>
<td>21.8</td>
<td>145</td>
</tr>
<tr>
<td>1987</td>
<td>0.61%</td>
<td>806</td>
<td>41.2</td>
<td>22.3</td>
<td>180</td>
</tr>
<tr>
<td>1988</td>
<td>0.62%</td>
<td>922</td>
<td>41.5</td>
<td>22.8</td>
<td>210</td>
</tr>
<tr>
<td>1989</td>
<td>0.63%</td>
<td>713</td>
<td>41.0</td>
<td>22.8</td>
<td>163</td>
</tr>
<tr>
<td>1990</td>
<td>0.64%</td>
<td>933</td>
<td>36.2</td>
<td>20.7</td>
<td>194</td>
</tr>
<tr>
<td>1991</td>
<td>0.65%</td>
<td>971</td>
<td>37.3</td>
<td>21.6</td>
<td>209</td>
</tr>
<tr>
<td>1992</td>
<td>0.66%</td>
<td>785</td>
<td>36.6</td>
<td>21.5</td>
<td>169</td>
</tr>
<tr>
<td>1993</td>
<td>0.67%</td>
<td>690</td>
<td>36.3</td>
<td>21.7</td>
<td>150</td>
</tr>
<tr>
<td>1994</td>
<td>0.68%</td>
<td>936</td>
<td>33.6</td>
<td>20.5</td>
<td>192</td>
</tr>
<tr>
<td>1995</td>
<td>0.69%</td>
<td>2943</td>
<td>33.8</td>
<td>20.8</td>
<td>613</td>
</tr>
<tr>
<td>1996</td>
<td>0.70%</td>
<td>1991</td>
<td>37.8</td>
<td>23.3</td>
<td>465</td>
</tr>
</tbody>
</table>

# rounded to nearest whole number.
2.1.5 Discussion

This analysis suggests that Chinese immigrant cohorts to Victoria have included approximately 20-26% with LTBI. This is a significant proportion of new arrivals, particularly in light of the very low background rate of LTBI diagnosed in the Victorian-born population (158). Although further assessment of reactivation risk is necessary, a prevalence rate of this magnitude suggests that this and other similar groups may warrant consideration of public health intervention to prevent subsequent active TB infection.

This direct application of national TST survey and immigration data sources provides an estimate of LTBI prevalence in local immigrant cohorts. These estimates are useful for several reasons. In particular, they draw from representative and well-validated national tuberculosis survey data, and use a well-validated international approach to the diagnosis of tuberculosis infection in population studies. However, such data does not exist for all countries of interest, and it is likely that the use of regional or other less completely representative survey data would be required for this approach to be extended beyond Chinese immigrant cohorts.

This approach is limited by several important factors. First, no validation data specifically related to Chinese immigrant cohorts is available, and it may be that migrants are in some way systematically different from the Chinese population as a whole. However, the estimates of TST reactivity are clinically reasonable, and reflect published data from comparable groups. One report identified that 12.2% of a cohort of Chinese orphans were found to have positive TST results; a result somewhat higher than predicted by the national survey ARTI but in a group which is arguably expected to have higher risk of LTBI (159). Another study of newly arrived refugees in Australia found that 31% were TST reactive, in keeping both with their expected higher personal risk of exposure prior to arrival.

A deeper problem is that this approach assumes concordance between TST reactivity and LTBI, which, as reviewed in Chapter 1, imperfectly reflects the actual performance of the TST. Given the recognised occurrence of false positive and
negative TST results, the possibility of adjustment for test performance will be explored in section 2.2.

2.2 Adjusting LTBI prevalence estimates using a latent-class, random effects approach

As reviewed previously, the uncertain relationship between TST-reactivity and LTBI is problematic for optimal understanding of LTBI prevalence. In recent years, there has been interest in mathematical approaches to the problem of estimating test characteristics in the absence of a gold standard. One of these approaches, latent class analysis (LCA), considers the outcomes of multiple tests applied to a given population in order to estimate the performance of each test in detecting the true underlying population of interest(160). This is estimated by assuming that the probability of a positive test (ie reactive TST or positive Quantiferon Gold) is a composite function reflecting both the presence of a group of truly LTB-infected individuals (the latent class) as well as false-positive results in the group of uninfected subjects, and vice versa for negative test results. While previous approaches to latent class analysis have assumed independence of the tests performed, more recent approaches have been extended by the use of a random effects model to consider the possibility of conditional dependence(161). This is important in the case of LTBI diagnostic tests, as it is highly likely that TST and IGRA are positively associated given the similarity of the immunologic responses they evaluate.

The challenges of LTBI diagnosis in the absence of a gold standard have resulted in interest in applying this approach to improving estimates of existing test characteristics. One recent publication from Sadatsafavi et al used data drawn from a systematic review and meta-analysis of LTBI test literature in order to perform random effect, latent class analysis(162). In so doing, estimates of TST test characteristics, such as sensitivity and specificity, have been offered, which, if accurate, could allow for adjustment of existing TST data. This section, then, explores the implications of applying these estimated TST test characteristics to the LTBI prevalence calculated for Chinese immigrant cohorts in the previous section.
2.2.1 Aims

To review the literature related to latent class approaches to improving estimates of LTBI test performance. To explore the impact of adjusting LTBI prevalence estimates based on TST-reactivity through the application of LCA.

2.2.2 Methods

Estimates of the sensitivity and specificity of TST for LTBI were obtained from the published literature as described above. Statistical analysis was planned in two phases. First, the implications of sensitivity and specificity estimates were explored through application to simulated cohorts of 100,000 subjects with a range of TST prevalence from 0.1% to 100%, at 0.1% intervals. A series of virtual 2*2 tables for each cohort were constructed using MATLAB (R2012a, The MathWorks, Nowick, MA, USA). The primary outcome of interest was the likely underlying ‘true’ LTBI prevalence corresponding to a measured prevalence of TST-reactivity. Following this exploratory analysis, a second phase of analysis applied the estimated sensitivity and specificity values to the previously described cohorts of Chinese immigrants to Victoria.

All data used in this analysis is from published literature and publically available sources, and relates to non-identifiable information. According to the rules of our institutions, no application for Human Research Ethics Committee consideration was necessary.

2.2.3 Results

The approach of Sadatsafavi et al, as described above, offered an overall estimate of TST sensitivity and specificity of 0.709 (95% CI 0.658-0.761) and 0.683 (0.522-0.844) respectively.

Figure 2.2.1 shows the resulting calculated TST prevalence for a range of true LTBI prevalence, given assumed test characteristics.
2.2.1 Calculated proportion of immigrants with tuberculin test reactivity given a range of true latent tuberculosis infection prevalence.

Although the trend in figure 2.2.1 is linear, the relationship between a given LTBI prevalence and corresponding TST reactivity changes dramatically over the range of prevalence evaluated. For instance, a population prevalence of 52% will return a TST reactivity rate of roughly 52%; a ratio of approximately 1:1. Figure 2.2.2 shows the ratio of TST reactivity/LTBI prevalence over lower LTBI prevalence ranges. At lower prevalence, an exponentially more significant change is seen, with increasingly large magnitude of difference seen in settings where prevalence is less than 2%.

2.2.2 Ratio of TST reactivity to latent tuberculosis infection for simulated cohorts with <50% prevalence of LTBI
The initial phase of analysis demonstrated that published estimates of sensitivity and specificity were incompatible with the calculated prevalence of TST reactivity in the Chinese immigrant cohort described previously. Moreover, the expected TST positivity on an entirely TB uninfection population is estimated to be 32%, which is higher than all estimates arising from the population surveys in China. Accordingly, the planned second phase of analysis was abandoned.

2.2.4 Discussion

Given the estimates of TST test characteristics, it has been demonstrated that the maximum range of TST positivity would be between approximately 31.7-70.9%. This reflects the growing number of false positive reactions at low LTBI prevalence, and means that populations with either larger or smaller rates of TST reactivity are simply inconsistent with the stated test accuracy.

These results highlight several of the issues involved with applying test accuracy in different settings. Most significantly, it is highly improbable that a test such as the TST will have consistent sensitivity and specificity across a range of populations being influenced, as it is, by factors such as BCG immunisation status, interpreter variability, influence of non-TB mycobacteria and age at which the TST was performed. The issue of setting-specific test accuracy is not related to any particular approach, but will be an inherent limitation of any attempt to offer a sensitivity and specificity of a diagnostic test applicable to a variety of settings.

Latent class analyses are likely to be most use when applied to situations where test performance is consistent. Ideally, this may be a situation where a substantially uniform cohort is evaluated with multiple tests, or perhaps meta-analysis where sufficiently similar cohorts are compared, particularly underlying disease prevalence is static. Results from LCA may be generalisable across such conditions, however, it appears unlikely that a single composite assessment of sensitivity and specificity could ever be readily generalised, especially into situations where LTBI prevalence is not already known to be comparable with the reference standard.
Given this theoretical impasse, section 2.3 will consider an alternative approach, bypassing the elucidation of true LTBI prevalence by considering instead the country- and immigration-cohort specific risk of active TB disease.

2.3 Estimating risk of tuberculosis reactivation in Australian immigration cohorts.

2.3.1 Aims
To estimate the risk of tuberculosis in immigrants to Victoria, Australia. To consider this risk as a function of time since arrival and stratify by age group and region of origin.

2.3.2 Methods
Data on immigration to Victoria was obtained from the Australian Bureau of Statistics in order to define the arrival cohorts from 1975 to 2007. Each annual cohort consisted of all immigrants to Victoria with data collected on age (in 5 year groupings), region of birth (as defined by ABS) and year of arrival to Australia.

The tuberculosis control program database of the Victorian Department of Health (formerly Department of Human Services Victoria) was searched to extract all notified cases of TB from 1995 to 2010. TB notification data was excluded before 1995 due to incomplete records prior to this time. Age at notification, region of birth and year of arrival in Australia (where relevant) was obtained. For the purposes of this analysis, cases were excluded where year of arrival was prior to 1975. New Zealand notifications were not included in the study as denominator data is not reflected in the ABS immigration figures owing to the large number of new Zealanders in Australia not seeking immigration status.

All data used in this analysis was de-identified prior to extraction, with approval for use provided by relevant data managers. According to institutional policy, no review by Human Research Ethics Committee was required.

Statistical Methods
The data were analysed using a survival analysis with proportional hazards assumptions. In order to develop a survival analysis with these data, the aggregate immigration data were transformed into individual-level data according to the following assumptions:

1. death of a proportion of the cohort was incorporated by assuming that after arrival in Australia, immigrants adopted the Australian age-matched population risk of death\(^{(163)}\). Age at death was drawn randomly from Australian life expectancy tables conditional on age at arrival.

2. For the cohort who did not develop active TB, the period of study ended (was censored) either at the imputed year of death or 2010, whichever was earliest.

Once the entire cohort of immigrants was specified, the cohort of notified cases was added. A matched (by age at arrival, year of arrival and region of origin) group of immigrants was deleted from the initial cohort to avoid double entry of immigrants who went on to develop TB.

Survival for the purpose of this study is defined as TB-free survival. The entry point of individuals into the analysis is 1995 or the year of arrival, whichever is the later. For those arriving prior to 1995, the origin point of the risk is taken as the arrival year. For example, a person immigrating in 1990 would be included in the analysis from 1995 but would be assumed to be at risk for tuberculosis for 5 years prior to entry into the analysis.

Classical survival analysis was used to determine the hazard of TB reactivation. The exit point from the study was year of notification for those who developed active TB, or year of study end or imputed year of death for those who were censored (did not develop TB). A Cox proportional hazard assumption was used in estimating the effect of region on risk of reactivation and this was tested visually and using Schoenfeld residuals\(^{(164)}\). The associated factors tested in the proportional hazards analysis were age and region. Age was defined as age at the beginning of the analysis (1995 or year of arrival) and grouped into 5-year age categories. At-risk years (denominators for measure of risk) were adjusted for expected deaths in this cohort. This adjustment was according to age at study entry, following Australian life expectancy tables. A
sensitivity analysis was performed examining the estimated incidence rate of tuberculosis in each age group under different death/attrition assumptions. Calculations were performed using STATA/SE 11.0™.

2.3.3 Results

The data obtained from the Australian Bureau of Statistics, showed the total number of immigrants who arrived into Victoria between 1975 and 2007 (inclusive) from the regions of interest was 768,000. This provided an estimated 9.9 million at-risk years over the study period; i.e. from 1995 to 2010 inclusive. During this time 5347 notifications of tuberculosis were made to the Department of Health, Victoria of which 3712 had recorded information that pertained to this cohort. These were notifications of active tuberculosis in immigrants documented arrival times between 1975 and 2007. Demographic characteristics of those notified and not notified are shown in Table 2.2.

The risk of TB reactivation in Victorian immigrants from high risk areas of Asia, Africa and the Pacific is 100-150 per 100,000 person years for the first 6 years following immigration. The shape of the incidence rate (risk per year) as a function of time since arrival is given in Figure 2.3.1. The risk reduces to around 50 per 100,000 person-after 12 years and then a subsequent risk settles at around 25 per 100,000. Of those who develop tuberculosis during the first 35 years following arrival to Australia, an estimated 50% present within 7 years and only 20% present within 2 years. Figure 2.3.2 shows the cumulative risk profile by country.

| Table 2.2 Demographic characteristics of immigrants who were/were not notified with active tuberculosis in Victoria, 1995-2010 |
|-------------------------------------------------|-----------------|------------------|
| Notified with active TB 1995-2010              | Not notified with active TB |
| Median age at arrival (interquartile range)    | 27 (21-38)      | 26 (13-35)       |
| Proportion of the group that came from:        |                 |                  |
| Europe                                         | 4%              | 31%              |
| Asia Pacific                                   | 77%             | 49%              |
| Africa                                         | 18%             | 15%              |
| America                                        | 1%              | 5%               |
2.3.1 Risk per year of active tuberculosis for immigrants from highest and lowest risk countries of origin.
2.3.2 Cumulative probability of tuberculosis over 35 years after arrival in Victoria, stratified by regions of origin.

The incidence rate of TB reactivation is highly region dependent, as seen in Figure 2.3.2. The regions with highest observed risk are central Asia (predominantly India) and sub-Saharan Africa, with lowest risk seen in immigrants from Europe and North America.

The incidence of tuberculosis in all immigrants stratified by age is given in figure 2.3.3. A bimodal pattern is seen with modes in the 20s and in older age. Fewer observations in the oldest age categories explain the large credible intervals in these groups.
Sensitivity analysis

There was a maximum of 20 years prior to entry into the study observation period, with a mean of 5.5 and a median of 4 years. The method of survival analysis used in this study takes this into account, provided the individuals survive to the observation period. However, if attrition takes place and is not observed (left-truncated data) the resulting incident rate is an estimate necessitating some assumptions (see (165) for a description of left censored data).

The sensitivity of the outcome results to the study assumptions was tested. The first assumption relaxed was that the denominator (all permanent residents to Victoria arriving between 1975 and 2007 inclusive) would undergo attrition at a rate similar to Australian death rates. This assumption could either under or over-estimate the denominator. It could under-estimate the denominator because, studies of immigrants find that in fact the risk of death adjusted for age and sex is actually up to 15% lower for immigrants than for Australian born people (166). Additionally, net migration into the state is also possible. It could over-estimate the at-risk group because death rates may be higher in immigrants in this particular cohort, or there may be a net
migration out of Victoria by these immigrants either interstate or overseas or they may have acquired TB prior to the observation period (reducing their risk of presenting within the observation period).

The dataset was then re-examined under two extreme assumptions. The first sensitivity test was to assume that there was no death or attrition of this cohort at all. The second sensitivity test was to assume that there was a 3% attrition rate per year. To put this into the context of the study, this rate of attrition is approximately the death rate of a 79 year old Australian woman in the year 2000. Hence both of the above sensitivity tests are likely to lie well outside the true range of possibilities.

Figure 2.3.4 shows the results, with the effect of no attrition not markedly different from the baseline assumption. With the 3% attrition assumption, the effect becomes substantial in the over 60 age groups.

![Estimated risk by age group under three assumptions](image)

**2.3.4 Estimated risk by age group under various assumptions regarding death and attrition**

Figure 2.3.5 shows a similar effect on the cumulative risk with higher estimates in the group in whom greater attrition of the denominator (person years at-risk) is assumed, evident after 20 years from arrival in Australia.
2.3.5 Cumulative risk of tuberculosis following immigrant arrival into Australia under three different assumptions.

Regarding the notified cases of active tuberculosis; missed diagnoses are unlikely unless people return home, move interstate or die before their tuberculosis is diagnosed. Excess diagnoses may occur in the case when students - planning to return and never registered as permanent residents - are included in the notified cases.

The second component of the sensitivity analysis assessed the potential impact of student/temporary visitor cases of incident tuberculosis on the analysis. 200 cases (3.7%) were notified and included in the study from individuals who arrived within 2 years of the diagnosis and who were aged 20-29 years. A proportion of these could have been students. All of these people were excluded from the study followed by re-examination of the data. The effect of excluding all possible student cases in these age groups was to reduce the incidence rate from 69 to 58 per 100,000 person years in the 20-24 age-group and from 52 to 44 per 100,000 person years in the 25-29 age-group.
Other age groups were unaffected. Hence there is an 18% reduction in incident rate if all immigrants of this age group who present within two years are excluded. This clearly overstates the number of incident cases that are temporary residents as it includes all immigrants. Figure 2.3. shows the effect of excluding all early presenters with TB on the cumulative risk curve. The bottom line tracks lower than the baseline assumptions because the number of notifications is reduced by 3.7%.

2.3.4 Discussion

This study demonstrates that the risk of active tuberculosis is moderately high in Australian immigrants and this rate is reflective of incidence in regions of origin. The incidence of active tuberculosis soon after arrival is 100-150 per 100,000 in high risk immigrant groups and this is maintained for 5-6 years following arrival in Australia. In the subsequent decade, the risk reduces but remains higher than the Australian born population (estimated 1.5 per 100,000 person-years (167)) for at least 35 years after immigration. The risk of active tuberculosis is age-dependent, with a bimodal increase in incidence in the 20s and after 60 years of age. This finding differs from that of Donald et al. who did not observe a higher rate of tuberculosis in the older group (168, 169). Half the risk of tuberculosis occurred within 6.8 years of arrival to Victoria and 20% within the first two years, a similar result to an earlier study in which half of the risk was in the first five years and 30% in the first 2 years (167).

The strengths of this study include the establishment of a complete immigration cohort as denominator for assessing risk of reactivation of tuberculosis. This method has also allowed assessment of dynamic hazard of TB disease as a function of age, region of origin and time since arrival. This study is limited by its retrospective nature and incomplete capacity to account for short-term visitors; however, continuous statewide data collections have been used in order to minimise reporting bias. Intrastate travel following migration to Australia may potentially introduce discrepancy between location of immigration and TB diagnosis.

Sensitivity analysis shows that if the rates of net migration out of Victoria are much higher than anticipated, this could have led to a substantial under-estimate of risk of tuberculosis in the elderly and those in Australia for greater than 10 years. However,
the qualitative conclusions are the same; namely, that the risk of tuberculosis is age dependent with a second peak in the elderly and that the incidence rate of tuberculosis is highest after arrival but is maintained for many decades above the Australian rate. If this immigrant cohort has death rates lower than the Australian average, the risk of tuberculosis will be only marginally over-estimated in this study. Additionally, there are some limitations intrinsic to the data sources used in this analysis. In particular, denominator data are those provided by immigration statistics and do not capture short-term visitors from these regions.

As expected, it can be seen that region of origin into is an important predictor of subsequent tuberculosis risk. Many regions’ immigrants fall well below the global average incidence of 130 per 100,000, including all regions of Europe, North and South America. South Asian and sub-Saharan African immigrants have the highest incidence, reflecting the incidence in their country of origin. However, it should be noted that risk of progression to active TB disease is not perfectly correlated with risk in countries of origin, which may reflect factors such as socio-economic differences between immigrants and non-immigrants or a ‘healthy-traveller’ bias. Overall, TB incidence in the study cohort is broadly proportional to, but considerably lower than, the incidence in the country of origin. For example, South Asian and sub-Saharan African immigrants have the highest incidence of around 140 and 100 per 100,000 respectively in this study. This compares with the WHO estimates of incidence within these regions of 420-2000 (Pakistan-India) and 490 per 100,000 respectively (171). Our estimates of incidence in South-East Asia are higher than those estimated using Victorian notification data from 1987 to 1992 (170). This earlier study estimated an incidence of 47.5 overall, compared with our estimate of 64 per 100,000 in South-East Asia. The discrepancy could reflect a different mix of immigrants to the region over time, with changes in immigration patterns and higher rates of refugee intake from these populations in recent years.

Age, too, has been demonstrated to be important predictor of risk. Age-specific risk of active tuberculosis in this study shows a peak in the 20s, as in other studies (169). The incidence in under 5 year olds is very low in this study compared with other studies measuring rates of tuberculosis in native populations, probably reflecting the very low risk of primary tuberculosis infection in the Victorian immigrant group. The
incidence in the elderly is very high in this cohort, a feature that has been absent in many studies of developing countries in the past (172). Although the data are sparse for this age group, leading to uncertainty regarding the true incidence in the elderly, the effect size is large; larger in fact than the peak in the 20s.

These findings have several consequences for physicians and public health policy makers in Australia. First, we must revise the notion that risk of reactivation is principally in the first two to three years following arrival in Australia. Second, the marked regional variation in incidence suggests that countries and regions of origin need more refined stratification than simply high, medium and low incidence for TB incidence. Finally, the efficacy and cost-benefit of treatment of latent tuberculosis is highly dependent on risk of reactivation and therefore the findings in this study should be incorporated into a cost-effectiveness analysis in order to determine risk thresholds for the use of various public health strategies for preventing TB disease.

The results of this study are ready to be incorporated into a dynamic model to predict subsequent rates of TB that can be expected in Australia given particular immigration regions and numbers. This can be used to inform policies regarding the strategies to reduce TB in Australia. Although low by global standards, it should be remembered that Victoria TB incidence remains 70 times higher than the WHO Millennium Development Goal target; a situation that is unlikely to improve without the implementation of well-targetted public health strategies incorporating treatment of LTBI.

2.4 Summary of approach to estimating TB risk for public health evaluation

This chapter has considered several novel approaches to improving estimates of LTBI prevalence and tuberculosis risk for potential use in a model evaluating public health strategies. Section 2.1 provided estimates of LTBI prevalence based on Chinese national TST reactivity surveys, while section 2.2 attempted to extend this approach through the use of a mathematical adjustment for test performance. These approaches were demonstrated to be sub-optimal for inclusion in public health evaluation, both on pragmatic and theoretical grounds. Subsequently, an alternative approach has been
presented in section 2.3, which bypasses the problematic issue of LTBI diagnosis through the use of cohort-specific risk of subsequent tuberculosis reactivation. This approach has been shown to perform well in an Australian context, and provides a basis for models evaluating public health strategies, particularly those relating to future tuberculosis disease in immigration cohorts.

The use of regional cohort-specific risk of tuberculosis reactivation has a number of additional advantages from a modelling perspective. Historical data can be incorporated into the baseline model, with the opportunity to continue to refine future evaluations based on trends in tuberculosis risk and other emerging factors. As has been demonstrated in this analysis, such data can also be used to consider cross-cohort issues of significance, including the effects of aging or gender on tuberculosis risk.

