**Sydney Medical School**

**Faculty of Medicine and Health**

# Drug-resistant tuberculosis (TB) and latent TB infection in high and low incidence setting

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***This thesis is presented for the degree of***

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# STATEMENT OF ORIGINALITY

I certify that the work in this thesis entitled “Drug-resistant tuberculosis (TB) and latent TB infection in high and low incidence setting” has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself. In addition, I certify that all information sources and literature used are indicated in the thesis.

Dr Wai Lai Chang (470436329)

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| TB | tuberculosis |
| TBI | latent TB infection |
| MDR/RR-TB | Rifampicin-resistant or multidrug-resistant tuberculosis |
| XDR-TB | extensively drug-resistant tuberculosis |
| *M.tb* | *Mycobacterium tuberculosis* |
| WHO | World Health Organization |
| COVID-19 | coronavirus |
| HIV | Human immunodeficiency virus |
| TST | tuberculin skin test |
| IGRA | interferon-gamma release assays |
| TPT | tuberculosis preventive therapy |
| 3HP | three months of weekly rifapentine plus isoniazid |
| 4RIF | four months of daily rifampicin |
| 6-9H | six to nine months of daily isoniazid |
| DST | drug susceptibility test |
| AFB | acid-fast bacilli |
| HHCs | household contacts |
| BCG | Bacillus Calmette–Guérin |
| AE | adverse event |

# ABSTRACT

**Background.**

Tuberculosis (TB) remains the world's second leading cause of death from a single infectious agent in 2022 after COVID-19[1]. The global number of people newly diagnosed with TB was over 10 million in 2022 [1]. There were an estimated 450 000 incident cases of MDR/RR-TB in 2021, with an estimated 191 000 deaths due to MDR/RR-TB[2].

The overall aim of this thesis was to evaluate the prevention and treatment of people affected by drug-resistant and drug-susceptible TB. (i) Evaluate the current programmatic management of patients receiving individualised antibiotic therapy for MDR/ RR-TB in the city of Sydney, Australia and the treatment outcomes. (ii) Evaluate the management of people at high risk of MDR/RR-TB in NSW with multidrug-resistant tuberculosis in New South Wales, Australia. (iii) Identify risk factors for TBI in the HHC of MDR/RR-TB patients and the prevalence of TBI among MDR/RR-TB contacts in Vietnam. (iv) To evaluate the feasibility and acceptability of weekly rifapentine and isoniazid (3HP) using digital treatment adherence reminders in Sydney, Australia.

**Methods.**

In Chapter 2 and 3, we performed a retrospective cohort study of patients treated for MDR/RR-TB using individualised treatment based upon molecular drug susceptibility test (DST) results in Sydney, Australia, and we evaluated the prevalence of TBI and active TB disease amongst contacts.

In Chapter 4, we conducted a cross-sectional survey among HHC of patients with MDR/RR-TB in Vietnam and evaluated the prevalence and risk factors for developing TBI amongst the HHC.

In Chapter 5, we determined patient acceptability of treatment for TB infection, nested within a randomised trial of preventive therapy for contacts of people with drug-susceptible TB infection in Australia.

**Results.**

In Chapter 2 and 3, our retrospective cohort identified 55 patients with MDR/RR TB were treated with individualised treatment in Australia and 93% (51/55) achieved treatment completion. It showed individualised treatment has a high rates of treatment success within the public treatment programme. It also found a high prevalence of TBI 96/247 (38.9%) among contacts of patients diagnosed with MDR/ RR TB. More than half of the contacts were offered prophylactic treatment with extensive variation observed in the medications, doses, and durations,

In Chapter 4, the cross-sectional survey among contacts of patients with MDR/RR-TB in Vietnam found a prevalence of TB infection of 71.2% (2721/3823). Factors associated with a positive TST in the multivariable model included, HHCs with older age groups had a higher prevalence of infection. Other factors associated with an increased prevalence of infection included: normal BMI (aOR = 1.33, 95% CI: 1.06- 1.66), smoking history (aOR = 1.76, 95% CI: 1.39- 2.23), a prior history of TB (aOR = 4.56, 95% CI: 2.49- 8.35), the presence of a BCG scar (aOR = 1.23, 95% CI: 1.02-1.50 ), and more than 8 hours spent each day on average over the previous 3 months with the index patient (aOR = 1.52, 95% CI: 1.28-1.81).

In Chapter 5, our interim analysis of the randomised trial showed 111 patients were enrolled, 58 (52.3%) were allocated to the 3HP intervention arm, and 53 (47.7%) were allocated to the 4RIF comparator arm and the treatment completion rate was 86/111 (77.5%).

**Conclusions.**

These findings demonstrate the effectiveness of individualised therapy for drug-resistant TB in a high-income setting. We demonstrated the prevalence of TB infection in a high-burden setting, Vietnam, was high - in contrast to the low number of individuals with TB infection among those contacts of MDR/RR-TB patients in Australia. Finally, we have shown high completion of preventive therapy among people with TBI in Australia. These are only a small part for the roadmap to achieve the End TB Strategy.

Further research is required to for different country to achieve the WHO End TB strategy by 2035, it is not a “one size fits all” approach and its success depends on adaptation for diverse country settings.

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# CHAPTER ONE

# 1. INTRODUCTION

### 1.1 Is TB still a public health problem?

On March 24, 1882, Dr. Robert Koch announced the discovery of *Mycobacterium tuberculosis*, the bacteria that causes tuberculosis (TB). Tuberculosis is transmitted via droplets exhaled from infected patients to contacts. In the nineteenth century, TB killed one out of every seven people living in the United States and Europe. After 140 years since discovery, TB remains the world's second leading cause of death from a single infectious agent in 2022(after COVID-19), and global TB targets have either been missed or remain off track[1].

### 1.2 The global prevalence of TB

According to the latest report from WHO, the global number of people newly diagnosed with TB was 7.5 million in 2022. This is the highest number since WHO began global TB monitoring in 1995, above the pre-COVID baseline (and previous historical peak) of 7.1 million in 2019, and up from 5.8 million in 2020 and 6.4 million in 2021[1]. The number in 2022 probably includes a sizeable backlog of people who developed TB in previous years, but whose diagnosis and treatment was delayed by COVID-related disruptions that affected access to and provision of health services [1]. Globally in 2022, TB caused an estimated 1.30 million deaths (95% UI: 1.18–1.43 million). This was down from best estimates of 1.4 million in both 2020 and 2021, and almost back to the level of 2019 [1].

### 1.3 Covid-19 and TB

The coronavirus (COVID-19) pandemic has caused enormous health, social and economic impacts since 2020 [2]. This includes impacts on the provision of and access to essential tuberculosis (TB) services, the number of people diagnosed with TB and notified as TB cases through national disease surveillance systems, and TB disease burden (incidence and mortality). As mentioned before, the reported global number of people newly diagnosed with TB was 7.5 million in 2022, which was higher than pre-COVID baseline of 7.1 million in 2019. And the global number of TB deaths is estimated to have increased in both 2020 and 2021, while the historic decline in the TB incidence rate slowed in 2020 and then increased in 2021. COVID-related disruptions are estimated to have resulted in almost half a million excess deaths from TB in the three years 2020–2022, compared with the number that would have occurred if pre-pandemic trends had been maintained. COVID-related disruptions in the three years 2020–2022, with increases in the number of people not detected and thus not treated for TB, also resulted in increases in the number of deaths caused by TB [2]. The impact of reduced case detection on TB mortality is severe and more immediately noticeable, since there are more people with untreated TB [2]. Negative impacts of broader TB determinants on TB incidence during the COVID-19 pandemic, such as poverty, income per capita and undernourishment are likely [2].

There was a major global recovery in the number of people diagnosed with TB and treated in 2022, after 2 years of COVID-related disruptions. This has started to reverse or moderate the damaging impact of the pandemic on the number of people dying from or falling ill with TB. However, after COVID-19, global TB targets have either been missed or remain off track.

# 2. THE BIOLOGY OF TB

*Mycobacterium tuberculosis* is an ancient bacterium that was first presented as the cause of tuberculosis (TB) in 1882. Despite the global introduction of a vaccine and the discovery of an effective four-drug treatment regimen, *M. tuberculosis* still likely infects approximately one-quarter of the world's population and is the leading infectious cause of mortality worldwide [3, 4].

### 2.1 The Spectrum of Tuberculosis Infection to Disease

A longstanding tenet of TB pathogenesis has been that *M. tuberculosis* exists in either a metabolically inactive latent state, or a metabolically active disease state. For individuals with latent TB infection (TBI), the host maintains a dynamic relationship with *M. tuberculosis* through the regulation of available nutrients as well as the innate and acquired immune systems [12, 13].

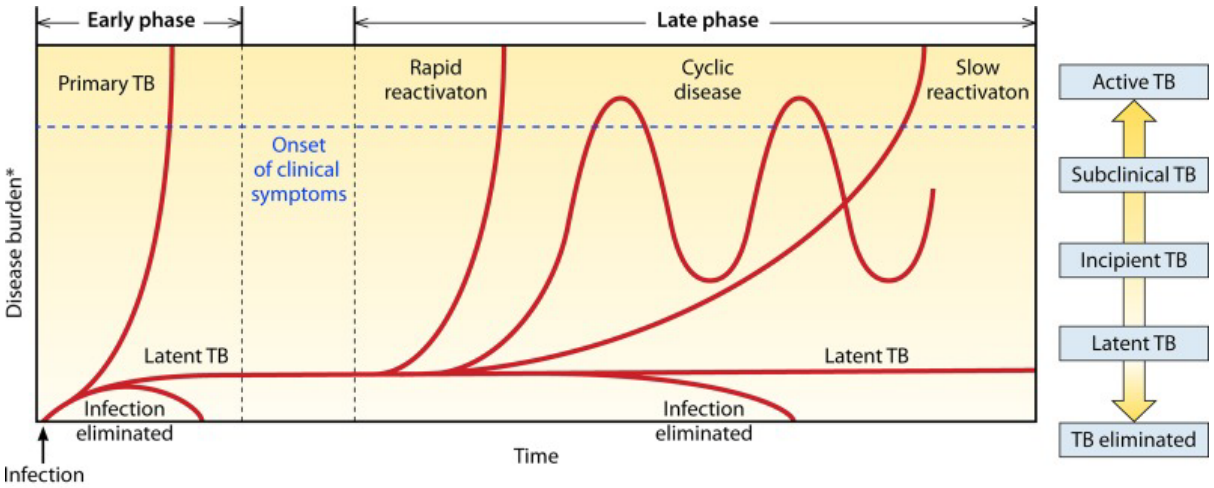
The current WHO definition considers LTBI "as having evidence of TB infection with positive reaction to the tuberculin skin test (TST) or interferon-gamma release assays (IGRA), and no clinical, radiological or microbiological evidence of active TB disease" [5-7]. It is estimated about 5% of people infected with TB progress rapidly to active disease, while the vast majority of people develop a latent infection and remain at risk for progression to active disease ("reactivation") [8]. Currently, there is no direct way of confirming LTBI or its microbiological load, as existing tests infer LTBI based on a T cell response to TB or TB-like antigens [9].

Recent research has demonstrated that human TB infection, from latent infection to active disease, exists within a continuous spectrum of metabolic bacterial activity and antagonistic immunological responses. Two additional clinical states were proposed in addition to TBI or active TB: incipient and subclinical TB [10]. "Incipient TB infection" is an infection with viable *M. tuberculosis* bacteria that is

likely to progress to active disease in the absence of further intervention, but has not yet induced clinical symptoms, radiographic abnormalities, or microbiologic evidence consistent with active TB disease [10]. Subclinical TB disease is disease due to viable *M. tuberculosis* bacteria that does not cause clinical TB-related symptoms, but causes other abnormalities that can be detected using existing radiologic or microbiologic assays [10] (Figure 1.1).

Following the establishment of latent infection, the pathways by which disease may naturally progress include (I) latency (the most common course, which encompasses persistent or eliminated disease burden), (ii) rapid or (iii) slow progression through incipient and subclinical disease to active TB, or (iv) a period of cycling through incipient and subclinical states that may precede the development of symptomatic disease or eventual disease resolution [11] (Figure 1.1).

**Figure 1.1 Pathways of tuberculosis disease progression [11].**




*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

### 2.2 Risk factors associated with progression from TBI to active TB

According to WHO, approximately one-quarter of the global population is or has been infected with TBI. Although recent studies have shown that the majority of TB-immunoreactive individuals have cleared their infection while retaining immunological memory of it [12]. Under the current definition of TBI, immunoreactive people who have cleared the bacteria meet the definition of "infection." Meanwhile, people who fail to meet the immunological definition of "infection" include patients with culture-confirmed TB, as well as individuals with noncanonical immune responses[12]. Healthy individuals can harbour TBI for a lifetime, and it is estimated about 5% of people infected with TB progress rapidly to active disease [12,17]. Reactivation occurs, often within the first 2 to 5 years following infection [13, 14]. The understanding of the underlying reasons for TBI reactivation is incomplete, but it does include bacterial, host and environmental factors [15]. The most potent risk factor is human immunodeficiency virus (HIV) infection [16]. Other comorbidities and conditions associated with LTBI reactivation include chronic renal failure requiring haemodialysis [17], transplant patients on immune suppressants [18] and patients with silicosis [19], among others. At moderate risk are patients treated with tumour necrosis factor alpha (TNF-α) inhibitors (used for many autoimmune and inflammatory conditions) [20] or glucocorticoids [21], those with diabetes and recently infected children under the age of four [22]. Other risk factors for TBI reactivation including patients who abuse alcohol [23], smoking cigarettes [24], or are underweight or malnourished [25].

### 2.3 Treatment for drug-susceptible TB

To minimize the ill health and mortality caused by TB, everyone who develops TB disease needs to be able to promptly access diagnosis and treatment. WHO recommends for the drug-susceptible DS-TB, a regimen containing rifampicin for 6 months. This 6-month treatment regimen, 2HRZ(E)/4HR, comprises isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and

rifampicin for 4 months [6]. People living with HIV who develop TB also require antiretroviral treatment (ART) for HIV, to avoid preventable deaths from TB and HIV [1]. Globally in 2020 (the latest annual patient cohort for which data are available), the treatment success rate for people treated for TB with first-line regimens was 86%, and ranged among WHO regions from 71% in the European Region to 92% in the Eastern Mediterranean Region [2].

**2.4 Management for TBI caused by drug-susceptible *M. tuberculosis***

Prevention of active TB disease by treatment of TBI is a critical component of the WHO End TB Strategy [26]. Tuberculosis (TB) preventive therapy (TPT) decreases the risk of developing TB disease and its associated morbidity and mortality. There are several antibiotics used individually or in combination which are currently recommended by WHO based upon clinical trials, including isoniazid, rifampicin and rifapentine (Table 1.1). The efficacy of currently available treatments ranges from 60% to 90% [27]. Due to limitations in the current available diagnostic tests such as TST and IGRA for diagnosing TBI, TST and IGRA do define an immune response. However, there is no other biomarkers representing people with viable bacteria that could subsequently progress to TB disease[28]. Individuals in the trials may include those who have cleared their infection while retaining immunological memory, as well as those who are recently infected, leading to the difference in their risk of developing TB. These factors explain the highly variable incident rates observed in the cited TPT trials.

WHO recommended treatment of TBI is recommended for people living with HIV [29] and for children under 5 years who are household contacts of people with pulmonary TB [30] in all settings including those with a high TB incidence, and for adult contacts of people with TB and other clinical risk groups living in settings with a low TB incidence [31-33]. The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events.

**Tuberculosis preventive treatment (TPT)**

**Daily isoniazid monotherapy**

Six months' daily monotherapy with isoniazid has been the standard treatment for both adults and children living in countries with either high or low TB incidence. Several systematic reviews have demonstrated its preventive efficacy. A systematic review of RCTs involving people living with HIV [34] showed that isoniazid monotherapy reduces the overall risk for TB by 33%, and the preventive efficacy reached 64% for people with a positive TST (Table 1.1).

Another systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (odds rat i o, 0.65; 95% CI 0.50;0.83) [35]. There were no controlled clinical trials comparing 9 months' to 6 months' isoniazid monotherapy. Re-analysis and modelling of the United States Public Health Service trials of isoniazid conducted in the 1950s and 1960s,showed that the benefit of isoniazid increases progressively when it is given for up to 9–10 months and stabilizes thereafter [36].

In the absence of a direct comparison, WHO recommended that 9 months' isoniazid is an equivalent option to 6 months of isoniazid in countries with a low TB incidence and a strong health infrastructure. It noted, however, that 6 months' isoniazid is preferable to 9 months from the point of view of feasibility, resource requirements and acceptability to patients [37] .

**Daily rifampicin monotherapy**

A previous systematic review conducted for the 2015 TBI guidelines [38], updated in 2017 [35], found similar efficacy for 3–4 months' daily rifampicin and 6 months of isoniazid (odds ratio, 0.78; 95% CI, 0.41;1.46). A trial by the Menzies group in nine countries demonstrated that 4 months of daily self-administered rifampicin is non-inferior to nine months of daily isoniazid (4RIF) [39]. Daily rifampicin at a dose of 10mg/kg (up to 600mg) is well-tolerated [40] and has a low cost. This regimen has been

recommended as the standard of care by the World Health Organisation (WHO) and other international guidelines for countries with a low TB incidence (Table 1.1).

**Daily rifampicin and isoniazid**

A systematic review [38] and its update in 2017 [35] showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid. The RCT performed in children found similar efficacy for 3–4 months' daily rifampicin plus isoniazid, compared to 6 months' isoniazid [41]. It also reported a lower risk for adverse events and a higher adherence rate [41].

WHO recommended that the benefits of 3 months' daily rifampicin plus isoniazid for infants and children < 15 years of age outweighs the harm, given its safety profile, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid [37] (Table 1.1).

**Weekly rifapentine plus isoniazid (3HP)**

Once weekly rifapentine and isoniazid for twelve weeks is recommended for TBI, based upon data from a phase 3 randomised trial [42]. A new systematic review was conducted to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid with that of isoniazid monotherapy [37]. The review covered four RCTs [42-45]. Two of the RCTs involving adults with HIV, found no significant difference in the incidence of active TB, between participants given a 3-month weekly regimen of rifapentine plus isoniazid and 6 or 9 months of isoniazid monotherapy [42-45]. The risk of hepatotoxicity was significantly lower and completion rate higher with the with the 3-month weekly regimen [42-45]. One RCT included a comparison between a 3-month weekly regimen of

rifapentine plus isoniazid and continuous isoniazid monotherapy in adults with HIV infection [43], which found no significant difference in TB incidence in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB infection or death in participants given continuous isoniazid. In mostof the studies, the 3-month regimen of weekly rifapentine plus isoniazid was given under direct observation (Table 1.1).

The 3HP regimen offers potential advantages of less cost and greater adherence, requiring just 12 once weekly doses rather than daily dosing. However, rifapentine is not a registered drug in Australia and therefore it has not been widely available and for most published studies of the 3HP regimen, treatment has been given under direct observation, which can be costly and impractical to scale-up. Recent study compared the 3HP treatment given by DOT versus self-administered therapy (SAT) and achieved similar treatment completion rates and safety outcomes [46]. Furthermore, treatment completion with 3HP therapy has not been compared to 4RIF using digital treatment adherence reminders. **In chapter 5**: **The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection**, we explore the effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF), upon adherence with treatment for latent TB infection.

**Table 1.1 Treatment for latent TB infection**

| Drug regimens | Duration | Evidence |
|---|---|---|
| **Daily Isoniazid** | 6 months | • Systematic review of RCTs involving people living with HIV [34] showed that isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51;0.87)<br>• Another systematic review of RCTs also showed a significantly greater reduction in TB incidence among |

| | | |
|---|---|---|
| | | participants given the 6-month regimen than in those given a placebo (odds ratio, 0.65; 95% CI 0.50;0.83) [35]. |
| **Daily Isoniazid** | 9 months | • No controlled trials to compare 6 months vs 9 months regimens.<br>• Recommendations based on re-analysis and modelling of previous trial from Comstock showed benefit of isoniazid increases progressively when given up to 9–10 months. |
| **Daily Rifampicin** | 4 months | • Systematic review in 2015 found similar efficacy 3–4 months' daily rifampicin and 6 months of isoniazid (odds ratio, 0.78; 95% CI, 0.41;1.46) [35, 38].<br>• 4 months of daily rifampicin was shown to be non-inferior to nine months of daily isoniazid of self-administered rifampicin (4RIF) [39]. |
| **Daily rifampicin plus isoniazid** | 3 months | • A systematic review in 2015 [47] showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid.<br>• The RCT [98] comparing of 3–4 months' daily rifampicin plus isoniazid to 6 months' isoniazid showed similar efficacy and reported a lower risk for adverse events (RR 0.33, 95% CI 0.20;0.56) and a higher adherence rate (RR 1.07, 95% CI 1.01;1.14) among children. |

| | | |
|---|---|---|
| | | • Similar findings were reported in the two observational studies [99, 100]. |
| **Weekly rifapentine plus isoniazid (under direct observation)** | 3 months | • Two of the RCTs involved adults with HIV from South Africa, Peru and in a number of countries with a low incidence of TB found no significant difference in the incidence of active TB between 3-month weekly regimen compared to 6 or 9 months of daily isoniazid monotherapy (RR 0.73, 95% CI 0.23;2.30), the risk for hepatotoxicity was significantly lower with the 3-month weekly regimen in adults with HIV (RR 0.26, 95% CI 0.12;0.55) and those without HIV (RR 0.16, 95% CI 0.10;0.27).<br>• The weekly regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01;1.55; adults without HIV: RR 1.19, 95% CI 1.16;1.22, children and adolescents: RR 1.09, 95% CI 1.03;1.15). |

# 3. DRUG-RESISTANT TB

### 3.1 The epidemiology of drug-resistant TB

Since 1994, the World Health Organization (WHO) has systematically collected and analysed data on levels of resistance to anti-TB drugs from countries and territories [48]. Rifampicin-resistant or multidrug-resistant TB (collectively referred to as MDR/RR-TB) is defined as resistance to both rifampicin and isoniazid, while extensively drug-resistant tuberculosis (XDR-TB), involves resistance to isoniazid and rifampicin, the fluoroquinolones, and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin) [49].

Globally, there were an estimated 450 000 incident cases of MDR/RR-TB in 2021, up 3.1% from 437 000 in 2020 [2], with an estimated 191 000 deaths due to MDR/RR-TB in 2021 [2]. The estimated proportion of MDR/RR-TB cases with pre-XDR (i.e. resistance to any fluoroquinolone for which testing was done) was 20% [2]. In 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected. This highlighted a capacity gap for either diagnosing or treating DR-TB, a gap that comes at the cost of continued transmission of drug-resistant strains.

### 3.2 Diagnostic challenge of drug-resistant tuberculosis

#### Phenotypic DST (conventional DST)

Diagnosing MDR/RR-TB is one of the most challenging aspects of the cascade of care. Definitive diagnosis of MDR/RR-TB requires that *Mycobacterium tuberculosis* bacteria be detected and resistance to anti-TB drugs determined. This can be done by isolating the bacteria by culture, identifying it as belonging to the *M. tuberculosis complex* (MTBc), and conducting drug susceptibility testing (DST) using solid or liquid culture media. Bacteriological confirmation of TB is necessary to test

for resistance to first-line and second-line anti-TB drugs; such testing can be done using rapid molecular tests, phenotypic susceptibility testing, or reference-level genetic sequencing. Conventional culture and phenotypic DST methods require prolonged lengths of time to confirm mycobacterial growth and detect drug resistance, during which patients may be inappropriately treated, drug-resistant strains may continue to spread, and amplification of resistance may occur [27]. In many settings, rapid molecular DST is not performed, so patients must not respond to therapy first.

**Genotypic DST**

In recent years, nucleic-acid amplification tests (NAATs), which are highly specific and sensitive, have helped to revolutionize the TB diagnostic landscape [50]. Line-probe assays (LPA) were the first molecular tests recommended by the World Health Organization (WHO) in 2008. They significantly reduce the time needed to diagnose multidrug-resistant and rifampicin-resistant TB (MDR/RR-TB), compared with culture testing. The next major step forward in 2010 was WHO's endorsement of the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real-time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance, directly from sputum specimens in less than two hours. WHO recommended the use of Xpert MTB/RIF as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, rather than smear microscopy/culture and phenotypic DST in adults with signs and symptoms of pulmonary TB [50, 51]. Adoption of Xpert MTB/RIF provided an opportunity to increase and expand access to accurate TB diagnostics, but it cannot be used as a replacement for smear and culture for monitoring the response of drug-resistant TB patients to therapy[52].

**Use of Xpert MTB/RIF**

Ideally, testing for drug resistance should be provided for all identified TB patients before the start of TB treatment, so that the most appropriate therapy for each individual can be determined. However, the goal of universal access to DST has not yet been realized for most of the world's TB patients, and

in many areas only patients considered at high risk for drug resistant TB have access to DST. Presently, in most low- and middle-income countries, DST is done only in a fraction of all cases. If done routinely, it is often only done in retreatment cases. This leads to a large number of undetected drug-resistant TB cases, or severely delayed diagnosis of the majority of drug-resistant TB cases.

### 3.3 Treatment for drug-resistant TB

The WHO recommendations for drug-resistant TB have changed substantially over the last decade, as evidence emerged from cohort studies and randomised trials [53-55] (Table 1.2). Until 2016, MDR/RR TB treatment was based on an injectable drug plus a fluoroquinolone (moxifloxacin, levofloxacin, or gatifloxacin), with a duration of 18–20 months or longer [56]. Currently, the treatment for drug-resistant TB requires use of at least four second line antibiotics (bedaquiline, pretomanid, linezolid and moxifloxacin) for a minimum of six months [53] (Table 1.2). More details are discussed at later section.

#### Individualised therapy for MDR/RR-TB

Historically, patients with MDR/RR-TB are treated with individualised regimens. Individualised regimens can be developed by evaluating the drug-resistance profile of the causative bacteria from DST, and patient-specific factors that may determine treatment toxicity. The composition of longer regimens is governed by the selection of individual medicines considered to be effective and by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity. Longer regimens require at least 18 months or more of therapy [31, 42]. The treatment combination would involve an injectable (group 2), a higher generation fluoroquinolone (group 3), together with a group 4, group 1, and group 5 drug (Table 1.2).

**Use of Bedaquiline in MDR/RR-TB**

Bedaquiline (Bdq) belongs to a new class of drugs called diarylquinolines. Bedaquiline is the first new drug developed specifically to treat TB in over 40 years. Bedaquiline has a novel mechanism of action. The drug specifically targets mycobacterial adenosine triphosphate (ATP) synthase, an enzyme that is essential for the supply of energy to Mycobacterium tuberculosis and most other mycobacteria [57].

Bedaquiline was granted accelerated approval by the USA Federal Food and Drug Administration (FDA) in December 2012 [58]. The approval is primarily based on an analysis of time to sputum culture conversion, from two controlled phase 2 trials in patients with pulmonary MDR/RR-TB [59], and double-blinded placebo-controlled trials, which demonstrated clinical efficacy with faster and lasting conversions in patients receiving bedaquiline for the first 24 weeks, when given on top of a WHO standard MDR/RR regimen, on a review of the safety data gathered in these studies [59].

