

Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases

Fox GJ¹, Schaaf HS², Mandalakas A³, Chiappini E⁴, Zumla A⁵, Marais BJ⁶

¹Sydney Medical School, University of Sydney, Sydney, Australia; ²Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; ³Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States; ⁴Paediatric Infectious Disease Unit, Meyer University Hospital, Department of Health Science, University of Florence, Florence, Italy; ⁵University College London and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom; ⁶The Children's Hospital at Westmead and the Marie Bashir Institute for Infectious Diseases and Biosecurity (MBI), University of Sydney, Sydney, Australia;

Correspondence to:

Dr Greg J Fox

Room 574 Blackburn Building

University of Sydney

Sydney, Australia, 2006

Tel: +61-412912538

E-mail: greg.fox@sydney.edu.au

Running title: TB prevention among DR-TB contacts

Keywords: Drug-resistant; tuberculosis; household contacts; children

Abstract: 192 words

Word count: 2,928

References: 65 in main text, 77 including tables.

Conflicts of interest: None to declare

Abstract

Prevention of multidrug (MDR) and extensively drug-resistant tuberculosis (XDR-TB) is a top priority for global TB control, given the need to limit epidemic spread and considering the high cost, toxicity and poor treatment outcomes with available therapies. We performed a systematic literature review to evaluate the evidence for strategies to reduce MDR/XDR-TB transmission and disease progression.

Rapid detection and timely initiation of effective treatment is critical to rendering MDR/XDR-TB cases non-infectious. The scale-up of rapid molecular testing has transformed the capacity of high-incidence settings to identify and treat MDR/XDR-TB patients. Optimised infection control measures in hospitals and clinics are critical to protect other patients and healthcare workers, while creative measures to reduce transmission within community hotspots require consideration. Targeted screening of high-risk communities may enhance early case-detection and limit the spread of MDR/XDR-TB. Among infected contacts, preventive therapy promises to reduce the risk of disease progression. This is supported by observational cohort studies, but randomised trials are urgently needed to confirm these observations and guide policy formulation.

Substantial investment in MDR/XDR-TB prevention and care will be critical if the ambitious global goal of TB elimination is to be realised.

Background

It is estimated that multidrug-resistant tuberculosis (MDR-TB; i.e. *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin) affects 480,000 people annually with only a fraction of these patients receiving appropriate treatment [1]. Given the poor outcomes of MDR-TB treatment and the need to contain its spread, preventing MDR-TB in contacts remains a top priority for global TB control [2]. This review explores current strategies for interrupting transmission and therapies to prevent infected contacts of MDR-TB cases from developing disease.

We performed a systematic review of the literature regarding the prevention of MDR and XDR-TB, using the following electronic databases: PubMed, the Cochrane Database of Systematic Reviews and EMBASE. We used the search terms "tuberculosis, multidrug resistant", AND "infection control" OR "prevention and control" OR "chemoprophylaxis" OR "transmission". English language papers were retrieved and bibliographic references of identified articles were examined for additional relevant studies. The search included papers published between January 2000 and May 2016. We also conducted a search of the websites of relevant institutions (World Health Organisation, American Thoracic Society, European Respiratory Society, United States Centers for Disease Control and Prevention, International Union Against Tuberculosis and Lung Disease, United Kingdom National Institute for Health and Care Excellence and other national advisory groups) for existing guidelines.

Primary MDR-TB transmission

Antibiotic resistance first arises when patients with drug-susceptible (DS)-TB receive inadequate or interrupted therapy, leading to the selection of drug-resistant bacteria and 'acquired' drug resistance [3]. However, once resistant bacteria have become established in an infectious patient, they may then spread to others through airborne droplets as 'primary' or transmitted drug resistance. Despite initial evidence that laboratory induced drug-resistant mutations were associated with a fitness cost and likely reduced transmissibility, evidence from multiple sources indicate that drug-resistant bacteria selected within clinical settings are readily transmissible [4]. Consequently, primary transmission of drug-resistant bacteria is now

recognised as the dominant mechanism sustaining the global MDR-TB epidemic [5]. Molecular epidemiological studies indicate that a high proportion of drug-resistant (DR)-TB arises from primary transmission [6-8], while programme data from 30 low and middle income countries showed that a median of 54% (interquartile range 45-67%) of MDR-TB occurred among patients who have never received TB treatment [9]. Dynamic transmission modeling using programmatic data estimated that 95.9% (95% confidence interval [CI] 68.0-99.6%) of incident MDR-TB is attributable to primary transmission, including 61.3% (95% CI 16.5-95.2%) of MDR-TB in previously treated individuals [5]. Limiting MDR-TB transmission requires rapid diagnosis and effective treatment, together with optimal infection control and prevention programmes to limit the number of secondary cases [10].