Although this approach has been shown to be robust at a population level, further modifications may be possible to provide less coarse assessment of risk. Within-cohort risk adjustments based on factors such as HIV status or the outcome of any diagnostic testing performed may offer further improvements, and will be explored in Chapter 5 prior to incorporation into a final model of tuberculosis in Australia.
3. **Current approaches to management of LTBI in Australasia**

As discussed in the first chapter, the risk of reactivation in patients diagnosed with LTBI can be substantially reduced through appropriate use of antituberculous medications, most commonly isoniazid. While efficacy of such treatment can be around 90% in some situations, there is little evidence regarding how preventative therapy is actually used in the Australian context. No national regulation or data collection mechanism exists, for instance, to monitor and evaluate treatment for latent tuberculosis infection. Neither has there been a systematic review of state and organisational level recommendations and guidelines to consider their prevalence and uniformity across regions. Finally, where various guidelines for treatment decisions do exist, it is not known to what extent individual practitioners act in concordance with them. This information would be valuable, as public health strategies that involve identification and treatment of LTBI are likely to result in decreased incidence of active TB infection. Identifying how LTBI is managed is therefore of considerable importance in low-prevalence settings such as Australasia, and would provide a basis for future interventions and altered treatment approaches.

This chapter, then, will first perform a systematic review of existing guidelines that may apply to latent tuberculosis diagnosis and management in Australasia, including those from regional Departments of Health and both local and international expert bodies. Then, the results of an Australasian survey of actual LTBI practice will be presented and discussed. Finally, the emerging consideration of multi-drug resistant LTBI will be considered, and evidence regarding current management approaches will be presented.

### 3.1 Existing guidelines for the management of LTBI

Australasian clinicians have a variety of guidelines and recommendations to consider when approaching the management of latent tuberculosis infection. Internationally, there are established guidelines from the United States and Britain, both of which have been broadly influential in other countries. Although New Zealand has developed its own national guidelines, no such broad panel of recommendations has been developed in Australia. Instead, most states and territories have produced their
own guidelines, which are supplemented periodically. The National TB Advisory Council of Australia, consisting of public health representatives from each state and territory, has also issued various comments and recommendations on aspects of LTBI, although no complete guideline. Finally, specific expert panels in various areas of clinical practice have also developed guidelines which may exert influence in specific situations; for instance, the Australasian Society for Infectious Diseases has released recommendations for LTBI testing and treatment in recently arrived refugees.

Complicating this situation is the impression that existing guidelines differ in significant ways. Although this has not been formally reviewed, informally clinicians and public health officers report being aware of such differences. The extent of such differences, and the degree to which various guidelines may influence practice, requires summarisation in order to appreciate the background for clinical decision-making in Australia today.

3.1.1 Aim
To review guidelines informing the diagnosis and management of latent tuberculosis infection in Australasia.

3.1.2 Methods
To identify potentially relevant published guidelines, a search of relevant databases was conducted. Scopus, Web of Science, Medline, Pubmed and Cochrane Collection were searched for the terms ‘tuberculosis OR tb’, ‘latent OR screening OR LTBI’ and ‘guideline OR management OR protocol and ‘Australia OR New Zealand OR Australasia’. In addition, references were then hand-searched to identify other relevant publications.

It was anticipated that many existing state and territory guidelines would not have been published in peer-reviewed literature. Accordingly, internet-based searches were conducted, targeting state and territory health departments and professional societies to consider guidelines which may have been employed. Where guidelines for such bodies were not available publicly, direct contact was made with relevant
organisations to clarify whether such guidelines were in existence, and if so, to obtain additional guidelines for review.

In addition to the Australasian guidelines which were the primary focus of this review, consensus guidelines from international organisations, particularly in the United Kingdom and United States, were also reviewed, both in order to contextualise Australasian recommendations and consider the possibility that international guidelines may be directly utilised by local clinicians.

3.1.3 Results

The systematic review of guidelines found 13 guidelines potentially relevant to Australasian clinicians (38, 173-185). Table 2 compares the major features of the identified guidelines, highlighting recommendations for risk groups, screening tests and treatment regimens employed.

Table 3.1 Summary of guidelines potentially relevant to Australasian management of latent tuberculosis infection

<table>
<thead>
<tr>
<th>Organisatio n</th>
<th>Who gets tested?</th>
<th>Special focus groups for treatment</th>
<th>What test is used?</th>
<th>Treatment if LTBI diagnosed? (HIV negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australasian Society for Infectious Diseases 2009(173)</td>
<td>All refugees within 2 months of arrival</td>
<td>&lt;34 years, HIV infected, abnormal CXR</td>
<td>Either TST or IGRA</td>
<td>6-9 months of isoniazid (H)</td>
</tr>
<tr>
<td>Queensland Health 2009 (175)</td>
<td>Close contacts of active TB (household or &gt;8 hours in same environment)</td>
<td>Migrants with abnormal CXR get treatment regardless of age.</td>
<td>TST</td>
<td>H</td>
</tr>
<tr>
<td>UK National Institute for Clinical Excellence (176)</td>
<td>Close contacts (household or &gt;8 hours), new entrants to UK from high prevalence countries. Casual contacts if a large number of positive close contacts found (ie seems more infectious)</td>
<td>&lt;36, HIV, healthcare workers (any age), abnormal CXR</td>
<td>2 stage - TST then IGRA (if &gt;6 and no BCG or &gt;15 and BCG)</td>
<td>6H or 3HR</td>
</tr>
<tr>
<td>WA</td>
<td>Refugees and migrants</td>
<td>IGRA, Mantoux</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

80
<table>
<thead>
<tr>
<th>Authority</th>
<th>Target Group</th>
<th>Test Type</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW Health (177)</td>
<td>Patients starting TNF inhibitors</td>
<td>TST</td>
<td>9H</td>
</tr>
<tr>
<td>NSW Health (180)</td>
<td>High risk contacts (household, close friends/colleagues), contacts with higher risk of progression regardless of degree of contact (&lt;5, HIV, &gt;15mg pred, immunosuppressives, medical conditions, gastrectomy)</td>
<td>TST</td>
<td>9H</td>
</tr>
<tr>
<td>National Tuberculosis Advisory Committee 2014</td>
<td>Close contacts</td>
<td>TST</td>
<td>9H</td>
</tr>
<tr>
<td>Ministry of Health NZ 2003 (181)</td>
<td>Close contacts, refugees &lt;16 years, increased risk due to medical therapy, HCW</td>
<td>Either TST or IGRA; TST if &lt;7</td>
<td>6H or 3HR</td>
</tr>
<tr>
<td>Ministry of Health NZ 2010 (182)</td>
<td>Close contacts, high risk populations</td>
<td>TST</td>
<td>9H</td>
</tr>
<tr>
<td>US Centres for Disease Control and Prevention 2000 (38)</td>
<td>Migrants/refugees, prisoners, recent contact, high risk medical conditions</td>
<td>IGRA</td>
<td></td>
</tr>
<tr>
<td>US Centres for Disease Control and Prevention 2010 (183)</td>
<td>Recent contacts, HIV, HCW, medical conditions, IVDU, immigrants from high prevalence countries</td>
<td>IGRA</td>
<td></td>
</tr>
</tbody>
</table>

3.1.4 Discussion

When comparing major guidelines relevant to an Australasian context, it can be seen that they differ in several important ways. First, although all guidelines currently
recommend isoniazid as first-line therapy for patients without known drug-resistance, they are not consistent on recommendations for the duration of therapy. All guidelines suggest that isoniazid therapy between 6-12 months is appropriate, however, while the British guidelines clearly recommend 6 months, US and several Australian states prefer 9 months. Several districts have opted to refer the decision to clinician preference, leaving open the debate regarding optimal duration of therapy. Finally, the US CDC has recently recommended the use of shorter-course isoniazid and rifapentine therapy as an alternative to 9 months of isoniazid; a recommendation which has not yet been included in other guidelines internationally.

Second, there is continued dispute with relation to the preferred test for the diagnosis of LTBI. Some jurisdictions, such as Queensland and NSW, have elected to continue to use the TST alone for diagnosis, while others such as West Australia have moved to IGRA as the preferred option. Several authorities recommend a mixed approach; the UK guidelines, for instance, suggesting a TST followed by IGRA if positive. Finally, while the US guidelines indicate that the tests may be used interchangeably, West Australia recommends TST only if IGRA is not possible, and the Northern Territories recommends IGRA only if TST is contraindicated. There is clearly a substantial degree of variation regarding the regional perceptions of IGRA introduction, while several districts have modified their use over the last 5 years (CDC, NZ).

Guidelines that discussed the use of TNF-inhibitors were uniform in their recommendations for pre-treatment testing and treatment. However, the majority of guidelines, particularly Australian state and territory guidelines, do not comment on this risk group.

Finally, while there is general uniformity concerning approaches to LTBI testing and treatment in high risk patients, there is variation and lack of specificity in most regarding establishing which moderate-risk patients should be tested and receive therapy.
3.2 LTBI management survey

As reviewed in the preceding section, there exist a range of guidelines to which clinicians in Australia and New Zealand may refer. In many cases these guidelines overlap, with some State and Territory guidelines potentially in conflict with national statements or influential international recommendations. However, until recently there was little evidence regarding actual practice in the management of LTBI in Australasia. In order to gain understanding of how LTBI is currently being managed in Australasia, and to appreciate the impact of the various guidelines outlined above, a survey was conducted of infectious diseases and respiratory physicians engaged in LTBI treatment(186). The aims of this survey were both to review current practice and to allow an assessment of concordance with existing guidelines in order to determine whether a de facto uniformity of approach predominated.

3.2.1 Methods

All currently practicing infectious diseases and respiratory physicians and trainees were eligible to participate in this study. Potential participants were contacted through existing email distribution lists for the relevant professional organisations (Australasian Society of Infectious Diseases and the Thoracic Society of Australia and New Zealand). Potential participants were invited to complete an internet-based questionnaire (presented here at the end of the methods section) if their usual clinical practice involved management of adult patients with known or suspected latent TB infection.

Respondents to the initial email contact were directed to an independent online survey site. Participant information was collected concerning type of training (infectious diseases or respiratory physicians) and extent of involvement with the management of latent tuberculosis infection (number of patients seen and years of practice). Participants were then asked to respond to 12 short scenarios related to latent TB infection.

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3 It should be noted that the material included in this section relates to a survey conducted by Dr Justin Denholm and Dr Emma McBryde, the doctoral candidate and primary supervisor respectively. Given the relevance to this discussion the work is presented here in summary form, however this work was conducted prior to commencement of PhD studies, and should not be considered as a contribution to this present thesis.
infection and management (Appendix 1). All responses were of a ‘best-answer’ type to four multiple-choice options.

Survey responses were recorded, and basic descriptive statistics were performed using Excel™. Responses were then combined into binary options for intra-group comparison, and two-tailed p values were calculated using $X^2$ testing or Fisher’s exact test for values <5.

This study was approved by the Melbourne Health Human Research Ethics Committee as a quality assurance activity. No individual identifying information was recorded or collected, and participation was voluntary.

Survey questions

Demographics
   a. Role (ID Registrar/Consultant)
   b. Number of patients seen for LTBI annually
   c. Years of practice (years)

Scenario 1. A 25 year old recent immigrant from mainland China is referred after a positive TST test (12mm). He is asymptomatic with a normal CXR. He reports a history of BCG vaccination. What is your next step in management?
   a. Treat with isoniazid for LTBI
   b. Repeat TST
   c. Perform γ-interferon (eg Quantiferon Gold) assay
   d. Review in 3/12

Scenario 2. A 32 year old nurse is being screened for LTBI 6/12 after an occupational exposure to active pulmonary TB. Quantiferon testing is strongly reactive to both mitogen and TB-specific antigens. He reports a dry cough and 1 kg loss of weight over the last 2/12. CXR demonstrates scarring in the right upper lobe. What is your next step in management?
   a. Treat with isoniazid for LTBI
   b. Empiric therapy for active TB
   c. Perform TST
   d. Bronchoscopy

Scenario 3. A 29 year old physiotherapist has been assessed for LTBI after exposure to a patient with known isoniazid-resistant TB. She is asymptomatic with a normal CXR, and a positive quantiferon test for both mitogen and TB-specific antigens. You elect to treat her LTBI with:
   a. Isoniazid 300mg for 9/12
   b. Isoniazid 600mg for 9/12
   c. Rifampicin 600mg for 4/12
Scenario 4. You have diagnosed LTBI in a 36 year old HIV positive man not currently on ARV therapy. His most recent CD4+ count is 190, with an HIV VL of >100,000. In addition to appropriate management of his HIV, his LTBI would be best managed by:

a. Isoniazid 300mg for 9/12
b. Isoniazid 300mg for 12/12
c. Isoniazid 300mg until CD4+ count is greater than 350
d. Isoniazid 300mg and Rifabutin 600mg for 4/12

Scenario 5. You have been managing a 46 year old man with LTBI, and started isoniazid treatment 1/12 ago. From a normal baseline liver function, his ALT has risen to 120 µg/dL (normal range <45). He is asymptomatic. It would be most appropriate to:

a. Continue isoniazid at current dose
b. Reduce isoniazid dose to 200mg daily and monitor LFT
c. Cease isoniazid and wait for LFT to normalise
d. Change isoniazid to rifampicin

Scenario 6. A 46 year old woman with rheumatoid arthritis has been diagnosed with LTBI. She has been prescribed methotrexate for 5 years, and has a baseline ALT of 65 (normal range <45). You decide to treat for LTBI; which regimen would be most appropriate?

a. Isoniazid 300mg for 9/12
b. Rifampicin 600mg for 4/12
c. Moxifloxacin 400mg 6/12
d. Isoniazid 150mg for 9/12

Scenario 7. You have screened a 51 year old Indonesian woman for LTBI. She is asymptomatic with a normal CXR, and has a positive quantiferon test. She was treated for pulmonary TB when she arrived in Australia 12 years ago with 2HRZE/4HR and has had no recurrent symptoms or known exposure.

a. Treat with isoniazid for LTBI
b. Perform TST
c. Treat with isoniazid and rifampicin for ?drug resistant LTBI
d. Observe without treatment

Scenario 8. You have decided to start a 33 year old man on isoniazid for LTBI, and are discussing potential side effects. He has no comorbidities and normal baseline liver function tests. How likely is he to get significant isoniazid-associated hepatitis (ALT >5 times ULN) during his treatment?

a. 0.1-0.5%
b. 1-2%
c. 2-5%
d. 5-10%

Scenario 9. You have been treating a 45 year old woman with isoniazid for LTBI. She has frequently missed doses, and when she presents for her 9/12 review pharmacy
records suggest that she has taken 220 doses over her 9/12 course (intended total 270 doses). She has tolerated isoniazid without significant side effects.

For her LTBI treatment, you will:

a. Cease isoniazid as planned
b. Continue isoniazid until 270 doses taken
c. Extend course to a total of 12/12
d. Repeat quantiferon testing

Scenario 10. You have been asked to assess a 55 year old woman prior to commencement of infliximab for severe rheumatoid arthritis. She was born in Egypt and has lived in Australia for 22 years. She has never had active tuberculosis and is unsure if she has had BCG vaccination. She has a normal CXR. Her quantiferon test is non-reactive to both mitogen and TB-specific antigen, and has been reported as indeterminate.

Your next step will be:

a. Repeat quantiferon in 3/12
b. Perform TST
c. Treat for LTBI
d. Proceed with infliximab and observe

Scenario 11. After exposure to a family member with active TB, a 14 week pregnant woman is reviewed for LTBI. She is asymptomatic and has a positive quantiferon test. Your next step of management will be:

a. CXR to exclude active TB
b. Treat for LTBI immediately
c. Treat for LTBI after second trimester
d. Delay treatment until after delivery

Scenario 12. A 40 year old man has been referred for assessment after recent migration from India. He had BCG vaccination in childhood. He is not known to have had active TB and has never been treated, but he reports that 2 immediate family members had confirmed TB several years ago. Currently, he has a normal CXR and is asymptomatic. Quantiferon testing is borderline-reactive to both mitogen and TB-specific antigen, and has been reported as indeterminate.

What is your next step in management?

a. Repeat quantiferon in 3/12
b. Treat for LTBI
c. Perform TST
d. Clinical review annually (+/- CXR)

3.2.2 Results

Participants

A total of 126 respiratory and infectious diseases clinicians completed the questionnaire. 95 participants were physicians, representing 9.6% of all infectious diseases and respiratory physicians in Australia and New Zealand (386 infectious
diseases physicians and 599 respiratory physicians; data supplied by relevant specialist societies). Participant information is shown in table 3.2 below.

Table 3.2 – Latent tuberculosis survey participant information

<table>
<thead>
<tr>
<th>Duration of practice (years)</th>
<th>ID Physician (n=45)</th>
<th>Respiratory Physician (n=50)</th>
<th>ID trainee (n=21)</th>
<th>Respiratory trainee (n=10)</th>
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<tr>
<td>&gt;10</td>
<td>18</td>
<td>22</td>
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<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients/month</th>
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<th>2 to 5</th>
<th>6 to 10</th>
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<td>6 to 10</td>
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<td>2</td>
</tr>
<tr>
<td>&gt;10</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

Respondents were generally experienced clinicians, with 95/126 (75.4%) being consultant physicians and 70/126 (55.6%) reporting having managed LTBI for more than 5 years. Currently, most clinicians were in relatively low-volume practice, with 79/126 (62.7%) seeing less than 5 patients for assessment of LTBI per month.

Responses to scenarios have been grouped below by theme.

**Diagnosis**

Overall, clinicians were more likely to use an IGRA than TST for the diagnosis of LTBI. Several questions offered a choice between the two tests in a variety of situations, with respondents opting for IGRA more frequently (62.8% vs 37.2%; p<0.05). Most clinicians would use an IGRA for diagnosis of LTBI in patients known to have had BCG vaccination, and while clinicians frequently reported using an IGRA after a positive TST (84/126, 66.7%), no respondent performed TST following a positive IGRA. Following an indeterminate IGRA, clinicians were more likely to perform TST (32.9%) than to repeat IGRA (24.2%). Additionally, a small number of
respondents (4/126, 3.2%) indicated that they would use IGRA becoming negative as a guide to successful therapy.

When presented with a 25-year old patient with a positive TST and a history of childhood BCG vaccination, 84/126 (66.7%) of clinicians reported that they would proceed to an interferon-gamma assay before considering whether treatment for LTBI was appropriate. 24 (19.0%) would review in 3 months, while 15 (11.9%) would start isoniazid therapy immediately.

An immigrant from a high-prevalence country being screened for LTBI prior to starting infliximab was found to have an indeterminate interferon-gamma response. 28.6% (36/126) of clinicians reported that they would proceed with infliximab therapy and observe, while 9.5% (12/126) would initiate LTBI therapy prior to infliximab. The remainder indicated they would perform further tests to diagnose LTBI, either repeating IGRA (17/78; 21.8%) or TST (61/78; 78.2%).

In a separate question, respondents were also asked how they would manage an indeterminate interferon-gamma test in a 40 year old recent immigrant from a country with high TB prevalence. 66/126 (52.4%) said they would perform another test (44/126 would repeat IGRA, 22/126 would perform TST), while 47/126 (37.3%) would review clinically and 13/126 (10.3%) would initiate treatment for LTBI.

*Initiating LTBI therapy*

Respondents were asked to choose appropriate therapy for confirmed LTBI in a patient exposed to known isoniazid-monoresistant TB. 77/126 (61.1%) prescribed rifampicin (600mg daily for 4/12), while 20/126 (15.9%) opted for an isoniazid-based regimen (300mg for 6 or 9/12). 23% (29/126) said they would prescribe combination therapy with ethambutol and pyrazinamide for 4/12.

A 14-week pregnant patient with recent exposure to a case of active tuberculosis was found to have a positive interferon-gamma assay. 41/126 (32.5%) indicated that they would delay management until after delivery, while the remainder suggested some earlier investigation or therapy. Of those who would proceed with management in
pregnancy, 66/85 would perform a CXR to exclude active TB, while the remaining 19/85 would immediately start treatment for LTBI.

**Side-effects of LTBI therapy**

Respondents were asked to estimate the likelihood of a young man developing severe hepatotoxicity (Alanine transaminase (ALT) >5 times ULN) while receiving isoniazid monotherapy. Responses differed considerably; while 52/126 (43.7%) believed the incidence was 0.1-0.5%, 21/126 (15.7%) thought it was >5%. A number of large studies and reviews of isoniazid monotherapy have concluded that the incidence of serious hepatitis (ALT >5 ULN) is between 0.1-0.56%; a figure taken as the correct answer to this question (73-75). Clinicians who reported seeing more than 5 patients/month for the management of LTBI were very likely to answer correctly (32/37, 86.5%). They were significantly more likely to respond correctly than clinicians who had more general experience (>5 years practice) but were assessing less than 5 patient/month for LTBI (20/51, 39.2%; p<0.0001) or the overall group (p<0.0001).

When managing an asymptomatic patient with an ALT that became elevated while receiving isoniazid, but remained less than 3 times the upper limit of normal, 84/126 (66.7%) elected to continue therapy without modification. Interestingly, 13/126 respondents reported that they would dose-reduce isoniazid in this setting. This strategy was more common in respiratory practitioners (11/60, 18%) than in infectious diseases practitioners (2/66, 3%; p<0.001), and was particularly common amongst respiratory trainees (5/10; 50%).

**Review and completing therapy**

Clinicians were asked how frequently they would routinely review asymptomatic young patients with normal baseline liver function testing (LFT), and whether they would routinely perform serial LFT during therapy. Results are shown in figure 3.1. No significant differences were seen between infectious diseases and respiratory physicians.
Respondents were also asked to consider a 45-year-old woman who was found to have missed 50 doses from a planned 9/12 course of isoniazid therapy. 55/126 (43.7%) of clinicians would cease therapy as planned, with the remainder extending the course. 43/126 reported that they would continue for a further 3/12, while 24/126 would continue until all planned doses had been administered.

3.2.3 Discussion

This study found that participating clinicians in Australia and New Zealand reported significant variation in a variety of common practices related to the diagnosis and management of LTBI. These variations included testing algorithms, treatment selection and duration, and follow-up strategies, as well as estimated frequency of adverse effects on therapy. Such variation is likely to detract from the public health
impact resulting from LTBI management, and appropriate strategies to improve practice should be considered.

Participants included both respiratory and infectious diseases clinicians, were recruited across all Australian states and territories and New Zealand and provided actual practice information about current clinical management of LTBI in Australia and New Zealand. Due to the ‘blanket’ distribution of the survey to members of the professional societies of infectious diseases and respiratory physicians, this study was limited by an inability to characterise non-responders and participant self-reporting. However, the survey captured approximately 10% of all infectious diseases and respiratory physicians in Australia and New Zealand, which is anecdotally consistent with the proportion conducting LTBI management, and potential subjects were asked to self-select on the basis of having clinical practices including regular management of LTBI. It is likely, therefore, that the group sampled in this study provides a more helpful assessment of actual LTBI management in Australia and New Zealand than a more complete survey of infectious diseases and respiratory clinicians would have done.