**Replacement of injectable antibiotics with oral Bedaquiline in MDR/RR-TB regimen**

Until 2019, the standard treatment for MDR/RR-TB was 18-24 months including a daily injectable antibiotic. The requirement for injectable antibiotics created significant barriers to completion of treatment. Since 2019, changes from the use of injectable antibiotics were based upon evidence from cohort studies that injectables were associated with significant toxicity. WHO recommended Bedaquiline (for 6 months) is recommended in longer MDR/RR-TB regimens for patients aged 18 years or more, based on the 2018 meta-analysis, including a large dataset from South Africa with many patients treated with bedaquiline-containing regimens [60-62]. The reclassified drugs group with levofloxacin or moxifloxacin, bedaquiline, and linezolid as Group A Drugs [63] (Table 1.2). The individualised regimen should include all three Group A agents, and at least one Group B agent should

be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. Individualised regimens have the advantage of selecting antibiotics that are known to be effective in the individual and avoids unnecessary toxicity of additional antibiotics to which the bacterium is not susceptible, to construct a sufficiently effective regimen. More details are discussed at later section.

**Standardised treatment for MDR/RR-TB**

In May 2016, WHO conditionally recommended a shorter regimen comprising 9–12 months for patients with pulmonary MDR/RR-TB under programmatic conditions [37]. This regimen consisted of 4–6 months of a later generation fluoroquinolone (such as gatifloxacin or moxifloxacin), the injectable antibiotic kanamycin, prothionamide, high-dose isoniazid, clofazimine, pyrazinamide and ethambutol, followed by 5 months of the fluoroquinolone, clofazimine, pyrazinamide and ethambutol alone [30-33]. This standardised regimen of 9–12 months reported an overall success rate of 87.9% in the treatment of a cohort of 206 MDR/RR-TB patients who had never received second-line drugs in Bangladesh, at a fraction of the cost of traditional regimens (only € 225/course) [52, 53]. Because of limited global capacity for DST, WHO does not require DST for second-line drugs to be performed prior to starting this shorter regimen. Treatment decisions will be guided by prior treatment history and the local surveillance data to guide eligibility for this regimen [56]. However, this was based upon observational data, and evidence was considered low certainty in the absence of randomisation (Table 1.2).

In 2019, WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month)

regimens in MDR/RR-TB patients [44, 52] (Table 1.2). More studies have assessed an all-oral (without using an injectable aminoglycoside) shorter new regimen with promising results. Consequently, the 2022 WHO guidelines for MDR/RR- TB treatment have substantially changed, recommending shorter all-oral treatment for MDR TB. WHO recommended the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients [53, 55](Table 1.2).

Standardised treatment for MDR/RR-TB are all-oral and have a better side effect profile than the previous regimens. In the latest WHO 2022 guidelines, all patients are recommended the same duration regardless of their burden of disease and early response to treatment (Table 1.2). This underscores the need that treatment for patients with MDR/RR-TB to be individually tailored. It is important to gather real world data for patients treated with the standardised treatments. This help to improve the management of MDR/RR-TB by maximizing the treatment success rates while minimizing adverse effects.

The following table shows the changing WHO guidelines for the empirical treatment of MDR/RR-TB since 2010. Australia lacks local RR/MDR-TB treatment guidelines. Therefore, the WHO guidelines informed treatment decisions made by clinicians in Australia during the period of the retrospective cohort study in Chapter 2. (Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia (Aust NZ J Public Health. 2021; Online; doi: 10.1111/1753-6405.13144) (Table 1.2).'

**Table 1.2: Summary of changing WHO guidelines for empirical treatment of MDR/RR-TB since 2010**

| Year of WHO guideline | WHO recommended treatment for MDR/RR-TB | Change compared to previous guideline |
|---|---|---|
| 2011 | • Recommended an intensive phase of 8 months for most MDR/RR-TB patients and total treatment duration of 20 months.<br>• The intensive phase of MDR/RR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective (including an injectable anti-TB drug), as well as pyrazinamide.<br>• Individualised regimen based on DST:<br>STEP 1- Choose an injectable (Group 2)<br>STEP 2- Choose a higher generation fluoroquinolone (Group 3)<br>STEP 3- Add Group 4 drugs | Compared to the guideline in 2008, the regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.<br>• Group 1= Pyrazinamide, Ethambutol<br>• Group 2= Kanamycin, Amikacin, Capreomycin<br>• Group 3= Levofloxacin, Moxifloxacin<br>• Group 4= Cycloserine/terizidone, Para-aminosalicylic acid (PAS), Ethionamide/prothionamide<br>• Group 5= Bedaquiline, Delamanid, Linezolid, Clofazimine, Amoxicillin/clavulanate, |

| | | |
|---|---|---|
| | STEP 4- Add Group 1 drugs<br>STEP 5- Add Group 5 drugs | Imipenem/cilastatin plus clavulanate, Meropenem plus clavulanate, High-dose isoniazid, Clarithromycin, Thioacetazone |
| 2016 | • A conditional recommendation of a shorter regimen comprising 9–12 months for patients with pulmonary MDR/RR-TB under programmatic conditions, which is largely standardized, this is discussed further in the above section.<br>• Longer MDR/RR-TB regimens last for 18 months or more and which may be standardized or individualized.<br>• At least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and 4 core second line TB medicines.<br>• 1 group A drugs and 1 Group B or 2 Group C drugs | • Reclassified drugs according to efficacy, with a hierarchy of recommended drugs<br>• Clarithromycin and other macrolides are no longer included among the medicines to be used for the treatment of MDR/RR-TB.<br>• Recommended to treat MDR/RR-TB into groups from A to D<br>• Group A = fluoroquinolones;<br>Levofloxacin, Moxifloxacin Gatifloxacin<br>• Group B = second-line injectable drugs;<br>Amikacin, Capreomycin, Kanamycin<br>• Group C = other core second-line agents; |

| | | |
|---|---|---|
| | • If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five | Ethionamide / prothionamide, Cycloserine / terizidone, Linezolid, Clofazimine<br>• Group D1–3 = add-on agents;<br>D1 Pyrazinamide, Ethambutol, High-dose isoniazid<br>D2 Bedaquiline, Delamanid<br>• D3 p-aminosalicylic acid, Imipenem–cilastatin, Meropenem, Amoxicillin-clavulanate |
| 2019 | • A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in MDR/RR-TB) patients with TB that is resistant to fluoroquinolones<br>• For longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three | • Bedaquiline should be included in longer MDR/RR-TB regimens for patients aged 18 years or more.<br>• Reclassified drugs group:<br>• Group A = levofloxacin or moxifloxacin, bedaquiline and linezolid<br>• Group B = clofazimine, and cycloserine or terizidone<br>• Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or |

| | | |
|---|---|---|
| | agents are included for the rest of treatment if bedaquiline is stopped. | prothionamide, and p-aminosalicylic acid. |
| 2022 | • Suggested the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients.<br>• For longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least 4 TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. | • Kanamycin and capreomycin are not to be included in the treatment of longer regimens.<br>• Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. |

### 3.6 The MDR/RR-TB incidence and treatment enrolment, coverage, and outcomes

#### MDR/RR-TB incidence and treatment enrolment

The global incidence of multidrug-resistant tuberculosis (MDR/RR-TB) has recently increased by an annual rate of more than 20% [64]. Since 2020, the use of Xpert MTB/RIF as the initial diagnostic test was 1.9 million (33%) of the 5.8 million people newly diagnosed with TB in 2020, up from 28% in 2019 [50].

Globally, the cumulative total number of people reported as enrolled on treatment for MDR/RR-TB from 2018 to 2022 was 824 988, only 55% of the 5-year target (2018–2022) of 1.5 million that was set at the United Nations General Assembly meeting to fight against TB in 2018 [1, 2]. The WHO regions with the highest levels of treatment coverage are the African Region and the Region of the Americas [1]. Among the 30 high MDR/RR-TB burden countries, only eight had treatment coverage levels of ≥50% in 2022 [1].

The numbers of people being detected with MDR/RR-TB and enrolled on treatment fall far short of the estimated number of people developing MDR/RR-TB (incident cases) each year [1] [2]. Closing the gap requires improvements in overall detection of people with TB, improvements in the percentage of those diagnosed with TB who are bacteriologically confirmed (necessary to test for drug resistance) and improvements in the coverage of testing for MDR/RR-TB [1] [2].

#### MDR/RR-TB treatment outcomes

According to the WHO, of the 156,000 persons treated for MDR/RR-TB in 2018, just 56% achieved a successful outcome [7] [8]. In the latest WHO TB report 2023, the success rate for people treated for MDR/RR-TB was 63%; this was an improvement from 60% in 2021 and up from 50% in 2012 [1].

Although treatment success rates have increased, almost 15% of patients with MDR/RR-TB are reported to die from the disease during treatment [9]. Treatment outcomes of MDR/RR-TB differ considerably between settings [60]. In some high-income settings, treatment outcomes for MDR/RR-TB approach those of drug-susceptible disease. However, globally the outcomes are poor. Among WHO regions, the treatment success rate in 2018 ranged from 56% in the European Region to 69% in the African Region [28].

By the end of 2020, 109 countries were using bedaquiline as part of treatment for drug-resistant TB (DR-TB), 90 were using all-oral longer regimens for the treatment of MDR/RR-TB and 65 were using shorter regimens for the treatment of MDR/RR-TB [28]. Determinants of poor outcomes include the high incidence of adverse events seen with second-line antibiotics, barriers to accessing care [65] and difficulties maintaining adherence during a prolonged course of treatment [66, 67].

**3.7 It is not one size fit all**

Management of patients with drug-susceptible TB has followed a standardized empirical management approach for the past decades in resource limited setting. Standardised therapy neglects to take into account the variability in the individual response to treatment. Factors that influence this variability include variation in immune function and its natural ability to withstand TB disease once it has developed, human susceptibility to infection, immune response, individual variation in drug pharmacokinetics, and the varying duration of treatment needed to achieve relapse-free cure [68]. A precision medicine-guided approach allows the individual selection of medicines, based upon the antimicrobial profile of the causative bacterium and host-related vulnerabilities and comorbidities, personalized drug dosing, and treatment durations based on different clinical settings [68]. Treatment for multi-drug resistant (MDR/RR-TB) is a model example of precision medicine in other infectious diseases[69]. Treatment for drug-resistant tuberculosis is largely delivered through standardised,

empirical combination regimens in low-resource, high-burden settings [70]. However, the use of individualised treatment, guided by detailed drug susceptibility testing, is the standard of care in high-income settings[70].

**MDR/RR-TB in Australia**

In Australia, the per capita rate of all TB notifications has remained relatively stable since 1986 [33]. In 2022, the estimated total TB incidence was 1500, including 41 incident cases of MDR/RR-TB (including the Torres Strait) [1]. Although rates of TB and transmission within Australia have remained relatively low, migration from countries of high TB burden is an ongoing potential source of new TB cases. Cases of primary drug resistance MDR/RR-TB defined as a person is directly infected by a drug-resistant *M.tb* strain. This may occur due to infection with drug-resistant M. tuberculosis in the high-burden settings from which migrants have come, or as secondary or acquired drug resistance, occurring due to the acquisition of resistance-conferring mutations during failed treatment of drug-susceptible TB [71].

The treatment for MDR/RR-TB in New South Wales, the most populous of Australia's states, is individualised and based upon molecular drug susceptibility test (DST) results. Empirical treatment is started for the patient being investigated for TB using nucleic acid amplification testing. All the patients with positive culture had the genotypic DST performed using whole-genome sequencing (WGS) to identify the full antibiogram [72]. Following an initial period of empirical therapy for MDR/RR-TB, an individual treatment plan is developed according to the DST profile. Meta-analyses of published studies have demonstrated that an individualised approach can improve treatment outcomes when compared to programs where empirical regimens were used. [73] [74, 75] [76] [77] [75, 78] [79]. For this reason, many high-income countries, including Australia, deliver individualised therapy for drug-

resistant TB that is based upon the drug-resistance profile of the causative isolates and patient factors [73] [75] [74].

The effectiveness of individualised approaches varies between settings. Programmatic outcomes of individualised approaches in NSW Australia have not been reported previously [80, 81]. Therefore, we undertook this study to evaluate the programmatic outcomes of patients receiving individualised antibiotic therapy for MDR/RR-TB in the city of Sydney, Australia in **Chapter 2: Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia (Aust NZ J Public Health. 2021; Online; doi: 10.1111/1753-6405.13144). This would contribute to MDR/RR-TB control in Australia and advance the ambitious goal of TB elimination by 2035 [24].** This study was performed before the latest guideline from WHO is released in 2022.

### 3.8 Management of contacts of MDR/RR-TB patients

#### Current recommendation by WHO

In many countries where MDR/RR-TB diagnosis and treatment are still scaling up, MDR/RR-TB patients face long delays before initiation of effective treatment [52]. This means that the family has been in close contact with a highly infectious MDR/RR-TB patient for months or years. The prevalence of active MDR/RR-TB in household contacts (HHC) is therefore likely to be higher than that of household contacts of drug-susceptible index cases, and that of extensively drug resistant TB (XDR-TB) even higher [82].

#### Screening for TB infections for contacts of MDR/RR-TB patients

As discussed in the last section, HHCs of a patient with active MDR/RR-TB are at high risk for a TB infection and disease as they have a prolonged exposure to the index cases [82]. A meta-analysis published by Shah and colleagues, showed that 47% of the MDR/ RR-TB patients' household contacts

were diagnosed with TBI [83]. The prevalence of a TB infection and disease is particularly high among children who are household contacts and exposed to MDR/RR-TB, reaching up to 57% in an observational study [84]. These transmission rates are even higher between mother and children in the household.

There are several risk factors known to be associated with developing active TB in close contacts, including malnutrition, untreated TBI, being a household contact, age under 5 years, acid-fast bacilli (AFB) positivity of source case, concomitant human immunodeficiency virus infection, and immunocompromised status [85, 86] . However, there is limited data about risk factors for TBI in the HHC of MDR/RR-TB patients and the prevalence of TBI among MDR/RR-TB contacts in Southeast Asian setting. Therefore, in **chapter 4: Factors associated with tuberculosis infection among household contacts of patients with multidrug-resistant tuberculosis in 10 provinces of Vietnam: a cross sectional study**, we sought to determine in a Vietnamese cohort of MDR/RR-TB contracts: (a) prevalence of TBI, stratified by age group; (b) factors associated with TBI in this population and (c) proportion of recent infection versus longstanding (conversion rate). TST conversion was defined as an increase of 6mm or greater between the first and second reading, plus a second TST size of at least 10mm. The second TST was repeated after 8 weeks (52 days).

**Management for latent MDR/RR-TB contacts**

The current WHO guideline recommended primarily to conduct strict clinical observation and monitoring for the early detection of symptoms of TB among contacts of MDR/RR-TB for at least two years over the provision of preventive treatment [52, 87]. WHO recommends deferring the decision to start MDR/RR-TB preventive therapy to the clinician based on an assessment of benefits to harms given the individual patient circumstances, but there are no standardized recommendations for MDR/RR-TB contacts due to lack of randomized clinical trials of TB preventive therapy in this

population[88] [89] [90]. Two clinical trials have been conducted evaluating the effectiveness of fluoroquinolone preventive treatment for MDR/ RR-TB and will be discussed further in section 4.

In Australia, there is no established consensus amongst local authorities and governments about the current practice among standard of care for MDR/RR-TB contacts in NSW [88] [89] [90]. We undertook an evaluation of the standard of care for contacts of MDR/RR-TB and evaluated the prevalence of TBI and TB amongst these contact in NSW. This is reported in **chapter 3: Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia (ERJ Open Res 2021; 0:00149-2021 [DOI: 10.1183/23120541.00149-2021)**.

**Rationale for TPT in contacts of patients with MDR/RR-TB**

Prevention is especially important for those at risk of MDR/RR-TB, given the difficulty of treating these cases once active MDR/RR-TB disease is established. Selecting an appropriate preventive therapy is a major challenge for treatment of contacts of patients with drug-resistant TB. It is often difficult to distinguish whether contact TBI arose from transmission from the recognised index case, or due to a prior remote infection. An effective preventive therapy for people likely to be infected with MDR/RR-TB from close contacts, such as household or workplace contacts, would be an important intervention with individual and public health benefits. There have been very few comparative studies of the use of second-line TB drugs to prevent disease in MDR/RR-TB contacts [91, 92].

**Randomised controlled trials using levofloxacin as TPT**

Two trials have evaluated the effectiveness of preventive therapy for drug-resistant TB among household contacts. The V-QUIN MDR/RR-TB trial was a placebo-controlled, double-blind trial, aiming to assess the role of levofloxacin in TPT for adult household contacts of MDR/RR-TB patients (ACTRN12616000215426) [93]. The population of the trial, performed in Vietnam, included patients

aged >15 years who were in contact with confirmed MDR/RR-TB cases, during the prior three months and had a positive tuberculin skin test (TST). The TB-CHAMP (Tuberculosis child multidrug-resistant preventive therapy, ISRCTN92634082) Phase III, cluster randomised controlled trial differs from the V-QUIN MDR TB trial, primarily for the inclusion criteria [94]. This study, set in South Africa, recruits only children aged <5 years who have been in contact with confirmed MDR-TB cases. The children were randomized into two treatment groups, receiving either 15–20 mg/kg/day of levofloxacin or a placebo, for 24 weeks.

The findings of the V-QUIN trial and TB CHAMP trial were presented at the annual conference of the International Union Against TB and Lung Diseases in October 2023. They showed that oral antibiotic-levofloxacin taken for six months once-daily substantially reduced the risk of developing drug-resistant TB. In the VQUIN trial, it included adults and children living with a person with MDR-TB in the household were given six months of levofloxacin and followed up for 30 months. The study took place in 10 provinces across Vietnam. The incidence of bacteriologically-confirmed TB was 6 (0.6%) in the levofloxacin group and 11 (1.1%) in the placebo group (incidence rate ratio 0.51; 95% CI 0.18 – 1.47, p=0.21). In the TB CHAMP trial, which was conducted in South Africa between 2017-2023, it included children <18 years old with household exposure to an adult (≥18 years) diagnosed in the preceding 6 months with bacteriologically confirmed pulmonary MDR-TB. The primary endpoint was incident TB (confirmed/unconfirmed) including TB death, by 48 weeks post-randomisation. It showed that five children (1.1%) in the levofloxacin and 12 children (2.6%) in the placebo arms developed TB (hazard ratio, respectively [HR] 0.44; 95% confidence interval [CI] 0.15-1.25; p=0.121). Both studies showed that a drug regimen of six months was both safe and effective in preventing the development of MDR/RR-TB in adult and children. Jointly, across both trials, it showed that levofloxacin reduced the risk of developing TB by 60%. [95, 96]. Updated WHO guidelines of the management of TB infection among MDR/RR-TB contacts will be released in August 2024.

# 4. WHO END TB STRATEGY

The “End TB Strategy” of the WHO is a global plan to end the tuberculosis epidemic by 2030 [97]. The strategy has three indicators: to reduce TB deaths by 95%, TB incidence by 90%, and catastrophic costs for TB-affected households by 2030 [97] .

The primary focus for achieving this goal involves enhancing efforts to detect and treat individuals with active TB, implementing universal screening for high-risk individuals, and providing preventive therapy to those susceptible to developing active TB [4]. The Strategy's 2020 milestones aim for a 20% reduction in TB incidence and a 35% reduction in TB-related deaths, while the 2025 goals target a 50% reduction in TB incidence and a 75% decrease in TB-related deaths compared to 2015 levels [45, 94]. These targets and milestones can be tailored by countries to suit their unique circumstances, considering factors such as starting points, local epidemic drivers, national policies on universal health coverage (UHC), social protection, and planned interventions.

Unfortunately, the COVID-19 pandemic coupled with ongoing crises such as armed conflict, increasing food insecurity, political and economic instability, has reversed years of progress made in the fight against TB. For the first time in nearly two decades, WHO reported an increase in the number of people falling ill with TB and drug resistant TB in 2021 [1, 47].

### 4.1 Progress in relation to WHO End TB strategy

Globally, the TB incidence rate was estimated to fall by 13.5% from 2015 to 2020, but by 2021, it was only 10% lower than in 2015, falling short of the 2020 milestone and far from the 2025 goal of a 50% reduction [95, 96]. Regional progress has varied, with mixed results in meeting the 2020 milestone. In

five of the six WHO regions, the TB incidence rate increased between 2020 and 2021 due to shortfalls in case detection in 2020 and incomplete recovery in 2021. Notably, the African Region surpassed the 2020 milestone in 2021 with a 22% reduction compared to 2015, while the European Region maintained a 25% reduction. Some countries, such as Ethiopia, Kenya, Lesotho, Namibia, South Africa, Tanzania, and Zambia, achieved the 2020 milestone by 2021 [2] demonstrating that tailored strategies based on local needs and conditions can lead to significant progress. However, many countries still face challenges, with increases in TB incidence in those experiencing major shortfalls in TB notifications and slowed declines or stabilization in others.

This variability highlighted the need for a "not one size fits all" strategy, where countries adapt global targets to their specific situations to effectively combat TB and achieve the End TB Strategy goals.

### 4.2 What do we need to do to achieve WHO End TB Strategy?

The End TB Strategy encompasses a package of interventions that fall under three pillars. The first Pillar – integrated patient- centred care and prevention - puts people living with TB at the heart of service delivery. The second Pillar – bold policies and supportive systems – requires intense participation across government, communities, and private stakeholders. The third Pillar – intensified research and innovation - is critical to break the trajectory of the TB epidemic and reach the global targets [47].

The long-standing global strategy for tuberculosis control focuses on improving access to diagnosis, treatment, and supportive services to ensure that patients with symptomatic tuberculosis disease receive an appropriate diagnosis and treatment [98]. The Strategy is not a “one size fits all” approach and its success depends on adaptation for diverse country settings.

**Overall approach of this thesis**

This thesis evaluates the treatment and prevention of drug-resistant TB and TBI in high and low-burden settings. It evaluates the standard of care regarding the treatment of patients with MDR/ RR-TB and their contacts in Australia, a low incidence setting for TB. It also evaluates the prevalence of TBI and its risk factors among HHC of the MDR/RR-TB patients in a high-burden setting, Vietnam. Finally, it explores the use of preventive therapy for TBI in Australia.

Accelerating the detection of disease among high-risk contacts for MDR/RR-TB patients, in order to maximize the opportunity to identify and treat latent infection to prevent disease, should be prioritised to achieve the End TB strategy [99].

**Hypotheses for this thesis:**

- That a high treatment success rate can be achieved using individualised treatment for MDR/RR-TB in a high-income low-incidence setting
- That the management of contacts of patients with MDR/RR-TB varies substantially in New South Wales, Australia.
- That HHC of MDR/RR-TB patients in a Southeast Asian setting (Vietnam) have a high prevalence of infection.
- That a high proportion of people taking weekly rifapentine and isoniazid (3HP) complete treatment for latent TB infection, in eight hospitals of New South Wales, Australia.

**Specific aims**

The specific aims of the thesis were to:

1. Evaluate the current programmatic management of patients receiving individualised antibiotic therapy for MDR/ RR-TB in the city of Sydney, Australia and the treatment outcomes.
2. Evaluate the management of high-risk contacts of patients diagnosed with MDR/RR-TB in New South Wales, Australia
3. Identify risk factors for TBI in the HHC of MDR/RR-TB patients and the prevalence of TBI among MDR/RR-TB contacts in Vietnam.
4. To evaluate the feasibility and acceptability of weekly rifapentine and isoniazid (3HP) using digital treatment adherence reminders in Sydney, Australia.

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# PREVALENCE AND PREDICTORS OF TB INFECTION AMONG MDR/RR-TB CONTACTS AND THE TREATMENT PRACTICES

In Australia, the per capita rate of all TB notifications has remained relatively stable since 1986 [1]. In 2022, the estimated total TB incidence was 1500, including 41 incident cases of MDR/RR-TB (including the Torres Strait) [2]. Although rates of TB and transmission within Australia have remained relatively low, migration from countries of high TB burden is an ongoing potential source of new TB cases. The following two chapters 2 and 3 have been published and focused on the management of MDR/RR-TB in the New South Wales TB program in Sydney, Australia.

The WHO recommendations for drug-resistant TB have changed substantially over the last decade, as evidence emerged from cohort studies and randomised trials [3-5] (summarised in Table 1.2 in Chapter 1). Treatment for drug-resistant tuberculosis is largely delivered through standardised, empirical combination regimens, in low-resource, high-burden settings [6]. However, the use of individualised treatment, guided by detailed drug susceptibility testing, was the standard of care in high-income settings till 2022[6]. **Chapter 2: Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia** (Aust NZ J Public Health. 2021; Online; doi: 10.1111/1753-6405.13144), evaluates the programmatic outcomes of patients receiving individualised antibiotic therapy for MDR/RR-TB in the city of Sydney, Australia. This study was performed before the latest guideline from WHO was released in 2022.

Our study demonstrated the high treatment success rate that can be achieved using individualised treatment for MDR/RR-TB in a well-resourced setting. With the new WHO 2022 guidelines for MDR/RR- TB, recommending shorter all-oral treatment, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM). For high-income settings like

Australia, looking at the use of new agents (like bedaquiline and delamanid), and developing strategies to ensure patients' preferences remain at the centre of the clinical decision-making, is essential.

MDR/RR-TB patients face long delays before initiation of effective treatment [7]. This means that the family has been in close contact with a highly infectious MDR/RR-TB patient for months or years. The prevalence of active MDR/RR-TB in household contacts (HHC) is therefore likely to be higher than that of household contacts of drug-susceptible index cases, and that of extensively drug resistant TB (XDR-TB) even higher [8]. A meta-analysis published by Shah and colleagues, showed that 47% of the MDR/RR-TB patients' household contacts were diagnosed with TBI [9]. In **chapter 3: Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia (ERJ Open Res 2021; 0:00149-2021 [DOI: 10.1183/23120541.00149-2021)**, we undertook an evaluation of the standard of care for contacts of MDR/RR-TB, and evaluated the prevalence of TBI and TB amongst these contacts in NSW. Our study demonstrated that there is a high prevalence of TBI 105/247 (42.5%) among the contacts of the MDR/RR-TB patients. More importantly, recent systematic review has showed the pooled TB prevalence was 3.8% among contacts of microbiologically confirmed index patients, and 4.1% among contacts of multidrug-resistant (MDR)/extensively drug-resistant (XDR)-TB index patients [10]. Another study looking at the TBI and disease in children following exposure to adults with MDR/RR-TB, showed 44.7% were classified as TBI, and 14.7% had TB disease at enrolment [10].

Previous cross-sectional studies have showed that child's age and previous TB treatment history were independent risk factors for infection. Increasing age of the MDR-TB source case was protective, and source case alcohol use was associated with increased odds of infection in adjusted analysis [10]. Another study has found higher risk of TB infection in child contacts with household MDR/RR-TB vs. DS-TB exposure, but a lower risk of TB disease [11]. Screening the high-risk contacts for MDR/RR-TB patients could increase case detection, and our study supports the WHO TBI guidelines recommending screening in this population [12].