The variation in practice seen in this study is likely to reflect several issues. Although some aspects of LTBI management are well studied, such as treatment-limiting side effects of chemotherapy, a paucity of data exists on certain issues, such as best practice follow-up strategies. Some discrepancies in practice may reflect a lack of awareness, particularly amongst less experienced clinicians. Additionally, approaches to LTBI management have changed considerably over several decades, and clinicians not actively involved in regular clinical practice may not be aware of recent changes.

Optimal management of LTBI has the potential to result in a variety of public health benefits. It should minimise the risk of reactivation TB infection, decreasing both the health burden of infection and the degree of secondary transmission. It may also assist in preventing the emergence of multi-drug resistant strains of TB, and be applied in ways that are both acceptable and cost-effective. In order to accomplish these aims, however, strategies must be rational and consistently applied. Several aspects of this study highlight current practice issues that have the potential to work against these goals, and require further comment.
A number of clinicians in this survey reported dose-reduction of isoniazid when managing isoniazid-associated hepatotoxicity. Dose-reduction of isoniazid has been demonstrated to decrease early bactericidal activity when doses less than 300mg/day are used, and such regimens are not recommended(189, 190). A minority of clinicians also reported using isoniazid-based regimens for the treatment of isoniazid-resistant LTBI infection, a practice that has been shown to be ineffective(191). Effective public health strategies for addressing LTBI require consistent and rational prescribing practices. Educational strategies related to rational therapeutic prescribing may be of value in strengthening such programs, particularly targeting less experienced prescribers.

As reviewed in chapter 1, rational assessment of the cost-effectiveness of any LTBI strategy is hampered by the lack of a gold-standard diagnostic test. Such difficulties may be further compounded by several aspects of the responses observed in this present study. For instance, significant variation was reported in the frequency of follow-up review and tests of liver function and damage (LFT) in patients on isoniazid. Little evidence exists to strongly support specific practices, which is reflected in variation between international guidelines. For instance, the American Thoracic Society recommends monthly clinical review without repeated LFT in low-risk patients, while British guidelines do not offer a specific review program(176,192). Different review programs are associated with substantial variation in cost, and New Zealand LTBI guidelines recommend clinical review and LFT be performed 3-monthly, based specifically on cost-effectiveness data(194). Cost-effectiveness issues also arise through the rational use of new diagnostic technologies such as IGRA. A small number of respondents reported using IGRA to determine whether LTBI therapy had been successful, an application for which evidence to date is not supportive of(195). A number of clinicians also reported performing TST following indeterminate IGRA, which would be expected to have a low yield based on published comparisons and unlikely to be cost-effective(196). Finally, there is some evidence that performing multiple diagnostic tests may interfere with individual test performance; a finding which would further impair rational approaches to ensuring cost-effective LTBI therapy(197).
3.2.4 Conclusion

This study found that participating clinicians in Australia and New Zealand reported significant variation in a variety of common practices related to the diagnosis and management of LTBI. These variations included testing algorithms, treatment selection and duration, and follow-up strategies, as well as estimated frequency of adverse effects on therapy. Such variation is likely to detract from the public health impact resulting from LTBI management, and appropriate strategies to improve practice will be considered in subsequent sections of this thesis.

3.3 Treatment of suspected multidrug resistant LTBI

As reviewed above, the considerable bulk of therapies investigated for the treatment of latent TB infection are intended for infections with isolates sensitive to first-line tuberculosis medications. It has been suggested that latent MDR TB may be less likely to reactivate than infection caused by drug-susceptible organisms, a finding supported by notification data in at least one national surveillance program(111, 112). It is presently difficult to quantify the likelihood of reactivation MDR TB, however, and the consequences of developing active infection are significant.

Even in settings where rates of active MDR TB are extremely high, such as countries of the former Soviet Union, it is unlikely that the routine use of second-line antituberculosis medications for LTBI will be justifiable given the risks of subsequent reinfection and contributing to further drug resistance. However, individualised treatment regimens may be considered in patients based on sensitivity testing in contact isolates and personal risk/benefit considerations.

3.4 Potential impact of optimizing current management practices on public health

The variations in practice described in this chapter are likely to reflect several issues. Although some aspects of LTBI management are well studied, such as treatment-limiting side effects of chemotherapy, a paucity of data exists on certain issues, such as best practice follow-up strategies. Some discrepancies in practice may reflect a lack of awareness, particularly amongst less experienced clinicians. Additionally,
approaches to LTBI management have changed considerably over several decades, and clinicians not actively involved in regular clinical practice may not be aware of recent changes.

Optimal management of LTBI has the potential to result in a variety of public health benefits. It should minimise the risk of reactivation TB disease, decreasing both the health burden to the individual and the degree of secondary transmission. It should also assist in preventing the emergence of multi-drug resistant strains of TB, through effective exclusion of active disease prior to LTBI treatment, and be applied in ways that are both acceptable and cost-effective. In order to accomplish these aims, however, strategies must be rational and consistently applied. Several aspects of this study highlight current practice issues that have the potential to work against these goals, and require further comment.

3.4.1 Limiting drug resistance in TB

A number of clinicians in this survey reported dose-reduction of isoniazid when managing isoniazid-associated hepatotoxicity. Dose-reduction of isoniazid has been demonstrated to decrease early bactericidal activity when doses less than 300mg/day are used, and such regimens are not recommended(189, 190). A minority of clinicians also reported using isoniazid-based regimens for the treatment of isoniazid-resistant LTBI infection. Both practices are likely to be ineffective and may contribute to reactivation of drug-resistant tuberculosis. Effective public health strategies for addressing LTBI require consistent and rational prescribing practices. Educational strategies related to rational therapeutic prescribing may be of value in strengthening such programs, particularly targeting less experienced prescribers.

3.4.2 Improved cost-effectiveness

Significant variation was reported in the frequency of follow-up review and liver function testing (LFT) in patients on isoniazid. Little evidence exists to strongly support specific practices and the guidelines of the American Thoracic Society recommend monthly clinical review without repeated LFT in low-risk patients, while British guidelines do not offer a specific review program(174, 176). Different review
programs are associated with substantial variation in cost, and New Zealand LTBI guidelines recommend clinical review and LFT be performed 3-monthly, based specifically on cost-effectiveness data(194). Cost-effectiveness issues also arise through the rational use of new diagnostic technologies such as IGRA. A small number of respondents reported using IGRA to determine whether LTBI therapy had been successful, an application for which evidence to date is not supportive of(195). A number of clinicians also reported performing TST following indeterminate IGRA, which would be expected to have a low yield based on published comparisons and unlikely to be cost-effective(196).

3.5 Conclusions

The majority of cases of active tuberculosis infection in Australasia are reactivation from latent infection, most commonly acquired in high-prevalence countries. Effective strategies targeting LTBI can reasonably be expected to reduce the burden of subsequent active infections. Such strategies must, however, be rational and consistently applied. Inconsistency in practice related to the management of latent TB infection is likely to initially affect immigrants and refugees disproportionately given that they bear the burden of TB infection and disease in Australasia today. Difficulties involved in managing LTBI in these populations may include cultural and linguistic barriers, co-existing medical conditions and geographic relocation, and should not be further compounded by unnecessary practice variation.

Recognition of significant differences surrounding many areas of current management of LTBI in Australasia is important, and should provide impetus for developing strategies to improve consistency. This review has shown that Australasian practice does not consistently follow published international guidelines, and indeed could not given the conflicts between various iterations in current use. Accordingly, the development, implementation and regular updating of guidelines specifically for the Australasian context are important. Such guidelines must be developed with input from a variety of stakeholders to assist with ensuring broad acceptability. The results of this study suggest that further education may be useful, particularly for registrars and less experienced clinicians. Finally, further research into the areas of practice for
which little data exist is critical and may ultimately be necessary to resolve differences in practice. In particular, very limited evidence exists to direct practice related to the management of MDR LTBI. In a local Australian context, it is also unclear currently how cases of LTBI acquired from MDR TB index cases are being managed, and what specific risks arise from exposure and any treatment provided. The next section of this thesis, then, will report an investigation of real-world outcomes following MDR TB exposure, including an evaluation of actual practice in Victoria, Australia, and estimated risk of active infection after acquisition of MDR LTBI.
4. Multidrug resistant LTBI in Victoria, Australia

As outlined in the previous chapter, evidence to direct optimal management following MDR TB contact is lacking. Additionally, while several studies have outlined management approaches and outcomes following close contact in countries with a high-prevalence of tuberculosis infection, little published data exists to describe current management in low-prevalence settings (198-200). Information arising from such settings is critical, particularly as it would allow more accurate estimation of progression to active disease without confounding by multiple episodes of infection. An improved understanding of current management approaches used locally would also be valuable in preparing an accurate model of tuberculosis infection in Australia, including an assessment of risk associated with MDR TB exposure and outcomes following any treatment provided.

Although MDR TB remains relatively uncommon in Australia, in 2008 an estimated 440,000 cases of multi-drug resistant tuberculosis (MDR TB) occurred worldwide (200). MDR TB is of high importance for a variety of reasons, including the need for prolonged therapy, worse treatment outcomes and side effects and increased cost of treatment for individuals and public health systems (186-188). Increasing rates of MDR TB in many countries have prompted concern to identify effective new management strategies for treating diagnosed cases and preventing new infections from arising (201-203).

MDR TB may occur in the setting of failed treatment of initially drug-sensitive infection, or may be acquired de novo from an MDR index case (204). However, the considerable bulk of management approaches for latent tuberculosis infection (LTBI), including contact identification, medical treatment and follow up protocols, are intended for infections with isolates sensitive to first-line tuberculosis medications (186). In the context of an increasing global burden of MDR TB, the presumption of infection caused by drug-sensitive TB isolates may not be justified in some clinical settings. Most commonly, this relates to people known to have been

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significantly exposed to a source of sputum smear-positive MDR TB. It has been suggested that latent MDR TB may be less likely to reactivate than infection caused by drug-susceptible organisms, a finding supported by notification data in at least one national surveillance program(111, 112) However, it is presently difficult to quantify the likelihood of latent MDR TB (MDR LTBI) progressing to active disease, partly because data regarding latent reactivation is confounded by superimposed reinfection in most areas internationally.

Victoria, Australia is a state with a population of around 5.5 million people. TB incidence is approximately 7/100,000 population/year, with 85% of cases occurring in residents born overseas. Victoria has a low prevalence of drug-resistant infection, with MDR TB consisting of approximately 0.5-2.4% of cultured isolates(206). Local contact tracing and genotypic data suggest that clustering is infrequent and the considerable majority of cases arise from reactivation of LTBI rather than local transmission. All cases of TB in Victoria are notified to the Department of Health TB program, with management of both active and latent infection provided free of charge via public hospital networks. Contact tracing is performed via the TB program, with subsequent referral to public hospital TB clinics where consideration of chemopreventative therapy is required. A state-wide reference laboratory (Victorian Infectious Diseases Reference Laboratory; VIDRL) performs drug susceptibility and molecular testing on all isolates of TB cultured from any laboratory in Victoria.

4.1 Aims

The primary aim of this study was to perform enhanced long-term follow up of people previously identified as contacts of MDR TB cases through routine contact tracing in Victoria, Australia. This study aimed to review management approaches and assess outcomes following exposure, particularly development of MDR TB disease.

4.2 Methods

A retrospective review of MDR TB contacts identified by the Victorian Department of Health from January 1995 to December 2010 was performed. Following notification of cases of active TB in Victoria, contact tracing is performed routinely.
By established Victorian Department of Health protocol, ‘contacts’ are considered to be those having more than 8 hours of cumulative exposure to potentially infective people. The designation of potential infectivity is applied to all patients with symptomatic pulmonary disease, whether smear positive or negative, and excludes those with extra-pulmonary disease only. Baseline and 3-month tuberculin skin testing (TST) is routinely performed for those considered contacts, with those testing positive referred for specialist medical review and consideration of preventative therapy. TST reactions of ≥10mm are considered positive, except in the case of children <5 or immunocompromised contacts, where a threshold of ≥5mm is employed. For the purposes of this review, a final determination of whether contacts had acquired LTBI was based on the outcome of specialist medical assessment, including clinical review and additional investigations where considered necessary.

Records for the TB Control Program were hand-searched to identify both cases of MDR TB and those identified as potential contacts by contemporaneous routine surveillance. No exclusion criteria were applied to contacts. A separate existing statewide TB database from the Victorian Infectious Diseases Reference Laboratory was also searched to identify MDR isolates, with results cross-checked to ensure complete identification.

Molecular evaluation of the MDR strains was performed on isolates since 2002, using conventional Mycobacterial Interspersed Repetitive Unit (MIRU) typing methods (207, 208). Initially 15 loci were amplified for each strain, with numbers of repeats estimated and profiles compared using BioNumerics Version 5.0. Strains that were found to have identical profiles but did not have a recognized epidemiological link were subjected to further typing using 7 extra loci to determine if the strains could be further discriminated (209).

For each contact identified through existing databases, follow-up information was sought in a variety of ways. First, computerized public hospital medical record and pharmacy databases were reviewed for contacts to identify any assessment or management following exposure. Medical and pharmacy records were then retrieved and hand-searched for information regarding the investigation and management after MDR TB exposure. If any management was performed outside of public hospitals,
records were sought from individual medical practitioners to supplement available data. Secondly, Victorian Department of Health and state laboratory databases were reviewed to identify any contacts subsequently diagnosed with active TB. Finally, wherever additional information from patients was required, telephone contact was sought to discuss their course since exposure and to provide additional information not routinely recorded in clinical databases. Total follow up periods were calculated from the date of exposure (as determined by initial contact tracing exercise) to the date of final data extraction from TB reference laboratory.

Statistical analysis was performed with Stata 10.1 (StataCorp, Tx, USA). Descriptive analysis was performed with frequency counts reported for each outcome of interest. Where possible, incidence rates were expressed as events/100,000 person/years of follow up. Incidence rates were also calculated separately for the first two years following exposure. Contacts were considered to have been diagnosed with LTBI based on the decision of contemporaneous treating clinicians, including CXR, TST and interferon-gamma release (IGRA) assay results. Contacts with LTBI were considered to have been treated with appropriate preventative therapy if the prescribed regimen contained at least one active agent on the basis of index susceptibility testing. Comparisons between groups were made with Fisher’s Exact Test.

Ethical review and approval of this study was performed by the Human Research Ethics Committees for Melbourne Health and the Victorian Department of Health.
Questions from telephone interview script

1. Have you [Has your child] ever had a TB vaccine (BCG vaccine)? If so, how old were you [they]?

2. Our records show that you were [your child was] tested for tuberculosis in [Month/Year]. Do you remember this occurring? Why were you [they] tested?

3. Did you [they] go to a clinic or hospital for further tuberculosis testing after this?

4. Did you [they] ever have a course of medication to treat tuberculosis? Do you remember what this involved?
   a. If so, did you [they] have any side effects or problems with the treatment?
   b. Did you [they] complete the treatment?

5. Since being tested with the Department of Health, have you [they] ever been unwell with tuberculosis?

6. Have you [has your child] travelled overseas since your testing? Where did you go and for how long?

7. Have you ever been told you [your child] had TB infection while outside Victoria?
   a. If so, where and when did this happen?
   b. Do you remember what tests and/or treatment you [they] received?

8. Do you [they] have any ongoing medical review for tuberculosis now?
4.3 Results

Forty-seven cases of MDR TB were identified in Victoria over a 16 year period (1995 to end 2010). Of these, 12 cases (25.5%) had extrapulmonary disease only. Amongst 35 cases of pulmonary MDR TB, 22 (62.9%) were sputum smear positive on initial presentation. One case was co-infected with HIV.

A mycobacterial dendrogram of isolates is shown in figure 4.3.1. Based on the initial 15 loci profiles, there were 5 apparent clusters identified. Three clusters involved 2 strains, one involved 3 strains and the final cluster involved 6 strains which were all found to be members of the Beijing lineage of *M. tuberculosis*. Two of the clustered strains were from the same patient who had isolations of MDR TB in 2003 and in 2010. The cluster involving 3 strains was a recognized cluster where contact tracing agreed with typing results and was considered to have involved recent transmission. The remaining strains that were subjected to further typing (figure 4.3.2) gave only 2 strains with identical typing patterns. These two strains were from unconnected patients with extrapulmonary disease only and different sensitivity patterns, not resident in Australia at overlapping times. These were found to be of the Beijing lineage, which are widespread highly clonal strains of *M. tuberculosis*, and are not considered closely related(210).
4.3.1 Mycobacterial dendrogram of MDR TB isolates in Victoria, 1995-2010.
4.3.2 Further MIRU/VNTR testing of unexpected potential clusters identified by 15 locus typing using another seven loci: Mtub04, QUB-11B, Mtub21, QUB-26, Mtub30, Mtub39, QUB-4156.

*MIRU/VNTR loci tested: ETR A, ETR B, ETR C, MIRU 2, MIRU 4 (ETR D), MIRU 10, MIRU 16, MIRU 20, MIRU 23, MIRU 24, MIRU 26, MIRU 27, MIRU 31 (ETR E), MIRU 39, MIRU 40. § The first two digits of the lab number represent the year. † INH isoniazid, RIF rifampicin, EMB ethambutol, PYZ pyrazinamide, ETH ethionamide, CIP ciprofloxacin, KAN kanamycin, AMK amikacin. Brackets indicate intermediate resistance.

MDR TB index cases had a total of 570 contacts identified by contemporaneous epidemiologic contact tracing, with a total follow-up period of 3,093 person years of observation (PYO) since exposure. Potentially infective cases had a median 7 epidemiologic contacts (IQR 4-22). No person was identified as a contact of more than one case, nor was any evidence of secondary transmission identified. Demographic description of contacts can be found in table 4.1, and contract tracing network in figure 4.3.3. Most index patients with MDR TB were born outside Australia (45/47; 95.7%), 44% of contacts were Australian-born, with only 4.9% of contacts having the same country of birth as the index case. Contacts were first reviewed at medical clinics a median 25 days after notification to Department of Health, while the likely period of exposure preceded notification by a median of 56 days.
4.3.3 Contact tracing network from Victorian MDR TB index cases, 1995-2010

Table 4.1 Demographic details of MDR TB contacts in Victoria, 1995-2010 (n=570)

<table>
<thead>
<tr>
<th>Region of birth</th>
<th>Contacts with LTBI (n=49)</th>
<th>Contacts without LTBI (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia/New Zealand</td>
<td>16 (33)</td>
<td>239 (48)</td>
</tr>
<tr>
<td>South East Asia</td>
<td>15 (31)</td>
<td>136 (27)</td>
</tr>
<tr>
<td>Africa</td>
<td>8 (16)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>North Asia</td>
<td>5 (10)</td>
<td>47 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (10)</td>
<td>57 (11)</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>27 (17-43)</td>
<td>28 (18-37)</td>
</tr>
<tr>
<td>Sex (female, %)</td>
<td>24 (49)</td>
<td>229 (46)</td>
</tr>
<tr>
<td>Median time from exposure to notification (days, IQR)</td>
<td>4 (1-30)</td>
<td>5 (1-14)</td>
</tr>
<tr>
<td>Median follow-up since exposure (months, IQR)</td>
<td>54 (30-59)</td>
<td>66 (47-79)</td>
</tr>
</tbody>
</table>

LTBI=latent tuberculosis infection; IQR=inter-quartile range.

Following contact tracing, the majority of contacts were considered to be at low risk for progression to active disease, with 49/570 (8.6%) considered likely to have acquired infection from index cases. Of the 49 considered likely to have MDR LTBI, 18 received some form of preventative therapy. 4/18 were prescribed preventative therapy targeting drug sensitive infection (3 received isoniazid, 1 rifampicin), as
clinicians were apparently unaware of the index susceptibilities at the time of initial presentation. 3/18 were prescribed regimens intended to treat MDR LTBI but which were revealed to contain no active agents when eventual drug susceptibility profiles were available. The remaining 11 contacts were prescribed a variety of regimens containing at least 1 active agent, with administration and side effects of potentially efficacious regimens summarised in table 4.2.

A variety of reasons were offered for the decision not to provide preventative therapy in 31 cases: 5 patients did not present for clinical follow up, 3 declined further follow up after consultation, 11 opted for serial CXR and clinical review, and in 4 cases preventative therapy was considered to be high risk due to medical comorbidities (eg hepatitis, advanced age). In 3 cases, patients had a past history of TB infection and treatment, and in 1 case active TB was diagnosed at medical review. In 4 cases no specific reason could be identified.

Table 4.2 Preventative therapy agents prescribed for MDR LTBI

<table>
<thead>
<tr>
<th>Number</th>
<th>Regimen prescribed</th>
<th>Intended duration, months</th>
<th>Actual duration, months</th>
<th>Number of active agents</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MXF</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>Mild nausea initially</td>
</tr>
<tr>
<td>2</td>
<td>MXF</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>Nil reported</td>
</tr>
<tr>
<td>3</td>
<td>RMP, PZA, EMB</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Nil reported</td>
</tr>
<tr>
<td>4</td>
<td>CFX, PZA</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Mild abdominal pain initially</td>
</tr>
<tr>
<td>5</td>
<td>INH, PZA</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>Nil reported</td>
</tr>
<tr>
<td>6</td>
<td>EMB, PZA</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>Nil reported</td>
</tr>
<tr>
<td>7</td>
<td>EMB, PZA</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Nil reported</td>
</tr>
<tr>
<td>8</td>
<td>MXF, EMB</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>Nil reported</td>
</tr>
<tr>
<td>9</td>
<td>MXF, EMB</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>Nil reported</td>
</tr>
<tr>
<td>10</td>
<td>CFX</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Persistent itch (ceased early)</td>
</tr>
<tr>
<td>11</td>
<td>CFX</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Persistent nausea (ceased early)</td>
</tr>
</tbody>
</table>

No cases of TB occurred in either the group with no evidence of LTBI or in the group with LTBI treated with preventative therapy following exposure to MDR *M. tuberculosis* over the follow up period (mean post-exposure follow up of 5.5 and 4.5 years respectively). Two cases of MDR TB occurred in the group not treated with preventative therapy following exposure to MDR *M. tuberculosis* (mean 4.7 years follow up), both genotypically identical to the same index case. Overall incidence of MDR TB in this group was 1,162/100,000 PYO (95% CI 140-4347/100,000).PYO
post exposure, while incidence in the first two years after exposure was 2,878/100,000 PYO (95% CI 364-10,362/100,000). A summary of groups and outcomes is in figure 4.3.4.

4.3.4 Summary of outcomes following MDR TB exposure in Victoria, 1995-2010.

LTBI=latent tuberculosis infection; MDR=multidrug resistant; TBI=tuberculosis infection; FTA=failed to attend.

The strains from the two contacts that developed active MDR TB were identical to those from the index case, a 23 year old Indian male who had recently arrived in Australia. In one case, an 11-year-old Australian-born boy of Indian ethnicity was found to have active pulmonary TB at the time of clinical review, 4 months after the likely time of exposure. During this period, a TST was recorded as 11mm. Due to his history of BCG vaccination, a Quantiferon Gold In-tube Assay (Cellestis, Carnegie, Victoria) was also performed and found to be positive. During the screening period, some neck discomfort developed, prompting CT imaging which revealed a small upper lobe cavity, later confirmed to be MDR TB following wedge resection. In the second case, the 19 year old Indian male contact declined further investigation after initial LTBI assessment suggested significant household contact had occurred. 15 months later, he presented spontaneously with cervical lymphadenopathy, later culture-confirmed as MDR TB following excisional biopsy. Both strains were
genotypically identical to the index case, and patients completed therapy for MDR TB successfully.