A key missing feature for TB control is a comprehensive program for prophylaxis for contacts of index cases with MDR/RR- TB. The current WHO guideline recommended primarily to conduct strict clinical observation and monitoring for the early detection of symptoms of TB among contacts of MDR/RR-TB, for at least two years over the provision of preventive treatment at the time when study is performed [7, 12]. In Australia, there is no established consensus amongst local authorities and governments about the standard of care for MDR/RR-TB contacts in NSW [13] [14] [15]. The current WHO guidelines have a conditional recommendation for fluoroquinolone preventive therapy for HHCs, due to a lack of randomized clinical trials of TB preventive therapy in this population[13] [14] [15]. Two clinical trials have been conducted evaluating the effectiveness of fluoroquinolone preventive treatment for MDR/ RR-TB, and will be discussed further in conclusion.

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# CHAPTER TWO

# INDIVIDUALISED TREATMENT FOR MULTIDRUG-RESISTANT TUBERCULOSIS IN NEW SOUTH WALES, AUSTRALIA

## 2.1 FOREWORD

This chapter evaluate the programmatic outcomes of patients receiving individualised antibiotic therapy for MDR/RR-TB in the city of Sydney, Australia and has been published:

**Chang V,** Ling R, Velen K, Fox G. Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia. *Aust N Z J Public Health. 2021 Oct;45(5):437-442. doi: 10.1111/1753-6405.13144. Epub 2021 Jul 26. PMID: 34309967.*

# Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia

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## Abstract

**Objective:** Multidrug-resistant tuberculosis (MDR-TB) presents a major global health challenge. In high-income countries, treatment is individualised to optimise efficacy and reduce toxicity. We aimed to evaluate the outcomes of patients with MDR-TB receiving individualised antibiotic therapy in Australia.

**Methods:** This retrospective cohort study was performed in the city of Sydney in Australia and included patients diagnosed with bacteriologically confirmed MDR-TB diagnosed between 2000 and 2016. The clinical characteristics of patients and treatment details were extracted from medical records. The incidence of adverse events and end-of-treatment outcomes were also evaluated.

**Results:** Fifty-five patients with MDR-TB were identified at TB clinics in seven hospitals. The median age was 32 years (interquartile range [IQR]: 27–36 years). The median duration of the intensive phase treatment was six months (IQR 6–7 months). All patients' treatment administration was directly observed. The commonest reported adverse event was ototoxicity (44%; 23/52) and successful treatment outcomes were achieved by 95% (52/55) of patients.

**Conclusion:** This study demonstrated the high treatment success rate that can be achieved using individualised treatment for MDR-TB in a well-resourced setting.

**Implications for public health:** The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.


**Key words:** drug-resistant tuberculosis, tuberculosis, management of MDR-TB

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide.[1,2] Among these, almost half a million people developed multidrug-resistant tuberculosis (MDR-TB), defined as disease caused by *M. tuberculosis* that is resistant to both rifampicin and isoniazid.[1-4] A diagnosis of MDR-TB presents a major challenge for patients due to prolonged treatment, a high incidence of adverse events, high mortality rates and substantial costs of treatment.[5,6] In Australia, the rate of TB notifications has remained relatively stable since 1986.[7] Although rates of TB and transmission within Australia have remained low, migration – often from countries of high TB burden – is an ongoing potential source of new TB cases, including drug-resistant ones.

Treatment outcomes of MDR-TB differ considerably between settings.[8] In some high-income settings, treatment outcomes for MDR-TB approach those of drug-susceptible disease. However, globally, the outcomes are poor. Of the 156,000 persons treated for MDR-TB or rifampicin-resistant TB (RR-TB) in 2018, just 56% achieved a successful outcome.[1,9] Determinants of poor outcomes include the high incidence of adverse events seen with second-line antibiotics, barriers to accessing care[10] and difficulties maintaining adherence during a prolonged course of treatment.[1,9] The programmatic use of individualised therapy may help to improve treatment completion by ensuring that treatment regimens have been optimised for each patient. Individualised regimens can be developed by evaluating the drug-resistance profile of the causative bacteria and patient-specific factors that may determine treatment toxicity. Meta-analyses of published studies have demonstrated that an individualised approach can improve treatment outcomes when compared to programs where empirical regimens were used.[5,6,11-15] For this reason, many high-income countries, including Australia, deliver individualised therapy for drug-resistant TB that is based upon the drug-resistance profile of the causative isolates and patient factors.[5,6,11]

This study aimed to evaluate the programmatic outcomes of patients receiving individualised antibiotic therapy for MDR-TB in the city of Sydney, in New South Wales, Australia. Some cases were reported in a recent study looking at the outcomes of MDR-TB diagnosed in Australia between 1998 and 2012.[16]

## Methodology

### *Study design and setting*

This retrospective cohort study included patients treated at the seven chest clinics at tertiary hospitals in Sydney, the most populous city in Australia. The country has a low annual incidence of TB, with the Commonwealth Department of Health reporting a rate of 5.8 cases per 100,000 population in 2018.[17] MDR-TB comprises

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less than 2% of diagnosed cases. Given it is a relatively low-prevalence disease, a prospective study is not feasible.

Treatment for MDR-TB in New South Wales is individualised and based upon molecular drug susceptibility test (DST) results. Empirical treatment is started for the patient being investigated for TB using nucleic acid amplification testing. During the study period, once a patient was found to have resistance to both RIF and INH, a full antibiogram using phenotypic drug susceptibility testing was performed. Following an initial period of empirical therapy for MDR-TB, an individual treatment plan was developed according to the DST profile, in consultation with a statewide expert panel. The panel included experienced respiratory physicians, TB nurses and public health staff.

All investigations and treatment for TB were provided free of cost to patients through government-funded chest clinics.[17] During the study period, government policies mandated the regular observation of patients taking treatment by healthcare workers throughout treatment – also known as Direct Observation of Therapy (DOT).[17,18] The principle of individualised treatment for MDR-TB relies upon the capacity of the healthcare system to delivering individualised treatment regimens including access to quality-assured drug susceptibility testing (DST), regimens including effective antibiotics, medications of good quality and outpatient management of adverse events.[19]

### *Eligibility and participant identification*

Eligible participants were consecutive patients with a laboratory-confirmed diagnosis of MDR-TB in the state of New South Wales (NSW) between 1 January 2000 and 31 December 2016. The study period was selected as the World Health Organization (WHO) released the update of policy recommendations on the treatment of drug-resistant TB in 2016.[20] Patients with confirmed MDR-TB were identified via the state Mycobacterial Reference Lab, which performs drug susceptibility testing for isolates from all patients in New South Wales.

### *Data collection*

Medical and pharmacy records were reviewed at each clinic to obtain clinical information about identified cases. Collected data included patient demographics, comorbidities, risk factors, TB diagnosis (pulmonary or extrapulmonary), prior TB treatment (with first-line drugs or second-line drugs), sputum culture conversion, the details of TB treatment including (intensive and continuation phrase) duration, complications and outcomes. Radiological findings (chest radiography and computed tomography) collected were based on reports by the radiologists. Cases were excluded if no details of the treatment were found. We were unable to exclude an influence of other potential risk factors due to the retrospective observational nature of the study.

### *Definitions*

The 'intensive phase' of treatment was defined as the period of treatment during which a second-line injectable drug was given (either an aminoglycoside, amikacin or kanamycin, or polypeptide, capreomycin). The 'continuation phase' comprised the remainder of treatment. The drug resistance of the bacterium to each antibiotic was documented as sensitive, resistant or not reported. A drug was considered an effective drug if it was given to patients with documented sensitivity to that drug.

Adverse events were evaluated based upon documentation by the treating physicians in patients' medical records. The grade of adverse events was determined from the available clinical information by one researcher (VC), according to standardised criteria.[21] Grade 1 adverse events comprised events with no symptoms or mild symptoms; Grade 2 events comprised adverse events for which local or non-invasive interventions were indicated; Grade 3 events were defined as those requiring hospitalisation or resulting in disability; Grade 4 events comprised events with life-threatening consequences and Grade 5 resulted in death.[21] Adverse events leading to changes to treatment were documented. The treatment outcomes for pulmonary MDR-TB were defined according to the Laserson Criteria.[22] The treatment outcomes for extra-pulmonary MDR-TB were defined as completed, died, failure, relapse and transfer out. The World Health Organization (WHO) defines 'cure' as 'treatment completion' with at least three negative cultures after the intensive phase of therapy in the absence of 'treatment failure'.[23]

### *Data analysis*

Descriptive analyses were performed to characterise the clinical and microbiological characteristics of patients. Quantitative variables were summarised using frequencies or median values, with interquartile ranges (IQR). Adverse events were classified by organ or system. Percentages were calculated for participants without missing values. Statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

### *Ethical considerations*

Ethical approval for the study was granted by the Sydney Local Health District Human Research Ethics Committee (HREC, LNR/17/CRGH/129). Site-specific approval to conduct the study was obtained from each hospital prior to the commencement of data collection.

## Results

Between 2001 and 2016, 76 patients with confirmed MDR-TB were identified by the state Reference Laboratory. Of these, 55 patients were treated within the seven participating urban chest clinics. Twenty-one cases were excluded from the study as we were unable to identify the complete documentation.

The median age of participants was 32 years (interquartile range [IQR]: 27–36 years). Patients' characteristics are shown in Table 1. Most patients (54/55; 98%) were born outside Australia (East Asia, 16; South Asia, 20; Southeast Asia, 14; North Africa, 3; Oceania, 1). Among 52 patients for whom HIV status was available, one (2%) tested positive and received concurrent anti-retroviral treatment (Table 2). Pulmonary TB was diagnosed in 65.5% (36/55) of patients; of these, smear microscopy was positive in 47.2% (17/36). The median duration of symptoms was eight weeks (IQR 4–12 weeks).

### *Drug susceptibility test results*

Rapid molecular testing for drug resistance was available in New South Wales in 2011 and it was performed for 14/21 patients (66.7%). The median duration between the availability of the rapid drug resistance testing and confirmatory second line (drug susceptibility testing) DST was 16 days (IQR 5–32 days). The median time from diagnosis of TB to the diagnosis of MDR-TB was 40 days (IQR 28–51 days). The proportion of resistance to first-line and second-line drugs is shown in Table 3.

**Table 1: Characteristics of patients with MDR-TB .**

| Characteristic | n (%) |
|---|---|
| Total | 55 (100) |
| Gender | |
| Male | 32 (58) |
| Female | 23 (41.8) |
| Age (years) | |
| less than 18 | 1 (1.8) |
| 18-24 | 5 (9.1) |
| 25-34 | 31 (56.4) |
| 35-44 | 10 (18.2) |
| 45-54 | 3 (5.5) |
| 55-64 | 4 97.3) |
| 65+ | 1 (1.8) |
| Employment status | |
| Working full time | 18 (32.7) |
| Working part-time | 11 (20) |
| Unemployed | 4 (7) |
| Studying | 13 (24) |
| Not stated | 9 (16.4) |
| Smoking status | |
| Lifelong non-smoker | 46 (84) |
| Current smoker | 6 (10.9) |
| Ex-smoker | 3 (5.5) |
| Alcohol (etoh) usage | |
| Does not drink etoh | 35 (63.6) |
| Social etoh use | 20 (36) |
| Excessive etoh use | 0 |
| Intravenous drug user (IVDU) | |
| Non-IVDU | 54 (98.2) |
| Current IVDU | 0 |
| Ex- IVDU | 1 (1.8) |
| Medical comorbidities | |
| HIV | |
| Yes | 1 (1.8) |
| No | 51 (92.7) |
| Not documented | 3 (5.5) |
| Diabetes Mellitus | |
| Yes | 5 (9.1) |
| No | 50 (90.9) |
| Not documented | 0 |
| Chronic hepatitis B | |
| Yes | 3 (5.5) |
| No | 47 (85.5) |
| Not documented | 5 (9.1) |
| Chronic hepatitis C | |
| Yes | 2 (3.6) |
| No | 48 (87.3) |
| Not documented | 5 (9.1) |
| Silicosis | |
| Yes | 0 |
| No | 6 (10.9) |
| Not documented | 49 (89.1) |
| Immunosuppression | |
| Yes | 3 (5.5) |
| No | 51 (92.7) |
| Not documented | 1 (21.8) |
| History of TB | |
| Yes | 11 (20) |
| No | 44 (80) |
| History of MDR/XDR-TB | |
| Yes | 1 (1.8) |
| No | 54 (98.2) |

**Table 2: Diagnostic classification of the site of disease for patients with MDR-TB.**

| Characteristic | Number of patients n (%) |
|---|---|
| Total | 55 (100%) |
| Site of tuberculosis | |
| Pulmonary TB only | 36 (65.5) |
| Extrapulmonary TB | 12 (21.8) |
| Lymphadenitis | 8 (14.5) |
| Pleura | 2 (3.6) |
| Abdominal | 1 (1.8) |
| Central Nervous System | 1 (1.8) |
| Pulmonary and extrapulmonary TB | 7 (12.7) |
| Microbiological status at diagnosis | |
| Sputum smear positive | 17 (39.5) |
| Sputum culture positive | 26 (60.5) |
| Chest radiography findings at diagnosis | |
| Cavities present | 13 (30.2) |
| Parenchymal present | 29 (67.4) |
| Military disease | 4 (9.3) |
| Normal | 11 (25.6) |
| Radiological changes on Computed Tomography | |
| Cavities present | 17 (39.5) |
| Parenchymal present | 17 (39.5) |
| Military disease | 3 (7.0) |
| Normal | 4 (9.3) |
| Not performed | 2 (4.7) |

**Table 3: Drug resistance profiles to first and second-line drugs.**

| Resistance profile for MDR-TB isolates n=55 (%) | Phenotypic resistance to the listed antibiotic(s) | Resistance to antibiotic(s) not documented |
|---|---|---|
| 1st line | | |
| HR | 55 (100) | 0 (0) |
| HRE | 12 (21.8) | 7 (12.7) |
| HRZ | 16 (29.1) | 13 (23.6) |
| HREZ | 4 (7.3) | 14 (25.5) |
| 2nd line | | |
| Group A- Fluoroquinolones | | |
| Moxifloxacin | 4 (7.3) | 33 (60) |
| Ciprofloxacin | 5 (9.1) | 6 (10.9) |
| Levofloxacin | 1 (1.8) | 48 (87.3) |
| Ofloxacin | 0 (0) | 49 (89.1) |
| Group B- 2nd line injectable agents | | |
| Amikacin | 1 (1.8) | 9 (16.4) |
| Capreomycin | 1 (1.8) | 8 (14.5) |
| Kanamycin | 0 (0) | 49 (89.1) |
| Streptomycin | 21 (38.2) | 21 (38.2) |
| Group C- other 2nd line agents | | |
| Ethionamide | 20 (36.4) | 9 (16.4) |
| Prothionamide | 0 (0) | 46 (83.6) |
| Cycloserine | 5 (9.1) | 19 (34.5) |
| Terizidone | 1 (1.8) | 48 (87.3) |
| Linezolid | 2 (3.6) | 32 (58.2) |
| Clofazimine | 8 (14.5) | 8 (14.5) |
| Others add on agents | | |
| PAS | 5 (9.1) | 43 (78.2) |
| Imipenum/ Cilastatin | 0 (0) | 49 (89.1) |
| Meropenum | 1 (0) | 50 (89.1) |
| Augmentin DF | 2 (0) | 51 (89.1) |
| Thioacetazone | 3 (0) | 52 (89.1) |
| Bedaquiline | 4 (0) | 53 (89.1) |

*Note:*

*H— Isoniazid, R— Rifampicin, E—Ethambutol, Z— Pyrazinamide*

Fluroquinolone resistance was present in 10/55 (18.2%) of cases (Table 3).

### *Hospitalisation and treatment regimens*

During the initial treatment period, 32/55 patients (58.2%) were hospitalised. All patients received their treatment under direct observation between three and five days a week. The median durations of inpatient and outpatient treatment were seven days (IQR 0–42 days) and 600 days (IQR 540–713 days), respectively. The median duration of the intensive phase treatment was six months (IQR 6–8 months), and the median duration of continuation phase treatment was 14 months (IQR 12–18 months).

Patients received between four and seven antibiotics. The median number of effective drugs which were given was five (IQR 4–5) for patients with documented sensitivities. The details of the MDR-TB regimens used during the acute and continuation phrase is shown in Table 4. The treatment was consistent with standard WHO guidelines at the time of the study, which included the use of four core second-line drugs with one being the secondary line injectable agents.[18,24] The WHO endorsed the shorter MDR-TB regimen for patients with rifampicin resistant-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or was considered highly unlikely in May 2016, but none of the patients in the study received the shorter regimens.

### *Treatment outcomes*

Table 6 shows treatment outcomes for the cohort. Two patients died before the treatment for MDR-TB treatment was started. One patient transferred out, leaving Australia four months after treatment started. The median duration from treatment commencement to sputum smear conversion was 58 (IQR 38–73) days and culture conversion was 59 (49–130) days. After two months of treatment, 51% (22/43) of patients became smear negative and 49% (21/43) were culture negative. No patient was smear positive at five months. A negative culture was documented for 35% (15/43) of patients who were initially sputum culture positive; however, 63% (27/43) patients were not able to expectorate sputum after they commenced treatment for five months. Only eight patients had sputum collected at seven months and at the end of treatment, of which both were culture negative. (Table 5). A total of 93% of the patients (51/55) achieved treatment completion as defined by the WHO.[23]

### *Treatment toxicity*

Adverse events were commonly reported, as shown in Table 7. The adverse events reported most often were ototoxicity (44%; 23/52 patients). Of the 54 patients taking an injectable antibiotic, more than half of the patients 59% (32/54 patients) had audiometric monitoring once they reported symptoms and only 37% (20/54) patients had audiometry within one month of treatment commencement. Hepatotoxicity (50%; 26/52 patients) and gastrointestinal symptoms (56%; 29/52 patients) were commonly reported. No reported grade four or five adverse events were reported.

**Table 4: MDR-TB treatment regimens .**

| | Intensive phrase | Continuation phrase |
|---|---|---|
| Total number of patients n (%) | 54 (100) | 52 (100) |
| Group A- Fluoroquinolones | | |
| Moxifloxacin | 52 (96.3) | 52 (100) |
| Ciprofloxacin | 2 (1.9) | 0 (0) |
| Group B- 2nd line injectable agents | | |
| Amikacin | 28 (51.9) | 0 (0) |
| Daily dose | 8 (14.8) | 0 (0) |
| 5 days per week | 20 (37) | 0 (0) |
| Capreomycin | 26 (48.1) | 0 (0) |
| Daily dose | 12 (22.2) | 0 (0) |
| 5 days per week | 10 (18.5) | 0 (0) |
| 3 days per week | 4 (7.4) | 0 (0) |
| Group C- other 2nd line agents | | |
| Ethionamide | 2 (1.9) | 0 (0) |
| Prothionamide | 20 (37) | 18 (34.6) |
| Cycloserine | 14 (25.9) | 13 (25) |
| Linezolid | 6 (11.1) | 4 (7.7) |
| Clofazimine | 27 (50) | 27 (51.9) |
| Others add on agents | | |
| Pyrazinamide | 30 (55.6) | 26 (50) |
| Ethambutol | 36 (66.7) | 32 (61.5) |
| High dose Isoniazid | 11 (20.4) | 10 (19.2) |
| PAS | 4 (7.4) | 2 (3.8) |
| Amoxycillin/clavulanic acid | 0 (0) | 3 (5.8) |
| Bedaquiline | 1 (1.9) | 1 (1.9) |

**Table 5: Results for repeat sputum microscopy and culture for patients on MDR-TB treatment.**

| Repeat sputum culture n=43 (%) | Sputum smear positive | Sputum smear negative | Sputum culture positive | Sputum culture negative | Not performed |
|---|---|---|---|---|---|
| 2 months | 8 (18.6) | 22 (51.2) | 9 (20.1) | 21 (48.8) | 13 (30.2) |
| 5 months | 0 | 16 (37.2) | 1 (2.3) | 15 (34.9) | 27 (63.0) |
| 7 months | 0 | 8 (18.6) | 0 | 8 (18.6) | 35 (81.4) |
| End of treatment | 0 | 8 (18.6) | 0 | 8 (18.6) | 35 (81.4) |

## Discussion

This retrospective cohort study of patients treated for MDR-TB in Sydney, Australia, over a 16-year period demonstrated a high rate of treatment success. Patients' treatment regimens were individualised and based upon molecular drug susceptibility test (DST)

**Table 6: Treatment outcomes for MDR-TB patients.**

| Treatment outcome | n (%) |
|---|---|
| Patients with pulmonary MDR-TB | |
| Total | 43 (100) |
| Cure | 1 (2.3) |
| Completed | 40 (93.0) |
| Died | 1 (2.3) |
| Failure | 0 (0) |
| Transfer out | 1 (2.3) |
| Patients with extrapulmonary MDR-TB | |
| Total | 12 (100) |
| Completed | 11 (91.6) |
| Died | 1 (8.3) |
| Failure | 0 (0) |
| Transfer out | 0 (0) |

**Table 7: Cumulative incidence of adverse events among patients treated for MDR-TB.**

| Adverse event | Grade of adverse event n (%) n=52 patients* | | | | | Treatment decision following adverse event n (%) | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | Treatment continued | Treatment modified | Treatment stopped |
| Cardiac arrhythmia | 0 | 0 | 0 | 0 | 0 | 52 (100) | 0 | 0 |
| Electrolyte abnormality | 7 (13.5) | 1 (1.9) | 2 (3.8) | 0 | 0 | 50 (96.2) | 1 (1.9) | 1 (1.9) |
| Haematological | 4 (7.7) | 0 | 3 (5.8) | 0 | 0 | 49 (94.2) | 0 | 3 (5.8) |
| Headaches | 2 (3.8) | 1 (1.9) | 1 (1.9) | 0 | 0 | 50 (96.2) | 0 | 2 (3.8) |
| Hearing impairment | 13 (28.3) | 7 (15.2) | 3 (6.5) | 0 | 0 | 38 (73.1) | 2 (3.8) | 11 (21.2) |
| Hypo/hyperthyroidism | 1 (1.9) | 1 (1.9) | 0 | 0 | 0 | 52 (100) | 0 | 0 |
| Liver toxicity | 15 (28.8) | 7 (13.5) | 4 (7.7) | 0 | 0 | 46 (88.5) | 1 (1.9) | 5 (9.6) |
| Myalgia _arthralgia | 9 (17.3) | 0 | 0 | 0 | 0 | 52 (100) | 0 | 0 |
| Nausea vomiting | 25 (48.1) | 4 (7.7) | 0 | 0 | 0 | 47 (90.1) | 3 (5.7) | 1 (1.9) |
| Peripheral neuropathy | 5 (9.6) | 0 | 3 (5.8) | 0 | 0 | 50 (96.2) | 2 (3.8) | 0 |
| Psychiatry | 0 | 0 | 0 | 0 | 0 | 52 (100) | 0 | 0 |
| Visual impairment | 2 (3.8) | 1 (1.9) | 0 | 0 | 0 | 52 (100) | 0 | 0 |

*Notes:*
**Adverse events for 52 patients were reported; 3 patients did not have adverse event data (1 transferred out and 2 died prior to treatment).*

results. Most included an injectable antibiotic during the intensive phase of treatment. Our cohort showed an excellent treatment completion rate – well above the WHO target of 75%, and similar to that achieved in other high-resource settings.[2,25,26] All patients received treatment under direct observation of healthcare workers. All 52 patients had at least one adverse event. The high treatment completion rates achieved indicated the ability of healthcare workers to continue supervising the MDR-TB treatment despite the frequent occurrence of side effects.

The reporting of drug-related adverse events was inconsistent. The grading of reported adverse events was not documented by clinicians in routine practice. Owing to the presence of multiple concurrent antibiotics, it was difficult to attribute a specific adverse event to a specific antibiotic. According to state policies, serious adverse events of medicine should be reported to the national Therapeutic Goods Administration. However, notification practices vary considerably across sites.[27] While patients were followed up monthly at the clinic by treating physicians, national monitoring guidelines for the monitoring of drug-resistant TB treatment are lacking. Considering the increasing use of the new or repurposed second-line drugs, local guidelines for standardised drug-safely monitoring are warranted. A few patients had repeat sputum collected during the treatment course; developing a standardised monitoring protocol for sputum analysis at regular intervals throughout treatment can improve the reporting of treatment outcomes.

This study had several limitations. As this was a retrospective study, documentation in the medical records was sometimes incomplete – particularly regarding patients' comorbidities. Furthermore, the data available to guide the classification of the severity of adverse events were limited. During the study period, the global treatment guidelines for MDR-TB continued to evolve. Recently, the WHO has endorsed the use of new drugs, such as bedaquiline, and repurposed anti-TB drugs as first-line therapies in the treatment of MDR-TB.[1] However, few patients in our cohort had access to these second-line drugs – bedaquiline only became available in Australia in 2017. Aminoglycosides are not recommended in the treatment of MDR-TB patients on longer regimens.[28] All patients in our study received their individualised MDR-TB treatment with DOT supervised by healthcare workers, which may also have contributed to the high treatment completion rate.

This study has important policy implications. Firstly, individualised therapy can result in excellent treatment outcomes and so should be considered in settings where this is feasible. Secondly, it shows that adverse events are almost universally observed. However, intensive monitoring can ensure that patients safely complete treatment. Lastly, in New South Wales, where just 2% of patients with TB have MDR-TB, further studies should look into the cost-effectiveness of performing rapid molecular testing to detect rifampicin-resistant TB for patients without a prior TB treatment history or other risk factor for drug-resistance.

## Conclusion

In conclusion, individualised treatment for patients with MDR-TB in Australia was associated with high rates of treatment success within the public treatment program. The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.[29] It is important for countries like Australia with high incomes and low TB incidence to continue using individualised treatment for MDR-TB, optimise the use of new agents like bedaquiline and delamanid, and develop strategies to ensure patients' preferences remain at the centre of the clinical decision making.

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# CHAPTER THREE

# LATENT TUBERCULOSIS INFECTION AMONG CONTACTS OF PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS IN NEW SOUTH WALES, AUSTRALIA

## 3.1 FOREWORD

This chapter evaluates the prevalence of TBI and active TB disease amongst contacts of patients with MDR/RR-TB screened in NSW and characterises the current approach to management of TBI in this population.

**Chang V,** Ling R, Velen K, Fox G. Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia. *ERJ Open Res. 2021 Sep 20;7(3):00149-2021.doi:10.1183/23120541.00149-2021.PMID:34549043;PMCID: PMC8450450.*

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ORIGINAL RESEARCH ARTICLE
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# Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia

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Shareable abstract (@ERSpublications)
**Given the high likelihood of multidrug resistance in strains responsible for LTBI among MDR-TB contacts, new research is needed to evaluate preventive therapies for this patient population**
https://bit.ly/2Tf4LLY

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## Abstract

*Background* Contacts of an individual with active tuberculosis (TB) disease have a higher risk of developing latent TB infection (LTBI) or active TB disease. Contact tracing is a public health measure that seeks to identify exposed contacts, screen them for co-prevalent TB and consider prophylactic treatment to prevent progression from LTBI to active TB disease. The investigators sought to determine the prevalence of LTBI and active TB disease among contacts of patients with multidrug-resistant (MDR)-TB in New South Wales, Australia.

*Methodology* A retrospective cohort study was performed among the contacts of patients diagnosed with MDR-TB between 2000 and 2016, inclusive, at seven chest clinics. Medical records were used to identify eligible contacts. Outcomes of screening and prophylactic treatment regimens offered to MDR-TB contacts with LTBI were characterised. Collected data included demographic information, screening tests results and initial management.

*Results* In total, 247 contacts of 55 MDR-TB patients were identified. LTBI was identified in 105 contacts (42.5%). Preventive treatment was received by 20 contacts with LTBI (32.3%) in the form of various regimens, ranging from one to three antimicrobials, with various doses and durations. One contact with LTBI who was untreated progressed to active TB disease during the study period, according to clinic notes.

*Conclusion* Contacts of MDR-TB patients have a high prevalence of LTBI. Management of these contacts varies substantially in New South Wales, reflecting a lack of definitive evidence for preventive therapy. Further research is required to determine the optimal management of this population.

## Introduction

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide [1, 2]. Among these, almost half a million people developed multidrug-resistant (MDR)-TB, defined as disease caused by *Mycobacterium tuberculosis* that is resistant to both isoniazid and rifampicin [1–4]. A diagnosis of MDR-TB presents a major challenge for patients, owing to the prolonged treatment, high incidence of adverse events, high mortality rates and substantial costs of treatment [5, 6].

TB is transmitted *via* droplets that are coughed up by infected patients and inhaled by susceptible contacts. The World Health Organization (WHO) aims to eliminate this disease by 2035 [7]. In high-income countries with low rates of TB, contact tracing is the primary method used to find those at risk of developing TB. However, the prevalence of latent tuberculosis infection (LTBI) and TB disease among contacts of patients with MDR-TB and drug-susceptible TB are not well understood. Systematic reviews and meta-analyses have shown that contacts of MDR-TB patients have a high risk of developing TB, with disease commonly diagnosed within 12 months of the index patient's diagnosis [8, 9]. A recent prospective cohort study found a higher prevalence of LTBI among household contacts of MDR-TB patients than

among contacts of patients with newly diagnosed TB that was presumed not to be drug resistant [10]. Accelerating the detection of disease among high-risk contacts of MDR-TB patients could maximise the opportunity to identify and treat latent infection to prevent disease, and should be prioritised to achieve the End TB Strategy [11].

Identifying MDR-TB contacts with LTBI is clinically useful only if there is an approach to reducing the risk of developing active TB disease. This is the rationale for prophylactic treatment regimens for LTBI [12]. However, established consensus among global authorities and governments has yet to be reached with regards to managing LTBI in MDR-TB contacts [13–15]. In the absence of definitive guidelines in New South Wales (NSW), Australia, the provision of prophylaxis lies with a respiratory physician's clinical judgment, based upon the individual clinical features of each patient. A contact tracing study conducted in Victoria, Australia, reported substantial variability in prescribed prophylaxis for MDR-TB contacts, in terms of antimicrobial regimens as well as treatment duration [16]. Current practices regarding effective regimens to prevent TB among contacts of patients with MDR-TB have not yet been established [17].

This study aimed to determine the prevalence of LTBI and active TB disease among contacts of patients with MDR-TB screened in NSW and to characterise the current approach to managing LTBI in this population.

## Methodology

### *Study design and setting*

This retrospective cohort study was performed for contacts of patients with MDR-TB in NSW between 2000 and 2016. MDR-TB was defined as bacteriologically confirmed TB with resistance to isoniazid and rifampicin. Patients were excluded if they did not have bacteriologically confirmed MDR-TB (with proven isoniazid and rifampicin resistance). We collected quantitative data from the medical records of contacts of the MDR-TB index patients attending chest clinics within NSW. Variables of interest included demographic information, age, gender, country of birth and contact exposure to a person with known TB (an "index" patient). We also recorded disease status of the contacts, and the outcomes of the contact screening. Tuberculin skin test (TST) and interferon-γ release assay (IGRA) test results of the contacts were recorded. Immunological evidence of TB infection was defined as a TST reaction size of ⩾10 mm or a positive IGRA, upon which LTBI status was determined and the use of prophylactic treatment regimens was reported. Contacts were defined as having completed screening if they completed a TST or IGRA and clinical follow-up at the TB clinic.

### *Participant identification*

A list of all patients with a laboratory-confirmed diagnosis of MDR-TB in NSW from January 1, 2000, to December 31, 2016, was identified from the state-wide mycobacterial reference laboratory at the Institute for Clinical Pathology and Medical Research Mycobacterium Reference Laboratory. In total, 55 patients were identified from seven participating urban chest clinics in NSW where patients received treatment at the TB clinics. We visited the chest clinics of these seven hospitals to identify the records of these MDR-TB patients, which contained documentation of routine contact tracing performed for each case of active TB disease.

Contact tracing was managed differently across different chest clinics, with some keeping paper records and others using specialised computer software. Generally, for each MDR-TB patient, a list of contacts would be identified and an attempt made to screen these individuals with follow-up at the chest clinic. The sample of MDR-TB contacts examined by this study included all individuals identified through chest clinic contact tracing programmes and comprised the population of identifiable MDR-TB contacts. No identified contacts were excluded at the data collection stage. Existing electronic and hard copy contact records maintained by chest clinics were obtained and manually searched for relevant quantitative data.

### *Outcome measures*

Outcomes of contact screening were also of interest. Contacts with positive TST results obtained from contact screening, without a prior history of LTBI or TB, were considered to have new LTBI. We also recorded the use of prophylactic treatment regimens, including the medications used and their doses, durations and documented adverse effects. Adverse events were evaluated based upon documentation by the treating physicians in the patients' medical records. The grade of adverse events was determined from the available clinical information by two researchers (VC and RL), according to standardised criteria [8]. Grade 1 adverse events comprised events with no symptoms or mild symptoms; Grade 2 events comprised adverse events for which local or noninvasive interventions were indicated; Grade 3 events were defined as those requiring hospitalisation or resulting in disability; Grade 4 events comprised events with

TABLE 1 Demographics of contacts of patients with MDR-TB, New South Wales, Australia, 2000–2016

| | |
|---|---|
| **Total contacts commenced screening** | 247 (100) |
| **Gender** | |
| Male | 107 (43.3) |
| Female | 140 (56.7) |
| **Age, years** | |
| <18 | 27 (10.9) |
| 18–24 | 16 (6.4) |
| 25–34 | 76 (30.8) |
| 35–44 | 43 (17.4) |
| 45–54 | 38 (15.4) |
| 55–64 | 29 (11.7) |
| 65+ | 18 (7.3) |
| **Country of birth** | |
| Africa | 12 (4.9) |
| East Asia | 18 (7.3) |
| South Asia | 26 (10.5) |
| Southeast Asia | 65 (26.3) |
| West Asia | 4 (1.6) |
| Europe | 4 (1.6) |
| South America | 1 (0.4) |
| North America | 1 (0.4) |
| Australia and New Zealand | 81 (32.8) |
| Not documented | 35 (14.2) |
| **Employment status** | |
| Working full-time | 87 (35.2) |
| Working part-time | 91 (36.8) |
| Unemployed | 23 (9.3) |
| Studying | 31 (12.6) |
| Not stated | 15 (6.1) |
| **Smoking status** | |
| Lifelong non-smoker | 185 (74.9) |
| Current smoker | 12 (4.9) |
| Ex-smoker | 15 (6.1) |
| Not documented | 35 (14.2) |
| **Alcohol usage** | |
| Does not drink | 159 (64.4) |
| Social usage | 58 (23.5) |
| Excessive usage | 8 (3.2) |
| Not documented | 22 (30.9) |
| **IVDU** | |
| Non-IVDU | 222 (89.9) |
| Current IVDU | 0 (0) |
| Ex-IVDU | 3 (1.2) |
| Not documented | 22 (30.9) |
| **Bacille Calmette–Guérin scar** | |
| Yes | 57 (23.1) |
| No | 30 (12.1) |
| Not documented | 160 (64.8) |
| **Medical comorbidities** | |
| HIV | |
| Yes | 0 (0) |
| No | 221 (89.5) |
| Not documented | 26 (10.5) |
| Diabetes mellitus | |
| Yes | 30 (12.1) |
| No | 209 (84.6) |
| Not documented | 8 (3.2) |
| Immunosuppression | |
| Yes | 0 (0) |
| No | 231 (93.5) |
| Not documented | 16 (6.5) |

Continued

TABLE 1 Continued

| | |
|---|---|
| **Types of contact** | |
| Household | 94 (38) |
| Institutional/healthcare | 71 (28.7) |
| Other | 10 (4) |
| Not documented | 72 (29.1) |

Data presented as n (%). MDR: multidrug resistant; TB: tuberculosis; IVDU: intravenous drug user.

life-threatening consequences; and Grade 5 events resulted in death. Adverse events leading to changes in treatment were documented.

### *Data analysis*

Descriptive analyses were performed. Quantitative variables are summarised using frequency (%) and median (interquartile range (IQR)). Adverse events were stratified by organ or system. Proportions were based upon the number of non-missing values. Statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, NY, USA).

### *Ethical considerations*

Ethical approval for the study was granted by the Sydney Local Health District Human Research Ethics Committee (LNR/17/CRGH/129). Site-specific permission was obtained from each hospital prior to commencement of data collection.

## Results

We reviewed the medical files of 55 MDR-TB patients from seven chest clinics in Sydney, NSW, through which 247 MDR-TB contacts were screened (table 1). The number of contact cases per index patient ranged from one to 115 with a median of two contacts per case. Most of the contacts (131 of 247, 53.0%) were born overseas. All patients with Bacille Calmette–Guérin (BCG) scars (57 of 247, 23.1%) were born overseas.

247 contacts with chest clinic records commenced screening, of which 215 completed screening. TST was the predominant mode of TB exposure screening. Only three contacts were documented to have had an IGRA test. Immunological evidence of TB infection was found in 105 contacts (42.5%). 96 (38.9%) were diagnosed with LTBI by the specialist medical assessment. 62 contacts (25.1%) were classified as having LTBI due to recent exposure (*i.e.* newly diagnosed) and 34 (13.8%) were classified as having LTBI due to remote exposure. Of the 62 newly diagnosed LTBI contacts, 11 (4.5%) were born in Australia/New Zealand, 28 (11.3%) in Southeast Asia, 13 (5.3%) in South Asia, eight (3.2%) in East Asia and two (0.8%) in Africa. One contact had co-prevalent extrapulmonary TB that was fully sensitive to first-line antibiotics (figure 1). The index case isolate had different drug susceptibility test results from this contact. Table 2 shows the screening outcomes of contacts.

More than half of the contacts with newly diagnosed LTBI were offered prophylactic treatment (table 3). Extensive variation was observed in the medications, doses and durations making up the prophylactic treatment regimens offered to contacts with LTBI. Table 4 reports the documented regimens used in the treating hospitals. In two contacts, isoniazid preventive therapy was commenced before patients' drug susceptibility results were known. Treating clinicians stopped therapy once it was recognised to be ineffective. These two contacts went onto chest X-ray surveillance. 14 of the index cases with MDR-TB had organisms that were susceptible to high-level isoniazid, and 11 contacts were offered isoniazid as part of their prophylactic regimens. Adverse events from the prophylactic treatments were rarely reported.

## Discussion

This retrospective cohort study found a high prevalence of LTBI among contacts of patients diagnosed with MDR-TB over a 16-year period. In low-incidence countries, including Australia, that have low background transmission rates of TB, transmission among contacts born in those countries most likely results from the recognised exposure to a patient with MDR-TB. The calculated LTBI prevalence in our study was 96 of 247 (38.9%), which is comparable to a reported 52.6% prevalence of LTBI in a meta-analysis of contacts of patients with MDR-TB or extensively drug-resistant TB in other high-income countries [8]. One contact had concurrent extrapulmonary TB that was not drug resistant. More than half

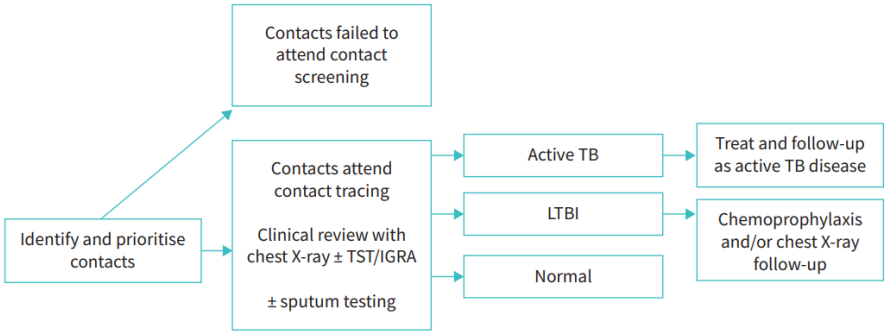


FIGURE 1 Algorithm for contact tracing and management in New South Wales, Australia. TST: tuberculin skin test; IGRA: interferon-γ release assay; TB: tuberculosis; LTBI: latent TB infection.

of the contacts with LTBI (33 of 62, 53.2%) were offered prophylactic treatment but only 20 of 62 (32.3%) of the contacts accepted preventive therapies. The majority of the contacts (42 of 62, 67.7%) accepted chest X-ray surveillance.

Selecting an appropriate preventive therapy is a major challenge in treating contacts of patients with drug-resistant TB. It is often difficult to distinguish whether contact LTBI arises from transmission from the recognised index case or from a prior remote infection. For those born in Australia, a setting with a low incidence and low background transmission of *M. tuberculosis*, most cases of LTBI are likely to have occurred owing to their close contact with active MDR-TB disease. However, in our study, many contacts were born overseas, meaning that it was difficult to definitively exclude remote infection.

This study had several limitations. First, because this was a retrospective study, documentation in the medical records was sometimes incomplete. By relying on chest clinic records, the investigators are unable to exclude the possibility that some contacts were not documented in available records. Second, with the small number of contacts treated, the variation in regimens used and the absence of a control group, we

TABLE 2 Screening outcomes of contacts of patients with MDR-TB, New South Wales, Australia, 2000–2016

| | |
|---|---|
| **Contacts who commenced screening** | 247 (100) |
| **Completed screening (total)** | 215 (87) |
| Tested positive for LTBI | 105 (42.5) |
| TST positive (≥10 mm) | 104 (42.1) |
| IGRA positive (≥0.35) | 1 (0.4) |
| Tested negative for LTBI | 110 (44.5) |
| TST negative (<10 mm) | 108 (43.7) |
| IGRA negative (<0.35) | 2 (0.8) |
| **Did not complete screening** | 32 (13.0) |
| Did not attend | 26 (10.5) |
| Transferred out before completing screening | 3 (1.2) |
| Deceased before completing screening | 3 (1.2) |
| **Chest X-ray findings** | |
| Abnormal | 8 (3.2) |
| Normal | 207 (83.8) |
| Not documented | 32 (13.0) |
| **Final diagnosis** | |
| LTBI | 96 (38.9) |
| Newly diagnosed LTBI | 62 (25.1) |
| Prior history of LTBI | 34 (13.8) |
| Active TB disease | 1 (0.4) |
| Previous inactive TB (treated or not treated) | 8 (3.2) |

Data presented as n (%). MDR: multidrug resistant; TB: tuberculosis; LTBI: latent tuberculosis infection; TST: tuberculin skin test; IGRA: interferon-γ release assay.

**TABLE 3** Management of contacts diagnosed with LTBI

| | Contacts |
|---|---|
| **Contacts with newly diagnosed LTBI** | 62 (100) |
| **Preventive therapy offered** | 31 (50) |
| Accepted | 18 (29) |
| Refused | 13 (21.0) |
| **Preventive therapy not offered** | 31 (50) |
| **Chest X-ray surveillance offered** | 31 (50)[#] |
| Accepted[¶] | 44 (71.0) |
| Refused | 0 |

Data presented as n (%). LTBI: latent tuberculosis infection. [#]: isoniazid preventive therapy was commenced before patients' drug susceptibility results were known, stopped by clinicians once it was recognised to be ineffective, and contacts offered chest X-ray surveillance; [¶]: including contacts refusing preventive therapy.

were unable to assess the effectiveness of different regimens to treat LTBI. The undertaking of this study has so far corroborated the utility of contact tracing programmes demonstrated by the existing body of literature and has characterised a substantial degree of contact transmission in NSW. Even if contacts do not receive treatment, they can be monitored for incipient disease following their known exposure. This is likely to accelerate diagnosis of early disease and reduce potential ongoing transmission in the community.

This study has important policy implications. First, given the significant role of contact transmission in LTBI development, efforts to detect and treat contacts with MDR-TB infection play an important role in the control of TB in this low-prevalence setting. LTBI is a significant risk for developing infectious active TB disease. It is often stated that the lifetime risk of developing active TB after an index infection is 5–10%; a recent study has shown the 1650-day cumulative hazard is up to 11.5% [18]. Hence, identifying contacts and screening them for LTBI can effectively break the cycle of TB transmission. Prevention is especially important for those at risk of MDR-TB, given the difficulty of treating these cases once active MDR-TB disease is established. Second, identifying contacts with LTBI is clinically useful only if there is an approach to reducing the risk of development into active TB disease. Regular clinical and radiological surveillance accelerate diagnosis of early disease and reduce potential ongoing transmission in the community [1], but they are labour intensive and do not reduce the risk of potential development into active TB disease. This is the rationale behind prophylactic treatment regimens for LTBI; however, currently available guidelines for treating LTBI in MDR-TB contacts lack uniformity and are based upon limited evidence of effectiveness of the commonly used preventive therapies in this population [2, 19, 20]. Another important consideration unique to our population of MDR-TB contacts would be individualising

**TABLE 4** Antibiotic treatment of infected contacts of patients with MDR-TB

| Regimen recommended by treating physicians | Contacts commencing treatment | Contacts completing recommended treatment | Contacts reporting adverse events during treatment |
|---|---|---|---|
| **Total** | 18 (100) | 18 (100) | 1 (5) |
| **One drug** | | | |
| Moxifloxacin | | | |
| 6 months | 7 (35) | 7 (35) | 0 (0) |
| **Two drugs** | | | |
| Isoniazid and rifampicin | 7 (35) | 7 (35) | 0 (0) |
| 4 months | 3 (15) | 3 (15) | 0 (0) |
| 6 months | 3 (15) | 3 (15) | 0 (0) |
| Unknown duration | 1 (5) | 1 (5) | 0 (0) |
| Isoniazid and pyrazinamide | | | |
| 9 months | 2 (10) | 2 (10) | 1 (5) |
| **Three drugs** | | | |
| Isoniazid, rifampicin and pyrazinamide | 2 (10) | 2 (10) | 0 (0) |
| 5 months | 1 (5) | 1 (5) | 0 (0) |
| 6 months | 1 (5) | 1 (5) | 0 (0) |

Data presented as n (%).

therapy based on the drug-resistance profile of the index patient. Given the high likelihood of MDR in strains responsible for LTBI among MDR-TB contacts, prophylactic treatment regimens should ideally be guided by drug susceptibility profiles of M. *tuberculosis* strains.

### *Conclusion*

This study has characterised the current practice relating to contact investigation for MDR-TB in NSW, and has shown a high prevalence of LTBI in close contacts of patients with MDR-TB. Further research is required to shape clinical guidelines relating to the appropriate management of LTBI among MDR-TB contacts. Attention should be given to identifying strategies that enhance uptake of screening, as well as chemoprophylaxis to advance the ambitious goal of TB elimination [7].

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# CHAPTER FOUR

# FACTORS ASSOCIATED WITH TUBERCULOSIS INFECTION AMONG HOUSEHOLD CONTACTS OF PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS IN 10 PROVINCES OF VIETNAM: A CROSS SECTIONAL STUDY

## 4.1 FOREWORD

This chapter evaluates risk factors for TBI in the HHC of MDR/RR-TB patients and the prevalence of TBI among MDR/RR-TB contacts in Southeast Asian setting.

This chapter is being prepared for submission.

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**Factors associated with tuberculosis infection among household contacts of patients with multidrug-resistant tuberculosis in 10 provinces of Vietnam: a cross-sectional study.**

**Abstract**

Background:

In 2021, an estimated 450 000 incident people developed Rifampicin-resistant (RR) or multidrug-resistant (MDR)-TB (defined as resistance to both rifampicin and isoniazid) worldwide. Given that the commonly used rapid molecular diagnostic test, GeneXpert, only detect resistance, programmatic reporting groups MDR/RR-TB together. Household contacts (HHCs) of a patient with active MDR/RR-TB are at high risk for a TB infection (TBI) and disease, as they have a prolonged exposure to the index cases. This study aimed to establish the prevalence of TBI and factors associated with TB infection among HHCs.

Methods:

A cross-sectional survey was conducted among close contacts of patients with MDR/RR-TB, who participated in screening for TB infection, as a part of the VQUIN multidrug-resistant tuberculosis (MDR-TB) trial. TBI status was defined based upon a tuberculin skin test result (TST) of at least 10mm. Logistic regression was used to evaluate the relationship between the characteristics of HHCs or the index case, and HHCs with positive TST. The primary outcome was the prevalence of TBI amongst the HHCs, and the risk factors associated with TBI in this population.

Results: 3823 HHCs of 1758 MDR/RR-TB index cases participated in screening. The prevalence of TB infection at baseline was 71.2%, comprising 2309 (60.4%) individuals with baseline positivity, and an additional 283 (7.4%) demonstrating TST conversion after 8-12 weeks. Factors associated with a positive TST in the multivariable model included, HHCs with older age groups had a higher prevalence

of infection. Other factors associated with an increased prevalence of infection included: normal BMI (aOR = 1.33, 95% CI: 1.06- 1.66), smoking history (aOR = 1.76, 95% CI: 1.39- 2.23), a prior history of TB (aOR = 4.56, 95% CI: 2.49- 8.35), the presence of a BCG scar (aOR = 1.23, 95% CI: 1.02-1.50 ), and more than eight hours spent each day on average over the previous three months with the index patient (aOR = 1.52, 95% CI: 1.28-1.81).

Conclusion:

This study identified that HHCs amongst the MDR/RR-TB patients had a high TBI prevalence and identified a number of risk factors of contracting TBI. Evidence for the effectiveness of preventive therapy to treat TB infection in MDR/RR-TB contacts is urgently needed.

**Background**

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide [1, 2]. Among these, almost half a million people developed Rifampicin-resistant or multidrug-resistant TB (defined as resistance to both rifampicin and isoniazid), collectively referred to as MDR/RR-TB [1]. A diagnosis of MDR/RR-TB presents a major challenge for patients, owing to prolonged treatment and high incidence of adverse events, high mortality rates, and substantial costs of treatment [2] [3]. Tuberculosis infection (TBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* (*M.tb*) antigens, with or without evidence of the clinical manifestation of active TB [4]. On average, 5–10% of people who are infected will develop active TB over the course of their lives, with the highest risk in the first year after infection [5]. The global burden of TBI is about one-quarter of the world's population, representing a reservoir of approximately 2 billion people [6]. In the WHO regions, the estimated prevalence of TBI in 2018 was 36% in South-East Asia. However, the prevalence of infection with strains that are resistant to first line anti-TB drugs (isoniazid and/or rifampicin) are not available, as infecting strains of *M.tb* cannot be isolated and tested for resistance [7]. Previous mathematical model estimated that globally, 19.1 million people were latently infected with MDR/RR-TB strains in 2014 [8], with a higher burden in children younger than 15 years [8].

Household contacts (HHCs) of a patient with active rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) are at high risk for a TB infection and disease. [9, 10]. Previous meta-analysis showed that 47% of the MDR/ RR-TB patients' household contacts are infected [11]. The prevalence of a TB infection and disease is particularly high among children who are household contacts and exposed to MDR/RR-TB, reaching up to 57% in an observational study [12]. Contact tracing has been the core strategy for preventing drug- susceptible TB in many high and low income settings [13] [14],where effective preventive therapy is available. However, for drug-resistant TB, contact tracing alone will not suffice without effective preventive therapy. Currently, there are ongoing clinical trials focusing on the efficacy of levofloxacin as tuberculosis preventive therapy (TPT) in MDR/RR-TB contacts. The "End TB

Strategy" of the World Health Organization (WHO) seeks to reduce TB incidence to fewer than 10 cases per 100,000 people per year by 2035 [15]. Central to this goal is to improve the detection and offer treatment of TB infection, for people at risk of progressing to active TB disease [15]. However, there is limited data about risk factors for latent TB infection (TBI) in the HHCs of MDR/RR-TB patients and the prevalence of TBI among MDR/RR-TB contacts in Southeast Asian setting. This study aimed to identify factors associated with TBI and evaluate the prevalence of TBI among the HHCs of the MDR/RR-TB patients in the rural and urban provinces in Vietnam.

**Methods**

*Study design*

A cross-sectional survey was conducted among household contacts of patients with MDR/RR-TB, who agreed to be screened for participation in a clincial trial evaluting the effectiveness of levofloxacin preventive therapy for MDR-TB, the VQUIN MDR Trial. The study was conducted in Vietnam, a lower-middle income country of over 100 million people in Southeast Asia. Vietnam ranks amongst high-prevalence countries for both TB and MDR/RR-TB, and has a low population prevalence of HIV. Participants were recruited in ten urban and rural provinces: Hanoi, Ho Chi Minh City, Can Tho, Da Nang, Quang Nam, Thanh Hoa, Khanh Hoa, An Giang, Tien Giang and Nam Dinh. Participating regions included the provinces with the highest numbers of MDR-TB cases, comprising rural and urban sites throughout the northern, central and southern regions of Vietnam. Study sites were clinics participating in the public Programmatic Management of Drug-Resistant TB Program, managed by the Vietnam National TB Program. The study was undertaken between April 2016 and July 2019. We aimed to determine (a) prevalence of TBI, stratified by age group; (b) factors associated with TBI in this population and (c) proportion of recent infection versus longstanding (conversion rate).

*Study population and eligibility*

We recruited consecutive patients with bacteriologically confirmed pulmonary MDR/RR-TB who lived with at least one other person. Bacteriologically confirmed pulmonary TB was defined as the presence of sputum that has tested positive for tuberculosis, either by acid-fast bacilli on smear microscopy, or a positive test for *M. tuberculosis* on culture or PCR. In addition, to be eligible the index case required a positive test for rifampicin resistance (RR) on PCR (GenXpert MTB/RIF), or resistance to both rifampicin and isoniazid on phenotypic or genotypic drug susceptibility testing (DST). The first person diagnosed with RR-MDR-TB in in a house during the study period was the 'index patient'.

Household contacts (HHCs) were defined as people living within the same household as the index case during the preceding 3 months, having shared the living space for at least one night per week. Tuberculin tests were conducted on all contacts, including those with a history of TB disease. People with prior MDR/RR-TB were excluded from the study, however people with presumed drug-susceptible disease were eligible. A TST increase of at least 6mm, combined with the second TST measurement of 10mm or more, would be considered indicative of conversion, distinguishing recent infection from longstanding cases.