4.4 Discussion

Contacts who acquired LTBI from index cases of MDR TB were at high risk of progression to active disease if not given preventative therapy. Although numbers in this group were small, the observed incidence rate of 2,878/100,000 (95% CI 364-10,362/100,000) person-years in the first two years after exposure is comparable to rates of disease found by household contact investigation in high prevalence settings such as Peru and South Africa (198, 199). By contrast, background rates of MDR TB in Victoria are extremely low; 0.085 cases/100,000 person-years observed during the period of this study. While previous estimates of reactivation risk have been hampered by uncertainty regarding the relative contribution of reinfection in high prevalence regions, the evident low background rate and minimal local transmission in our setting allows for improved clarity in assessment of reactivation rates following exposure.

Although an increased risk of MDR TB amongst close contacts is not surprising, the low background incidence makes the more than 30,000-fold increased risk observed especially striking. Further, the risk outside of the first two years following exposure may be underestimated, given the potential for lengthy periods of latency prior to reactivation(149). It has been suggested that latent MDR TB may be less likely to reactivate than infection caused by drug-susceptible organisms, a finding supported by notification data in at least one national surveillance program(111, 112). This present study has not compared reactivation from drug-susceptible infections. However, the observed rates of disease described here suggest that if a reduction in reactivation risk existed, it would be of insufficient magnitude to justify the avoidance of preventative therapy in appropriate clinical settings.

Routine epidemiologic contact tracing appeared effective in this context. No cases of TB were observed during follow up of the 503 contacts considered low risk following screening. The observed ratio of approximately 13 contacts to 1 transmission of M. tuberculosis per case is consistent with other published data, although values vary
considerably depending on local conditions and diagnostic criteria (198, 211). Local contact tracing and genotypic data related to drug-susceptible infections suggest that clustering is infrequent and that the considerable majority of TB cases arise from reactivation of LTBI rather than recent transmission. The results of this present study reinforce this perspective, and do not suggest the occurrence of unrecognized community transmission.

This study is limited by the possibility of undiagnosed TB infections in the Victorian community, and by its retrospective design. Undiagnosed TB infections are considered unlikely due to the availability of statewide TB services providing free treatment through public hospital networks and the maintenance of a mandatory central clinical and laboratory service and database. Unrecognized loss to follow-up, including subsequent TB diagnosis made overseas, would impact these findings. However, 97.5% of contacts had at least one clinical review or phone interview following exposure. It is also possible that close contacts may have been missed by initial public health investigation. To consider this possibility, MDR TB isolates have been compared genotypically, with dendrograms demonstrating no evidence of unrecognized transmission. However, as only a minority of cases lead to active disease, we cannot exclude the possibility of unrecognized acquisition of LTBI during this period.

During the time that this study operated, no uniform guidelines dealing specifically with the management of MDR TB exposure existed. This is reflected in the various approaches taken by clinicians, particularly in relation to the prescribing of preventative therapy. Although relatively little evidence exists for the efficacy of MDR LTBI treatment regimens, where is it to be prescribed it is evident from first principles that agents to which the isolate is susceptible should be used. The discordance observed in our study between isolate sensitivity and choice of preventative therapy is significant, and may reflect a number of factors. In some cases, it appeared that preventative therapy was prescribed before sensitivity testing was available, while in others clinicians were evidently unaware of drug-resistance in initial isolates. This reinforces the need for rapid molecular testing of drug susceptibilities to ensure that treating clinicians are aware of the sensitivity profile of index cases in a timely fashion.
4.5 Summary and implications for public health evaluation

In this low-prevalence setting, the risk of MDR TB transmission to close contacts was significant. While no cases of active disease were observed amongst contacts who received post-exposure preventative therapy, regimens used were highly variable and no conclusions can be drawn regarding effectiveness. Further studies, some currently underway, are needed to better clarify the effectiveness of MDR LTBI preventative therapy (114). Overall, our findings highlight the importance of careful follow-up of close contacts and further investigation into the effectiveness of preventative therapy, particularly in low-prevalence regions where relative risk difference is heightened. These findings also emphasise the importance of rapid diagnosis of drug resistance and effective communication between public health, laboratory and clinical practitioners, to allow early and appropriate decision-making regarding chemoprophylaxis for contacts of MDR tuberculosis, particularly in light of the recognised risk of subsequent MDR transmission amongst families and other at-risk groups in a variety of settings (212, 213).

In addition to these direct clinical and public health implications, these findings also provide a number of critical parameters to inform a mathematical model for evaluating public health strategies in Australia. As international rates of MDR TB are expected to rise in coming years, an increasing number of immigrants will arrive with MDR LTBI strains, against which standard preventative therapies will be ineffective. The rates of progression to primary disease observed in this study will inform the model outcomes for those infected with MDR LTBI, and assist in predicting their contribution to overall tuberculosis incidence in Australia. In addition, understanding risk of progression following infection with MDR LTBI allows more robust modelling of competition between drug resistant and drug sensitive strains of tuberculosis. As increasing numbers of MDR TB cases occur globally, this issue of strain competition will become more important, particularly given expanding efforts to control drug sensitive LTBI in various settings.

This chapter has presented novel, local data which allows outcomes relating to MDR LTBI to be incorporated, including risk of reactivation, secondary transmission and
side effects of preventative therapy for multi-resistant isolates. These findings will directly inform a mathematical model for evaluation of public health strategies relating to LTBI, which will be presented in chapter 6.
5. Risk factors for tuberculosis reactivation

Previous chapters have considered the risk of developing active TB disease following exposure or LTBI test conversion. This discussion has so far focused on population and average rates of reactivation, however individual risk of reactivation may vary from population means. Such variation has the potential to greatly impact public health interventions related to TB. For instance, if population sub-groups are at significantly different risk of active infection following the acquisition of LTBI, public health strategies may be made more effective by targeting high risk groups for screening or intervention. This section will review established and emerging risk factors for TB, with an emphasis on emerging genetic polymorphisms conferring altered risk of disease, and consider the potential impact of various factors within the Australian context.

As with any complex disease process, a variety of potential factors have been proposed in different contexts and isolated cohorts. In order to concentrate on well-established risk factors likely to represent genuine associations across a range on contexts, this section will focus on risk factors where sufficient data exists that meta-analysis has been performed to establish association and clarify the magnitude of risk conferred. Some associations have also been included where meta-analysis is not available but factors are well-described and supported by significant data, for instance multiple large observational cohorts.

Of particular interest in the context of this thesis are factors likely to be significant enough to be relevant in constructing an accurate mathematical model of TB in Australia. For this to be the case, factors must both confer a meaningful alteration of individual risk and be prevalent enough in Australian or immigrant populations to affect overall rates of active TB disease. Although some authors have suggested that strong associations with risk are required for individual factors to be considered as important (eg OR>5.0(214)), the importance of any factor will also be partly determined by its frequency of occurrence in relevant populations. Some well-

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5 Sections of this chapter have been published as Denholm JT, McBryde ES, Eisen DP. Mannose-binding lectin and susceptibility to TB: a meta-analysis. *Clinical and Experimental Immunology*, 2010;162:84-90 (Appendix 4) and Denholm JT, McBryde ES, Meta-analysis and risk factors for tuberculosis susceptibility in Walker SE, Martin DF (eds). *Tuberculosis: Risk Factors, Drug Resistance and Treatment* (Appendix 5).
established associations, such as in those with silicosis or receiving TNF-α inhibitor therapy, may be relevant in some specific individuals but are unlikely to be prevalent enough to be important for population-level modelling. Therefore, this review focuses predominantly on factors demonstrated to be associated with an OR for TB of at least 1.5 and a population prevalence of >1%.

5.1 HIV

Perhaps no other factor had as much impact on tuberculosis control worldwide than the spread of HIV infection (215, 216). Uncontrolled HIV infection leads to a progressive decline in CD4+ T-cells and associated immune dysfunction, leading to the development of a variety of opportunistic infections and malignancies (217). HIV and TB are recognised to interact in a number of directions, including TB-associated acceleration of HIV progression and substantial interaction between treatment regimens (218, 219).

HIV remains a relatively low-prevalence infection in Australia, with a national prevalence of approximately 0.1% (220, 221). However, within population subgroups, HIV infection rates may vary considerably. Of greatest significance in this region is HIV infection in men who have sex with men (MSM). MSM account for more than 80% of new HIV diagnoses, and conversely, prevalence of HIV amongst MSM is up to 8-10% in some Australian cities (222, 223). Intravenous drug users (IVDU), a group heavily impacted in many countries, have been relatively less affected in Australia. Although global estimates suggest that around 10% of HIV infection may be related to IVDU, Australian data suggests an HIV prevalence of approximately 1-1.5% in IVDU (224).

Estimates of LTBI acquisition in HIV-infected individuals are hampered by increased anergy to TST (225, 226). However, data from some TST surveys in high prevalence countries have suggested that annual risk of TB infection is similar between HIV positive and negative people, indicating that the majority of increased risk is likely to result from higher rates of reactivation, rather than acquisition of LTBI (227). Although formal meta-analysis of the association between HIV and active TB risk is not available, large observational studies in many countries have confirmed the
association and quantified levels of risk. A summary of the available evidence from the World Health Organisation concludes that the incidence rate ratio for active disease (TB incidence rate in HIV+/HIV- individuals) is approximately 6.0 (range 3.5-8.0) in non-industrialised countries, and 60 (range 41-77) in the developed world. This large difference in risk is to some degree predicted by the divergent baseline TB risk in low- vs high-prevalence regions, perhaps because of pooling of individuals at risk for both HIV and TB in low prevalence settings, or different patterns of progression to disease in varying populations. Overall, the larger figure is likely to more accurately reflect the impact of HIV in an Australian context.

Overall, while the prevalence of HIV infection in Australia is low, the magnitude of the increased risk for TB conferred by HIV is substantial. This is likely to mean that risk associated with HIV will need to be incorporated into a robust model of TB in Australia.

5.2 Diabetes mellitus

Diabetes mellitus (DM) has been linked to various impairments of cellular immune responses, particularly T helper cell function. DM has been associated with an increased risk of a range of infectious conditions, including post-operative wound infections, pneumonia and sepsis, as well as increased mortality and complications associated with infection. Observational reports over several decades have suggested an association between diabetes and tuberculosis, both related to increased risk of infection and poor outcomes following disease. However, in recent decades there has been controversy regarding the association, particularly as to whether tuberculosis infection was likely to precipitate diabetes and so confound the connection.

DM is a common condition in the Australian population, with a recent Federal Government agency report concluding a national prevalence of 3.6%. This figure represents diagnosed cases of DM however it is well recognised that many people with the condition have not been investigated or received a formal diagnosis. Accordingly, this figure is likely to be conservative. DM prevalence is also high and rising in many international surveys. A recent Indian national survey,
for instance, found 12.1% and 14.0% met diagnostic criteria for DM and impaired glucose tolerance, respectively. Overall, then, these figures suggest a substantial burden of disease in Australia.

Although DM is a well-established risk factor for many infectious conditions, then, it has only been relatively recently that substantial evidence for increased risk of tuberculosis has been accumulated, and the association has become generally accepted(228, 229). A meta-analysis of the association between DM and TB disease included 13 studies, set primarily in developed countries, and suggested a RR of 3.11 (95% CI 2.27-4.26) for PTB(237). Published data concentrates on active TB infection and treatment outcomes, and insufficient data exists to consider the risk of LTBI acquisition or prevalence.

5.3 Tobacco smoke

There are a number of plausible mechanisms by which tobacco smoking may predispose to increased risk for TB, including dysfunction of respiratory tract cilia and impairment of both cellular and humoral immunity(238, 239). Although the proportion of Australians who smoke has fallen steadily in recent decades, approximately 20% of the adult population continues to smoke tobacco(240). In addition, smoking rates are higher in the countries of origin of many immigrants to Australia. For instance, recent national estimates of smoking rates in India and China found that, respectively, 37 and 71% of adult males were current smokers(234, 235).

Several meta-analyses of published data have been conducted to consider the strength of association between smoking and TB. The first included 24 individual studies, and considered risk of both LTBI and TB disease, concluding that current smoking conferred RR of 1.73 (95% CI 1.46-2.04) and 2.66 (95% CI 2.15-3.28), respectively(241). This analysis also suggested that, based on these estimates, smokers with LTBI had a RR 1.6 for progressing to active TB disease. The second meta-analysis included 38 studies, and sought to consider the impact of indoor air pollution in addition to personal smoking risk(242). This study suggested that current smokers had a RR of 1.83 (95% CI 1.49-2.23) for LTBI and 2.01 (95% CI 1.63-2.48) for PTB, although these conclusions are impacted by multiple adjustments. In summary, then,
both meta-analyses conclude that smoking is a significant risk factor for both LTBI and TB disease, with roughly comparable estimates for the magnitude of risk conferred.

5.4 Vitamin D deficiency

Vitamin D is involved in regulation of monocyte and macrophage activity, known to be critical for TB control\textsuperscript{(243, 244)}. In addition to in vitro effects on cellular immunity, vitamin D deficiency states have been associated with a range of infectious conditions, particularly upper respiratory tract infections\textsuperscript{(245)}.

The Australian prevalence of vitamin D deficiency is high. Studies in various Australian contexts suggest that up to 80\% of people in some high risk groups may have deficiency states, while several studies have found 10-20\% in even low-risk populations\textsuperscript{(246, 247)}. High risk groups include those with poor sun exposure due to veiling, dark skin or residence in nursing homes, as well as disproportionate effect in the Southern Australian states\textsuperscript{(246, 248, 249)}.

7 studies comparing vitamin D in patients with new active tuberculosis infections and controls have been included in a meta-analysis\textsuperscript{(250, 251)}. A summary effect size of 0.68 was calculated, indicating that serum vitamin D levels were 0.68 SD lower in those with tuberculosis infection. While this meta-analysis convincingly demonstrates an association between low serum vitamin D levels and active tuberculosis infection, it cannot establish a direction of effect; that is, whether low vitamin D levels contribute to TB susceptibility or occur as a result of infection. Interestingly, Gibney et al have also demonstrated a significant difference between vitamin D deficiency in African immigrants with active versus latent TB\textsuperscript{(252)}. This analysis suggested an OR of 0.41 for active disease with every doubling of serum vitamin D; that is, vitamin D sufficiency may be protective against progression to active disease following LTBI acquisition.

In general, it appears likely from the accumulated evidence that vitamin D deficiency does play a role in TB susceptibility, particularly in the reactivation of LTBI. The impact of vitamin D supplementation on LTBI reactivation remains unclear, however,
given the significant amount of vitamin D deficiency in the Australian population, this is a factor likely to be considering during mathematical modelling.

5.5 Genetic factors

Hereditary factors that predispose to tuberculosis infection have been speculated about long before genetic mechanisms were clearly understood (253). As technology for evaluating and comparing genetic code has been developed, interest in eliciting the specific gene polymorphisms has grown (254, 255).

Although associations have been suggested between TB infection and many polymorphisms in small cohorts and case-control studies, there has frequently been difficulty in reproducing findings across populations and generalising the importance of individual gene polymorphisms in alternative settings (256). As increasing number of studies are published, however, more robust meta-analytic techniques have been able to be performed in order to increase the significance and reliability of these proposed associations. Accordingly, this section will concentrate on review of meta-analyses of the association between gene polymorphisms and TB, before offering conclusions regarding the impact genetics may have on the development of the proposed mathematical model in an Australian context.

To identify meta-analyses of the association between genetic polymorphisms and TB susceptibility, a systemic search of relevant databases was conducted. Scopus, Web of Science, Medline, Pubmed and Cochrane Collection were searched for the terms ‘tuberculosis OR tb’ and ‘genetic OR gene OR polymorphism’ and ‘metaanalysis OR meta-analysis OR systematic OR review’. In addition, searches were carried out specifically directed towards previously identified genotypes associated with tuberculosis, including HLA-DR, INF-y, SLC11A1, MAL/TIRAP and CCL2. References were then hand-searched to identify other relevant publications. The primary search was conducted by the candidate, with a second reader cross-checking manuscripts for inclusion. Manuscripts were included if they reported the association of a genetic polymorphism with tuberculosis infection or disease in a human population. No restrictions for publication language were imposed.
Using this search strategy, 17 meta-analyses of gene polymorphisms and TB risk were identified (table 5.1). 11 gene polymorphisms were found to have a significant association with TB infection, representing three clusters of interest: human leukocyte antigens (HLA), vitamin D receptor genes (VDR) and solute carrier genes (SLC). Risk and significance of each cluster is reviewed below.

<table>
<thead>
<tr>
<th>Author</th>
<th>Polymorphism</th>
<th>OR for TB (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacheco et al</td>
<td>IFNG T874A</td>
<td>0.75 (0.63-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacheco et al</td>
<td>IL-10 1082G</td>
<td>0.92 (0.67-1.26)</td>
<td>ns</td>
</tr>
<tr>
<td>Pacheco et al</td>
<td>TNF G308A</td>
<td>0.88 (0.69-1.12)</td>
<td>ns</td>
</tr>
<tr>
<td>Kettaneh et al</td>
<td>HLA DR8</td>
<td>1.72 (1.21-2.46)</td>
<td>0.003</td>
</tr>
<tr>
<td>Kettaneh et al</td>
<td>HLA DR2</td>
<td>1.67 (1.16-2.41)</td>
<td>0.006</td>
</tr>
<tr>
<td>Kettaneh et al</td>
<td>HLA B13</td>
<td>0.64 (0.5-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kettaneh et al</td>
<td>HLA DR3</td>
<td>0.72 (0.59-0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>Kettaneh et al</td>
<td>HLA DR7</td>
<td>0.65 (0.53-0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Li et al (2006)</td>
<td>3UTR</td>
<td>1.33 (1.08-1.63)</td>
<td>0.008</td>
</tr>
<tr>
<td>Li et al (2006)</td>
<td>D543N</td>
<td>1.67 (1.36-2.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Li et al (2006)</td>
<td>SLC11A1 INT4</td>
<td>1.14 (0.96-1.35)</td>
<td>0.13</td>
</tr>
<tr>
<td>Study</td>
<td>Gene</td>
<td>SNP</td>
<td>OR</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Li et al (2006)</td>
<td>SLC11A1</td>
<td>5GTN</td>
<td>1.32</td>
</tr>
<tr>
<td>Gao et al (2010)</td>
<td>VDR</td>
<td>FokI ff</td>
<td>2.0</td>
</tr>
<tr>
<td>Gao et al (2010)</td>
<td>VDR</td>
<td>BsmI bb</td>
<td>0.5</td>
</tr>
<tr>
<td>Xiao et al (2010)</td>
<td>P2X7</td>
<td>A1513C</td>
<td>1.44</td>
</tr>
<tr>
<td>Xiao et al (2010)</td>
<td>P2X7</td>
<td>762T</td>
<td>1.01</td>
</tr>
<tr>
<td>Miao et al (2011)</td>
<td>TIRAP</td>
<td>S180L</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### 5.5.1 Human leukocyte antigens (HLA)

HLA are a class of protein expressed on cell surfaces, involved in immune stimulation and recognition of self-antigen(257, 258). A large number of HLA types exist, and vary substantially between different ethnic populations. Accordingly, HLA types have been investigated as a possible contributor to worldwide variation in TB prevalence(259-261).

The meta-analysis of Kettaneh et al considered 22 published articles considering 60 HLA types and TB susceptibility(262). 5 HLA types were found to have significant association with TB risk, with 3 antigen types decreasing risk (HLA B13, DR3 and DR7) and 2 associated with increased risk (HLA DR2 and DR8).

HLA types vary considerably in different ethnic populations, and the relevance of these antigens will differ across immigration cohorts. However, HLA DR2 has been noted to be a common antigenic type in Australia, with blood donor testing suggesting a prevalence of 27-30%(263).

### 5.5.2 Vitamin D receptor (VDR)

Gene polymorphisms related to vitamin D metabolism and action are of particular interest, given that evidence, reviewed previously, also exists for a direct link between
vitamin D deficiency and tuberculosis risk(250, 252). Polymorphisms of the vitamin D receptor, then, have also been of interest in relation to tuberculosis susceptibility. A meta-analysis of VDR polymorphisms included 23 studies, and suggested several gene variants were significantly associated with TB risk(251). In particular, the *FokI* ff genotype was associated with an OR of 2.0 (95% CI 1.3-3.2) for TB disease, while the *BsmI* bb genotype was associated with an OR of 0.5 (95% CI 0.4-0.8), although these effects were noted only in Asian patients.

Studies reporting the frequency of these polymorphisms suggest that these polymorphisms occur frequently. The *BsmI* bb genotype was found in 30% of German cardiac patients and 50.7% of Asian control patients, while the *FokI* ff was identified in 10% of Asian and 15% of Caucasian subjects(251, 264, 265). It is difficult to appreciate the likely impact of these polymorphisms currently, however, given that their association appears limited to the Asian populations studied. While this may indicate more complex genetic pathways are involved, these results may also be confounded by issues such as serum vitamin D levels and bias in control recruitment.

### 5.5.3 SLC11A1

The *SLC11A1* (formerly known as NRAMP1) gene encodes a soluble protein transporter involved in macrophage activation(266). Murine models of infection have identified genetic polymorphisms of *SLC11A1* as being associated with increased susceptibility to a range of intracellular pathogens, including mycobacteria and *Salmonella* sp(267).

A meta-analysis of *SLC11A1* and tuberculosis risk reviewed 17 studies, and identified several polymorphisms with OR between 1.32 (95% CI 1.03-1.68) and 1.67 (1.36-2.05)(268). European controls were unlikely to have these polymorphisms (0.5-3%), while Asian controls were more likely (10-20%).
5.6 Novel meta-analysis of mannose-binding lectin gene (MBL2) polymorphisms and TB susceptibility

In addition to the meta-analyses of gene polymorphisms identified above, review of current literature in this area indicated that a number of cohort studies had been conducted considering the association between MBL2 gene polymorphisms and TB disease. An association between MBL2 gene and TB would be of considerable interest, as a high frequency of polymorphisms has been observed in the Australian population(269). However, initial review of existing published data demonstrated conflicting findings regarding the nature and magnitude of any impact of MBL2 gene polymorphisms and tuberculosis susceptibility. No synthesis of this data had been conducted to date and so novel meta-analysis was undertaken(270). The following section details the methodology and results of this analysis.

5.6.1 Methods

Identification of studies

For the meta-analysis, all published studies that considered the association between tuberculosis and MBL2 polymorphisms were included. A literature search for the MeSH terms “tuberculosis OR TB OR mycobacteria” and “MBL OR mannose-binding lectin OR mannose-binding protein” was performed using Medline and PubMed and abstracts were reviewed for relevance. No language restrictions were applied to the search strategy. References of articles were also reviewed for additional relevant citations not included in the original search protocol. The full text of all articles was reviewed to ensure they met preset criteria for inclusion.

Nomenclature and data extraction

The primary outcome considered in the meta-analysis was the association between pulmonary tuberculosis infection and the presence of MBL2 polymorphisms in patients without HIV. For the primary analysis, and to allow appropriate comparison of all studies, cases and controls were classified as AA (wild-type MBL2 genotype), AO (structural gene polymorphism heterozygous MBL2 genotype) or OO (compound heterozygote MBL2 genotype). Although studies may have also analysed the potential
influence of MBL on the site or severity of tuberculous disease, to meet inclusion criteria all required a direct comparison between subjects with active pulmonary TB and healthy, non-TB diseased controls.