*Data collection*

Data regarding index patients included demographic details, first-line drug resistance profile of the *M. tuberculosis* (if the culture was positive), medical comorbidities (such as diabetes, HIV, chronic lung disease), and treatment details. A structured questionnaire consisting of patient characteristics and demographic information was used. HHCs were interviewed to collect information about demographic factors, prior exposure to a person with TB, symptoms, and the relationship of contacts with the index case.

All HHCs underwent clinical assessment, including a physical examination, and plain chest radiography. All HHCs were asked to attempt to produce sputum for sputum Xpert MTB/Rif (Xpert)

to exclude co-prevalent TB. TST was performed for all contacts, using 0.1ml of the purified protein derivative (PPD) 1mL vials. TB infection (TBI) was defined as a tuberculin skin test (TST) of 10mm or greater at the first reading, or TST conversion, defined as an increase of 6mm or greater between the first and second reading, plus a second TST size of at least 10mm. The second TST was repeated after 8-12 weeks in HHCs in whom the initial TST result was negative to account for the long TST conversion window. TST size was measured based upon the lateral size of the induration on the forearm 48-72 hours after placement. A digital photograph was taken of the TST and reviewed by study staff during their initial performance of TST to maintain quality. Vernier calliper was used to measure the size of the TST to avoid cut point bias.

In the presence of clinical, radiographic or Xpert-based evidence of possible TB, two additional expectorated sputum samples were sent for both smear and liquid cultures. If the culture was negative at eight weeks, a repeat chest radiograph was performed to exclude incident TB. HHCs who did not complete screening or were diagnosed with co-prevalent-TB with positive sputum samples (Xpert/culture), were excluded from the analysis.

*Management of household contacts*

HHCs with evidence of latent TB infection, without the presence of active disease, were invited to participate in the parent study (VQUIN MDR trial). Eligible HHCs with TBI, or significant immunosuppression, were randomised to self-administered oral levofloxacin once per day, or an indistinguishable placebo [16]. Patients who were not eligible were followed up with serial chest radiography for 30 months to detect incident TB. Outcomes of the parent trial will be reported separately.

*Statistical analysis*

Descriptive analyses were used to describe characteristics of the enrolled household contacts and their index cases. The prevalence of TBI was calculated as a proportion of HHCs with TST of 10mm or

greater at the first reading, or an increase of 6mm or greater between the first and second reading, plus a second TST size of at least 10mm, compared with all the HHCs who completed screening with valid TST readings and no evidence of co-prevalent TB with positive sputum samples.

Quantitative variables were summarised using frequencies or median values, with interquartile ranges (IQR). To investigate the relationship between potential factors associated with the risk of TB diagnosis, we utilised DAGitty 3.1 [17] to generate directed acyclic graphs (DAGs) to visually represent the interconnections. Mixed effects logistic regression models were developed to statistically explore the relationship between the identified potential factors associated with the risk of TB diagnosis, allowing for random effect at the household level. In addition to the outcomes of the univariate models, multivariate models were built using variable selection technique with a liberal significance criterion of 0.2 and change-in-estimate (CIE) approach, along with the consideration of information criteria such as AIC and BIC when deciding between competing models. Model fit was assessed by using Hosmer-Lemeshow test and Pearson's residual plots. The proportion of missing values was minimal, constituting less than 0.1%, with no missing values for the primary outcomes. While a complete-case analysis is a valid option, we chose to enhance the utilisation of available data by employing a random-forest imputation method, grounded in the data patterns of all characteristic variables outlined in Table 4.1. To assess the robustness of our findings, we conducted a sensitivity analysis, comparing outcomes between the complete-case approach and the imputation method, revealing a close alignment between the two approaches. The imputation process was executed using the 'missRanger' package (Version: 2.4.0) in R Studio (Version: 2023.12.0+369). The results are presented by illustrating the estimated effect sizes and their 95% confidence intervals (CIs), accompanied by p-values at the 0.05 significance level.

*Ethical issues*

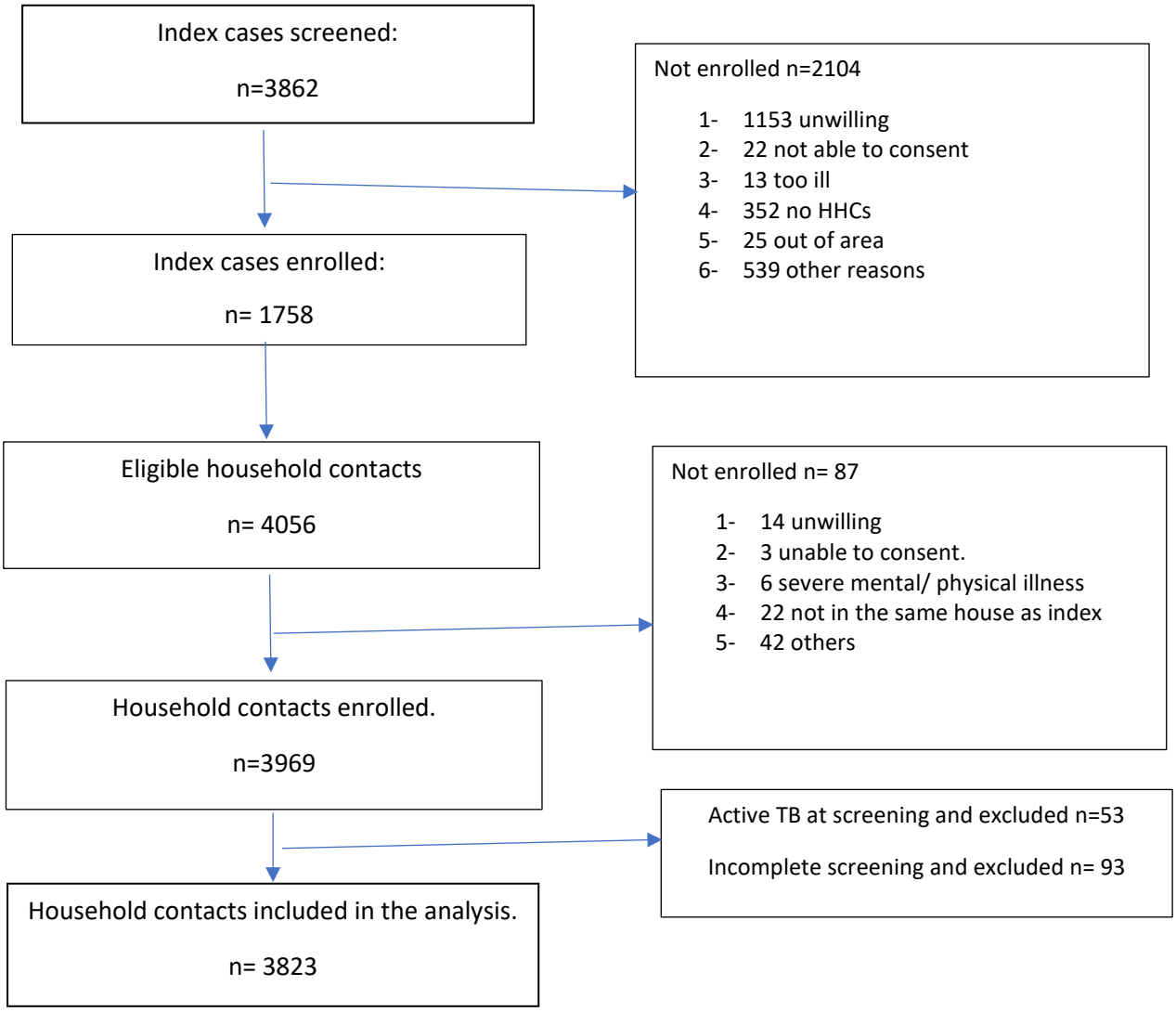
All study participants, or their parents if aged under 15 years, provided voluntary written informed consent. Children aged under 15 years required written parental consent and asked to give verbal assent. Ethics approval was obtained from the Human Research Ethics Committee at Sydney University, Sydney, NSW, Australia (Protocol 2014/929), the Institutional Review Board of the National Lung Hospital, Hanoi, Vietnam and the Ministry of Health.

**RESULTS**

*Characteristics of the Study Population*

Between March 2016 and October 2019, 1758 MDR-TB index cases and 3969 HHCs were enrolled in the study. A consort diagram summarising participant recruitment is shown in Figure 4.1. Within these households, 53 (1.3%) individuals were diagnosed with co-prevalent microbiologically confirmed TB, and 93 (2.3%) individuals did not complete the screening and they were excluded from this analysis. Table 4.1 shows the characteristics of index cases and household contacts. The majority of the HHCs were female (60.9%), and 494 (12.6%) were aged less than 10 years. There were 20 (0.5%) HHCs who reported having had a positive HIV test, 159 (4.1%) reported a prior history of TB and 2171 (55.4%) had a BCG scar present. The majority of the HHCs 2744 (70.1%) spent less than eight hours each day on average over the previous three months with the index patient. The median TST size was 12.0mm (IQR 8-15mm) Figure 4.2.

Figure 4.1 Consort diagram showing participants included in screening of the household contacts of index cases.




HHC=household contact

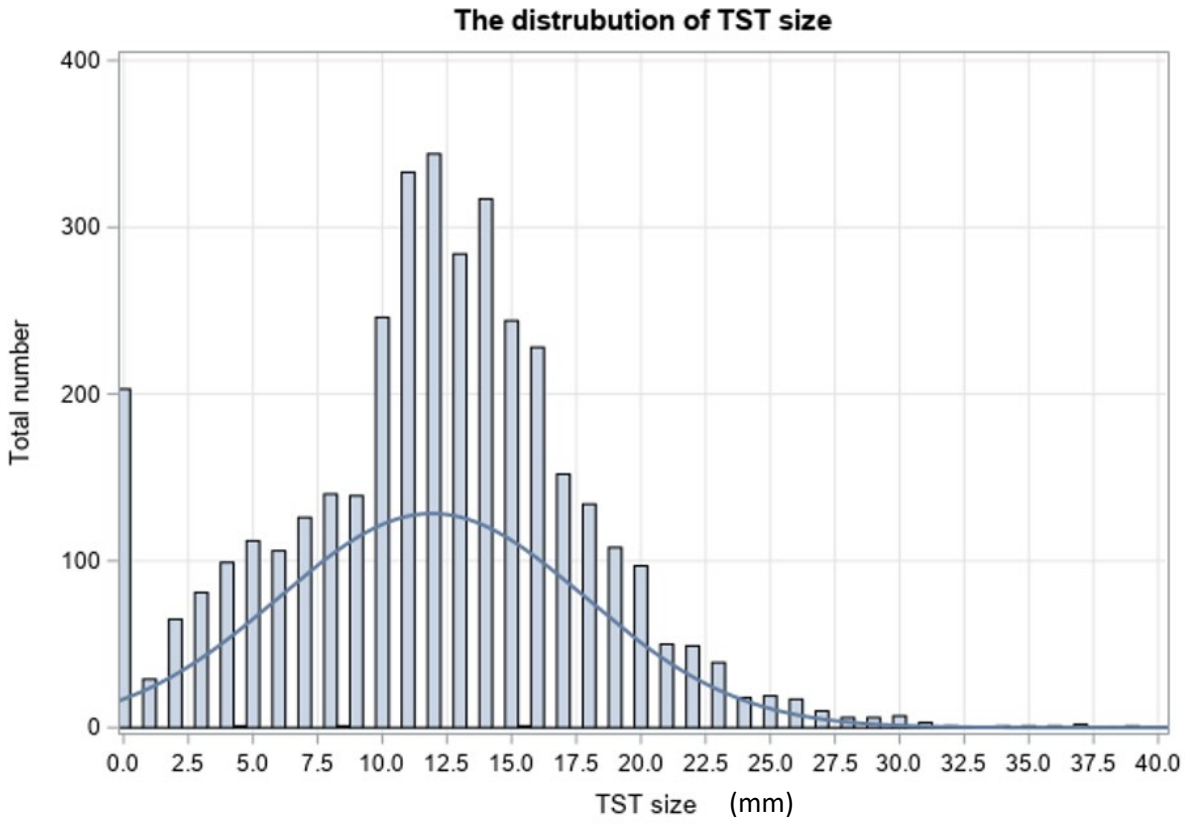
Table 4.1 Characteristics of household contacts

| Characteristics | n (%) |
|---|---|
| **Total** | 3916 (100) |
| Male | 1531 (39.1) |
| Female | 2385 (60.9) |
| **Age (years)** | |
| Median (IQR) | 34.0 (18-50) |
| <10 | 494 (12.6) |
| Oct-19 | 576 (14.7) |
| 20- 29 | 571 (14.6) |
| 30- 39 | 648 (16.6) |
| 40- 49 | 619 (15.8) |
| 50- 59 | 582 (14.9) |
| 60- 69 | 346 (8.8) |
| ≥70 | 80 (2.0) |
| **BMI (kg/m2)** | |
| Median (IQR) | 21.2 (18.7-23.6) |
| <18.5 | 946 (24.2) |
| 18.5-25 | 2391 (61.1) |
| 25-30 | 505 (12.9) |
| >30 | 74 (1.9) |
| **Ethnicity** | |
| Kinh | 3778 (96.5) |
| Chinese | 101 (2.6) |
| Muong | 2 (0.1) |
| Thai | 2 (0.1) |
| Other | 23 (0.6) |
| Not documented | 10 (0.3) |
| **Provinces** | |
| North provinces | |
| Hanoi | 974 (24.9) |
| Nam Dinh | 221 (5.6) |
| Central provinces | |
| Thanh Hoa | 150 (3.8) |
| Da Nang | 203 (5.2) |
| Quang Nam | 66 (1.7) |
| Khanh Hoa | 150 (3.8) |
| South provinces | |
| An Giang | 231 (5.9) |
| Can Tho | 146 (3.7) |
| Ho Chi Minh City | 1626 (41.5) |
| Tien Giang | 149 (3.8) |
| **Education status** | |
| Less than primary education | 673 (17.2) |
| Primary education | 791 (20.12 |

| Characteristics | n (%) |
|---|---|
| **Total** | 3916 (100) |
| Lower secondary education | 1004 (25.6) |
| Upper secondary education | 821 (21.0) |
| University degree or equivalent or higher | 617 (15.8) |
| Not documented | 10 (0.3) |
| **Smoking status** | |
| Current smoker | 526 (13.4) |
| Former smoker | 146 (3.7) |
| Never smoker | 3234 (82.6) |
| Not documented | 10 (0.3) |
| **Alcohol consumption in the past month** | |
| Never | 2971 (75.9) |
| Once a month or less | 375 (9.6) |
| 2-4 times/month | 261 (6.7) |
| 2-3 times/week | 136 (3.5) |
| More than 4 times/week | 163 (4.2) |
| Not documented | 10 (0.3) |
| **Prior history of tuberculosis** | |
| Yes | 159 (4.1) |
| **BCG scar present** | |
| Yes | 2171 (55.4) |
| No | 1734 (44.3) |
| Not documented | 11 (0.3) |
| **Medical comorbidities** | |
| None reported | 2634 (67.3) |
| Diabetes mellitus | 116 (3.0) |
| Chronic Kidney Disease | 6 (0.2) |
| Liver Disease | 105 (2.7) |
| Chronic lung disease | 34 (0.9) |
| HIV | 20 (0.5) |
| Other | 1135 (29.0) |
| Not documented | 15 (0.4) |
| **Relationships to Index patient** | |
| Child | 1234 (31.5) |
| Sibling (brother or sister) | 441 (11.3) |
| Spouse (husband or wife) | 938 (24.0) |
| Parent | 535 (13.7) |
| Grandparent | 20 (0.5) |
| Other relative | 324 (8.3) |
| Friend | 41 (1.0) |
| Other | 373 (9.5) |
| Not documented | 10 (0.3) |

| Characteristics | n (%) |
|---|---|
| **Sleeping proximity to the index patient** | |
| In the same bed | 602 (15.4) |
| In the same room | 414 (10.6) |
| In the same building | 2213 (56.5) |
| In a different building | 677 (17.3) |
| Not documented | 10 (0.3) |
| **Time spent with the index patient in the past 24 hours** | |
| Median (IQR) | 5.0 (2-10) |

Figure 4.2 The TST size distribution of TST size in the cohort



*Prevalence of TBI*

Among the 3823 HHCs included in the analysis, TBI was present for 2721 among (72.1%). 2438 people (63.8%) had a positive TST at the baseline reading. With the 1385 people (36.2%) with negative TST at baseline, an additional 283 people (7.4%) converted to positive after 8-12 weeks (Table 4.2). The baseline demographics for participants with positive and negative Tuberculin Skin Test (TST) results are showed in Supplementary appendix Table 4.1

Table 4.2 Tuberculin Skin Test positivity among household contacts

| | **n (%)** |
|---|---|
| **Total screened** | 3823 (100) |
| Tuberculin skin test result* | |
| **10mm and above** | **2721 (71.2)** |
| ≤5mm | 478 (12.5) |
| 6-9mm | 624 (16.3) |
| 10mm and above | 2721 (71.2) |
| HHCs with positive TST as baseline | 2438 (63.8) |
| HHCs with initially negative TST | 1385 (36.2) |
| Conversion** | 283 (7.4) |
| No conversion | 1102 (28.8) |

*Based upon first reading, or second reading after 8-12 weeks if conversion occurred.

**an increase of at least 6mm, and ≥10mm

HHC= household contact

*Factors associated with TBI among household contacts.*

In the multivariable analyses (Table 4.3), HHCs with older age groups had a higher prevalence of infection. Other factors associated with an increased prevalence of infection included: normal BMI (aOR = 1.33, 95% CI: 1.06- 1.66), smoking history (aOR = 1.76, 95% CI: 1.39- 2.23), a prior history of TB (aOR = 4.56, 95% CI: 2.49- 8.35), the presence of a BCG scar (aOR = 1.23, 95% CI: 1.02-1.50), and more than eight hours spent each day on average over the previous 3 months with the index patient (aOR = 1.52, 95% CI: 1.28-1.81).

Among index patient's status (Table 4.3), in the adjusted analysis, smoking history (aOR= 1.31, 95 % CI: 1.09- 1.59) and persistent cough more than 2 weeks (aOR= 1.23, CI: 1.02- 1.49) were associated with TBI.

Table 4.3 Adjusted and unadjusted analyses of factors associated with tuberculin skin test positivity among household contacts (n=3823)

| | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| Variables | n (%) | cOR | 95% CI | P-value | aOR | 95% CI | P-value |
| **Household contact factor** | | | | | | | |
| **Age** | | | | | | | |
| < 15 | 753 (19.7) | ref. | | | ref. | | |
| 15 – 29 | 821 (21.5) | 1.98 | 1.56-2.52 | <0.001 | 1.75 | 1.34-2.27 | <0.001 |
| 30 – 44 | 934 (24.4) | 2.52 | 2.00-3.18 | <0.001 | 2.13 | 1.59-2.86 | <0.001 |
| 45 – 59 | 894 (23.4) | 3.03 | 2.37-3.88 | <0.001 | 2.58 | 1.90-3.49 | <0.001 |
| ≥60 | 421 (11.0) | 1.98 | 1.48-2.64 | <0.001 | 1.65 | 1.16-2.34 | 0.005 |
| **Gender** | | | | | | | |
| Male | 1485 (38.8) | ref. | | | | | |
| Female | 2338 (61.2) | 1 | 0.86-1.17 | 0.983 | | | |
| **BMI*** | | | | | | | |
| Underweight (<18.5) | 894 (23.4) | ref. | | | ref. | | |
| Normal (18.5-22.9) | 1745 (45.6) | 1.85 | 1.52-2.25 | <0.001 | 1.33 | 1.06-1.66 | 0.014 |
| Overweight and obese (≥23) | 1184 (31.0) | 1.77 | 1.43-2.19 | <0.001 | 1.19 | 0.93-1.53 | 0.176 |
| **Education** | | | | | | | |
| Less than primary education | 615 (16.1) | ref. | | | | | |
| Primary education | 815 (21.3) | 1.2 | 0.92-1.55 | 0.176 | | | |
| Lower secondary education | 988 (25.8) | 1.39 | 1.08-1.80 | 0.011 | | | |
| Upper secondary education | 773 (20.2) | 0.96 | 0.74-1.24 | 0.734 | | | |
| University degree or equivalent or higher | 632 (16.5) | 0.62 | 0.47-0.81 | <0.001 | | | |
| **Use of alcohol** | | | | | | | |
| Never | 2903 (75.9) | ref. | | | | | |
| Once a month or less | 370 (9.7) | 1.5 | 1.14-1.97 | 0.004 | | | |
| 2-4 times per month | 255 (6.7) | 1.67 | 1.21-2.31 | 0.002 | | | |
| 2-3 times per week | 135 (3.5) | 1.8 | 1.16-2.82 | 0.01 | | | |
| More than 4 times per week | 160 (4.2) | 1.66 | 1.11-2.49 | 0.014 | | | |
| **Smoking history** | | | | | | | |
| Never | 3162 (82.7) | ref. | | | ref. | | |
| Yes | 661 (17.3) | 2.08 | 1.67-2.60 | <0.001 | 1.76 | 1.39-2.23 | <0.001 |
| **Past TB** | | | | | | | |
| No | 3669 (96.0) | ref. | | | ref. | | |
| Yes | 154 (4.0) | 5.5 | 3.04-9.94 | <0.001 | 4.56 | 2.49-8.35 | <0.001 |
| **BCG scar** | | | | | | | |
| No | 1716 (44.9) | ref. | | | ref. | | |
| Yes | 2017 (55.1) | 0.8 | 0.68-0.93 | 0.005 | 1.23 | 1.02-1.50 | 0.034 |
| **Time spent with index patient** | | | | | | | |
| Less than 8 hours | 2332 (61.0) | ref. | | | ref. | | |
| 8 hours and more | 1491 (39.0) | 1.45 | 1.23-1.72 | <0.001 | 1.52 | 1.28-1.81 | <0.001 |

| | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| Variables | n (%) | cOR | 95% CI | P-value | aOR | 95% CI | P-value |
| **Smoking history** | | | | | | | |
| Never | 1553 (40.6) | ref. | | | ref. | | |
| Yes | 2270 (59.4) | 1.18 | 0.98-1.41 | 0.083 | 1.31 | 1.08-1.59 | 0.006 |
| **Persistent cough** | | | | | | | |
| Less than 2 weeks or no persistent cough | 1952 (51.1) | ref. | | | ref. | | |
| More than 2 weeks | 1871 (48.9) | 1.2 | 1.00-1.44 | 0.045 | 1.23 | 1.02-1.49 | 0.03 |
| **Sputum production** | | | | | | | |
| No | 1783 (46.6) | ref. | | | | | |
| Yes | 2040 (53.4) | 1.14 | 0.95-1.36 | 0.163 | | | |
| **Haemoptysis** | | | | | | | |
| No | 3317 (86.8) | ref. | | | | | |
| Yes | 506 (13.2) | 1 | 0.75-1.28 | 0.874 | | | |
| **Night sweat** | | | | | | | |
| No | 2740 (71.7) | ref. | | | | | |
| Yes | 1083 (28.3) | 1.05 | 0.86-1.29 | 0.61 | | | |
| **Weight loss** | | | | | | | |
| No | 2176 (56.9) | ref. | | | | | |
| Yes | 1647 (43.1) | 1.07 | 0.89-1.28 | 0.499 | | | |
| **Appetite loss** | | | | | | | |
| No | 2617 (68.5) | ref. | | | | | |
| Yes | 1206 (31.6) | 1.04 | 0.86-1.26 | 0.68 | | | |

*World Health Organization (WHO) Regional Office for the Western Pacific Region BMI definition [18] normal, 18.5–22.9 kg/m2; overweight, 23–24.9 kg/m2; moderate obesity, 25–29.9 kg/m2; and severe obesity, ≥30 kg/m2

cOR= crude odd ratio  aOR= adjust odd ratio

*Factors associated with TST conversion (developing TBI) among household contacts.*

In the multivariable analysis (Table 4.4), HHCs with normal BMI (aOR = 1.66, 95% CI: 1.04- 2.64), HHCs with history of TB (aOR = 3.45, 95% CI: 1.14- 10.40), and more than eight hours spent each day on average over the previous three months spent with the index patient (aOR = 1.43, 95% CI: 1.01- 2.01)

were associated with TST conversion. No index patient factors (Table 4.4) were associated with conversion.

Table 4.4 Household contact and index patient characteristics associated with TST conversion among household contacts (n=1514)

| | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| Variables | n (%) | cOR | 95% CI | P-value | AOR | 95% CI | P-value |
| **Household contact factor** | | | | | | | |
| **Age** | | | | | | | |
| < 15 | 399 (26.4) | ref. | | | ref. | | |
| 15 – 29 | 316 (20.9) | 1.5 | 0.91-2.46 | 0.111 | 1.15 | 0.67-1.97 | 0.612 |
| 30 – 44 | 327 (21.6) | 1.69 | 1.05-2.73 | 0.032 | 1.09 | 0.60-1.96 | 0.785 |
| 45 – 59 | 292 (19.3) | 2.37 | 1.44-3.88 | <0.001 | 1.43 | 0.78-2.62 | 0.246 |
| ≥60 | 180 (11.9) | 2.28 | 1.31-3.97 | 0.004 | 1.33 | 0.68-2.59 | 0.402 |
| **Gender** | | | | | | | |
| Male | 577 (38.1) | ref. | | | | | |
| Female | 937 (61.9) | 1.28 | 0.92-1.78 | 0.145 | | | |
| **BMI*** | | | | | | | |
| Underweight (<18.5) | 417 (27.5) | ref. | | | | | |
| Normal (18.5-22.9) | 654 (43.2) | 2.02 | 1.34-3.03 | <0.001 | 1.66 | 1.04-2.64 | 0.034 |
| Overweight and obese (≥23) | 443 (29.3) | 1.73 | 1.11-2.70 | 0.017 | 1.34 | 0.80-2.27 | 0.27 |
| **Education** | | | | | | | |
| Less than primary education | 248 (16.4) | ref. | | | | | |
| Primary education | 305 (20.2) | 1.23 | 0.73-2.09 | 0.435 | | | |
| Lower secondary education | 337 (22.3) | 1.32 | 0.79-2.21 | 0.298 | | | |
| Upper secondary education | 309 (20.4) | 0.82 | 0.47-1.42 | 0.479 | | | |
| University degree or equivalent or higher | 315 (20.8) | 0.78 | 0.45-1.34 | 0.361 | | | |
| **Use of alcohol** | | | | | | | |
| Never | 1208 (79.8) | ref. | | | | | |
| Once a month or less | 131 (8.7) | 1.58 | 0.94-2.68 | 0.088 | | | |
| 2-4 times per month | 76 (5.0) | 0.66 | 0.29-1.46 | 0.3 | | | |
| 2-3 times per week | 46 (3.0) | 1.89 | 0.83-4.29 | 0.13 | | | |
| More than 4 times per week | 53 (3.5) | 1.52 | 0.69-3.36 | 0.301 | | | |
| **Smoking history** | | | | | | | |
| Never | 1327 (87.7) | ref. | | | | | |
| Yes | 187 (12.4) | 1.42 | 0.91-2.23 | 0.126 | | | |
| **Past TB** | | | | | | | |
| No | 1490 (98.4) | ref. | | | ref. | | |

| | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| Variables | n (%) | cOR | 95% CI | P-value | AOR | 95% CI | P-value |
| Yes | 24 (1.6) | 4.3 | 1.45-12.73 | 0.009 | 3.45 | 1.14-10.40 | 0.028 |
| **BCG scar** | | | | | | | |
| No | 665 (43.9) | ref. | | | ref. | | |
| Yes | 849 (56.1) | 0.56 | 0.40-0.78 | <0.001 | 0.71 | 0.48-1.05 | 0.083 |
| **Time spent with index patient** | | | | | | | |
| Less than 8 hours | 975 (64.4) | ref. | | | ref. | | |
| 8 hours and more | 539 (35.6) | 1.46 | 1.04-2.05 | 0.028 | 1.43 | 1.01-2.01 | 0.043 |
| **Index patient factor** | | | | | | | |
| **Smoking history** | | | | | | | |
| Never | 637 (42.1) | ref. | | | | | |
| Yes | 877 (57.9) | 1.15 | 0.79-1.66 | 0.461 | | | |
| **Persistent cough** | | | | | | | |
| Less than 2 weeks or no persistent cough | 800 (52.8) | ref. | | | | | |
| More than 2 weeks | 714 (47.2) | 1.29 | 0.90-1.86 | 0.166 | | | |
| **Sputum production** | | | | | | | |
| No | 714 (47.2) | ref. | | | | | |
| Yes | 800 (52.8) | 1.3 | 0.90-1.88 | 0.161 | | | |
| **Haemoptysis** | | | | | | | |
| No | 1318 (87.1) | ref. | | | | | |
| Yes | 196 (13.0) | 0.78 | 0.45-1.36 | 0.381 | | | |
| **Night sweat** | | | | | | | |
| No | 1078 (71.2) | ref. | | | | | |
| Yes | 436 (28.9) | 1.34 | 0.89-2.00 | 0.16 | | | |
| **Weight loss** | | | | | | | |
| No | 857 (56.6) | ref. | | | | | |
| Yes | 657 (43.4) | 1.26 | 0.87-1.82 | 0.213 | | | |
| **Appetite loss** | | | | | | | |
| No | 1039 (68.6) | ref. | | | | | |
| Yes | 475 (31.4) | 1.14 | 0.78-1.68 | 0.5 | | | |

*Duration between index case diagnosis with TB and screening of contact*

The median number of days between enrolment to the study of the index case and contact was three (IQR 0-3). Looking at the patients with -ve TST at the baseline screening, the median number of days for between commencement of treatment of the index case and screening of the HHCs was 18 days (IQR 3-37) for patients with conversion compared to 20 days (IQR 6-48) for patients without conversion. Comparing the different groups of exposure time for the HHCs to the index cases before they were commenced on TB treatment had no significant correlation to the TST conversion rate of the contacts (Table 4.5).

Table 4.5 Exposure time to index case before commenced on TB treatment and TST conversion rate among HHCs.

| | cOR | 95% CI | P-value |
|---|---|---|---|
| TST conversion | | | |
| **Exposure time to index case** | | | |
| 0-29 days | ref | ref | ref |
| 30-59 days vs 0-29 days | 0.863 | 0.530-1.405 | 0.553 |
| 60-90 days vs 0-29 days | 0.577 | 0.303- 1.101 | 0.095 |

*Stratified analyses*

Table 4.6 shows the different TST size groups stratified by age group, provinces and gender. The TST size groups varied by age. For patients ≤10 years, only 128 (24.9%) had TST ≤5mm and majority of the group 269 (52.3%) had TST ≥10mm. The proportion of people with a positive TST (>=10mm) increased with age. There were 2110 HHCs from the Southern provinces compared to 555 HHCs from the central provinces. 1517/2721 (55.8%) of the patients with TST ≥10mm came from Southern provinces.

Table 4.6 TST size group stratified by age group, province and genders.

| | **Tuberculin skin test size*** | | | **Total no.** |
|---|---|---|---|---|
| | ≤5mm | 6-9mm | ≥10mm | **n (%)**** |
| **Age** | | | | |
| <10 | 128 (24.9) | 117(22.8) | 269 (52.3) | 514 (100) |
| 10-19 | 69 (13.8) | 93 (18.6) | 338 (67.6) | 500 (100) |
| 20- 29 | 60 (10.7) | 83 (14.8) | 417 (74.5) | 560 (100) |
| 30- 39 | 70 (10.9) | 99 (15.5) | 471 (73.6) | 640 (100) |
| 40- 49 | 71 (1.9) | 68 (1.8) | 478 (77.5) | 617 (100) |
| 50- 59 | 47 (1.2) | 81 (2.1) | 443 (77.6) | 571 (100) |
| 60- 69 | 22 (0.6) | 60 (1.6) | 261 (76.1) | 343 (100) |
| ≥70 | 11 (0.3) | 23 (0.6) | 44 (56.4) | 78 (100) |
| **Gender** | | | | |
| Male | 182 (12.3) | 246 (16.7) | 1057 (71.2) | 1485 (100) |
| Female | 296 (12.7) | 378 (16.2) | 1664 (71.2) | 2338 (100) |
| **Province#** | | | | |
| North | 216 (18.7) | 161 (13.9) | 781 (67.4) | 1158 (100) |
| Central | 61 (11.0) | 71 (12.8) | 423 (76.2) | 555 (100) |
| South | 201 (9.5) | 392 (18.6) | 1517 (71.9) | 2110 (100) |

# North provinces included Hanoi and Nam Dinh.

Central provinces included Thanh Hoa, Da Nang, Quang Nam and Khanh Hoa.

South provinces included Ho Chi Minh City, Tien Giang, An Giang and Can Tho

**Row percents shown.

*Sensitivity analyses*

Table 4.7 shows the prevalence of TBI stratified by age group using cut-points of either ≥5mm or ≥15mm. WHO recommends using different cut-points depending on the epidemiological and clinical conditions of the patients [19]. 3345 (87.5%) of the study population had TST ≥5mm, 1514 (39.6%) of the cohort had TST ≥15mm, and the result was similar across different age groups.

Table 4.7 The prevalence of TBI stratified by age group using cut-points of either ≥5mm or ≥15mm.

| | **Defined TBI using different cut-points of TST size** | | | |
|---|---|---|---|---|
| **Age** | **≥5mm** | **≥10mm** | **≥15mm** | **Total in each age group n (%)** |
| <10 | 386 (75.1) | 269 (52.3) | 134 (26.1) | 514 (100) |
| 10- 19 | 431 (86.2) | 338 (67.6) | 154 (30.8) | 500 (100) |
| 20- 29 | 500 (89.3) | 417 (74.5) | 238 (42.5) | 560 (100) |
| 30- 39 | 570 (89.0) | 471 (73.6) | 268 (41.8) | 640 (100) |
| 40- 49 | 546 (88.5) | 478 (77.5) | 284 (46.0) | 617 (100) |
| 50- 59 | 524 (91.8) | 443 (77.6) | 268 (46.9) | 571 (100) |
| 60- 69 | 321 (93.6) | 261 (76.1) | 141 (41.1) | 343 (100) |
| ≥70 | 67 (85.9) | 44 (56.4) | 27 (34.6) | 78 (100) |
| **Total of the cohort n (%)** | 3345 (87.5) | 2721 (71.2) | 1514 (39.6) | 3823 (100) |

*Based upon first reading, or second reading after 8-12 weeks if conversion occurred.

**Discussion**

This cross-sectional study identified that HHCs amongst the MDR/RR-TB patients in 10 Provinces of Vietnam showed that the prevalence of TB infection was 71.2%, including 7.4% converting to positive 8-12 weeks after initial screening. Risk factors for TBI included duration of exposure to infectious TB (index patient with persistent cough more than two weeks, spent eight hours or more each day on average over the previous 3 months with the index patient), HHCs aged more than 15 years, HHCs with normal BMI, smoking history, history of TB, and the presence of a BCG scar.

MDR/RR-TB patients often face long delays before initiation of effective treatment [20]. This means that the family may have been in close contact with a highly infectious MDR/RR-TB patient for months or years. Our study demonstrated a prevalence of TBI of 71.2%. This was higher than published systematic reviews which found a pooled proportion of TBI was between 51% and 61% in MDR-TB contacts [11, 21]. The proportions were higher in settings with high, compared to low, TB burdens. The high prevalence of TBI at the first reading indicated that infection had occurred before screening for TBI took place. Interesting, looking at the HHCs with -ve TST at the baseline screening, comparing the exposure time for the contacts to the index cases before they were commenced on TB treatment has no significant correlation to the TST conversion rate of the contact. There has been limited studies looking at MDR/RR-TB transmission in the households setting. Previous studies in Peru looking at the "fitness" of an infectious pathogen is defined as the ability of the pathogen to survive, reproduce, be transmitted, and cause disease [22, 23]. These studies compared the fitness of the MDR/RR-TB to drug-susceptible tuberculosis, and looked at the incidence of tuberculosis disease among the household contacts of MDR/RR-TB index patients compared to that among the contacts of drug-susceptible index patients. They designed a household structured, stochastic mathematical model to estimate the fitness costs and fitting the model to data from a large prospective cohort study of TB disease in household contacts undertaken in Lima, Peru between 2010 and 2013. They found the average relative fitness of the MDR-*M.tb* circulating within households was significantly lower than

concurrent susceptible *Mtb,* and 3.3% of the HHCs contacts of MDR/ RR-TB index cases developed tuberculosis disease, while 4.8% HHCs of drug-susceptible index patients developed tuberculosis disease[22, 23]. But there was emerging evidence which points to a greater risk of transmission with drug resistant TB when compared to drug susceptible disease [24].

Our study showed the prevalence of TBI in HHCs <20 years old was 607/1014 (59.9%) It was much higher than the estimated prevalence of TST positivity of 16.7% for children aged 6–14 years in the first national tuberculin survey in Vietnam [25]. It was expected to have a higher prevalence of TBI in the HHCs than the community and due to the lower socioeconomic status being in households of patients with MDR/RR-TB. Our study also had more adolescents than younger children compared to the cohort in first National Tuberculin Survey. In our cohort, age influenced the proportion of HHCs found to be TB positive. For HHCs aged ≥20 years old, 2114/2809 (75.3%%) were diagnosed with TBI. This was similar to previous meta-analysis which found a pooled TBI prevalence in HHCs among children of 27%, and increased to 52% among adults [11] .

Our study has showed several factors associated with TBI in HHCs of MDR/RR-TB patients: HHCs age more than 15 years, smoking history, normal BMI and the presence of a BCG scar. These were consistent with risk factors identified in previous studies done in Vietnam and found being a household contact, increased age, low educational level and the high body mass index were associated with developing TBI [25, 26]. Several risk factors that influence TBI in household contact from various literature are gender, age, close relationship with TB patients, contact duration with the patients, room-sharing with patients, education level, smoking behaviour, alcohol use, and HIV serostatus [27]. The odds of TST positivity were high among those with a prior history compared to those with no prior history of TB (aOR = 4.56); however, this could be attributed to the immune response generated by the initial infection. The presence of a BCG scar could lead to a false-positive result on the TST because the BCG vaccine contains antigens to which the TST will react. In our study, HHCs with normal BMI (aOR = 1.66) was associated with TST conversion and HHCs who were underweight might have a lower

conversion rate due to their impaired immunity. Interestingly, HHCs with a prior history of TB (aOR = 3.45) were associated with TST conversion, although we could not rule out the potential boosting effect related to waning immunity from remote infection.

In our study, 7.4% of the HHCs converting to TST positive 8-12 weeks after initial screening. This was consistent with recent study looking at household contact investigations of TB in Brazil and 7.4% had TST conversion[28]. The median TST size was 12.0mm in our study and we used 10mm as the cutoff point for TBI diagnosis.

In our study, we used TST to diagnose TBI. TST measured the delayed type hypersensitivity reactions to purified protein derivative (PPD), which was not specific to *M. tuberculosis* infection, and positive results may be due to BCG vaccination or exposure to environmental mycobacteria [29]. TST positivity is an indirect measurement of TB infection. Although it may indicate current infection, a positive test also could indicate prior exposure to other mycobacteria. In our cohort, the prevalence positive TST results increased with age could suggest the importance of longstanding infection. TST conversion suggests recent infection, although it may also reflect a boosting phenomenon if there has been remote prior infection. Both TST positivity and conversion may occur among individuals who have cleared their infection but retained immunological memory[30]. Nevertheless, for the HHC with TST conversion, previous TB history (aOR = 3.45) was also high in our study.

The strengths of the study included a very high completion of screening, and rigorous training and quality control of TST placement. Vernier calliper was used to measure the size of the TST and avoided any cut point bias (Figure 4.2). We have included HHCs from both urban and rural populations across 10 provinces likely to be representative of MDR/RR-TB contacts nationally, and we evaluated the characteristics of index cases and HHCs prospectively.

This study has a number of limitations. The HIV status of the HHCs were self-reported based on history, it could have some misclassification. Only 0.5% of the HHCs reported history of HIV. In addition,

previous study has showed in high–tuberculosis (TB) incidence area, the age-adjusted incidence rate of TB attributable to reinfection after successful treatment was four times that of new TB [31, 32]. In our cohort, we could not conclude transmission occurred from the identified index case. In the high transmission setting, the prevalent TB was not just due to the household exposure, but also the community transmission, and that we were not able to distinguish between these with a test for TBI.

This study has several important policy implications. The high prevalence of TBI was evident among the HHCs contacts of the MDR/RR-TB patients. It supports the WHO LTBI guidelines recommending screening in this population [19], and contact tracing provides an important opportunity to accelerate the detection of active disease amongst high-risk contacts for MDR-TB patients, therefore it should be prioritised to achieve the End TB strategy [33]. A key missing feature for TB control is a comprehensive program for prophylaxis for contacts of index cases with MDR/RR- TB. Recently completed [16, 34] and ongoing clinical trials [35] have evaluated the effectiveness of preventive therapy for infected household contacts of patients with MDR/RR-TB. If preventive therapy (TPT) is found to be effective, there will be clear benefits in high prevalence areas, and perhaps giving TPT without doing TST could be considered given the prevalence of TBI in HHCs is so high. Latest WHO guidelines recommended a regimen of 6 months of levofloxacin should now be used as TPT for contacts of MDR/RR-TB in light of new evidence from two well-conducted randomized controlled trials in South Africa and Vietnam supporting the use of levofloxacin of this regimen in people of all ages [36].

**Conclusion**

TBI is highly prevalent among HHCs of people diagnosed with MDR/RR-TB in Vietnam. HHCs with increasing age, normal BMI, past smoking history, prior history of TB, presence of BCG scar, spent 8 hours or more each day on average over the previous three months with index patient, index patient with smoking history and persistent cough more than two weeks had statistically significant positive

association with TBI. Identifying and treating latent infection, with the upcoming evidence from the trials, should be prioritised to achieve the End TB strategy [33].

Supplemental appendix

Figure 4.1 The directed acyclic graphs (DAGs) for each potential causal factor for TBI diagnosis

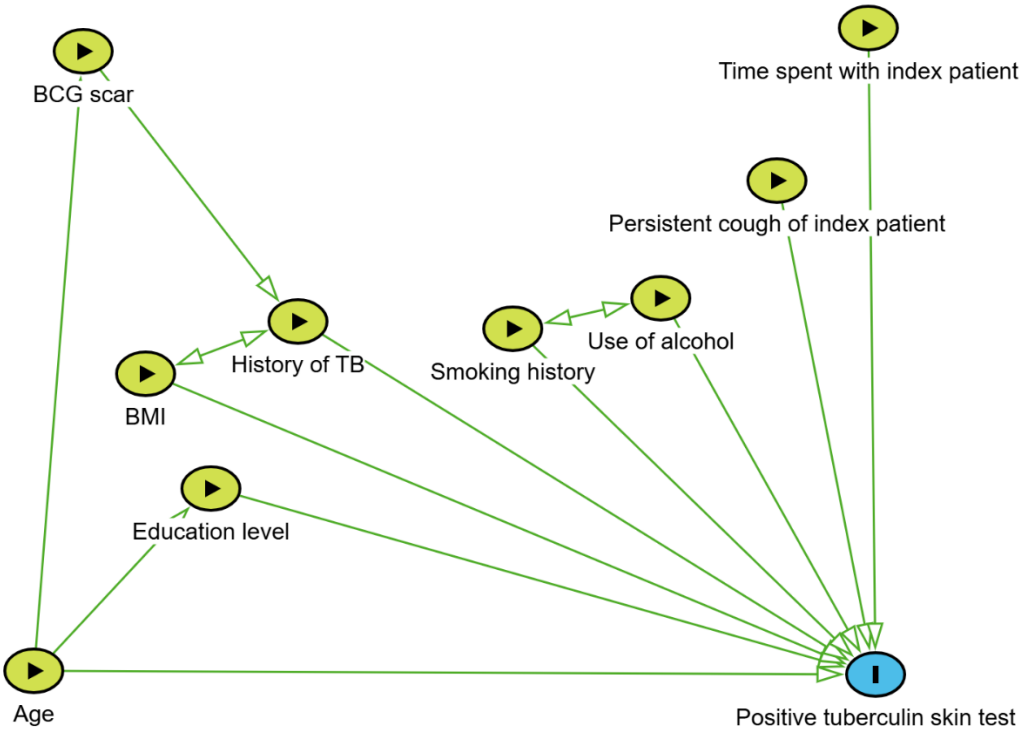


Table 4.1 The baseline demographics for participants with positive and negative Tuberculin Skin Test (TST) results among HHCs of MDR-TB patients in 10 provinces in Vietnam

| | TST results | | |
|---|---|---|---|
| | Positive | Negative | Total |
| | n(row %) | n(row %) | n=3823 (100) (row %) |
| **Age** | | | |
| < 10 | 269 (52.3) | 245 (47.7) | 514 (100) |
| 10 – 19 | 338 (67.6) | 162 (32.4) | 500 (100) |
| 20 – 29 | 417 (74.5) | 143 (25.5) | 560 (100) |
| 30 – 39 | 471 (73.6) | 169 (26.4) | 640 (100) |
| 40 – 49 | 478 77.5) | 139(22.5) | 617 (100) |
| 50 – 59 | 443 (77.6) | 128 (22.4) | 571 (100) |
| 60 – 69 | 261 (76.1) | 82(23.9) | 343 (100) |
| > 70 | 44 (56.4) | 34 (43.6) | 78 (100) |
| **Gender** | | | |
| Male | 1007 (67.8) | 478 (32.2) | 1485 (100) |
| Female | 1585 (67.8) | 753 (32.2) | 2338 (100) |
| **BMI*** | | | |
| Underweight (<18.5) | 533 (59.3) | 366 (40.7) | 899 (100) |
| Normal (18.5- <25.0) | 1657 (70.4) | 698 (29.4) | 2355 (100) |
| Overweight (25- <30) | 355 (71.3) | 143 (28.7) | 498 (13.0) |
| Obese ( ≥30) | 47 (66.2) | 24 (33.8) | 71 (100) |
| **Highest level of education** | | | |
| Less than primary | 413 (67.4) | 200 (32.6) | 613 (100) |
| Primary | 572 (70.3) | 242 (29.7) | 814 (100) |
| Lower secondary | 724 (73.4) | 262 (26.6) | 986 (100) |
| Upper secondary | 515 (66.6) | 258 ( 33.4) | 773 (100) |
| University degree or higher | 366 (57.9) | 266 (42.1) | 632 (100) |
| **Frequency of alcohol use in the past month** | | | |
| Never | 1907 (65.8) | 991 (34.2) | 2898 (100) |
| Once a month or less | 272 (73.5) | 98 (26.5) | 370 (100 |
| 2-4 times per month | 189 (74.1) | 66 (25.9) | 255 (100) |
| 2-3 times per week | 102 (75.6) | 33 (24.4) | 135 (100) |
| More than 4 times per week | 120 (75.0) | 40 (25.0) | 160 (100) |
| **Smoking history** | | | |
| Never | 2073 (65.6) | 1085 (34.4) | 3158 (100) |
| Yes | 517 (78.3) | 143 (21.7) | 660 (100) |
| **HIV status (self-reported)** | | | |
| Negative | 2570 (67.7) | 1225 (32.3) | 3795 (100) |
| Positive | 19 (95) | 1 (5.0) | 20 (100) |
| **Prior TB*** | | | |
| No | 2450 (66.9) | 1214 (33.1) | 3664 (100) |
| Yes | 140 (90.9) | 14 (9.1) | 154 (100) |

| | TST results | | |
|---|---|---|---|
| | Positive | Negative | Total |
| | n(row %) | n(row %) | n=3823 (100) (row %) |
| **BCG scar** | | | |
| No | 1198 (69.9) | 515 (30.1) | 1713 (100) |
| Yes | 1392 ( 66.1) | 713 (33.9) | 2105 (100) |
| **Time spent with index patient during infectious period** | | | |
| <8h | 1753 (65.7) | 917 (34.3) | 2670 (69.8) |
| 8- <15h | 537 (74.3) | 186 (25.7) | 723 (18.9) |
| 15- <24 | 182 (68.2) | 85 (31.8) | 267 (7.0) |
| ≥24 | 120 (73.6) | 43 (26.4) | 163 (4.3) |

* People with past RR/MDR-TB were not eligible for enrolment.

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# CHAPTER FIVE

# USE OF RIFAPENTINE AND ISONIAZID COMPARED TO RIFAMPICIN FOR LATENT TB IN AUSTRALIA

## 5.1 FOREWORD

This chapter examines the effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF), ontreatment adherence for latent TB infection. (Interim date analysis indicates that the trial is ongoing, and recruitment expected to conclude in February 2024)

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**Use of rifapentine and isoniazid compared to rifampicin for latent TB in Australia**

**Abstract**

Background:

Prevention of active tuberculosis (TB) disease by treatment of latent TB infection (TBI) is a critical component of the WHO End TB Strategy. The most used treatment for current treatment for TBI is either of six to nine months of daily isoniazid (6-9H) or 4 months of daily rifampicin (4RIF). Recent trials have shown combination regimen of isoniazid and rifapentine administered weekly for 12 weeks ('3HP') under direct observation was at least as effective as 4RIF or 9H, while also having higher rates of treatment completion and lower rates of adverse events. However, no randomized controlled trials have compared 3HP with four months of rifampicin (4RIF)..

Methods:

A multi-centre, prospective, open-label, randomised trial, was conducted among individuals with TBI in 8 clinics in New South Wales. Initial analyses were conducted for the enrolled participants between July 2019- September 2022, the trial will aim to finish in June 2024. Patients were randomised to weekly rifapentine and isoniazid administered for 12 weeks, or daily self-administered rifampicin for 4 months. The 3HP arm was monitored via SMS, while the 4RIF arm was self-monitored with standard clinic follow-up. The primary outcome was treatment completion. Descriptive analyses and the primary intention-to-treat analyses were performed on pooled study outcomes. Comparative statistics will be performed at the conclusion of the trial.

Results:

During the study period, 210 patients were enrolled and randomised within eight chest clinics. Of these, 106 (50.5%) were allocated to the 3HP intervention arm, and 104 (49.5%) were allocated to the 4RIF comparator arm. The treatment completion rate was 86/111 (77.5%). Eight patients stopped the treatments following grade 1-2 AEs, and one person stopped due to a grade 3 AE.

Conclusion:

This study demonstrated treatment with once weekly rifapentine plus isoniazid for three months (3HP), with SMS monitoring and self-administered daily rifampicin for four months (4RIF), achieved a high completion rate and high patient satisfaction.

**Background**

*Mycobacterium tuberculosis* is a major global public health problem, affecting 10.6 million people in 2021 worldwide [1]. According to WHO, approximately one-quarter of the global population is infected with TBI [1]. Healthy individuals can harbour TBI for a lifetime, it is estimated about 5% of people infected with TB progress rapidly to active disease [2]. Prevention of active TB disease by treatment of TBI is a critical component of the WHO End TB Strategy [2].

Multiple regimens are recommended to treat TBI, including six to nine months of daily isoniazid (6-9H) [3], or 4 months of daily rifampicin (4RIF) [4, 5] or 3–4 months' daily rifampicin plus isoniazid [6] or 3-month weekly regimen of rifapentine plus isoniazid (3HP) [7]. Randomised controlled trial have shown no significant difference in the incidence of active TB between participants given 3HP and 6-9H [8]. 3HP is associated with significantly lower hepatotoxicity and higher rates of treatment completion than INH [8-11]. A systematic review was conducted and showed same effectiveness of 3HP compared to 6-9H monotherapy [7]. The review covered four RCTs [11-14]. Two of the RCTs involved adults with HIV [11-14]. The risk for hepatotoxicity was significantly lower and high completion rate with the with the 3-month weekly regimen [11-14]. The 3HP regimen offers potential advantages of less cost and adherence, requiring just 12 once weekly doses rather than daily dosing. However, it has not been widely available in Australia. Rifapentine is only available via a Special Access Scheme[5]. The regimen involving 4RIF at a dose of 10mg/kg (up to 600mg) is well-tolerated [12] and has a low cost. This regimen has been recommended as the standard of care by the World Health Organisation (WHO) and other international guidelines for countries with a low TB incidence [4, 5], and previous randomised trial has shown 4RIF was non-inferior to 9H [13]. There was a retrospective cohort study showed a higher completion rate with self-administered 3HP therapy compared to 4RIF, however this was not a randomised study, and it was a single-site programmatic evaluation. The treatment completion was determined by pharmacy and clinic dispensing data, so the completion

rates were likely overestimates of the actual treatment completion. All these factors may have contributed to the difference [14]. All the RCTs comparing the 3HP regimens have included pairwise comparisons that use 9H as a standard comparator and the 3HP regimen was given under direct observation. Trials directly comparing patient-important outcomes among two recently approved regimens are lacking (3HP vs 4RIF).

WHO's guidelines recommend that 3HP be administered under direct observation, based upon the practice followed in the clinical trial evaluating the effectiveness and tolerability of 3HP [8, 11]. In person observation can be costly and impractical to replicate, taking up the valuable time of healthcare workers, as well as requiring the patient to travel to their health care centre. The requirement for routine DOT of preventive therapy is a substantial barrier to care, particularly for patient populations with a low income who may have difficulty taking time off work to attend the clinic.

The iAdhere study evaluated the proportion of people taking 3HP who completed treatment among those given therapy under DOT compared to those receiving self-administered treatment (SAT) [15]. It showed treatment completion in the DOT group (87.2%) was higher than in either SAT group (74.0% without reminders; 76.4% with reminders)[15]. When the analysis was restricted to participants in the USA only, 'SAT no reminder' was non-inferior to DOT [15]. Another study compared standard treatment for TBI (control) with standard treatment plus two-way weekly text messaging (intervention) [21]. The treatment duration in the study was either 12 months (isoniazid) or 6 months (rifampin). While weekly two-way text messaging did not enhance completion rates for latent TB infection compared to standard care, completion rates remained high in both treatment arms [16]. We propose this as a more pragmatic alternative to direct observation, while also expecting that it will encourage better adherence rates than self-monitoring. This approach is a practical and simple way to encourage and remind patients to take their medication, and weekly SMS messages have been

demonstrated to improve antiretroviral treatment adherence for HIV patients[17]. Therefore, we undertook a study to compare treatment completion amongst patients with TBI assigned to the weekly 3HP using SMS monitoring, with patients assigned to daily self-administered 4RIF.