**Statistical analysis**

Primary and secondary analyses were performed using STATA 10.1 (Stata Corporation, College Station, TX, USA). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the association between tuberculosis infection and MBL2 polymorphism in each study.

To consider evidence of publication bias, funnel plots of the studies included in the final analysis were prepared. Chi-squared tests were performed to assess the degree of heterogeneity between trials, and both fixed and random-effects metaregression models were used.

5.6.2 Results

*Studies included in the primary meta-analysis*

Seventeen publications relating to MBL and tuberculosis infection in human subjects were identified (271-286). Two were excluded as they only provided data on MBL serum levels and not MBL2 polymorphisms (271, 272). One study was excluded as it considered only population prevalence of tuberculosis and polymorphisms without individual data (273). One study was excluded as it did not provide sufficient individual raw data for analysis (274). One study was excluded as data from patients with pulmonary and extra-pulmonary disease could not be separated for MBL2 polymorphism analysis (276). Data from the remaining twelve studies were included in the primary analysis of MBL2 genotype frequency in HIV-negative patients with pulmonary TB versus healthy controls, containing a total of 1815 patients and 2666 controls. Summary data from the included studies are shown in table 5.2.
Table 5.2 Summary of studies considering MBL2 polymorphisms and TB susceptibility

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patient population</th>
<th>Case subjects</th>
<th>Control</th>
<th>Serum MBL levels</th>
<th>MBL polymorphisms included</th>
<th>Polymorphisms found in TB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>India [31]</td>
<td>Adult TB patients</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pakistan [20]</td>
<td>HIV+ adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thailand [25]</td>
<td>HIV+ adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>USA [22]</td>
<td>HIV+ adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Spain [31]</td>
<td>HIV+ adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tanzania [19]</td>
<td>HIV+ adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>South Africa [27]</td>
<td>HIV- adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mali [34]</td>
<td>HIV- adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Turkey [32]</td>
<td>HIV- adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>USA [22]</td>
<td>HIV- adults</td>
<td>Healthy adults</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Legend:
- HIV+: HIV+ patients
- HIV-: HIV- patients
- TB: Tuberculosis
- MBL: Mannose-binding lectin
- MBL2: Mannose-binding lectin 2

Note: The table represents the summary of studies considering MBL2 polymorphisms and TB susceptibility. The information includes the setting, patient population, case subjects, control, serum MBL levels, and MBL polymorphisms found in TB patients.
To examine the effect of the degree of MBL deficiency, pooled data were considered according to genotype in two different manners. As outlined above, twelve studies contained sufficient data for primary analysis of wildtype vs any MBL2 variant allele (OA/OO) genotype, representing a wide range of intermediate and extremely low MBL levels. Ten studies (275-278, 280, 281, 283, 285-287) contained sufficient information for wildtype vs compound heterozygote (OO) genotype frequency in cases and controls, representing a comparison between normal and extremely low MBL levels alone.

**Primary analysis**

Chi-squared testing of the included studies demonstrated a high degree of heterogeneity (p<0.001). Due to the high degree of heterogeneity, a random-effects metaregression model was considered to be most appropriate and was applied throughout.

Figure 5.6.1 shows the odds ratios (OR) for tuberculosis infection between subjects with wild type MBL2 genotypes (AA) and those with either single (AO) or compound heterozygous (OO) MBL2 mutations. OR’s from individual studies ranged from 0.18-3.94 with a combined OR of 0.87 (95% CI 0.59-1.28). Figure 5.6.2 shows the OR for tuberculosis infection comparing subjects with AA genotypes and those with OO MBL2 variants. OR from individual studies ranged from 0.14-2.30 with a combined OR of 0.55 (95% CI 0.22-1.34). Both figures highlight the considerable variation in effect size and direction, and suggest a high degree of heterogeneity between studies. Neither analysis, then, demonstrates a significant difference between groups, suggesting that MBL2 genotype relying on structural gene variant allele alone does not significantly influence tuberculosis susceptibility.
5.6.1 Meta-analysis of MBL2 gene polymorphism on tuberculosis susceptibility: AA vs OA/OO forest plot

5.6.2 Meta-analysis of MBL2 gene polymorphism on tuberculosis susceptibility: AA vs OO forest plot
An additional ad hoc meta-analysis was performed on studies that reported complete MBL2 genotypic profile inclusive of promoter polymorphisms. Although only a minority of studies reported such data, this group was chosen as such genotype profiles are considerably more strongly associated with MBL serum levels than structural genotypes alone. Using this subset, patients and controls were reanalysed based on frequency of high or low MBL-producing genotype. O/O and XA/O were considered low MBL-producing genotypes in this analysis, with other genotypes considered to be high MBL-producing. This analysis, shown in figure 5.6.3, did not demonstrate a significant effect of MBL2 genotype on likelihood of pulmonary TB infection (275, 277, 281, 283), with results influenced significantly by a single outlying study.

5.6.3 Meta-analysis of influence of MBL2 genotype with promoter regions on tuberculosis susceptibility.

5.6.3 Conclusion

This meta-analysis is limited by the large degree of heterogeneity in the designs of the studies identified for analysis, and conclusions drawn may be less applicable to
specific sub-populations. It has also been suggested that the high degree of genetic heterogeneity in the populations studied may account for some degree of the conflict between results (275). However, this meta-analysis employed a random effects model designed to counter these variations and found no overall effect of MBL2 genotype on TB susceptibility.

It should also be noted that this meta-analysis is limited by a lack of systematic assessment for bias in included studies(288). It is possible that a stratification of studies on the basis of quality would yield differences in reported association between MBL2 genotype and tuberculosis susceptibility, however, given the large degree of heterogeneity between studies and variation in reported findings, it is considered unlikely that such an analysis would suggest a statistically significant association.

5.7 Mycobacterial factors

5.7.1 Strain-specific

Individual strains of M. tuberculosis have been associated with greater than expected risk of transmission, and large surveillance programs have suggested that factors related to strain diversity may be important in understanding risk of infection and disease(289, 290). The impact of individual strains, however, may be difficult to appreciate given the significant variability in transmission risk between hosts, and the number of circulating strains in many contexts(289). While some strains, such as the Beijing strain GC1237, may be associated with increased risk of infection in some settings, the relative contribution from transmission and propensity to active disease are incompletely understood(291, 292). In addition, it is recognised that patients may be frequently co-infected with multiple strains of M. TB(293).

Strain diversity in Australia is related significantly to the country of origin of those infected. The impact of strain-specific risk of transmission is unknown in this context, however appears likely to be less relevant in low-transmission regions such as this. Potentially, strains associated with high risk of reactivation may be less likely to
emerge in Australia, as immigrants may be more likely to develop disease prior to travel. On the basis of current evidence, however, strain-specific factors are insufficiently predictive of tuberculosis risk to be used to guide public health interventions, particularly in a setting where the majority of infecting strains (causing LTBI) will be unknown.

5.7.2 Drug-resistance

Controversy continues regarding the impact of drug-resistance mutations on Mycobacterial fitness and transmission(289). Experience from other pathogens suggests that increasing resistance mutations are associated with a variable loss of organism fitness, and some in vitro and animal studies suggest this is true for at least some resistance mutations in M TB(294, 295). However, other mutations do not appear affected(296). Most recently, guinea pig studies have confirmed that human patients with highly resistant strains of TB remain readily infectious, suggesting that fitness costs of maintaining these mutations may be relatively unimportant in a public health context(297). Furthermore, data presented in Chapter 4 regarding MDR TB transmission and reactivation in Victoria is consistent with that associated with drug sensitive strains in previous work, suggesting that drug resistance does not appear to substantially reduce mycobacteria fitness or virulence in vivo.

5.7.3 Composite organism/host genetics

Given the complexity of the interaction between host and Mycobacterial pathogen, it is perhaps unsurprising that researchers have begun to consider the impact of individual host/pathogen associations for infection risk(298). Such investigation is fraught due to the large number of potential interactions to be considered, and the possibility of spurious connections identified through multivariable investigations. Nonetheless, this is a plausible and important future direction for understanding tuberculosis infections, albeit one unlikely to impact public health considerations substantially.
5.8 Summary of impact of risk factors on evaluating public health strategies

This chapter has reviewed a range of factors that potentially may influence individual risk of TB reactivation. HIV infection, smoking and diabetes are key risk factors that have been identified for inclusion in a model of TB in Australia. All confer significant risk increase and are present in a substantial proportion of many populations from which immigration cohorts are comprised. Although other factors such as silicosis or TNF-α inhibition clearly increase risk of tuberculosis considerably, they are uncommon risk factor and unlikely to be present frequently enough in immigrants for incorporation to be worthwhile.

Despite the significant advances made in understanding genetic influences on tuberculosis reactivation this analysis has identified no polymorphism significant enough to be included in a population-based model. There are several reasons for this. First, no individual polymorphism, either alone or in combination, has been found to confer more than a 2-fold risk of tuberculosis disease. Although this may not be a negligible risk increase in an individual, on a population level it appear to be of insufficient magnitude to warrant inclusion, particularly in light of the genetic screening required to identify the minority of individuals carrying various polymorphisms. Although in future rapid assessment of multiple gene polymorphisms may allow for better risk evaluation, on the basis of current evidence no genetic factors will be incorporated into the evaluation of public health strategies for LTBI.
6. Mathematical model of public health approaches targeting LTBI

Previous chapters of this thesis have considered a variety of elements necessary for optimal understanding of tuberculosis infection and control in environments such as Australia. Following review and survey of existing evidence, information pertaining to some of these elements has been gathered from available literature, while in other areas, novel and local data has been obtained in order to optimally inform an understanding of tuberculosis in an Australian context.

This chapter will bring together all of the input data generated in the preceding chapters and utilise it to develop and evaluate a mathematical model of tuberculosis infection in Australia. Following a review of mathematical modelling in infectious diseases and evaluation of appropriate modelling strategies for this present work, a general model will be described and evaluated. Finally, the implications of this model for public health management will be elucidated and discussed, including focused consideration on the potential for eradication of tuberculosis as a public health issue in Australia.

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6 Sections of this chapter have been published as
6.1 Introduction to infectious diseases modelling

Mathematical models consider relationships between input variables and outputs under specified conditions(299). Modelling infectious diseases is a process by which characteristics of infectious agents and epidemics may be quantified and explored. In the setting of infectious diseases, modelling assumes especial importance given the ethical and practical limitations involved in the prospective study of infectious agents in humans.

Mathematical models of infectious diseases may be useful for a variety of objectives. They may predict outcomes of infectious epidemics, such the proportion of population likely to be infected by a novel virus, or the peak incidence of cases during an influenza season. They may also be used to consider the likely impact of various interventions, such as vaccination or infection control strategies(300, 301). Alternatively, they may be used following epidemiologic description of outbreaks in order to characterise features of the infective agent, such as basic reproductive rate(302). All of such models can provide novel insight into the expected behaviour of infectious diseases under various circumstances, which is increasing employed in developing and evaluating public health strategies(303).

Determining the appropriateness of various mathematical modelling approaches for a specific application in infectious diseases requires consideration of a number of factors. These factors may relate to the infectious agent itself, the host, environment or some combination. For example, the degree of infectiousness of an agent is a critical factor which will significantly impact the rate of spread through a given community. Pre-existing population immunity may, however, proportionally impede spread through a reduced number of susceptible hosts. Measles, for instance, is a highly contagious organism which typically spreads rapidly through naïve populations, but can be effectively contained when high proportions of the population are vaccinated(304). In the context of tuberculosis, host capacity for re-infection and partial immunity due to immunisation may make incorporation of such factors complex.
Within any modelling approach judgements regarding the complexity of assumptions and inputs to be included are required. Increasing the number and detail of included factors may potentially improve the predictive ability of a model; however imprecision inherent in any imported data assumptions may result in decreasing reliability as complexity increases. There is therefore a frequent trade-off to be made between parsimony and adequacy of any given model. In this context, adequacy means that all relevant information is incorporated and that outputs are calibrated to available data, while the principle of parsimony refers to the selection of the simplest possible adequate model (305).

A variety of stages are required to determining how a model of an infectious condition should be constructed. The following section uses an approach elucidated by Vynnycky and White, after initial work by Habbema et al, and is summarised in figure 5.8.1 (299, 306). In the context of this present work, approaches are discussed with specific reference to tuberculosis however it should be noted that the method is a general one with applicability to other infectious agents and situations.

5.8.1 Steps in the development and use of a model. Reproduced from Vynnycky (279)
6.1.1 Identify the question

A clear elucidation of the question of interest is key to effective model design. Models related to tuberculosis may be predominantly interested in infection control strategies, vaccine efficacy, public health interventions or any number of different questions. Each may require additional relevant information for adequate modelling, while in some cases alternative model design will be preferable. In the context of this thesis, the central questions of interest relate to Australia’s capacity to achieve the WHO Millennium Development Goal for 2050, by reducing TB incidence to less than one case per million population per year.

6.1.2 Identify relevant facts about the infection in question

Key information about the infection under consideration must be relevant both to the organism in question and the population of interest. For some infections, this may include rates of vaccination or pre-existing immunity amongst the population, as well as basic biological facts regarding duration of infectious period after transmission and likelihood of death or recovery after infection occurs.

For tuberculosis, social factors such as the number and duration of contact episodes within the population will also assume significance. Such information may be highly variable amongst different populations, and may need to be explored in specific terms where a model is intended to be relevant to a particular geographic or social setting.

Given the specific question identified here, additional critical information may also include details of immigration patterns from high-prevalence regions, rates of tuberculosis reactivation amongst immigration cohorts and dynamic prevalence of important risk factors such as diabetes and HIV infection in the Australian and immigrant populations.

6.1.3 Choose type of modelling method

Specific details of the variety of modelling methods available will be explored in the subsequent section. It should be noted, however, that a range of modelling options exist, with relative strengths and weaknesses for specific situations and conditions.
Some decisions about optimal approaches to modelling may be related to the particular infection of interest, while others will be more related to the type of question identified at the outset of the modelling process. In the case of tuberculosis infection, for example, the lack of durable immunity generated following infection means that some standard approaches to modelling may not be valid without substantial modification. Even when considering a single condition like tuberculosis, a number of different modelling approaches may be indicated depending on the specific question to be asked. Network models may be preferential when considering issues related to interaction and isolation amongst relatively small groups, for example, while deterministic compartmental models may be more appropriate when detailed individual data is not readily available or basic parameters need to be estimated. In general terms, it should be noted that there is rarely a single modelling approach which is ‘correct’, and different models may make varying contributions to our understanding of complex phenomena and relationships.

6.1.4 Specify model input parameters

The parameters necessary for model construction vary depending on the approach chosen. Network models require information to be obtained or estimated regarding factors such as frequency of effective contact between individuals, while such factors are either not included or subsumed into other composite parameters in other approaches to modelling. Common parameters for many approaches include: the risk of a susceptible individual becoming infected during a given time (‘force of infection’), the number of secondary cases generated by each infectious individual (‘basic reproductive rate’, or $R_0$ for immunologically naïve populations) and the rate at which infectious individuals recover, although there are many others.

For some conditions and situations, basic information regarding appropriate parameters is readily available for inclusion into new models. Historical epidemiologic investigation into outbreaks of novel influenza viruses or measles into susceptible populations have provided a great deal of knowledge regarding basic parameters for these infections(307, 308). For some novel infections, parameters must either be assumed on the basis of similar conditions or measured empirically prior to modelling(309, 310). In the case of tuberculosis, a combination of factors means that,
despite extensive historical investigation, basic parameters remain controversial. The absence of a gold standard for latent infection, long periods of latency, incomplete progression to active disease and less than total immunity following resolution of infection are just a few of the factors that mean input parameters for tuberculosis infection may be difficult to assess and vary between models.

6.1.5 Set up model

Setting up a model involves assembling the input parameters within the modelling approach chosen. In addition to constructing the various equations governing the relationships between different aspects of the model, in practical terms this step also includes factors such as determining the most appropriate format for operating the model within. For some very simple models this may be performed manually however most mathematical models require a computer-based program for operation.

6.1.6 Model validation

Validation of a model consists of comparison of the outcome data generated with observed outcomes. Validation ensures that the predictions of a model are concordant with observations, and therefore likely to accurately reflect the behaviour of a given infectious disease. Due to the wide variety of variability in settings and conditions of infectious outbreaks, it is unlikely that any model will predict outcomes perfectly. However, predictions should be sufficiently accurate to suggest that the model will be useful in relation to a particular context.

For validation to be conducted, observed data must be available for comparison. This may not be possible in some circumstances, for example, when considering the outcomes following an outbreak of a hypothetical infectious agent, or the impact of a novel vaccine or treatment strategy. As has been highlighted elsewhere, the primary purpose of many models is to predict unknown outcomes where experimental data is not available(311). For many mathematical models, then, complete validation may not be possible at the time of construction, and alternative approaches to validation may be required. For example, some authors have proposed methods for comparing the outcomes of multiple mathematical models as an alternative approach to validation.
where experimental data is unavailable or incomplete (312). Other, less formal approaches to validation are often combined with available data, including assessment of biological plausibility of observed outcomes and analogy with apparently similar infectious agents and situations.

Where available data is used for validation, it should be distinct from the data used to inform the development of model parameters. If the same data set was used to develop the model and validate it, a very strong concordance would be observed despite the lack information gained regarding the usefulness of model predictions.

6.1.7 Prediction and optimisation

Finally, once models have been constructed and validated, they can be employed for evaluation of outcomes under a variety of conditions. Of central importance to most models is prediction of how outcomes of interest change given altered inputs, such as introduction of a new vaccine strategy, change in drug susceptibility of the infectious agent or change in pattern of social interaction (e.g., school closure during outbreak). As new information becomes available, models can be continuously updated. A feedback loop is generated, where new information arising from epidemiological observation can be incorporated into improving the predictions made by the model prior to the next opportunity to gather validation and optimisation data.

6.2 Survey of major approaches to modelling

This section surveys some of the major approaches to mathematical modelling of infectious diseases currently in use, with a particular emphasis on applicability to modelling tuberculosis infection in Australia. It should be noted that the following categories are representative and not mutually exclusive; for example, models may contain both deterministic and stochastic elements, and factors such as age-structure may be incorporated into either compartmental, individual-based or network models.
6.2.1 Difference/ordinary differential equation models (SIR/SEIR)

SIR (‘susceptible, infected, recovered’) models involve the allocation of individuals to one of three states, with movement between states governed by equations. In a simple example, all individuals start in the ‘susceptible’ state, with a certain likelihood of progressing to the ‘infected’ state during each time-step of the model. This likelihood of changing states (ie, becoming infected) may be a constant (eg 10% of infection each month), or a more complex function (eg proportional to the number of currently infected individuals in the population). Following infection, another equation determines the rate of movement into the ‘recovered’ state. In some circumstances, individuals may be able to move directly from susceptible to recovered, such as following effective vaccination, or asymptomatic infection that does not lead to infectiousness. Figure 6.2.1 shows a schematic diagram with one example of progression through the susceptible, infected and recovered states.

For these models, difference or differential equations may be employed. In difference equations time is discrete, while in differential equations time is continuous and functions give the rate of change between compartments.
SIR models are common and useful for epidemic assessment of a variety of infectious diseases. Use of this approach for tuberculosis, however, has variety of difficulties. First, the latency period of TB is long and variable, meaning that the average progress of individuals once ‘infected’ is not meaningful as a dependent variable. Secondly, basic SIR models assume that ‘recovered’ individuals are immune to further infection; however this assumption is not justified in relation to tuberculosis.

Some attempts to model aspects of tuberculosis epidemiology with SIR models have been made. For instance, Gomes and colleagues constructed a modified SIR approach which included partial susceptibility to reinfection in order to consider vaccine efficacy in a variety of contexts(313). An adaptation of the SIR model that is more commonly applied to tuberculosis is the SEIR model, which introduces an additional category of ‘exposed’ prior to ‘infected’. This category allows for the variable progression of the latent period, including the biological reality that many individuals exposed to TB will not progress to active disease. As shown in figure 6.2.3, the interactions between states can be constructed in a variety of ways. Some models assume that susceptible individuals may develop either active disease or latent infection following exposure (A)(314), while others assume that the individual must become latently infected before progressing to active disease (B or C). Models must also determine the likelihood of progression from latent infection to active disease, in the face of evidence that the majority of infected individuals will never develop active infection. Some researchers have approached this through the creation of latent sub-classes, in which sub-populations progress at different rates to active infection(315).

6.2.2 Several possible schematic models for SEIR models of tuberculosis infection. Note ‘L’ for ‘latent’ is used as a surrogate for ‘exposed’ in this context. Taken from (297)
6.2.2 Partial differential equation models

Partial differential equation (PDE) models are distinct from ordinary differential equations by the incorporation of more than one independent variable (316). In the context of tuberculosis infection, independent variables might commonly include age, for instance, and the risk of progressing to active disease vary according to the age of the individual at a given point in the model. Other aspects of such models may also vary; one model, for example, also varied risk of transmission based on age (317).

6.2.3 Individual based-models

One characteristic of difference and differential equation models is that they are compartmental. The models are based on evaluation of the various mutually exclusive categories or compartments (or ‘states’) that it is possible to fall into, and determining how many individuals are in each category at any given time. These models consider overall, average outcomes in populations however they do not provide information on the outcomes for any specific individual. Such outcomes are not relevant for these models, as it is the proportion and distribution of individuals which are of interest rather than the outcomes of specific individuals within compartments.

Individual-based models are of course different in that their focus is on the progress of each individual through the course of a simulation. Although similar population outcomes can be calculated, these represent the sum total of individual outcomes, rather than averages. While there are many ways to construct an individual-based model, these are predominantly stochastic with a predefined set of probabilities governing the likelihood of each individual moving from their current state to another.

Individual-based models have a number of advantages that make them attractive for a variety of infectious diseases models. They allow consideration of a large number of potentially interacting parameters which may be relevant on an individual level, such as age, household size and composition, occupation and patterns of social interaction. There may be too many of these variables to develop parsimonious compartment
models however they may be incorporated into an individual-based model with relative ease, by assigning individuals characteristics drawn from variables with pre-specified distributions. A disadvantage of individual-based models that should be noted is their computational complexity, which may be unnecessary for situations where only a small number of variables are dominant, or when average population outcomes are sufficient.

6.2.4 Age-structured models

Age-structured models modify parameters based on the age of individuals being considered. For models considering short periods of time, this may be limited to fixed differential risk of infection across age categories, while for models evaluating larger durations, individuals may age during within the timeframe of the model with substantial implications, such as risk of death from non-tuberculosis causes, for example.

Age stratification in tuberculosis is a significant issue for a number of reasons. The long duration of tuberculosis latency mean that serial intervals are typically measured in years rather than very short times appropriate to other diseases. Risk of tuberculosis infection varies considerably with age; an effect that has been demonstrated in original work for this thesis also. Age-structure may be influential in other ways also, depending on modelling approach; for example, a household, contact-modified compartmental (WAIFW; who acquired infection from whom) or network model may take into account altered transmission pressures associated with reproductive age and likely household contact with children.