**Methods**

*Study design and setting*

A multi-centre, prospective, open label, phase four randomised controlled trial was conducted in eight chest clinics in Sydney, New South Wales (NSW), Australia. NSW has a network of tuberculosis prevention and control services, with chest clinics funded by the state government. These clinics provide a service that is free to all people across the state, regardless of immigration status. The chest clinics reviewed patients for assessment and diagnosis for TB or TBI, and arranged screening, follow-up, and providing treatment.

*Study population and eligibility*

The study population comprised patients aged 2 and above attending participating clinics with a diagnosis of TBI, that were recommended for treatment by a Respiratory Physician, were invited to participate. TBI was defined as a Tuberculin test (TST) of 10mm or greater, or positive interferon gamma release assay (IGRA). Eligible participants also included individuals with HIV regardless of infection status. Eligible participants are required to have access to either a mobile phone or landline telephone. Patients who were currently pregnant confirmed by Urinary pregnancy test (BHCG), planning to become pregnant, breastfeeding, and under consideration for solid organ transplantation

were excluded. A structured questionnaire was completed at enrolment, consisting of patient characteristics and demographic information.

Prior to randomisation, eligible patients underwent clinical assessment and chest radiography (CXR) to exclude co-prevalent TB according to the standard practice. Patients diagnosed with TB were treated according to routine clinical care.

*Randomisation and blinding*

Eligible participants were randomised in a one-to-one ratio using computer-generated sequences.. Owing to the inherent differences in treatment frequency and duration, participants and investigators were not blinded to group allocation.

*Intervention and comparator regimens*

The intervention regimen comprised 3HP (intervention arm) given once weekly for 12 weeks. Dosing was based on weight (Table 5.1) [18]. For patient weight more than 50kg, the weekly Rifapentine dose (once weekly) was 900mg. Isoniazid dosing (once weekly) was based on age and weight. In the 3HP arm, patients weighing 60kg or more would require nine of the 100mg Isoniazid tablets and three of the 300mg Rifapentine tablets with total of 12 tablets. Adherence was supported through once-weekly SMS sent by clinic staff to the participant's mobile phone or phone call for those unable to use SMS. Participants were asked to respond, otherwise a follow-up phone call was performed. The comparator regimen was daily self-administered rifampicin regimen (4RIF) (weight-based dosing, up

to 600 mg) (120-dose). Adherence to treatment in both groups was measured at each visit using pill counting by healthcare workers, pharmacy records of prescription fulfilment or via patient self-report.

*Safety monitoring*

Prior to commencement of the LTBI treatment, all patients had baseline liver function tests, and complete blood count performed. Urinary pregnancy test (BHCG) was performed for women aged 15-45 years commencing the 3HP regimen. Patients were assessed by the treating physician at 1 month after commencement of treatment. This included a medical assessment and repeat blood tests. At each clinic visit, participants were asked about the presence of side effects. This approach followed the standard practice in participating clinics. At end of treatment, patients were asked to complete an end of treatment questionnaire related to adverse events and their satisfaction about the treatment they received all patients were asked about acceptability of the regimen, and their experience of SMS monitoring (in the 3HP group). If patients developed symptoms of an immunological reaction during treatment, they were asked to suspend treatment. During the covid-19 pandemic, telehealth appointments were performed instead of face-face appointments.

*Study outcomes*

The primary outcome was comparing the proportion of participants completing treatment in 3HP and the 4RIF arm. This was defined as taking at least 90% of the required doses within no more than one month longer than the prescribed treatment period. For those in the 3HP arm, this comprised at least 11 doses taken within 16 weeks of randomisation. For the 4RIF arm, this comprised at least 108 of 120 doses taken within 5 months of randomisation.

Secondary outcomes for the study included the proportion of people with at least one adverse event (AE) which occurred between the date of randomisation and the end of treatment: defined according to the National Cancer Institutes (US) Common Terminology Criteria for Adverse Events [19].

AEs were graded and managed by the treating clinician, in accordance with usual practice at the clinics. Adverse events of special interest (AESI), unexpected Adverse Events or other clinical issues raised by the treating physicians were reviewed by local site investigators participating in the study.

*Monitoring for systemic drug reactions / hypersensitivity*

Systemic reactions have been reported in 3.5% of patients taking rifapentine[20]. This classified as AESI. In a recent study, symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours. If a patient developed this adverse event, then further tests were performed characterise the immunological nature of the adverse event further.

The definition of a systemic drug reaction followed the definition used in the PREVENT TB trial [20]. The PREVENT Tuberculosis sub-study protocol team established two broad criteria for such a drug reaction; (1) hypotension (systolic blood pressure <90 mm Hg), urticaria (hives), angioedema, acute bronchospasm, or conjunctivitis (red eyes); and (2) at lease>4 of the following symptoms occurring concurrently (>1 of which had to be grade 2 or higher): weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills. AE that met either of the above criteria were termed systemic drug reactions (SDR).

For patients who developed this syndrome, we collected additional blood tests (including full blood count, C-reactive protein and liver function tests) to characterise this further. Serum was stored at baseline and after the adverse event for subsequent analysis.

*Statistical analyses*

The primary intention-to-treat analyses were performed for all participants randomised to therapy regardless of whether they commenced on therapy. Descriptive analyses described the characteristics of all the enrolled participants and pooled study outcomes. Safety analyses included participants who took at least one dose of study drug.

For the analyses of study outcomes and AEs, they were presented combined across arms for participants enrolled prior to September 30, 2022 as the study follow-up is ongoing. Quantitative variables were summarised using frequencies or median values, with interquartile ranges (IQR). Adverse events were reported for participants who took at least one dose of study drug, stratified by system and the treatment decisions after AEs were reported. Statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

*Sample size and power*

The sample size for the main RCT was calculated based upon the comparator 4-month regimen of rifampicin has been demonstrated to have a completion rate of 74%[12]. The 3-month regimen has been shown to have a completion rate around 85%, when delivered by DOT [21], although the two have not previously been compared. We expected adherence support for 3HP using SMS would result in higher treatment completion rates (87%) than 4RIF (74%) [22]. To achieve a one-sided lower limit

95% confidence interval with a power of 80%, a one-sided p-value < 0.05 for superiority, while allowing for a 10% loss to follow-up, and without accounting for clustering, we required including 105 patients per arm. Therefore, this required an overall sample size of 210 participants across all sites.

*Site monitoring and quality assurance*

Site monitoring was conducted at each site within 6 weeks of commencing recruitment, and every six months subsequently or as needed. Quality assurance of the investigational product was undertaken by clinical trials pharmacies at each site.

*Ethical issues*

The trial was registered prospectively with the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au; ACTRN12618001672246). Ethical approval for the study was granted by the Sydney Local Health District Human Research Ethics Committee (HREC/17/RPAH/229). A Clinical Trials Notification from the Therapeutic Goods Administration (TGA) was obtained (CT-2019-CTN-01472-1), to enable the use of rifapentine, which was not licensed by the TGA. The study sponsor was Sydney Local Health District.

Prior to consent, potential participants aged 18 years and over were given a Participant Information Statement. Written informed consent was obtained from participants aged 18 and over. For participants under 18 years of age, a parent or guardian was asked to sign the Participant Consent Form. Participants between 10 and 17 years of age were also asked to sign an assent form.

*Financial interests*

The rifapentine used for this study was provided by Sanofi Aventis Australia Pty Ltd (Sanofi). Sanofi did not contribute financially to the conduct of the study, and was not involved in the study design, data analysis or interpretation, or dissemination of findings.

**Results**

Between July 2019 and July 2024 2022, 210 patients were enrolled and randomised within eight chest clinics. Of these, 106 (50.5%) were allocated to the 3HP intervention arm, and 104 (49.5%) were allocated to the 4RIF comparator arm. Across the two study arms, most participants were overseas born 189/210 (90/0%) and 97/210 (46.2%) were male. The median age of participants was 35.7 years (interquartile range [IQR]: 28.2-46.1 years). One of the patients was known to be HIV positive. Most of the patients 188/210 (89.5%) reported no medical comorbidities (Table 5.2).

110/210 patients were included analyses of the study outcomes and AEs as the study follow up is ongoing. Overall, 86/111 (77.5%) of the patients completed treatment as per the protocol. Among these, 60/86 (69.8%) of patients felt their LTBI regimen was not too long. A total of 78/111 (90.7%) patients stated they would recommend their assigned treatment to others (Table 5.4). In the intervention group, 46/58 people received SMS monitoring, and 42/46 (91.3%) responded 100% of the weeks during the treatment. 43/46 (93.5%) found the SMS monitoring very helpful, and 40/46 (87.0%) of the group indicated they would choose SMS monitoring for tuberculosis preventive treatment in the future (Table 5.5).

The treatment completion rate was 86/111 (77.5%). There were 25/111 (22.5%) patients who did not completed the treatment as per the protocol, 11/25 (44%) of them did not start treatment once they

were told which group they were in. Among the 14/111 (12.6%) patients who commenced treatment but did not complete, one completed 75% of the treatment and stopped due to pregnancy. 10/111 (9.0%) of the patients completed <10% of the treatment (Table 5.3).

We included 100/111 (90.1%) of the patients who took at least one dose of the study drug in the safety analysis (Table 5.6). Across the two groups, 25/100 (25.0%) of the patients reported at least one AE during treatment. More than one AE was reported by 2 of the 25 (8.0%) patients. Most AE's were grade 1-2 (Table 5.6). There was one grade 3 AE that was a systemic reaction that was classified as a hypersensitivity reaction. The patient presented to an emergency department with angioedema, fatigue, nausea, vomiting, and dizziness, a few hours after taking the 3HP for the first time. The patient was given IM adrenaline in the ambulance and treated with hydrocortisone and went home after 8 hours of observation and made a full recovery. The patient was not offered further preventive therapy.

For the 25 patients who reported having an AE, 16/25 (64%) of the patients had no interruptions to their treatments, and 6/25 (24%) of the patients refused further treatments. (Table 5.7). Treating physicians stopped 3 (12%) the treatments for three (12%) patients, and two (8%) of them were started on alternative LTBI treatment (Table 5.7).

**Discussion**

This phase four pragmatic randomised trial evaluated the treatment completion rate and tolerability of three months of weekly rifapentine-isoniazid or four months of daily rifampicin, for the treatment of LTBI in Australia.

According to pooled outcome of the interim analyses from this trial, treatment with either once weekly rifapentine plus isoniazid for three months with digital treatment adherence reminders, or self-administered rifampicin for four months, had a high completion rate (77.5%) and high overall patient satisfaction (90.7%). Adherence was broadly in keeping with data from previous studies, which found similar treatment completion rates for both of the LTBI regimens [23]. This confirmed the feasibility of these shorter regimens (3HP and 4RIF) for treatment of LTBI.

In our study, one in four patients reported at least one adverse event (AE's) during treatment (25.0%). However, most reported AEs were classified as grade 1-2, and most of patients were able to resume treatment successfully after reporting an AE. The incidence of systemic drug reactions/hypersensitivity reactions was only 1% in our study, across the two groups. This is consistent with recent individual patient data demonstrating that the treatment-related grade 3 or 4 adverse events for 3HP and 4RIF that led to permanent drug discontinuation was 0.8 and 2.2% respectively [24].

In our study, adherence with 3HP was primarily monitored using two-way SMS messaging. This approach is a practical and simple method to encourage and remind patients to take their medication. This approach has been shown to improve antiretroviral treatment adherence for HIV patients [11]. The use of SMS monitoring in our study was found to be highly acceptable by almost all patients, and was a preferred method of treatment for future use. Therefore, the results to date suggested that that using SMS monitoring is a feasible alternative to direct observation.

The study had several limitations. We excluded patients who were pregnant and being worked up for solid organ transplantation. None of the patients included in the study were known to be HIV positive, although HIV testing was not performed. This may limit the generalizability in this population. This study included a large number of healthcare workers undergoing pre-employment screening and patients intended for immunosuppressive therapy. The inclusion criteria for the study were broad, and the people who were enrolled reflect those given TPT in NSW. The acceptability and adherence to TPT were reflective of the population of people referred for preventive therapy. Most of the patients in our study were young and had no reported comorbidities. We reported 25.0% of AE with the majority classified as grade 1-2. These interim data suggest that the 4RIF and 3HP treatment regimens are feasible, tolerable, and acceptable options for LTBI treatment. Among those patients monitored with SMS, they found it acceptable. The completed study will be adequately powered to assess the difference in treatment completion rate between two arms.

This study may have implications for public policy in Australia. One key aspect of tuberculosis (TB) control in the country, and a crucial component of the Australian Government's TB elimination initiative, is the treatment of latent TB infection (LTBI) to prevent the onset of active disease [2]. Considering the growing effort to promote LTBI treatment uptake in Australia, the use of reduced doses and short-course therapy is poised to play a critical role in realizing the goals of the End TB Strategy. Our interim data demonstrate that the once weekly rifapentine plus isoniazid treatment for three months with SMS monitoring, and self-administered rifampicin for four months, have high patient completion rates and satisfaction. However, the relative adherence and acceptability by arm remain to be evaluated. These findings provide further support for these short course LTBI treatments, particularly when implemented at scale and in conjunction with community-based adherence support approaches.

The health system costs of treatment for LTBI are also an important consideration. Denholm et al. conducted a pragmatic trial demonstrating that from a health systems perspective, self-administered 3HP therapy was less costly than that of self-administered 9H therapy in Victoria, Australia [14]. However, the study was not powered to assess differences in treatment completion. A previous systematic review compared 3HP, 6 to 9 months of isoniazid, 3 to 4 months of daily isoniazid with rifampicin, and 4RIF, which showed regimens of 3–4 months duration are more likely to be completed than longer regimens [16]. To further evaluate the cost-effectiveness of 3HP and 4RIF as LTBI regimens with community-based adherence support approaches, future studies are necessary. These studies could also investigate the impact of these approaches on reducing TB transmission in the community. The cost of some rifapentine formulations also curtailed the drug's accessibility. WHO has encouraged generic drug manufacturers to develop quality-assured formulations of rifapentine, and submit them for product evaluation to the WHO Prequalification Unit to increase their access and affordability [25].

A number of further research questions remain. Firstly, new regimens must be developed to reduce the pill burden for patients taking the 3HP regimen. In our study, most patients weighing 60kg or more required 12 tablets each week. This can be reduced by manufacturing tablets of higher strengths, and combination packs of treatment that can simplify the weekly dosing. Secondly, shorter treatments may further improve adherence. A recent study has showed that 1 month of daily rifapentine plus isoniazid was noninferior to daily isoniazid for 9 months, for the prevention of tuberculosis in HIV-infected adults, with a lower incidence of AE, and patients were more likely to complete treatment in the 1 month group [26]. Ongoing research in looking for novel shorter and more patient friendly options for LTBI in different population group will be crucial to increase the uptake of LTBI treatment among high-risk populations.

In low-incidence settings like Australia, where TB re-infection is unlikely due to low community transmission of *M. tuberculosis*, there is great benefit from the protection offered by preventive

therapy as people are unlikely to be re-exposed. Most of the patients referred for LTBI treatment in our study were born overseas. This highlights the importance of identifying strategies to enhance screening uptake, offering treatment in immigrant populations, and having patient centred approaches.

**Conclusion**

Among the first 111 people participating in this trial, treatment completion rate and patient acceptability were high for both 3HP and 4RIF treatments . Our interim findings suggest that treatment with once weekly rifapentine plus isoniazid for three months, with SMS monitoring and self-administered daily rifampicin for four months, achieved a high completion rate and high patient satisfaction. Expanded availability of short-course therapies for LTBI treatment will play a crucial role in government efforts to promote preventive therapy for TB in Australia and other comparable settings.

Figure 5.1 Consort diagram showing group allocation and follow-up

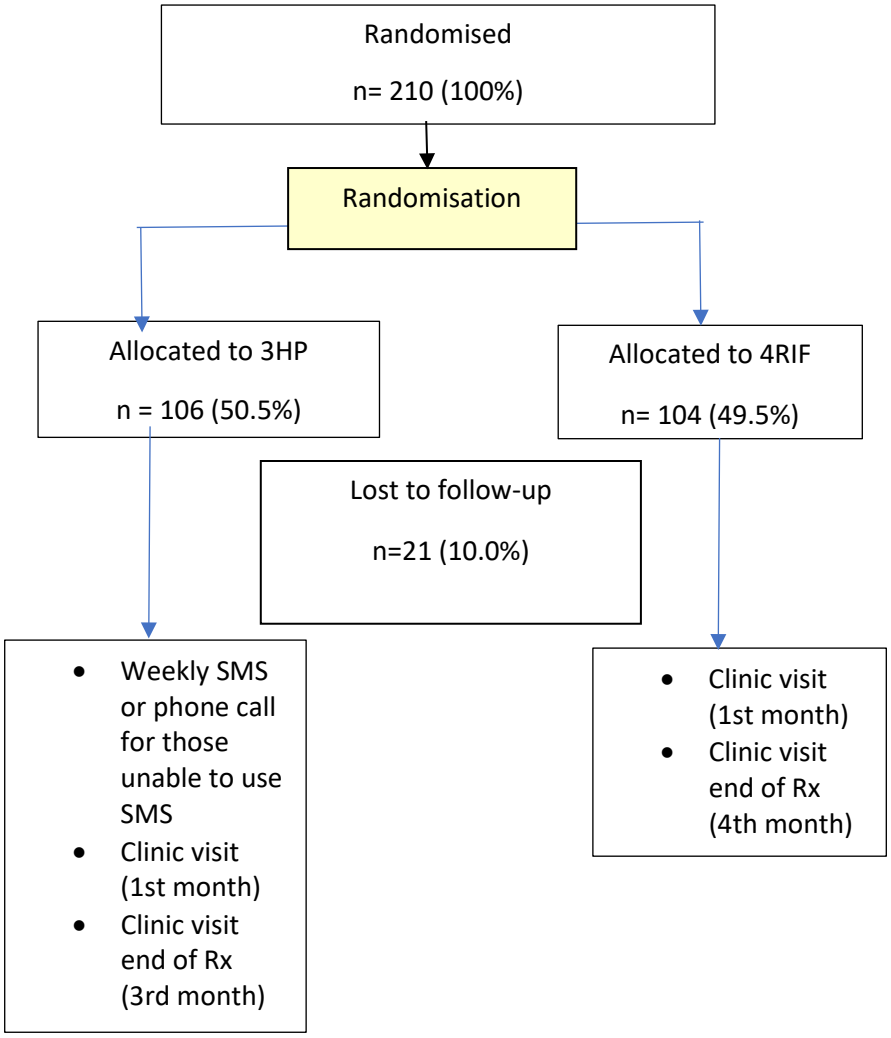

Table 5.1 Weight-based weekly rifapentine dosing [14]

| Weight | Weekly dose of rifapentine | Dose (mg/kg) |
|---|---|---|
| 10-14kg | 300mg | 21.4-30.0 |
| 14.1-25kg | 450mg | 18.0-31.9 |
| 25.1kg-32kg | 600mg | 18.8-23.9 |
| 32.1kg-50kg | 750mg | 15.0-23.4 |
| >50kg | 900mg | ≤18.0 |

**Weight-based weekly rifapentine dosing**

**Isoniazid dosing (once weekly)**

- Persons 2-11 years old received isoniazid 25 mg/kg (rounded up to the nearest 50 or 100 mg; 900 mg max) once weekly.
- Persons > 12 years old received isoniazid 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg max) once weekly.

Table 5.2 Characteristics of enrolled participants in 3HP and 4RIF groups (combined)

| Characteristics | n (%) |
|---|---|
| **Total enrolled** | 210 (100) |
| Male | 97 (46.2) |
| Female | 113 (53.8) |
| **Age** | |
| Median (IQR), years | 35.7 (28.2-46.1) |
| Less than 10 years | 1 (0.5) |
| 10-19 years | 6 (2.9) |
| 20-29 years | 60 (28.6) |
| 30-39 years | 70 (33.3) |
| 40-49 years | 33 (15.7) |
| 50-59 years | 23 (11.0) |
| 60-69 years | 11 (5.2) |
| more than 70 years | 6 (2.9) |
| **BMI (kg/m$^2$)** | |
| Median (IQR) | 24.1 (22.4-26.7) |
| <18.5 | 5 (2.4) |
| 18.5-25 | 123 (58.6) |
| 25-30 | 58 (27.6) |
| 30-35 | 20 (9.5) |
| >35 | 4 (1.9) |
| **Country of origin** | |
| Africa | 6(2.9) |
| Australia and New Zealand | 21 (10.0) |
| Europe | 2 (1.0) |
| North America | 1 (0.5) |
| South America | 4 (1.9) |
| Southeast Asia | 168 (80) |
| Middle east | 8 (3.8) |
| **Alcohol use in the past month** | |
| None | 139 (66.8) |
| Once a month or less | 24 (11.5) |
| 2-4 times/month | 33 (15.9) |
| 2-3 times/week | 7 (3.4) |
| More than 4 times/week | 5 (2.4) |
| **No. of alcohol consumed on drinking day** | |
| Median (IQR) | 0(0-1) |
| 1 standard drink | 34 (16.4) |
| 2 standard drinks | 21 (10.1) |
| 3 standard drinks | 7 (3.4) |
| >3 standard drinks | 9(4.3) |

| Characteristics | n (%) |
|---|---|
| **HIV status*** | |
| Positive | 1 (0.5) |
| Negative | 66 (31.6) |
| Not tested | 142 (67.9) |
| **Medical comorbidities** | |
| None reported | 188 (89.5) |
| Diabetes mellitus | 8 (3.8) |
| Chronic Kidney Disease | 2 (1.0) |
| Causes of impaired immunity | 1 (0.5) |
| Transplant anti-rejection drugs | 2 (1.0) |
| Other immunosuppressive condition | 5 (2.4) |
| Other# | 4 (1.9) |
| **Reason for testing for TB infection** | |
| Health worker pre-employment screening | 109 (51.9) |
| Contact investigation | 45 (21.4) |
| Migration screening | 22 (10.5) |
| Intended use of immunosuppressive therapy | 24 (11.4) |
| Other | 10 (4.8) |
| **Test for tuberculosis infection** | |
| Positive TST** | 30 (14.3) |
| Positive IGRA results** | 206 (98.1) |
| **Chest Xray findings** | |
| Normal | 169 (80.5) |
| Probable TB-related abnormality | 30 (14.3) |
| Fibronodular disease ≥2cm | 4 (1.9) |
| Granuloma | 22 (10.5) |
| Pleural thickening | 4 (1.9) |
| Abnormality not related to TB | 11 (5.2) |
| **Baseline LFT** | |
| ALT within normal range | 200/210 (95.2) |
| AST within normal range | 202/210 (96.2) |
| **Own mobile phone** | |
| Yes | 210 (100) |
| No | 0 (0) |
| **Own a landline phone** | |
| Yes | 62 (29.5) |
| No | 148 (70.5) |
| **Site of enrolment** | |
| Canterbury Hospital | 5 (2.4) |
| Concord Hospital | 18 (8.6) |
| Liverpool Hospital | 3 (1.5) |
| Prince of Wales Hospital | 5 (2.4) |
| Parramatta Chest Clinic | 95 (45.2) |

| Characteristics | |
|---|---|
| Royal Prince Alfred Hospital | 68 (32.4) |
| St George Hospital | 0 (0) |
| St Vincent Hospital | 16 (7.6) |

TST: Tuberculin test, positive TST is defined as 10mm or greater
IGRA: positive interferon gamma release assay IGRA; IQR: interquartile range; LFT: liver function test.
ALT: alanine transaminase, normal range is within 5-40 units per litre of serum)
AST: aspartate transaminase, normal range is within 7-56 units per litre of serum.
[#] one patient has hypercholesterolaemia, one has depression, one has autoimmune disease
*HIV status was based on upon history
**12/111 (10.8%) patients had both positive IGRA and TST

Table 5.3 Total no. of patient completed assigned treatments.

| **Total no. of pt enrolled** | **% of the therapy taken** | n (%) n= 111 patients |
|---|---|---|
| Therapy complete | 100% | 83 (74.8) |
| | ≥ 90 % | 3 (2.7) |
| Therapy not complete | Never commenced on the therapy | 11 (9.9) |
| | Completed <20% | 11 (9.9) |
| | 20-39% | 2 (1.8) |
| | 40-59% | 0 |
| | 60-79% | 0 |
| | 70-89% | 1 (0.9) |

Table 5.4 Patients' satisfaction with treatment for LTBI.

| **Total number of participants commencing treatment** | | n (%) n=86 patients |
|---|---|---|
| Convenience rating | Very inconvenient | 1 (1.2) |
| | Inconvenient | 3 (3.5) |
| | Convenient | 45 (52.3) |
| | Very inconvenient | 37 (43.0) |
| Recommend LTBI treatment to others | Strongly recommend | 48 (55.8) |
| | Recommended | 30 (34.9) |
| | Neither recommend for nor against | 8 (9.3) |
| | Recommend against | 0 |
| | Strongly recommend against | 0 |

Table 5.5 Patients' satisfaction with using weekly SMS adherence reminders, among those receiving the reminders.

| **Total** | | n (%) n=46 patients |
|---|---|---|
| Did you find SMS helpful during your treatment? | Not at all helpful | 2 (4.3) |
| | Not helpful | 1 (2.2) |
| | Helpful | 15 (32.6) |
| | Very helpful | 28 (60.9) |
| Did SMS reminders help you remember to take treatment? | Not at all | 5 (10.9) |
| | Sometimes | 15 (32.6) |
| | Often | 10 (21.7) |
| | Always | 16 (34.8) |
| Did you have any concerns about breaching your privacy by using SMS? | Very concerned | 1 (2.2) |
| | Somewhat concerned | 1 (2.2) |
| | Not concerned | 8 (17.4) |
| | Not at all concerned | 36 (78.3) |
| Would you choose SMS monitoring in future? | Yes | 40 (87.0) |
| | No | 5 (10.9) |
| | Don't know | 1 (2.24.3) |

Table 5.6 Types and grading for AEs for patients on treatments

| Adverse event | Grading of AE | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Rash | 2 | 1 | 0 | 0 |
| Headache | 3 | 0 | 0 | 0 |
| Gastrointestinal problem | 8 | 3 | 0 | 0 |
| Itchy skin | 2 | 0 | 0 | 0 |
| Sleeping or mood problems | 4 ) | 0 | 0 | 0 |
| Liver toxicity / hepatitis | 1 | 0 | 0 | 0 |
| Haematological abnormality | 2 | 0 | 0 | 0 |
| Systemic drug reaction/hypersensitivity reaction * | 0 | 0 | 1 | 0 |
| **Total no. of AE n (%) n=27** | 22 (81.5) | 4 (14.8) | 1 (3.7) | 0 |
| **No. of patients reported any AEs n (%)** n=100** | 20 (20) | 4 (4) | 1 (1) | 0 |

Table 5.7 Treatment decision for patients reported any AEs.

| | Treatment decision for patients following AEs n (%) | | |
|---|---|---|---|
| Adverse event | n=25 (%) | | |
| | Treatment continued | Treatment stopped | |
| | | participant's decision | medical officer's decision |
| Rash | 2 (8.0) | 1 (4.0) | 0 |
| Headache | 2 (8.0) | 0 | 0 |
| Gastrointestinal problem | 4 (16.0) | 5 (20) | 1 (4.0) |
| Itchy skin | 2 (8.0) | 0 | 0 |
| Sleeping or mood problems | 4 (16.0) | 0 | 0 |
| Liver toxicity / hepatitis | 1 (4.0) | 0 | 0 |
| Haematological abnormality | 1 (4.0) | 0 | 1 (4.0) |
| Systemic drug reaction/hypersensitivity reaction * | 0 | 0 | 1 (4.0) |
| **No. of patients reported any AEs n (%) n=25** | 16 (64) | 6 (24) | 3 (12) |

* The definition of a systemic drug reaction followed the definition used in the PREVENT TB trial [11]. The PREVENT Tuberculosis sub-study protocol team established two broad criteria for such a drug reaction; (1) hypotension (systolic blood pressure <90 mm Hg), urticaria (hives), angioedema, acute bronchospasm, or conjunctivitis (red eyes); and (2) at least 4 of the following symptoms occurring concurrently (>1 of which had to be grade 2 or higher): weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills. AE that met either of the above criteria were termed systemic drug reactions (SDR).