Incorporation of age-structure into mathematical models can alter its realism and accuracy considerably, as has been demonstrated specifically for tuberculosis infection. One report considered the impact of incorporating demographic profiles into tuberculosis transmission models, and found that inclusion of at least a constant mortality rate made predictions of infection dynamics more consistent. (318)
6.2.5 Stochastic models

Both difference and differential equation models are deterministic; that is, progress of a population through the states is governed by a series of set formula where outcomes are unchanging for a set of given initial conditions. A stochastic approach to modelling, however, involves uncertainty of outcome. Instead of rates governing transition through states, it is probabilities that govern the behaviour of models (316). Stochastic events are usually treated as discrete, where a single individual either moves from one state to the next in a small time increment or they do not. Markov Chains are the most commonly used stochastic models, as the behaviour of an individual in any state is independent of its history. That is, an individual in the ‘latent’ class, for instance, has the same likelihood of progressing to active disease regardless of how long ago that individual moved from ‘susceptible’ to ‘latent’ initially.

Stochastic models may themselves adopt various approaches to probabilistic reasoning. Most commonly, classical (or ‘frequentist’) probability theory has been used to assign a probability for each possible outcome, with the summary likelihood of a given event occurring being the multiplicative probability of all of the preceding events. Non-classical probability, however, has increasingly become recognised as useful in many modelling contexts. Amongst these approaches, Bayesian probability has been the most commonly used in biomedical contexts (319, 320). Within a Bayesian framework, probability of all model parameters is regarded as uncertain, with this uncertainty expressed through a probability density function probability distribution of the parameter space for the parameter of interest. Posterior probability distributions are the probabilities of the parameter given the prior probability and the data that are currently available. This can be serially updated as new information is available, with uncertainty diminishing as increasing amounts of data are incorporated. Bayesian methods have a number of advantages over frequentist approaches to modelling, including an allowance for the real-time updating of prior beliefs regarding likelihoods.

Stochastic models offer some intuitive advantages when modelling likely future outcomes. Real-world choices rarely have closely defined, deterministic
consequences, and some degree of uncertainty regarding outcome is a realistic assumption. Stochastic models are well-positioned to consider questions such as ‘how likely is [outcome X]?’, and to consider relevant thresholds for risks or outcomes. They also provide, through analysis of multiple simulations using the same initial conditions and parameters, the likely variability of outcomes that could occur due to chance.

6.2.6 Spatiotemporal and network models

While previous models discussed allow consideration of presence of infection over time, spatiotemporal models also involve awareness of geographic location of individuals within a population. This may be important for a variety of reasons. In the setting of infectious diseases like tuberculosis, one potential factor of importance is the incorporation of a non-uniform risk of new infection. Risk may be proportional to the geographic or social closeness of two individuals, or may be absent without a particular spatiotemporal interaction. This is particularly evident within a network model, where both background risk and the impact of specific interactions (e.g., with a case of an infectious disease) affect the outcome for a particular individual (or node)(321). Other geographic factors, such as the likelihood of spread of infection to a distant locale in the setting of existing social behaviour patterns and interactions, may also be explored using these approaches(322).

Spatiotemporal and network models can be modified for relevance to particular groups where TB epidemiology may be of interest, as behavioural and social factors specific to local context can be incorporated. They may also incorporate deterministic and/or stochastic assumptions regarding factors within the model(323). The impact of changes in social behaviour can be demonstrated to have significant effect on measures of disease outcome. For instance, a uniform SEIR model will not allow recognition of the importance of clustering effects that are readily identified through models that incorporate interactions between individuals. These effects are frequently seen in real-world tuberculosis outbreaks, and network or spatiotemporal models may allow such effects to be more accurately considered(324). Network models may be particularly useful in these situations, as they allow for situations where there may be geographic but not social proximity, such as international borders(325).
Network models appear to have been adopted more frequently for considering tuberculosis transmission, while spatiotemporal models have been primarily employed for biologic modelling of immune responses to M. tuberculosis (326-328). One example of a network model of TB transmission is that of Cohen et al. (326). This model simulates a closed community, where individuals are randomly distributed and interactions subsequently determined on the basis of distance between individuals. Once the network was generated, a modified SEIR model of TB infection was used to generate estimates for risk of infection and transmission. The advantages of this particular approach included the capacity to consider re-infection and variable degrees of social contact, rather than the more uniform average risk estimates which would be employed in basic SEIR models. This approach also permits evaluation of strategies with target individuals differentially, including isolation or active case finding, and may be useful in determining optimal strategy in public health settings.

These models tend to be utilised more for smaller groups rather than large-scale populations. This is partially due to their computational complexity, and partly due to the necessity to measure or accurately estimate social interactions and other relevant factors where data may be imprecise in larger populations. For modelling a large population such as the Australia-wide evaluation planned for this thesis, there are a number of limiting factors to the use of network or spatiotemporal approaches. First, insufficient data exists currently to accurately estimate important parameters such as community interaction, particularly between relevant groups such as newly arrived immigration cohorts. Such parameters could be estimated but would be subject to inaccuracies, potentially magnified by the large scale of the modelling exercise. Second, as allude to above, the computational complexity of these models increases exponentially as the size of the population (and so the number of potential interactions) expands.

6.2.7 Choice of modelling approach

Consideration was given to the use of compartment-based models such as ordinary or partial differential equation models. Although such models have the advantage of simplicity in model construction, the degree of population heterogeneity and low
frequency of tuberculosis infection suggested that an individual-based model was likely to be the most rewarding for accurate modelling of infection in this context. Although computationally more demanding, data to inform a reliable individual-based model was available through the incorporation of actual individual immigration records, augmented through imputed characteristics where necessary.

Age-structure was considered to be an important factor, given the long durations of time included in the planned model. Both the changing risk of reactivation and background risk of mortality should vary with age, and this model will age-structure parameters in order to incorporate this.

A model intended for evaluation of public health policies requires not only an assessment of the average outcomes for a given approach, but also a robust understanding of the possible range of outcomes and their relative likelihood of occurrence. A deterministic model would not provide sufficient capacity to accurately demonstrate uncertainty in outcomes within a complex population-level framework such as the one required for these questions. A stochastic model was considered to be a more appropriate approach, in order that such complexity and range of possible outcomes be assessed clearly. In addition, since the emphasis of this model is on tuberculosis eradication, assessment of the behaviour of infection when only small numbers of cases remain is critical, and optimally evaluated using a stochastic approach.

Use of a network model was considered as such an approach has an increased degree of realism in terms of contacts and transmission risk. However network models are of most use when potential for local infection is high, as they provide more realistic assessment of significant contact and person-to-person transmission. In a Victorian setting, local data collected for this thesis has reinforced the concept that the substantial majority of local tuberculosis cases relate to reactivation of previously latent infection. Accordingly, the incorporation of network approaches to modelling would be unlikely to add significantly to accurate understanding of tuberculosis infection in this setting, as well as substantially increasing its complexity, and so this approach was not adopted.
Within the model approach chosen, a number of parameters were considered to be of key interest for evaluation. The central outcome of interest was TB incidence, with strategies related to identification and prevention of LTBI reactivation of chief importance. Accordingly, the model had to be able to consider a variety of immigration screening strategies, including alternative screening tools and management pathways following detection. It was felt desirable to include factors identified as increasing risk for tuberculosis infection. Data were available for this cohort on country of origin, HIV infection, diabetes, age-structure and smoking at either an individual level (country of origin, age) or in an aggregate form by country of origin and gender (smoking, diabetes, HIV infection). Finally, the risk of MDR TB introduction was identified as a central concern during the review process, and it was decided that this model must incorporate risk of MDR TB infection as part of the outcomes of interest associated with various strategies.

In summary, following consideration of the available modelling options, it was felt that the optimal approach to modelling tuberculosis in Australia would be an age-structured, individual-based, stochastic linear model. Key features for inclusion in the model parameters were as outlined above. The next section details the construction and validation of this model, and explores its predictions regarding tuberculosis incidence in Australia.

6.3 Developing a mathematical model of tuberculosis infection in an Australian context

An individual-based, stochastic model with discreet time intervals of tuberculosis reactivation in immigrants was developed using MATLAB (R2012a, The MathWorks, Nowick, MA, USA). MATLAB code for this model is included at the end of the methods section. Individuals populating this model were derived initially from immigration records of permanent arrivals to Victoria, Australia between 1975-2007. Individual level data on age, year of arrival and region of origin were available for approximately 750,000 arrivals over this period, with additional characteristics (HIV status, diabetes mellitus, smoking status, sex) stochastically assigned according to an initial randomization process weighted by regional risk estimates and adjusted by age and sex. Future arrivals were subsequently generated based on demographic
profiles of the most recently available immigrant cohorts, of 2007. Population incidence calculations used 2006 census data to provide a total population denominator, adjusted by +1.3% annually in accordance with historic population growth trend.

For each time-step of the model, age and other time-dependent variables were updated and new arrival cohorts integrated. Summary risk estimates for tuberculosis reactivation were then generated through adjustment of regional risk by individual modifiers. Regional risk of tuberculosis reactivation was taken from historical cohort-specific risk in the Victorian setting, as described in chapter 2 of this present work. Region-specific risk was adjusted to account for an annual 3.4% proportionate decline in global TB incidence, in accordance with most recent estimates from the World Health Organisation(329). Risk ratios in the presence of HIV infection, smoking, diabetes and age were taken from published estimates. Details of risk ratios for individual variables are provided at the end of the methods section of this thesis. An age-specific risk of mortality was applied based on Australian life expectancy tables, with subjects removed from subsequent time-steps following tuberculosis infection or death. Model outputs were fitted to pre-2007 historical tuberculosis notifications in immigrant cohorts to Victoria, with the period 2007-2011 used to validate model predictions against data. Baseline scenarios assumed that no transmission or secondary cases occurred following disease, with the impact of transmission subsequently explored in sensitivity analyses. Consistent with current data, 0.5-2.4% of TB disease was expected to be multidrug resistant at baseline, with sensitivity analyses performed to consider future trends(206).

Following consideration of baseline expectations for future tuberculosis incidence, a variety of strategies relating to latent tuberculosis infection were evaluated. Strategies focused on interventions during the immigration process, using combinations of tuberculin skin testing or interferon-gamma release assays and treatment with isoniazid or isoniazid plus rifapentine preventative therapy regimens. All strategies were initiated beginning January 1, 2013, and assume immediate (step-wise) application in relevant immigrant cohorts. Test characteristics were taken from meta-analysis of published literature. Treatment efficacy estimates were also taken from published literature, and are detailed in Table 6.1-6.3 at the conclusion of this section.
In addition to application of currently available approaches, this model was also used to evaluate the impact of potential future intervention approaches. Accordingly, a hypothetical therapeutic vaccine was also evaluated across a range of effectiveness and coverage, with sensitivity analysis performed to consider relevant thresholds for effectiveness. For all strategies, the primary outcome of interest was overall tuberculosis incidence in 2050, with secondary outcomes including proportion of multi-drug resistant disease associated with each strategy. Following exploratory analyses involving 1-1000 iterations of the model, each scenario or strategy examined conducted 100 iterations of the model, with mean annual tuberculosis cases and 95% confidence intervals calculated and reported.

Data on immigrant demographics was obtained from the Australian Bureau of Statistics. Data on country-specific risk of was obtained from the TB Control Program of the Department of Health Victoria, as described in chapter 2 of this present work. All data used in this analysis was de-identified prior to extraction, with approval for use provided by relevant data managers. According to institutional policy, no review by Human Research Ethics Committee was required.
MATLAB code

clear
% load and construct datasets; obsmat, observed ABS data, & fixedmat, stochastically imputed
% characteristics of individuals that do not change with time
load('workspace550pm20Feb2012extrayears50.mat');
obsextramat=obsmat;
fixedextramat=fixedmat;
load('workspace14Feb2012.mat');
p=size(obsmat, 1);
obsextramat(:, 1)=obsextramat(:, 1)+p;
obsmat=[obsmat; obsextramat];
fixedmat=[fixedmat; fixedextramat];

% fixedmat= male smoker diabetesever diabetesageonset HIV agedeath yeardeath
% obsmat= id ageofarrival region year_of_arrival
reg=obsmat(:, 3);
smoker=fixedmat(:, 2);
dbever=fixedmat(:, 3);
dbage=fixedmat(:, 4);
allagedeath=fixedmat(:, 6);
arrivetodeath=fixedmat(:, 6)-obsmat(:, 2);
totaloutcome=[];
evertb=ones(size(obsmat, 1), 1);

% hazard ratio compared with youngest group 0-5 years in Australia, derived from Chapter 2
agerelatedrisk=[1.087119 1.909857 5.113362 7.708005 4.996850 3.831604
17.684330 18.875500 18.293420];

% compared with region Oceania minus ANZ, the hazard ratio
regionalrisk=[0.0640615
0.3156295
0.7669089
1.9408880
0.9504696
2.5993110
0.1736536
0.2400387
2.5505520
];
yeardeath=obsmat(:, 4)-obsmat(:, 2)+allagedeath;

% hazard ratio for
smokingrisk=2.01;
diabetesrisk=3.11;
hivvec=fixedmat(:, 5);

% baseline hazard of tb modelled on data as a function of time since arrival into Australia
% y=(2.5*10^-4)*exp(-0.1192*x)+2*10^-5;
baselinerisk0=10*(10^-5)*ones(size(obsmat, 1), 1);
baselinerisk10=3*(10^-5)*ones(size(obsmat, 1), 1);
%end year for the simulations
finalyear=2090;
\begin{verbatim}
a= -1;
for hivrisk=[1:59:60];  % try 2 different assumptions about impact of HIV, no hazard versus 60 hazard ratio
hivrisk
a=a+1
arrivalyear=obsmat(:, 4);
attritionyear=arrivalyear-2012;  % time since 2012 to adjust for reduced global TB incidence
attritionyear=attritionyear.*(attritionyear>0);  % only adjust if arrived after 2012
globalreductionrate=0.966;
\end{verbatim}

% Start the timesteps loop
\begin{verbatim}
for year =1976:1:finalyear
year
% update time-dependent variables
\begin{verbatim}
timesincearrival=year-obsmat(:, 4);
agenow=obsmat(:, 2)+timesincearrival;
\end{verbatim}
% the following lines updates the entire population odds ratio according to timedependent and fixed %personal characteristics
\begin{verbatim}
OR=(smokingrisk.^smoker);
dbnow=dbage<agenow;
\end{verbatim}
% time since 2012 to adjust for reduced global TB incidence
% x is a variable used to consider a range of population-wide factors reducing TB reactivation % risk.
\begin{verbatim}
if year>2012,
OR=OR.*(globalreductionrate.*(attritionyear.*(attritionyear>0))).* ((1-x).*(attritionyear>0)+(1-attritionyear>0));
end
\end{verbatim}
\begin{verbatim}
OR=OR.*(diabetesrisk.^dbnow);
OR=OR.*ageterminedrisk(1).^((agenow>4)&(agenow<10));
OR=OR.*ageterminedrisk(2).^((agenow>9)&(agenow<15));
OR=OR.*ageterminedrisk(3).^((agenow>14)&(agenow<20));
OR=OR.*ageterminedrisk(4).^((agenow>19)&(agenow<25));
OR=OR.*ageterminedrisk(5).^((agenow>24)&(agenow<30));
OR=OR.*ageterminedrisk(6).^((agenow>29)&(agenow<35));
OR=OR.*ageterminedrisk(7).^((agenow>34)&(agenow<40));
OR=OR.*ageterminedrisk(8).^((agenow>39)&(agenow<45));
OR=OR.*ageterminedrisk(9).^((agenow>44)&(agenow<50));
OR=OR.*ageterminedrisk(10).^((agenow>49)&(agenow<55));
OR=OR.*ageterminedrisk(11).^((agenow>54)&(agenow<60));
OR=OR.*ageterminedrisk(12).^((agenow>59)&(agenow<65));
OR=OR.*ageterminedrisk(13).^((agenow>64)&(agenow<70));
OR=OR.*ageterminedrisk(14).^((agenow>69)&(agenow<75));
OR=OR.*ageterminedrisk(15).^((agenow>74)&(agenow<80));
\end{verbatim}
OR=OR.*agrelatedrisk(16).^(agenow>79&agenow<85);
OR=OR.*agrelatedrisk(17).^(agenow>84&agenow<90);

OR=OR.*regionalrisk(1).^(reg==3);
OR=OR.*regionalrisk(2).^(reg==4);
OR=OR.*regionalrisk(3).^(reg==5);
OR=OR.*regionalrisk(4).^(reg==6);
OR=OR.*regionalrisk(5).^(reg==7);
OR=OR.*regionalrisk(6).^(reg==8);
OR=OR.*regionalrisk(7).^(reg==9);
OR=OR.*regionalrisk(8).^(reg==10);
OR=OR.*regionalrisk(9).^(reg==11);

OR=OR.*(hivrisk.^hivvec)*(1);

% this is a 3 parameter model of the baseline hazard
riskvec=(timesincearrival>=0).*(2.5*10^-4).*exp(-0.1192*timesincearrival)+2*10^-5;

% convert baseline hazard to odds of infection
oddstb=riskvec./(1-riskvec);
oddstb=oddstb.*nevertb;

% update odds using the final odds ratio
oddstb=oddstb.*OR;
risktb=oddstb./(ones(size(oddstb))+oddstb);

% only those who have arrived, have never been observed to have tb and are still alive can get active TB
isliving=yeardeath>year;
risktb=risktb.*isliving;

%determine who gets TB using a random number generator, risktb is the vector, size of the whole cohort
%0<=risktb<=1

tbthisyear=risktb>rand(size(risktb));
nevertb=nevertb-tbthisyear; % exclude the incident cases of TB from subsequent timesteps

totaloutcome=[totaloutcome, tbthisyear]; %collect all of the incident cases for each time-step
end
s=sum(totaloutcome) %sum all of the incident cases for each time-step
figure(1)
plot([1976:finalyear], s((115*a+1):(115*(a+1))), 'color', 'b')
hold on
end
Table 6.1 Assumptions and risk modification included in mathematical model of tuberculosis infection in Victoria

<table>
<thead>
<tr>
<th>Risk modifier</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
</table>

**Interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months of weekly isoniazid and rifapentine versus no treatment</td>
<td>0.176</td>
<td></td>
</tr>
</tbody>
</table>

**Demographic factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV prevalence</td>
<td>Regionalised; see table</td>
<td>UNAIDS and the WHO’s Report on the Global AIDS Epidemic.</td>
</tr>
<tr>
<td>Sex</td>
<td>Random allocation, equally distributed</td>
<td></td>
</tr>
</tbody>
</table>
Sensitivity of tests for latent tuberculosis infection

Tuberculin skin test 73

Quantiferon gold 76

T-spot TB 88


Additional demographic information


Annual growth trend 1.30%

Table 6.2 Regional estimates of HIV and smoking rates

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence of HIV, total (% of population ages 15-49)</th>
<th>Smoking (% male &gt;16)</th>
<th>Smoking (female &gt;16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 New Zealand</td>
<td>0.1</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>2 Oceania</td>
<td>0.1</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>3 North-West Europe</td>
<td>0.23</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>4 South-East Europe</td>
<td>0.38</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>5 North Africa/Med</td>
<td>0.14</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>6 SEA</td>
<td>0.18</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>7 Northeast Asia</td>
<td>0.1</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>8 South Asia</td>
<td>0.26</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>9 North America</td>
<td>0.55</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>10 Latin/South America</td>
<td>0.47</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>11 Sub-Saharan Africa</td>
<td>5.45</td>
<td>23</td>
<td>8</td>
</tr>
</tbody>
</table>

Data extracted from (197, 312)

Table 6.3 Diabetes prevalence in Australia, 2007.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number</th>
<th>Per cent</th>
<th>Proportion with diabetes in the population (%)</th>
<th>Number</th>
<th>Per cent</th>
<th>Proportion with diabetes in the population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–44</td>
<td>50,400</td>
<td>10.1</td>
<td>0.8</td>
<td>60,400</td>
<td>14.7</td>
<td>0.9</td>
</tr>
<tr>
<td>45–49</td>
<td>27,800</td>
<td>5.5</td>
<td>3.7</td>
<td>37,800</td>
<td>9.3</td>
<td>4.8</td>
</tr>
<tr>
<td>50–54</td>
<td>51,900</td>
<td>10.4</td>
<td>7.6</td>
<td>28,400</td>
<td>7.1</td>
<td>4.1</td>
</tr>
<tr>
<td>55–59</td>
<td>71,000</td>
<td>14.2</td>
<td>11.5</td>
<td>62,500</td>
<td>15.7</td>
<td>9.9</td>
</tr>
<tr>
<td>60–64</td>
<td>84,600</td>
<td>10.9</td>
<td>15.2</td>
<td>40,200</td>
<td>10.2</td>
<td>7.5</td>
</tr>
<tr>
<td>65–69</td>
<td>94,600</td>
<td>16.0</td>
<td>21.2</td>
<td>42,600</td>
<td>10.7</td>
<td>10.4</td>
</tr>
<tr>
<td>70–74</td>
<td>80,200</td>
<td>12.0</td>
<td>16.6</td>
<td>34,100</td>
<td>8.6</td>
<td>10.3</td>
</tr>
<tr>
<td>75–79</td>
<td>40,100</td>
<td>8.0</td>
<td>18.3</td>
<td>36,400</td>
<td>9.2</td>
<td>12.9</td>
</tr>
<tr>
<td>80 and over</td>
<td>31,000</td>
<td>6.2</td>
<td>12.0</td>
<td>57,600</td>
<td>14.6</td>
<td>15.5</td>
</tr>
<tr>
<td>All ages**(a)**</td>
<td>591,300</td>
<td>100.0</td>
<td>4.9</td>
<td>397,500</td>
<td>100.0</td>
<td>3.8</td>
</tr>
</tbody>
</table>

(a) Based on survey participants’ self-reported information.
(b) Total includes people who did not know which type of diabetes they have but excludes gestational diabetes.

Source: AIHW analysis of the ABS 2007–08 NHS Confidentialised Unit Record File.
6.4 Results

6.4.1 Baseline scenario

Without additional intervention, the baseline scenario from this model predicts that approximately 14,700 cases of tuberculosis will occur in 1.5 million immigrants to Victoria during the period 2013-2050, with an expected 318 (95% CI 316-321) cases in 2050. Adjusting for expected population growth, this is equivalent to an incidence of 34.5 (95% CI 34.3-34.8) cases/million population in 2050. Figure 6.4.1 shows the baseline scenario incorporating variation (+/- 50% predicted) in global decline of tuberculosis incidence. Figure 6.4.2 shows validation of the model through comparison with diagnoses of tuberculosis in Victoria during the period 1991-2010 compared with actual TB notification data for this period.
6.4.1 Number of annual TB cases in Victoria under baseline conditions, including 3.4% decline in global TB incidence. Upper and lower variations shown depict model predictions given global TB decline varying by +/- 50% WHO predictions (1.7-5.1% annual decline).
6.4.2 Predicted and actual number of Victorian TB cases, 1991-2010. (Dashed line demonstrates derivation versus validation years)

Based on current rates of multidrug resistance, a mean of approximately 225 cumulative MDR TB cases are anticipated between 2012-2050, with 2-9 cases occurring in 2050. Sensitivity analyses explored the impact of 1-5% annual increase in the MDR proportion of global TB cases. A 5% proportionate increase per year resulted in approximately 665 cumulative cases over this period, with a mean of 32 new cases of MDR TB in 2050.