** Total no. of patients who took at least one dose of treatmentReferences

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# 6. CONCLUSION

This thesis focuses upon the programmatic management of MDR/ RR-TB patients and their contacts in the low incidence setting of Australia, evaluated the epidemiology of tuberculosis infection among the household contacts of patients with TB in Australia and Vietnam, and demonstrated the feasibility and acceptability of weekly Rifapentine with isoniazid for 3 months treatment for TB infection. Together, these findings demonstrate the importance of screening and treatment for TB disease and infection among this high-risk population and support the use of Individualised treatment for MDR/RR-TB in low burden countries. For different countries to achieve the WHO End TB strategy by 2035, it is not a "one size fits all" approach and its success depends on adaptation for diverse country settings.

### 6.1 Implications for countries with high burden of MDR/RR-TB

This thesis has demonstrated that HHCs amongst the MDR/RR-TB patients had a high TBI prevalence, and it supports the WHO TBI guidelines recommending screening in this population [1].

In Chapter 4, Factors associated with tuberculosis infection among household contacts of patients with multidrug-resistant tuberculosis in 10 provinces of Vietnam: a cross-sectional study, we demonstrated a high prevalence of TBI among HHC of the MDR/RR-TB patients in a Southeast Asian setting, Vietnam. In our cross-sectional survey of household contacts in 10 provinces, the prevalence of TBI was 71.2% (2721/3823) amongst the HHCs. The prevalence of active TB disease was 1.3% (53/3969) In the WHO regions, the estimated prevalence of TBI in 2018 was 36% in South-East Asia [2]. This has confirmed HHCs were the high priority group for contact tracing. We have identified several risk factors for TBI diagnosis after adjustment. These include increasing age, normal BMI, past smoking history, prior history of TB, presence of BCG scar, 8 hours or more spent with index patient for the last 24 hours, index patient with smoking history and persistent cough more than 2 weeks, had a statistically

significant positive association with TBI. These were consistent with previous studies done in drug-susceptible TB [3]

Our study demonstrated that there is a high prevalence of TBI among the HHCs of the MDR/RR-TB patients, which supports the WHO TBI guidelines recommending screening in this population [1]. Screening the high-risk contacts for MDR/RR-TB patients could increase case detection. This is the cornerstone focus for the first pillar of WHO END TB strategy[4]. A key missing feature for TB control is a comprehensive program for prophylaxis for contacts of index cases with MDR/RR- TB. The current WHO guidelines have a conditional recommendation for fluoroquinolone preventive therapy for HHCs due to lack of randomized clinical trials of TB preventive therapy in this population[5] [6] [7]. Two clinical trials have evaluated the effectiveness of preventative therapy for household contacts of patients with MDR/RR-TB, including the VQUIN MDR Trial and the TB child multidrug-resistant preventive therapy (TB-CHAMP).If preventive therapy (TPT) is found to be effective, there will be clear benefits in high prevalence areas, and perhaps giving TPT without doing TST could be considered, given the prevalence of TBI in HHCs is so high. Furthermore, the evaluation of risk and benefits for treating people with no (or mild) symptoms with drugs that have side-effects will need to be addressed.

**6.2 Implications for countries with low burden of TB/ MDR-RR TB**

This thesis has demonstrated a high treatment success rate using individualised treatment for MDR/RR-TB in a high-income low-incidence setting, and the importance of integrated patient- centred care is the main theme of the first pillar of the WHO End TB strategy [8].

It also showed the prevalence of TBI among contacts of patients diagnosed with MDR/RR-TB was high (38.9%). Because of the low community transmission, efforts to detect and treat contacts with

MDR/RR-TB infection plays an important role in the control of TB in this low-prevalence setting, as clinical trial results for effective preventive therapy are available.

In Chapter 2 Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia, we evaluated outcomes of individualised treatment for MDR/RR-TB in a high-income low incidence setting and showed it could achieve a high treatment success rate. We performed a retrospective cohort study of patients treated for MDR-TB in Sydney, Australia, over a 16-year period. Patients' treatment regimens were individualised, based upon molecular drug susceptibility test (DST) results. Most included an injectable antibiotic during the intensive phase of treatment, consistent with the WHO guideline at the time of the study period. This cohort showed the proportion of patients with treatment success was 51/55 (93%), well above the WHO target of 75%, and similar to that achieved in other high-resource settings[9, 10]. The high treatment completion rates achieved indicated the ability of healthcare workers to continue supervising the MDR-TB treatment despite the frequent occurrence of side effects. Individualised treatment for MDR/RR-TB is a model example of precision medicine in infectious diseases[11]. It is developed by evaluating the drug-resistance profile of the causative bacteria from DST, and patient-specific factors that may determine treatment toxicity. The importance of integrated patient- centred care is the main theme of the first pillar of the WHO End TB strategy [8]. The increasing availability of whole genome sequencing close to the time of diagnosis will further strengthen the capacity of TB programs to individualise therapy and sustain a high proportion of successful treatment for MDR/RR-TB.

In Chapter 3, latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia, we showed in a retrospective cohort study that the prevalence of TBI among contacts of patients diagnosed with MDR-TB over a 16-year period was high (38.9%). Low incidence countries including Australia, have low background transmission rates of TB. Among contacts born in Australia, transmission most likely resulted from the recognised exposure to a patient with MDR-TB. In our study, 105 (42.5%) patients tested positive for LTBI (based on a positive

IGRA or TST ≥ 10mm), and among them, 62 (25.1%) were newly diagnosed. More than half of the contacts with newly diagnosed TBI were offered prophylactic treatment, with extensive variation observed in the medications, doses, and durations. The majority of the contacts 42/62 (67.7%) went on CXR surveillance. Given the significant role of contact transmission in TBI development, efforts to detect and treat contacts with MDR/RR-TB infection plays an important role in the control of TB in this low-prevalence setting, because of the low community transmission. Secondly, identifying contacts with TBI is most useful if effective preventive therapy is available. Two clinical trials have evaluated the effectiveness of preventative therapy for household contacts of patients with MDR/RR-TB [12, 13]. More updated WHO guidelines on management of DR/RR-TB contacts will likely be released in 2024.

These findings contrast with our findings among household contacts in Vietnam, where the prevalence of TB infection was much higher at 71.2%. The high prevalence of TBI could reflect an ongoing transmission at the household before the index patient was diagnosed to have MDR/RR-TB, or some of the positive TSTs in older patients could represent the previous exposure. This has significant implications on contact tracing policy for high burden settings. Contact tracing' refers to a set of interventions including active case finding in contacts of patients with tuberculosis, and then proceeds to the application of specific interventions in those identified contacts[14, 15]. In high burden countries, people may have other opportunities for infection (or re-infection), and the overall population impact of contact tracing will be more limited to active case finding as a more valid intervention but not the treatment of TBI[15]. This is in contrast to low transmission settings, where contacts are going to have a relatively higher likelihood of infection and comprise a greater proportion of the total incident cases[15]. A focus on scaling-up of existing strategies for active case-finding among HHCs in high burden countries will improve early detection of MDR/RR-TB, and there are extra benefits to reducing transmission by detecting MDR/RR-TB early. And the next step could be scaling up screening for TBI and treatment with effective regimens in low burden countries as clinical trial results are available.

### 6.3 Use of TPT for individuals at risk of developing active TB

Considering the growing effort to promote TBI treatment uptake in low incidence settings like Australia, the use of reduced doses and short-course therapy, with digital treatment adherence reminders focused on implementation research for Digital Technologies and TB, supports the third pillar of WHO End TB strategy[8]. Adherence to the full course and completion of TPT are important determinants of clinical benefit to individuals and to the success of TB programmes[16].

In Chapter 5, use of rifapentine and isoniazid compared to rifampicin for latent TB in Australia, we demonstrated the feasibility of treating TBI with weekly rifapentine and isoniazid therapy for three months, with adherence supported using SMS. The pooled outcome of the interim analyses from our trial showed treatment with either once weekly rifapentine plus isoniazid for three months with digital treatment adherence reminders, or self-administered rifampicin for four months, had a high completion rate (77.5%) and high overall patient satisfaction (90.7%).

Our findings provide further support for these short course TBI treatments, particularly when implemented at scale and in conjunction with community-based adherence support approaches. The comparison of 3HP with 4RIF will also enable clinicians to determine preferable regimens for patients in this setting.

### 6.4 Future research questions

A number of research questions remain. Ending catastrophic costs in TB-affected households is one of the targets of the World Health Organization (WHO) end-TB strategy[14]. However, the widespread dissemination of MDR/RR TB- and XDR-TB continues to be a significant obstacle to achieving these ambitious targets [17]. In 2022, WHO guidelines for MDR/RR- TB treatment have substantially changed, recommending shorter all-oral treatment, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM). Future operation research to

scale up the shorter regimens and the ongoing trial Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB) trial (MSF ERB-1555) would give us more information about the efficacy and safety of these new, all-oral, shortened regimens for MDR/RR-TB. For countries like Australia with high-income and low-TB-incidence to continue using individualised treatment for MDR/RR-TB, looking at the use of new agents like bedaquiline and delamanid, and developing strategies to ensure patients' preferences remain at the centre of the clinical decision-making, is essential.

A key missing feature for TB control is a comprehensive program for prophylaxis for contacts of index cases with MDR/RR- TB. Two clinical trials have evaluated the effectiveness of preventative therapy for household contacts of patients with MDR/RR-TB [12, 13]. With the ongoing PHOENIx clinical trial (NCT03568383), comparing delamanid with isoniazid monotherapy, these will help us to evaluate the regimens as preventative measures for contacts of patients with MDR/RR-TB.

Use of TPT is recommended for different groups of individuals with TBI in high and low prevalence settings [16]. Future development of even shorter treatments for TPT is occurring, with ongoing trials such as the Asteroid study looking at 6 weeks of daily rifapentine. The 1HP trial has showed the safety and feasibility of 1 month of daily rifapentine plus isoniazid in children and adolescents[18], and the 2R2 trial has showed the safety of high dose rifampin monotherapy to shorten the duration of 4RIF [19]. These novel shorter and more patient friendly options for TBI in different population group will be crucial to increase the uptake of TBI treatment among high-risk populations.

### 6.5 COVID-19 and TB control

Although the COVID-19 pandemic has reversed years of progress made in the fight against TB, it provided us some lessons learnt from the COVID-19 pandemic. It highlighted the importance of integrated health care system and technology.

Previous study has identified the influence of the COVID-19 pandemic on HIV and TB services in Africa and Asia-Pacific[20]. There were instances of staff shortages, reduced access to TB care, and postponements of the follow-up visits for patients with TB during the pandemic[20]. It highlighted the importance of the use of digital tools in medical services delivery.

The COVID-19 pandemic hit in 2020 during our study in Chapter 5, use of rifapentine and isoniazid compared to rifampicin for latent TB in Australia. During the pandemic, face to face appointments at the outpatient's clinics were changed to telehealth, and during that period patients in the study were followed up with teleconferences. The interim analyses showed a high completion rate (77.5%) and high overall patient satisfaction (90.7%) in both arms and provide support for the use of digital delivery of healthcare services. Future study looking at use of digital tools would improve the efficiency of the management and treatment of TB patients, and also ensuring the data reliability and strengthening the information systems landscape[21].

**Summary**

In conclusion, this thesis highlights the management of MDR/RR-TB across diverse epidemiological settings. Our findings showed the high prevalence of TBI among household contacts of MDR/RR-TB patients, emphasizing the need for targeted screening and treatment strategies, as recommended by WHO guidelines. In high-burden countries like Vietnam, where household transmission is prevalent, rigorous contact tracing and prompt treatment initiation is crucial for disease control.

In low-incidence countries such as Australia, our study demonstrates the feasibility and success of individualized treatment approaches tailored to patient-specific factors, achieving high treatment success rates. There is an increasing focus on promoting TBI treatment uptake through reduced doses and short-course therapies. Our preliminary study results showed that implementing short-course

regimens such as rifapentine with isoniazid for TB treatment, bolstered by digital adherence tools, effectively enhances treatment completion rates and improves patient satisfaction.

Looking ahead, the adaptation of these findings into national TB control strategies is important for achieving the WHO End TB Strategy by 2035. Drawing lessons from the COVID-19 pandemic, there should be a focus on shaping patient-centred approaches in both high-burden and low-incidence settings to further refine TB management practices and reduce the global burden of tuberculosis.

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# APPENDIX ONE: THESIS PUBLICATIONS

## Publications arising from this thesis

1. **Chang V**, Ling RH, Velen K, Fox G. Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia. ERJ Open Res. 2021 Sep 20;7(3):00149-2021. doi: 10.1183/23120541.00149-2021. PMID: 34549043; PMCID: PMC8450450.

2. **Chang V**, Ling R, Velen K, Fox G. Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia. Aust N Z J Public Health. 2021 Oct;45(5):437-442. doi: 10.1111/1753-6405.13144. Epub 2021 Jul 26. PMID: 34309967.

## Publications during the PhD candidature

3. Greg J Fox, Lisa Redwood, **Vicky Chang**, Jennifer Ho. The Effectiveness of Individual and Environmental Infection Control Measures in Reducing the Transmission of Mycobacterium tuberculosis: A Systematic Review. Clinical Infectious Diseases, ciaa719, https://doi.org/10.1093/cid/ciaa719

4. Zhiyi Lan, Nafees Ahmad, Parvaneh Baghaei, Linda Barkane, Andrea Benedetti, Sarah K Brode, James C M Brust, Jonathon R Campbell, **Vicky Wai Lai Chang**, Dennis Falzon, Lorenzo Guglielmetti, Petros Isaakidis, Russell R Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange, Rafael Laniado-Laborín, Payam Nahid, Denise Rodrigues, Rupak Singla, Zarir F Udwadia, Dick Menzies, and The Collaborative Group for the

Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis"- Zhiyi Lan, Nafees Ahmad, Parvaneh Baghaei, Linda Barkane, Andrea Benedetti, Sarah K Brode, James C M Brust, Jonathon R Campbell, Vicky Wai Lai Chang, Dennis Falzon, Lorenzo Guglielmetti, Petros Isaakidis, Russell R Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange, Rafael Laniado-Laborín, Payam Nahid, Denise Rodrigues, Rupak Singla, Zarir F Udwadia, Dick Menzies, and The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017. The Lancet Respiratory- Published online March 16, 2020 https://doi.org/10.1016/S2213-2600(20)30047-3

# APPENDIX TWO: ABSTRACT PUBLICATIONS

## International Conference Abstracts

Poster presentation

1. **Vicky Chang**, Thu-Anh Nguyen, Binh Nguyen, Nhung Nguyen, Greg Fox. Characteristics of Household Contacts of Rifampin and Multidrug-resistant Tuberculosis Cases at High Risk of Progression to Tuberculosis Disease in Vietnam. *European Respiratory Journal Sep 2023, 62 (suppl67) PA2795; DOI: 10.1183/13993003.congress-2023.PA2795*

2. **Vicky Chang**, Greg Fox. The use of weekly rifapentine and isoniazid (3HP) for latent TB infection in Australia. *European Respiratory Journal* Sep 2023, 62 (suppl 67) PA4537; DOI: 10.1183/13993003.congress-2023.PA4537

## National (Australia) Conference Abstracts

Oral presentation

1. **Chang V**, Ling R, Velen K, Fox G. Individualized treatment for multidrug-resistant tuberculosis in New South Wales, Australia. Abstracts. *Respirology*, 26: 21-122. https://doi.org/10.1111/resp.14021

Poster presentation

2. **Chang V**, Ling R, Fox G. Latent tuberculosis infection among contacts of patients with drug-resistant tuberculosis Abstracts. Respirology, 26: 123- 207. https://doi.org/10.1111/resp.14022

3. **Chang V** , Ling R, Chiam D, Britton W, Fox G. Characterising the outcome and toxicity of treatment for drug resistant Tuberculosis in NSW (2019), Abstracts. Respirology, 24: 103-206. https://doi.org/10.1111/resp.13492

4. **Chang W**, Ling R, Chiam D, Britton W, Fox G. CHARACTERISING THE TREATMENT AND PREVENTION OF DRUG RESISTANT TUBERCULOSIS IN NSW (2018), TSANZ Poster Presentations. Respirology, 23: 104-215. https://doi.org/10.1111/resp.13268

## APPENDIX THREE: ETHICS APPROVAL LETTER

For study: **Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia** and **Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia.**

*Contact:* Sydney Local Health District Human Research Ethics Committee – CRGH
*Concord Repatriation General Hospital (CRGH)*
*Concord NSW 2139*
*Telephone:* *(02) 9767 5622*
*Email:* *crgh.ethics@sswahs.nsw.gov.au*

***Our Ref:***

CONCORD
REPATRIATION GENERAL
HOSPITAL

15 June 2017

Dr Greg Fox
C/- Dr Vicky Chang
Sydney Medical School Foundation
The University of Sydney
92-94 Parramatta Road
CAMPERDOWN NSW 2050

Dear Dr Fox,

**Re: LNR/17/CRGH/129 CH62/6/2017-088**
**Characterising the treatment and prevention of drug resistant Tuberculosis in NSW**

Thank you for submitting the above project for single ethical and scientific review. This project was first considered by the Sydney Local Health District Human Research Ethics Committee – CRGH at its meeting held on 18 May 2017. This Human Research Ethics Committee (HREC) has been accredited by the NSW Ministry of Health as a lead HREC under the model for single ethical and scientific review.

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and final ethical approval has been granted.

The Ethics Committee granted a waiver of the usual requirement for the consent of the individual to the use of their health information in a research project, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW).

The documents reviewed and approved include:

| | IDENTIFICATION NUMBER | DATE |
|---|---|---|
| **Low & Negligible Risk Research (LNR) Ethics Application Form** | **Submission code AU/6/91EC26** | **Replaced by LNR dated 14/06/2017** |
| **Protocol** | **Version 2** | **25/05/2017** |
| **Questionnaire 1 – MDR-TB index patient** | **Version 3** | **25/05/2017** |
| **Questionnaire 2 – Facility_MDR-TB patient** | **Version 4** | **25/05/2017** |
| **Questionnaire 3 – MDR-TB contacts** | **Version 4** | **25/05/2017** |

The HREC has provided ethical and scientific approval for the following sites:
1. Concord Repatriation General Hospital

**You are reminded that this letter constitutes ethical approval only. You must not commence this research project at Concord Hospital until a Site Specific Application has been reviewed and approved and separate authorisation from the Chief Executive or delegate has been obtained**

2. Westmead Hospital
3. Royal Prince Alfred Hospital
4. Prince of Wales Hospital
5. St George Hospital
6. The Sutherland Hospital

**Please forward a copy of this letter to all site investigators for submission to the relevant Research Governance Officer**

Please note the following conditions of approval:

1. You will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project, (including Serious Adverse Events).

2. Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review in the specified format.

3. You will notify the HREC, giving reasons, if the project is discontinued at a site before the expected date of completion.

4. You will provide an annual report to the HREC, and at completion of the study in the specified format.

5. You will adhere to the study protocol at all times.

HREC approval is valid for five (5) years subject to the supply of an annual progress report. The first report should be sent to the Concord Hospital Research Office by **30/06/2018.**

Should you have any queries about the HREC's consideration of your project please contact the Executive Officer - (02) 9767-5622. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the website: www.sswahs.nsw.gov.au/concord/ethics.

We wish you every success in your research.

***Please quote the above file number in all correspondence.***

Yours sincerely,

**Professor Andrew McLachlan**
*Chairman*
**Sydney Local Health District Human Research Ethics Committee – CRGH**

**Please complete the boxes below and return a copy of this page to the Concord Hospital Research Office:**

☐ *I acknowledge and accept the Conditions of Ethical Approval.*

☐ *I will not commence this project at any site until separate written authorisation from the Chief Executive or delegate of that site has been obtained*

| **Printed Name** | **Signature** | **Date** |
|---|---|---|
| Chief Investigator | | |

For study: **The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection**

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: X17-0157 & HREC/17/RPAH/229
9.43/JUN18

Health
Sydney
Local Health District

21 June 2018

A/Prof Gregory Fox
Respiratory Physician
Room 5216, Level 2
Medical Foundation Building
University of Sydney
Camperdown NSW 2050

Dear Professor Fox,

**Re: Protocol No X17-0157 & HREC/17/RPAH/229 - "The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection in Sydney Local Health District"**

The Executive of the Ethics Review Committee, at its meeting of 21 June 2018 considered your correspondence of 20 May 2018 and gave its approval of the following:

- Trial Protocol (Version 8.2, 20 May 2018)
- Follow-up Information Card (3HP Arm) (Version 2, 20 May 2018)
- Follow-up Information Card (4RIF Arm) (Version 2, 20 May 2018)
- Form 1: Enrolment form (Version 2, 20 May 2018)
- Form 2: End of Treatment Form (Version 2, 20 May 2018)
- Form 4: 3HP/4RIF Study Adverse Event Reporting Form (Version 2, 20 May 2018)
- Participant Information Sheet for Adults (Master Version 3, 20 May 2018)
- Participant Information Sheet (Parent of Child under 18 years) (Master Version 3, 20 May 2018)

- Adolescent Assent Information Sheet (Master Version 3, 20 May 2018)
- Participant Consent Form (Parent of Child under 18 years) (Master Version 3, 20 May 2018)
- Participant Consent Form (Master Version 3, 20 May 2018)

The inclusion of Liverpool Hospital and the Parramatta Chest Clinic as additional study sites is noted and approved. It is noted that authorisation will be sought to conduct the study at these sites.

It is also noted that you have obtained support from Sanofi Pharmaceuticals to supply the Rifapentine required for this study.

Yours sincerely,

Sanaa Thomas
**Executive Officer, Clinical Trials Sub-committee (RPAH Zone)**

for:

Merela Ghazal
**Acting Executive Officer**
**Ethics Review Committee (RPAH Zone)**

HERC\EXECOR\18-06

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
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TELEPHONE: (02) 9515 6766
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REFERENCE: X17-0157 & HREC/17/RPAH/229
9.38/NOV18

Health
Sydney
Local Health District

23 January 2019

A/Professor Gregory Fox
Respiratory Physician
Room 5216, Level 2
Medical Foundation Building
Camperdown NSW 2050

Dear Professor Fox,

**Re: Protocol No X17-0157 & HREC/17/RPAH/229 - "The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection in Sydney Local Health District"**

The Executive of the Ethics Review Committee, at its meeting of 23 January 2018 considered Ms V Chang's emailed correspondence of 2 January 2019 and gave its approval of the following:

- Protocol (October 2018 – December 2020) (Version 9.21, 13 November 2018)
- Information for Parents/Guardians (Master Version 3.4, 20 December 2018)
- Information for Adult Participants (Master Version 3.2, 31 December 2018)
- Information for Children Aged 10-13 Years (Master version 1, 31 December 2018)

Yours sincerely,

Sanaa Thomas
**Executive Officer, Clinical Trials Sub-committee (RPAH Zone)**

for:

Merela Ghazal
**Acting Executive Officer**
**Ethics Review Committee (RPAH Zone)**

HERC\EXECOR\18-11

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: X17-0157 & HREC/17/RPAH/229

NSW GOVERNMENT Health
Sydney Local Health District

22 March 2019

A/Professor Gregory Fox
Respiratory Physician
Room 5216, Level 2
Medical Foundation Building
Camperdown NSW 2050

Dear Professor Fox,

**Re: Protocol No X17-0157 & HREC/17/RPAH/229 - "The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection"**

Thank you, on behalf of the Ethics Review Committee for Ms V Chang's emailed correspondence of 21 March 2019. The following is noted and apprcved:

- Assent Information Sheet (14-17 Year olds) (Master Version 3.', 21 March 2019)

Yours sincerely,

Merela Ghazal
**Acting Executive Officer**
**Ethics Review Committee (RPAH Zone)**

HERC\EXECOR\19-03

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Health
Sydney
Local Health District

1 April 2019

A/Professor Gregory Fox
Respiratory Physician
Room 5216, Level 2
Medical Foundation Building
Camperdown NSW 2050

Dear Professor Fox,

**Re: Protocol No X17-0157 & HREC/17/RPAH/229 - "The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection"**

Thank you, on behalf of the Ethics Review Committee for your emailed correspondence of 29 March 2019. The following is noted and approved:

- Child Consent Form (14-17 Year olds) (Master Version 1, 27 March 2019)

Yours sincerely,

Merela Ghazal
**Acting Executive Officer**
**Ethics Review Committee (RPAH Zone)**

HERC\EXECOR\19-03

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EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: X17-0157 & 2019/ETH07006

NSW GOVERNMENT Health
Sydney
Local Health District

16 March 2020

Dear Professor Fox,

**Re: Protocol No X17-0157 & 2019/ETH07006 – "The effect of weekly rifapentine and isoniazid (3HP), compared to 4 months of daily rifampicin (4RIF) upon adherence with treatment for latent TB infection"**

The Executive of the Ethics Review Committee, at its meeting of 16 March 2020 considered Ms V Chang's emailed correspondence of 9 and 16 March 2020.

The following is noted and approved:

- Protocol (Version 9.22, 16 March 2020)
- Assent Information Sheet (14-17 year olds) (Master Version 3.2, 5 March 2020)
- Information for Children Aged 10-13 years (Master Version 1.1, 5 March 2020)
- Parent/Guardian Information Statement (Master Version 3.5, 5 March 2020)
- Participant Information Statement – Adult (Master Version 3.3, 5 March 2020)

Yours sincerely,

Sanaa Thomas
**Executive Officer**
**Clinical Trials Sub-committee (RPAH Zone)**

for:

Patricia Plenge
**Executive Officer**
**Ethics Review Committee (RPAH Zone)**

HERC\COR\20-03