Tuberculosis risk associated with concomitant HIV infection was varied in sensitivity analyses to consider the range of relative risk estimates associated with different settings. Reducing relative risk from 60 to 6-fold increase over baseline was associated with a small reduction in TB incidence, with a mean 316 (95% CI 312-319) cases in 2050, equivalent to 34.3 cases/million (95% CI 33.9-34.6).

Sensitivity analysis considering the impact of secondary transmission was performed. A 1% risk of secondary case per index case resulted in 322 cases in 2050 (35.0 cases/million), while a 5% risk was consistent with 334 cases in 2050 (36.2
cases/million. A 5% risk would result in an additional 1156 cases during the period 2013-2050.

6.4.2 Screening and chemopreventative therapy

The use of either tuberculin skin testing, Quantiferon or T-spot TB testing was evaluated in conjunction with the use of a 9 month course of isoniazid or a 12 dose (3 month) course of weekly isoniazid and rifapentine. Figure 6.4.3 shows a comparison of different screening and treatment strategies applied to all immigrants from 2012, while Table 6.4 presents the total number of cases and TB incidence for the target year 2050. These approaches would involve screening and/or treatment for the entire immigration cohorts, totally approximately 1.5 million people during the period 2012-2050.

Combinations of screening and chemopreventative therapy for all immigrants resulted, overall in a reduction of approximately one-third to one-half of the number of TB cases in 2050. For any strategy, the proportion of cases relating to MDR TB strains would be expected to rise to approximately 1-5%, as immigrants with drug-resistant strains of LTBI continue to reactivate in the context of smaller numbers of cases overall.
6.4.3 Number of tuberculosis cases in Victoria, 1990-2090, following introduction of various screening and treatment interventions for all new permanent arrivals to Victoria.

TST=tuberculin skin test; QFT= Quantiferon Gold test; Tspot= Tspot TB test; INH= Isoniazid; RPT= rifapentine.
Table 6.4 Summary of screening/treatment interventions and TB incidence outcomes in 2050

<table>
<thead>
<tr>
<th>Test Combination</th>
<th>Mean cases of active TB, 2050</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST + INH</td>
<td>225</td>
<td>24.4</td>
</tr>
<tr>
<td>QFT + INH</td>
<td>221</td>
<td>24.0</td>
</tr>
<tr>
<td>Tspot + INH</td>
<td>204</td>
<td>22.1</td>
</tr>
<tr>
<td>TST + INH/RPT</td>
<td>188</td>
<td>20.4</td>
</tr>
<tr>
<td>QFT + INH/RPT</td>
<td>179</td>
<td>19.4</td>
</tr>
<tr>
<td>Tspot + INH/RPT</td>
<td>156</td>
<td>16.9</td>
</tr>
<tr>
<td>Baseline</td>
<td>323</td>
<td>34.5</td>
</tr>
</tbody>
</table>

TST = tuberculin skin test; QFT = Quantiferon Gold test; Tspot = Tspot TB test; INH = Isoniazid; RPT = rifapentine.

In order to consider the potential for new diagnostic tests, hypothetical screening tests with sensitivity of 80-100% were evaluated in combination with isoniazid and rifapentine short-course therapy. Results are shown in figure 6.4.4 below.
6.4.4 Number of Victorian TB cases 2011-2050 following use of novel screening tool with varied sensitivity for LTBI for all new arrivals, followed by rifapentine/isoniazid short-course therapy if positive.
The most effective strategy identified in modelling whole population interventions, consisting of T-spot TB screening followed by isoniazid with rifapentine short course therapy following a positive result, was then further evaluated in sub-populations, including higher-incidence regions of origin and other groups with increased risk of disease. For regions of origin, 3 incidence thresholds were specified for stratification; regions with >1000, 400 and 200 cases per million population per year. Figure 6.8 compares the use of these incidence thresholds for inclusion in screening and treatment programs. In the target year of 2050, use of these thresholds resulted in TB incidence of 30.2, 29.6 and 27.2 cases/million respectively, compared with the baseline incidence of 34.5 cases/million. These thresholds include between 200-750,000 immigrants over the period 2012-2050, with details presented in figure 6.4.5 below.
6.4.5 Number of annual tuberculosis cases in Victoria, 2011-2050, following introduction of various tuberculosis incidence thresholds in regions of origin for inclusion in screening and treatment program using T-spot TB and isoniazid and rifapentine short-course therapy.
The impact of smoking reduction and cessation programs was also of interest, given the well-defined increased risk of reactivation and high prevalence of smoking in immigrant cohorts. In order to consider the potential impact of smoking cessation, a best-case scenario was explored through the simulation of a total smoking ban following arrival to Australia. This scenario, shown in figure 6.4.6, resulted in a mean 272 cases of tuberculosis in 2050, consistent with an incidence of 29.5 cases/million. A complete smoking ban would prevent an estimated 1650 cases of tuberculosis during the period 2013-2050.
6.4.6 Number of tuberculosis cases in Victoria, 2011-2050, following introduction of a complete ban on tobacco smoking commencing January 1, 2013, compared with baseline.
As an alternative to incidence thresholds for selecting a cohort for screening, the use of targeted screening programs for immigrants with diabetes and HIV infection were also explored. These approaches screened all new arrivals with diabetes (figure 6.4.7) or HIV (figure 6.4.8) with Tspot TB, followed by treatment with rifapentine and isoniazid short-course therapy for those testing positive. A screening program targeting immigrants with diabetes resulted in a mean of 289 (95% CI 286-290) cases in 2050, consistent with an incidence of 31.4 cases/million (95% CI 31.0-31.5). A screening program targeting HIV infected immigrants resulted in a non-significant reduction in 2050 TB incidence, with a mean 34.0 cases/million projected.
6.4.7 Number of tuberculosis cases in Victoria, 2011-2050, using diabetes status for inclusion in screening and treatment program using T-spot TB and isoniazid and rifapentine short-course therapy, compared with baseline.
6.4.8 Number of tuberculosis cases in Victoria, 2011-2050, using HIV status for inclusion in screening and treatment program using T-spot TB and isoniazid and rifapentine short-course therapy, compared with baseline.
The use of an age threshold for screening was also explored, with immigrants less than 35 or 50 years old included. Figure 6.4.9 compares the impact of age thresholds with the baseline scenario, which are consistent with resultant 2050 tuberculosis incidences of 22.9 and 18.2, with equate to 4120 and 5458 cases of tuberculosis prevented between 2012-2050, respectively.
6.4.9 Number of tuberculosis cases in Victoria, 2011-2050, using age at arrival thresholds for inclusion in screening and treatment program using T-spot TB and isoniazid and rifapentine short-course therapy, compared with baseline.
6.4.3 Therapeutic vaccination

For evaluation of hypothetical vaccine strategies, both vaccine efficacy and coverage was varied between 50-100% of new arrivals. Figure 6.4.10 shows tuberculosis incidence following introduction of a 50% or 100% efficacious therapeutic vaccine administered to all immigrants. Figure 6.4.11 shows predicted incidence of tuberculosis in 2050 across the considered range. In the optimal scenario, using a vaccine with 100% efficacy and coverage, a mean of 92 (95% CI 91-94) cases of tuberculosis would be expected in 2050, corresponding to an incidence of 10.0 (95% CI 9.9-10.2) cases/million. All cohort-wide strategies strategy would involve the administration of 1.5 million vaccine doses to be provided over the 38 year time period, with a mean of approximately 41,000 doses per year.
6.4.10 Number of cases of tuberculosis in Victoria, 2011-2050, following introduction of 50% or 100% effective therapeutic vaccination for all new immigrants.
6.4.11 Victorian tuberculosis incidence in 2050 following introduction of therapeutic vaccination with varying efficacy and coverage.

A summary of potentially effective strategies is shown in table 6.5, including comparison of number of immigrants screened and resultant 2050 TB incidence.
Table 6.5 Summary comparison of immigration-related LTBI interventions.

<table>
<thead>
<tr>
<th>Number of immigrants</th>
<th>Strategy</th>
<th>Infections</th>
<th>LTBI cases identified</th>
<th>LTBI cases proceeded</th>
<th>Case prevalence</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>0</td>
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</tr>
<tr>
<td>1.5</td>
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<td>3.45</td>
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<td></td>
<td>3.45</td>
<td>1.65</td>
<td>565</td>
<td>0.00</td>
</tr>
</tbody>
</table>
6.5 Discussion

Detailed discussion of various implications of this model follows in subsections below. Prior to application of these findings directly to public health policy, it should be noted that there are several limitations inherent to this approach. Predictions arising from this model are dependent on a number of underlying assumptions, particularly relating to future trends in immigration demographics and international TB control. This model also does not consider local transmission of disease or the possibility of infection/reinfection related to travel following arrival. However, the intention was to evaluate whether optimised immigration-related strategies may achieve sufficient TB incidence reduction towards the 2050 MDG, and as such, these exclusions are conservative. This study is also limited in focus on incidence of TB, rather than outcomes such as TB-related death, cost and QALY. This emphasis was appropriate given the central question of interest, however, further extension of the model will be required for inclusion into robust public health policy.

6.5.1 Screening tests

Three currently available screening tests were evaluated in this model: the tuberculin skin test and two interferon-gamma release assays, Quantiiferon and T-spot TB. Based on available estimates of test characteristics, T-spot TB performed best, with 2-5 fewer cases of TB disease per year by 2050 than if screening had been performed with Quantiiferon. Both IGRAs performed better than if tuberculin skin testing was used, with an additional benefit of approximately 10 cases per year. Overall, though, the use of any screening test led to a significant reduction in TB incidence, while differences between the various screening tests for latent tuberculosis were relatively minor.

Test characteristics, such as sensitivity and specificity, were taken from meta-analysis of published literature(330). Although this represents the best available evidence for test performance currently, these estimates are limited by several factors. First, the absence of a gold-standard for the diagnosis of latent tuberculosis means that there is a lack of appropriate comparator for assessment. Cohort studies often compare tests against each other, however discordance may be reflective of poor performance by either test or both in a given population. In order to establish a pseudo-gold-standard, many studies have opted to assess sensitivity in active infection, and consider this
effectively equivalent to performance in the setting of latent infection. This approach has significant limitations, particularly the risk of higher rates of falsely-negative tests, possibly due to migration of TB-specific T-cells to the site of active disease. Sensitivity for latent infection, then, may be higher than published estimates suggest. In order to consider this limitation, sensitivity analysis was performed to consider the impact of varying test characteristics, with relatively minimal impact found when test sensitivity was varied from 80-100%.

### 6.5.2 Chemopreventative therapy

The use of isoniazid and rifapentine combination therapy resulted in significant reduction in tuberculosis incidence, when compared with either current outcomes without routine treatment or the use of isoniazid alone. The additional benefit from the use of isoniazid and rifapentine was approximately 25-30 cases/year by 2050, regardless of which diagnostic test for LTBI had been employed.

The use of a step-wise function beginning in 2013 for the introduction of interventions may over-estimate the impact of putative intervention strategies. Actual interventions would require gradual implementation over a longer time frame. However, our interest in this model was to assess the maximum possible effectiveness for given strategies, with the aim of considering whether approaches may achieve the intended MDG target of <1 case/ million population. Although an immediate step-wise intervention will risk over-estimating the impact of a given approach, no strategy achieved the target despite this modelling choice.

### 6.5.3 Multidrug Resistance

An increased proportion of multidrug resistant (MDR) tuberculosis would be expected following the introduction of chemopreventative public health strategies. This increased proportion occurs as drug sensitive cases of LTBI are effectively treated with chemoprevention, while those with MDR LTBI continue to be at risk of reactivation. The use of the strategies considered here may result in an absolute increase of 1-2% MDR, however, should global rates of MDR TB continue to rise in future, such an effect may become even more prominent. Vaccine-based strategies,
which are expected to be equally effective against drug-resistant and drug-sensitive strains, reduce subsequent disease equally and so no altered proportions are evident.

Given this increase, it may be asked whether chemopreventative therapies effective against MDR LTBI should be used in such public health approaches. However, as reviewed earlier in this these, the evidence base for MDR LTBI chemoprevention is limited. Data presented in Chapter 4 of this thesis demonstrates the impact of MDR TB cases in low-prevalence regions such as Australia. Although such impact may be considerable, this data highlights the lack of recognised community transmission associated with MDR TB cases in the setting of effective public health management. In addition, current management of MDR TB in Australia appears effective, with successful treatment of individual cases and prevention of secondary transmission achieved. Accordingly, these findings would support the continued use of chemopreventative therapy for drug sensitive LTBI, apart from the specific setting of known close contact with an infectious case MDR TB.

6.5.4 Targetted screening

The majority of strategies considered here have been applied to the whole population of immigrants, regardless of personal risk factors or characteristics. This has been in keeping with the primary aim of evaluating strategies for maximal reduction in tuberculosis incidence, however, such strategies also result in screening and treatment for large populations at relatively lower risk of tuberculosis disease. In projected immigration cohorts between 2012-2050, such strategies would involve screening and treatment for approximately 1.5 million people, or a mean of 41,000 per year. In order to explore options for reducing the number of immigrants screened, various strategies considering screening and treatment for various sub-populations were secondarily evaluated. Improved strategies would preferentially select immigrants at high risk for subsequent tuberculosis disease, allowing the possibility of smaller screening/treatment programs with a relatively small loss in TB incidence reduction. The use of region of origin tuberculosis incidence thresholds for inclusion in immigration screening programs was effective in reducing Victorian tuberculosis incidence, with a decline from 34.5 to 30.2 cases/million seen in 2050 following implementation of screening for regions with more than 1000 cases of TB per million
population annually (ie Sub-Saharan Africa and South Asia). This strategy would prevent approximately 6050 cases of tuberculosis during the period 2013-2050. However, expansion of screening to thresholds of >400 and >200 cases/million resulted in a large number of addition immigrants included for relatively smaller marginal benefits (29.6 and 27.2 cases/million in 2050 respectively), suggesting that only the higher threshold may be worthwhile if targeted screening was to be employed. It is worth noting, however, that although new immigrants from these two regions represent the individuals at highest risk for reactivation, even combined they do not contribute an absolute majority of overall TB cases; in 2010, Sub-Saharan Africa and South Asia contributed 8.7% and 36.7% respectively.

The identification of subpopulations other than those related to region of origin were also explored. Of interest, a simulated introduction of a smoking ban was considerably effective, preventing around 1650 cases of tuberculosis between 2013-2050. This reduction is due to both the increased risk of TB reactivation in smokers and the large number of current smokers in many regions where tuberculosis is endemic. This combination of factors suggests that smoking cessation and reduction programs may be a valuable intervention for tuberculosis incidence reduction in immigration communities, and is deserving of further exploration.

Two age-specific thresholds for inclusion in screening and treatment interventions were considered; 35 and 50 years old. A substantial reduction in TB incidence was observed with the 35 year old threshold, reducing 2050 incidence from 34.5 to 22.9 cases per million. A further reduction in incidence was seen by increasing the age threshold from 35 to 50 however this additional benefit was relatively modest (22.9 to 18.2 cases/million).

It is notable that both varying relative risk associated with HIV infection and targeting HIV infected immigrants for screening resulted in minimal reduction in TB incidence. Although individuals with HIV and LTBI are at high risk of reactivation, the number of co-infected immigrants to Australia is very low, partially related to active screening and exclusion of HIV-positive individuals. Accordingly, while screening and treatment may be important in this group on the basis of personal risk,
as a public health strategy is it unlikely to be decisive, as may be the case in other regions globally.

Targetting interventions to immigrants with diabetes was had relatively limited effectiveness in reducing TB incidence, which is perhaps surprising given the large proportion of people who develop diabetes over their lifetime. Although people with diabetes have an increased risk of TB reactivation, diabetes risk increases with age while the average age of arrival in our cohorts was relatively lower. Accordingly, only a relatively few immigrants with diabetes were identified through the use of this as a criteria for inclusion. In addition, such an approach to screening may be hampered by those undiagnosed at the time of migration, even if diabetes is already biologically established prior to arrival.

6.5.5 Vaccination

The only vaccine currently available for the prevention of tuberculosis is the BCG vaccine, in widespread use since the 1920’s. Although the BCG is clearly effective in reducing severe complications of tuberculosis disease, particularly tuberculous meningitis in children less than 5 years old, its efficacy in adult immigrants is far less clear (331). Several meta-analyses have concluded that overall effectiveness may be around 50%, but that it may provide only 15% reduction in risk of pulmonary tuberculosis in adults (122, 332). Furthermore, no evidence exists that vaccination in adulthood, as would be required for many immigrants, impacts risk of future infection or disease (333). A novel, effective therapeutic vaccine would therefore potentially offer a significant benefit towards reduction of tuberculosis incidence in Australia. A number of candidate vaccines are under current evaluation however none have been clearly established as suitable in human clinical trials at this stage (334).

The results of this model suggest that caution is warranted regarding the potential impact of immigration-related vaccination strategies. Although mass vaccination as part of immigration entry to Australia would be likely to substantially reduce tuberculosis incidence, the pool of LTB-infected individuals already resident in Australia is predicted to experience ongoing reactivation for many decades, at rates exceeding 10 cases/million/year until well after the 2050 MDG timeline. Therefore, even completely effective vaccines employed during immigration would be
insufficient to achieve the 2050 MDG incidence target for tuberculosis. Furthermore, while an optimal vaccine was effective in reducing incidence, this was achieved with the administration of 1.5 million doses to a largely low risk population. Such a vaccine could be targeted at higher risk individuals, such as those from regions with >1000 incident TB diagnoses per million population; however, even an optimal vaccine for this group would require 200,000 doses administered in order to reduce 2050 TB incidence to 27 cases/ million/year.

Several different responses to these findings are possible. First, the demonstration that immigration screening and treatment is incapable of meeting the desired TB incidence goal may suggest that a public health strategy needs to consider expanding to incorporate the pool of LTB-infected individuals already resident in Australia. Alternative strategies may include targeted screening and treatment of people with a high likelihood of LTBI, including those who have emigrated from high prevalence countries, or subgroups such as refugees and asylum seekers. Evaluation of such approaches is beyond the scope of this present work, but could involve mathematical modelling or longitudinal pilot studies in selected populations. It must be acknowledged that such programs would be likely to involve considerably increased expenditure compared with immigration-focused approaches, due to the absence of established structures and processes for engaging with these populations. The evaluation of these strategies would also need to consider the ethical issues involved in targetted screening programs which would likely be stratified by country of birth.

Secondly, it may be acknowledged that the goal of <1 case/million population annual incidence is essentially an arbitrary one, both in terms of the absolute level of disease permissible and the timeline for success. Despite not meeting the MDG goal, immigration-related strategies appear to be relatively effective and would be expected to reduce the incidence of tuberculosis in Australia considerably. Although cost-effectiveness modelling has not been attempted here, given the processes already in place and relatively high-risk populations of interest, it would be reasonable to expect immigration-related approaches to perform well against alternative strategies. It remains to be seen, however, whether such strategies would be considered sufficiently cost-effective in order to warrant their adoption in this context.
6.6 Conclusions

In summary, immigration-related strategies are predicted to be effective in reducing tuberculosis incidence in this low-prevalence setting. Although no strategy evaluated was sufficiently beneficial to achieve the MDG goal of <1 case of TB disease per million population per year, both novel and currently available interventions could be used in this context to enhance and complement other strategies for reducing tuberculosis incidence in Australia. Although cost-effectiveness and implementation evaluation of such strategies is beyond the scope of this present work, those strategies outlined here and alternative, non-immigration related, approaches would benefit from such considerations in future.

Although hypothetical vaccine-related strategies have also been evaluated here, of the currently available approaches the use of either IGRA for screening, followed by treatment with a 12-week course of isoniazid and rifapentine, would appear to be optimal. Choice of chemopreventative therapy appears to have a more substantial impact on TB incidence than does screening tool in this analysis.

The focus in this chapter has been on modelling the potential effectiveness of immigration-related interventions targeting LTBI for reducing TB incidence. In keeping with this primary emphasis, strategies have aimed to maximise impact on incidence in a number of ways. For instance, test performance has been based on sensitivity, in order to assess the proportion of LTBI cases identified in order to initiate chemoprevention. Such evaluation, however, does not consider specificity closely, meaning that chemoprevention is likely to be given to immigrants not infected with LTBI at the time of arrival. Such people would be exposed to the risks of chemoprevention but not experience any personal benefit, and a more complete analysis of factors such as this would be required prior to implementation of such a public health strategy.

In addition to the considerations of effectiveness dealt with in this chapter, the introduction of any such immigration screening and/or treatment program requires considerable engagement with a raft of ethical issues as well. The next chapter will
consider the possible adoption of various immigration screening or treatment strategies for LTBI and propose a framework for consideration of such programs.
7. Ethical evaluation of LTBI immigration screening

Most applicants for immigration to Australia are currently required to undergo an assessment for active tuberculosis (TB). As was considered in Chapter 3, this requirement typically consists of a chest x-ray (CXR) and medical review, and is justified on two grounds; first, to protect the Australian community from public health and safety risks, and second, to limit the demand on the Australian health care system (335). Although some applicants, particularly those being considered for refugee or humanitarian visas, are not excluded from immigration on the basis of health care costs, screening for active TB is still required on the basis of ensuring that individuals are ‘fit to fly’ prior to travel, as well as on public health grounds (336).

Recently, there has been increasing interest in expanding immigration screening for TB to include consideration of latent infection (LTBI) (309, 310). Following primary infection of TB, tubercle bacilli may remain quiescent but viable for many decades prior to active infection (337). During this phase, preventative therapy may be given to eradicate infection and prevent active disease (108, 338). In low prevalence countries such as Australia, the considerable majority of new TB diagnoses arise from reactivation of previously latent infection in those born in high-prevalence regions. Under current policy, a history or CXR suggestive of LTBI may be discovered incidentally while screening for active disease however no specific testing is performed. The opportunity exists, therefore, to consider a systematic screening and treatment program where such infections could be identified and treated before clinical disease occurs.

In addition to any logistic considerations, such policies raise a number of ethical implications that require careful analysis prior to implementation. The focus of this chapter, then, is to review the potential alternatives for the introduction of LTBI screening into Australasian immigration policy, and consider approaches to evaluation of the ethical implications and acceptability of various strategies.

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7.1 Methods

This analysis comprised several interconnected elements. First, a review of current Australian immigration policies related to tuberculosis was conducted. This review aimed to clarify the policy and justification for tuberculosis screening currently applied during immigration to Australia, either for active or latent infection. Relevant Federal government department websites and publications were accessed in order to summarise immigration screening approaches to tuberculosis infection.

Second, a review of ethical frameworks for public health interventions was conducted. This review aimed to identify and present proposed alternative ethical frameworks for evaluating and assessing competing moral priorities with a public health sphere. This review was deliberately non-systematic, aiming to present a range of differing approaches to ethical policy development, and identify a coherent and appropriate option for subsequent application to possible LTBI-related interventions.

Finally, the introduction of screening and treatment for LTBI could be incorporated into new public health policy with a variety of permutations. Given the range of possible scenarios which could be adopted, key elements of such changes were extracted and described in order to allow ethical evaluation of various permutations in policy development.

7.2 Results

7.2.1 Existing Australian immigration policies

Currently, most applicants for immigration to Australia are required to undergo an assessment for active tuberculosis (TB)\(^{335}\). Requirements for immigration to Australia primarily consist of a chest x-ray prior to immigration. Children less than 11 years old and pregnant women are exempted from this investigation, and may be required to have a physical examination instead. Chest x-ray screening is intended to detect active tuberculosis, and if identified, treatment is mandated prior to travel. Evidence of past tuberculosis infection is not a barrier to travel however presentation for follow up medical assessment after immigration may be required.
Justification for these requirements is offered on two grounds; first, to protect the community from transmission of tuberculosis, and second, to limit the demand and costs for the local health care system\(^{(138, 335)}\). Although some applicants, particularly those being considered for refugee or humanitarian visas, are not excluded from immigration on the basis of health care costs, screening for active TB is still required in order to enable individuals to be treated before travel, ensuring that they are ‘fit to fly’ prior to immigration\(^{(336)}\).

7.2.2 Ethical frameworks for public health policy

A number of frameworks have been proposed for the ethical evaluation of public health policy, including immigration screening. Three contrasting approaches are presented here; frameworks based on national sovereignty, human rights and a principle-based approach. These frameworks are explored below with regards to their suitability and appropriateness for application to evaluating novel public health policy in relation to immigration screening for latent tuberculosis infection.

National sovereignty

Some approaches have emphasised national sovereignty, with its rights (or even obligations) to exercise immigration control on behalf of its citizens. One example of such a framework is that proposed by Myron Weiner\(^{(339)}\). Weiner considers the general question of international migration, and notes the conflict between an asserted human right to emigration (as expounded, for instance, in the United Nations Declaration of Human Rights, article 13) and national sovereignty as expressed in immigration control.

Although Weiner supports a right to freedom of movement within national borders, he argues that the moral basis on which this right is founded derives from the State, and that insufficient grounds exist for extending such a right to international law. He maintains that the responsibility of a State is to its citizens, and that it is a legitimate exercise of authority for a State to control immigration in ways that it judges will benefit, or at least not harm, existing citizens. While he concedes that such
an approach may be unjust in its treatment of citizens versus non-citizens, he argues that considerations of universal moral reasoning in public policy is impossible given the effective scope of the authority of the State, and that pragmatic considerations based on national sovereignty are both acceptable and preferable.

Weiner’s framework is explored predominantly in terms of economic inequality and outcomes; however this may readily be adapted to include health-related considerations such as latent tuberculosis. The national sovereignty approach would first assert the general legitimacy of States such as Australia to determine immigration policy on the basis of promoting the interests of existing citizens then seek to establish immigration control to this end. Weiner’s basic assertion that States have an essentially unlimited prerogative to determine immigration policy provide abundant scope for considerations based on health, as well as economic or other considerations.

In my view, the national sovereignty approach is unreasonably one-dimensional for a robust consideration of international migration policy. Although the national right to make determinations regarding immigration policy is acknowledged, it would appear that an approach limited to these considerations is likely to fail to give appropriate weight to the rights of, and appropriate care for, those seeking migration. I would argue that counter-balancing moral weight for potential migrants is required in order for an approach to immigration policy to be considered just. Accordingly, the following section will consider an alternative approach to immigration which concentrates on respect for human rights.

Human Rights

Other approaches have rejected national interests in favour of more universal considerations. Particularly influential in this regard have been approaches based on human rights considerations, such as the models adapted for assessment of mandatory HIV screening (340, 341). Such approaches emphasise limiting the burdens of screening on immigrants, particularly through appropriate targetting and adopting the least restrictive alternatives which achieve the desired public health benefit.
Laura Bisaillon explores one human-rights based approach to immigration policy in the context of HIV screening in Canada. Bisaillon begins her considerations with the observation that HIV testing is mandatory for all potential adult migrants, however testing positive does not necessarily lead to automatic exclusion from entry. Economic considerations, particularly the expected cost of anti-retroviral therapy (ARV) are subsequently employed in determining whether HIV-positive immigrants will be permitted entry.

Bisaillon argues that mandatory HIV screening is potentially unjust because testing is carried out under conditions of significant power imbalance, where applicants refusing to be tested would be denied entry automatically. She also highlights a number of more pragmatic concerns, including appropriate pre- and post-test counselling, provision of treatment and the availability of appropriate follow up for those refused entry. More generally, she proposes the use of a 7-point methodology for evaluating the human rights impact of a public health policy. This approach aims to identify the “least restrictive alternative – in terms of human rights – that will achieve the public health objective”. Human rights considerations are, in many circumstances, to be treated in preference to public health outcomes; although situations which pose a “significant risk” to the public are approached on a case-by-case basis.

Human rights-based frameworks for public health policy are laudable for their emphasis on the self-determination of individuals, and Bisaillon’s analysis highlights significant difficulties that arise from blunt application of a national sovereignty approach to immigration screening. However, I would argue that such frameworks are insufficient to account for the genuine tension between which autonomy and public health may operate. For robust consideration of immigration screening policy in relation to latent tuberculosis, we turn to a third framework, that employing a principle-based analytic for evaluation.

Principle-based Analytic

As has been reviewed above, a number of frameworks could be applied to the evaluation of public health immigration policy, with its evident tensions between
individual autonomy and national sovereignty around questions of transmissible infectious diseases. It is notable, however, that few have been developed specifically with this context in mind. One exception is the principle-based analytic approach proposed by Nancy Kass\textsuperscript{(342)}. This approach seeks to take into account the dynamic tension between harms and benefits to individuals and societies, and encourages systematic evaluation of public health policy on ethical grounds. The central concepts within this framework are the design of public health policy which minimises burdens and maximises benefits, and the fair allocation of those burdens and benefits. Critical to an appreciation of principle-based approaches is a recognition that no principle is \textit{a priori} to be understood as dominant or superior to others, but that conflicts between competing principles are resolved through a process of dynamic engagement.

Kass’ principle-based analytic framework employs a series of 6 questions for evaluation of public health policy. They are framed below in terms of evaluating programs already in existence, but may be readily adapted to consideration of potential policies through evaluation of expected outcomes initially and subsequent review following implementation.

The 6 questions are listed below, with additional explanatory comments.

What are the public health goals of the proposed program?

Goals should be expressed in terms of direct public health benefits, rather than surrogates; for example, a reduction in disease incidence or mortality is a more appropriate goal than an increase in testing performed or financial savings produced.

How effective is the program in achieving its stated goals?

This requires an active and recurring assessment of program effectiveness after implementation, which considers its impact on the relevant public health goal elucidated above. Should the program not be effective in meeting these aims, further consideration is unnecessary and the program should not be utilised further.

What are the known or potential burdens of the program?
If the program is or is expected to be effective on the basis of the above questions, considerations of harm or burden may then be assessed. Broad categories of such burdens include “risks to privacy and confidentiality”, “risks to liberty and self-determination” and “risks to justice”.

Can burdens be minimised? Are there alternative approaches?

Alternative approaches may permit public health goals to be met with less onerous impact, and should be considered within this framework.

Is the program implemented fairly?

Fair implementation requires that the burdens of a program are distributed reasonably, and the benefits do not accrue to only a sub-set of the population. Although some public health policy must be discriminatory, it is critical that such discrimination is based on sound justification, such as differing prevalence of disease in different groups.

How can the benefits and burdens of a program be fairly balanced?

The final question asks that there be an appropriate trade-off of benefits and burdens; that is, it requires assessment of whether the benefits of a program are sufficient to warrant the burdens which it imposes.

This framework is considered to be an appropriate one for assessing immigration public health policy. It is advantageous both because it offers a philosophical justification applicable to citizens and non-citizens, as well as providing a process via which analysis may proceed. This present review will therefore adopt this approach in order to consider the ethical implications of potential public health policy changes in relation to immigration screening for LTBI.
7.3 LTBI screening strategies

There are a variety of components to any screening strategy that require consideration. A screening program for LTBI needs to answer at least 4 primary questions: 1) what test(s) should be used for screening, 2) under what circumstances should such screening be conducted, 3) how should screening outcome affect the immigration process, and 4) what treatment and/or follow up strategies should be adopted?

7.3.1 What test(s) should be used for screening?

Currently, there are two types of candidate screening tool available for the diagnosis of LTBI. The tuberculin skin test (TST) involves intra-dermal injection of purified protein derivative (PPD), followed by observation of the size of local reaction after 48-72 hours. The interferon-gamma release assays (IGRA) are *in vitro* tests of T-cell reactivity following stimulation with *M. TB* specific antigens(343).

Ethically, minimising both costs and burdens for potential immigrants associated with screening tests is important. These considerations are not unrelated, as it is likely that screening costs would be borne by applicants in most situations. In general terms, it would be ethically problematic to adopt a screening test recognised to have a significant rate of false positive reactions, since this is an outcome that would impose unnecessary risk and burden on the person being screened, including risk of potential side effects from unnecessary treatment (see table 6). Although a false negative result may lead to a missed opportunities for prevention of subsequent TB disease, this merely fails to provide benefit rather than actively inducing harm. From an ethical perspective, then, it seems that a test with a low rate of false negative reactions is most important. Ultimately, though, both the positive and negative predictive value of any test need to be sufficiently robust to also ensure that screening is reasonably cost-efficient. It must also be recognised that only a minority of immigrants with LTBI will progress to active disease; a limitation which must be keenly appreciated until future tests are developed with better predictive power for progression.
Table 7.1 Implications of screening concordance and discordance with true latent tuberculosis state

<table>
<thead>
<tr>
<th>Test</th>
<th>LTBI +</th>
<th>LTBI -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>True positive; appropriate management</td>
<td>False positive; inappropriate management initiated</td>
</tr>
<tr>
<td>Test -</td>
<td>False negative; missed opportunity for appropriate management</td>
<td>True negative; appropriate management</td>
</tr>
</tbody>
</table>

7.3.2 Circumstances of screening

Once an appropriate test has been selected, it must then be determined how and when it should be employed. Screening could be performed in countries of origin or following arrival in Australia, although post-arrival screening may be associated with some loss to follow up and diminished efficacy of the program. Current policy relating to tuberculosis screening requires investigation and review prior to immigration. However, provision exists to require immigrants to present for post-arrival medical review in some circumstances (health undertaking), and established structures for both pre- and post-travel screening are already in operation.(344).

Screening policy may be applied to all immigrants, or could be limited to a subset (for instance, those from countries with a higher prevalence of tuberculosis infection, or those considered at higher personal risk, such as refugees and asylum seekers)(173). Any such limitation in the scope of screening policy would need to be justified on clear objective grounds to ensure that arbitrary discrimination did not occur. Although any non-uniform application of testing requirements may run the risk of unreasonable discrimination it is important to realise that broad use of screening amongst low-risk groups would likely result in an increased rate of false-positive results and diminished
cost-effectiveness of screening. This outcome would be suboptimal, and would add both to the cost and burden associated with a screening program.

7.3.3 Screening outcomes and immigration

Although there are a number of ways that a positive screening test for LTBI could affect the immigration process, two would seem most likely to be applied. First, in-country medical review and management could be required prior to immigration. Second, a health undertaking for presentation and appropriate management could be required.

LTBI presents some potential public health risk, as transmission following reactivation may occur. However, in contrast with active infection, such risks are potential rather than actual. Treatment of LTBI should thus not be required prior to travel on the grounds of ‘fitness to fly’ or imminent risk of transmission. Ethically, it would also appear difficult to justify imposing in-country LTBI treatment as a barrier to immigration when no immediate risk to public health exists.

Logistically, requiring management of LTBI prior to immigration would raise a number of difficulties. Many high prevalence countries do not routinely provide screening or treatment for LTBI, and local practitioners may be unfamiliar with its use in this context. Furthermore, treatment for LTBI in high-prevalence regions may be complicated by reinfection, especially where significant delays exist in immigration processes. Both of these difficulties could be avoided through management of LTBI in Australia following arrival, although this would require expansion of the existing health undertaking program and be associated with increased costs.

7.3.4 Treatment and follow up

Once LTBI has been diagnosed several strategies for management are in common use. Preventative therapy is most commonly provided with a course of isoniazid, although newer regimens including short-course isoniazid and rifapentine have been recently approved(109). All preventative therapy regimens are associated with risk of adverse effects, most significantly hepatotoxicity(73, 345). Risk of such complications of
preventative therapy varies considerably with age and additional comorbidities, and the balance of risk and benefit should be weighed for each individual with LTBI (76, 346). Choice of preventative therapy may also vary based on considerations such as drug interactions or likely infection with resistant tuberculosis.

For some immigrants with a positive screening test, LTBI therapy may not be indicated. This may be due to an unfavourable risk/benefit assessment, but detailed clinical review may also determine that no treatment is necessary; for instance, in the case of previously treated active TB. Appropriate management in the absence of preventative therapy may include clinical review during a higher-risk period (eg 2 years post arrival) however no further follow up may be indicated in some cases.

Treatment for active tuberculosis prior to immigration is mandated; that is, if a person with active tuberculosis is identified during screening, a documented treatment course is required before immigration will be permitted. Such a directive approach is justified by the imminent risk of TB transmission in the event of travel without effective treatment. However, LTBI presents no such immediate risk, and when combined with the considerable variation in appropriate management of individuals with LTBI, imposing a mandatory treatment approach appears difficult to justify. Overall, it would seem most appropriate to adopt the model of health undertaking rather than mandate a specific management program. This model would require presentation for medical review following immigration, and consider a tailored management approach, within the spectrum of general recommendations for LTBI.

### 7.3.5 Discussion

Introduction of immigration screening for LTBI involves a raft of logistic and ethical issues. At particular tension here is the sovereign exercise of power in interest of public health and the autonomy and dignity of those immigrating. The potential benefits of such a program, however, include prevention of a disease with significant morbidity and mortality for the individual with LTBI, and reduction in TB incidence and burden for Australia. Such benefits suggest that these issues are worth seeking to navigate.
In light of the issues outlined above, we would propose some general approaches to formulating optimal policy.

First, with regard to appropriate test choice, it is imperative to minimise false positive reactions while preserving acceptable overall accuracy. Amongst the diagnostic tests currently available, this would seem to suggest that use of IGRA would be preferable to TST, although advances in diagnostic technology may alter this in time. Screening could occur either prior to immigration or after arrival, and would likely be dictated by logistic considerations.

Secondly, LTBI does not present an immediate but merely potential future risk to individuals and others. As outlined above, we would contend that any attempt to exclude or defer potential immigrants on the basis of latent infection would therefore be disproportionate and unjustified. Mandatory testing for latent infection imposes little risk; however treatment for latent infection involves risk of adverse effects as well as individual benefits. These risks and benefits are highly dependent on individual circumstances, including age and pre-existing medical conditions. It would seem, then, that mandated testing followed by post-immigration medical review offers the opportunity for future treatment and personal benefit, and would seem a reasonable way to balance sovereignty and dignity.

Third, while testing and medical review could be mandated, a decision to be treated for latent infection should be voluntary. For a treatment decision to be voluntary, it should be separated from the immigration process in order to ensure that pressure, real or perceived, is not placed on potential immigrants to accept. This means that discussions regarding treatment should be conducted in Australia, by a medical professional independent to the immigration process. On medical grounds, it also appears more reasonable to offer treatment in Australia, as this eliminates the possibility of reinfection prior to travel if treatment was provided earlier.

A fourth point concerns the question of whether screening should be applied to all potential immigrants, or be limited to some groups; for instance, those from high-prevalence countries only. Although such limitation would be discriminatory (in the sense that not all potential immigrants would be treated the same), we would argue
that it could be justifiable provided that the basis on which policy was determined was not arbitrary. In this setting, it would be most reasonable to base such a policy on objective pre-screening risk of tuberculosis infection, for example on the basis of age and TB incidence in countries of origin, with appropriate thresholds set on the basis of cost effectiveness modelling.

Finally, any policy should be regularly monitored and evaluated following implementation. This is critical both for ensuring that policy is effective and conducted in an ethically appropriate manner and also to review developments in LTBI management which may change optimal future strategies. Safer and more effective treatment courses would change the risk/benefit equation for many individuals, for instance, while the availability of a gold standard test for LTBI may alter the pathways for management considerably. Future developments in LTBI screening and treatment will be likely to have a significant impact on the ethical acceptability of immigration screening, and should be part of ongoing policy review.

In summary, then, it could be ethically justifiable to introduce screening for latent tuberculosis infection into the immigration process, within appropriate guidelines. The question of the conditions under which such screening may be cost-effective has not been considered here, however, such testing could ethically be applied in a non-uniform way provided such an approach was not arbitrary. The results of testing should not influence immigration outcome, but be used to mandate medical review and consideration of treatment with an independent medical professional following immigration.
8. Conclusions

This thesis has evaluated a variety of aspects of latent tuberculosis infection, particularly in relation to public health considerations and policy. It has culminated in the development of both a mathematical model for quantitative evaluation and a proposed framework for ethical consideration of immigration-related public health interventions. In order to do so, review and assessment of a number of elements of tuberculosis latency with relevance to public health has been necessary. This has served to underscore the importance of latency in appreciating dynamic tuberculosis interventions, particularly in low-transmission regions such as Australia.

The first chapter of this thesis reviewed latent tuberculosis infection, and identified several key limitation in information required for the development of robust public health strategies incorporating latency. Four limitations were considered to be of particular importance. First, certain elements of latent tuberculosis natural history were uncertain, particularly risk of reactivation following acquisition. Secondly, factors altering the risk of reactivation required more detailed evaluation. Although some risk factors such as HIV infection were uncontested, the impact of host genetic factors on risk of tuberculosis reactivation in particular was inadequately understood, with uncertainty as to whether any factors were of sufficient importance to require inclusion in a population-level assessment of impact. Third, a lack of evidence regarding the impact of multi-drug resistant tuberculosis was evident, particularly in relation to optimal management of household contacts and others suspected of MDR LTBI. Finally, there were also operational problems in the diagnosis and management of LTBI in Australia, with a review of current guidelines highlighting the lack of concordance in treatment strategies employed by various clinicians and organisations.

In order to improve current understanding of risk of reactivation following acquisition of latent tuberculosis, several approaches were evaluated (Chapter 2). Mathematical approaches to adjusting existing tuberculin test surveys, particularly a latent-class, random effects model, were assessed and found to be deficient for the purpose of revising population prevalence estimates of latency. A novel study was therefore conducted to estimate reactivation risk in Australian immigration cohorts over a
prolonged period, with the result of producing dynamic tuberculosis risk hazards for incorporation into subsequent mathematical models.

A number of elements required for development of a mathematical model were available from published literature. However, the available evidence regarding multidrug resistant tuberculosis infection in low-prevalence regions was lacking. Such data is of significant to public health strategies targeting LTBI, as existing chemotherapeutic approaches are specific for drug-sensitive isolates, while rates of multidrug resistant infections are rising globally. Accordingly, a novel investigation was required, as presented in Chapter 4. This study provided quantitative information regarding the impact of multidrug resistant tuberculosis in Victoria, particularly highlighting the high risk to close contacts following exposure. Data from this study also provided a more complete appreciation of the impact of MDR TB cases in low-prevalence settings, which contributes to evaluating the importance of increasing prevalence of drug resistance in subsequent models of public health strategies.

In Chapter 5, a review of published risk factors for tuberculosis reactivation was conducted. Systematic review and meta-analysis data was collected from the published literature, and summary estimates of risk modification were presented to allow incorporation into a mathematical model. Following identification of conflicting evidence in the existing literature, a novel meta-analysis was also conducted to consider the impact of mannose-binding lectin deficiency on tuberculosis reactivation. Ultimately, this assessment of risk modifiers concluded that no host or mycobacterial genetic factor was of sufficient magnitude and frequency to warrant inclusion in a public health model, but that factors such as HIV infection, diabetes and tobacco smoking were suitable for incorporation into such a model.

The results of these investigations were then used in construction of a novel individual-based mathematical model of tuberculosis infection in Australia, with a special focus on immigration-related strategies for reducing tuberculosis incidence in Australia (Chapter 6). The results suggest that no immigration-specific strategy could lead to the achievement of the 2050 Millennium Development Goal of less that one case of active tuberculosis per million population. However, substantial reduction in incidence could be seen through the use of a variety of screening and/or treatment
approaches. Quantitative comparison of various strategies was possible through this model, demonstrating the superiority of interferon-gamma release assays for diagnosis and the additional benefit of isoniazid and rifapentine short course therapy for treatment of latent tuberculosis. This model also allowed the evaluation of various hypothetical vaccines, permitting some consideration of thresholds for effectiveness. These quantitative results highlight the most effective strategies for evaluation in future interventions, including clinical trials, operational research and cost-effectiveness analyses.

Technical details of policies must always be supported by consideration of ethical issues arising in the context of public health policy. Chapter 7 describes the application of a principle-based analytic framework applied to possible future policy in relation to latent tuberculosis screening and treatment via immigration. Such prospective considerations are critical given the significant tensions between national sovereignty and individual autonomy often seen in immigration policy, and the frequently heated public discourse regarding its application. This analysis suggests that appropriate balancing of these tensions is possible, and proposes the use of this approach for consideration of future public health policy proposals related to LTBI and immigration.

Overall, this present work has highlighted the critical importance of incorporating a robust consideration of latency in developing effective public health responses to tuberculosis. Previous models of tuberculosis-related public health interventions have been predominantly developed with prevention of secondary transmission as a central aim, which has led to emphasis on interventions focused on the identification of active tuberculosis and reduction in infectivity. These interventions are clearly beneficial in high prevalence regions, and contribute to substantial individual health benefits in addition to reducing population incidence. However, as has been demonstrated here, such strategies would not be expected to yield additional returns in contexts where tuberculosis transmission is uncommon. In low-prevalence regions such as Australia, the dominant pathway to active tuberculosis is reactivation of previously latent infection, acquired in higher-transmission regions internationally. Public health strategies in contexts such as this, then, must engage with the dynamic natural history
of latent tuberculosis infection, and consider interventions that primarily serve to reduce reactivation risk.

Given that the majority of individuals who acquire active tuberculosis in Australia do so following immigration from high-prevalence regions, the process of immigration represents a natural opportunity to identify people with latent tuberculosis infection, particularly those most likely to reactivate. Although assessment during immigration is likely to be the most efficient mechanism for any screening and/or treatment program, it should be remembered that such programs have significant limitations at present. These issues include the lack of gold-standard diagnostic test for latent tuberculosis, which serves to emphasise the fact that any screening program would both fail to identify some people at risk for future tuberculosis reactivation and erroneously diagnose others. When coupled with the reality that the large majority of those infected with latent tuberculosis will never progress to active disease, it is clear that any introduction of public health interventions of this type must progress carefully.

Finally, as outlined here, this thesis has attempted to build a foundation for the development and evaluation of defensible and effective public health approaches relating to latent tuberculosis in Australia. To do so has required consideration of the natural history of latency, within the particular context of a low-prevalence, low-transmission region. Although these methods are particularly focused on regions such as Australia at present, as international efforts to reduce tuberculosis infection continue, the relative importance of robust considerations of latency will increase in these, currently high-prevalence, contexts also. Latency is a key element to understanding tuberculosis infection and the dynamics of public health engagement. Although our understanding remains imperfect, in order for future interventions to be effective, the unique role of latency must be taken seriously. It is hoped that the tools developed herein will assist in the development and critical assessment of clinical and public health approaches to tuberculosis infection.
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