Infection and disease among MDR-TB contacts

In the absence of treatment, the natural history of MDR-TB is essentially the same as for DS-TB. Most infected contacts will mount an effective early immune response that contains the bacteria and prevents progression to TB disease [11]. If this occurs, mycobacteria may be undetectable in the lung, yet survive for prolonged periods in a dormant state called "latent tuberculosis infection" (LTBI). Bacterial reactivation and progression to disease can occur long after infection, particularly following immune compromise. TB disease and LTBI are not binary states, but rather are ends of a spectrum, with progression between the two states determined by the immunological control of the host and the virulence of the organism [12, 13]. In children, the term "TB infection" instead of LTBI is preferred, as they are usually recently infected and could still be in the phase of progression to disease [14].

Since individuals with LTBI are asymptomatic, the diagnosis relies upon immunological responses to *M. tuberculosis* antigens using either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA). TST quantifies the delayed cutaneous reaction to intradermally injected purified protein derivative (PPD), but cross-reactivity with environmental non-tuberculous mycobacteria and bacille Calmette-Guérin (BCG) vaccine may cause false positive results. Although IGRAs have greater specificity, this has limited clinical relevance in most settings and exhibits considerable within-subject variability. Neither test can differentiate

LTBI from active TB, or incipient disease [15]. Cohort studies from different settings indicate that 5% to 15% of people with LTBI will eventually develop TB disease, the vast majority within the first two to five years after exposure [11, 16]. The majority of infected children will progress to disease within 12 months, and almost all within two years. However, biomarkers to determine which individuals have the highest risk of progression to TB are lacking, although promising biomarkers of incipient disease in adolescents with documented TB infection have recently been reported [17].

The risk of LTBI and TB disease among contacts exposed to MDR-TB is considerable. In a meta-analysis of 25 studies, 7.8% of household contacts of MDR-TB patients developed TB, with most occurring within three years after enrolment. Furthermore, 47.2% of contacts had LTBI [18]. Healthcare workers exposed to MDR-TB also have a substantially increased risk of MDR-TB [19, 20]. In settings with uncontrolled TB transmission within the community, not all TB among contacts is necessarily attributable to the identified source case. In studies from Lima, Peru, 9% and 14% of contacts grew isolates which differed genetically from their presumed source case, indicating a likely alternative source of the infection [21, 22]. However, most MDR-TB cases result from recognized exposure and strategies to prevent MDR-TB among known contacts are critical to an effective public health response.

Strategies to curb transmission of drug-resistant TB

Rapid TB diagnosis with drug susceptibility testing

Similar to DS-TB, early diagnosis and effective treatment are crucial elements of an effective MDR-TB control strategy. Diagnostic delay is a major contributor to ongoing TB transmission. Diagnosis of DR-TB requires drug susceptibility testing (DST), which has been unavailable in most high-prevalence settings until the recent deployment of rapid genotypic DST using GeneXpert MTB/RIF® or Line Probe Assays (e.g. INNO-LiPA® and Genotype MTBDRsl®) [23]. However, a substantial case detection gap persists and it is estimated that three quarters of all MDR-TB cases remained undetected in 2014 [1]. Globally, only 12% of new bacteriologically confirmed TB cases and 58% of previously treated cases have DST performed. Universal DST for all TB patients at the time of initial diagnosis is a strong

recommendation of the 2016 World Health Organization (WHO) MDR-TB treatment guidelines [24]. This strengthened guidance applies to all settings and age groups [25] and is the centerpiece of the proposed “F-A-S-T” strategy – to Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid DST [25]. Further research is required to evaluate the effectiveness of such strategies, since substantial investment by health systems will be required to translate this vision into reality.

Enhanced case finding is a vital strategy to bridge the substantial MDR-TB case detection gap. Systematic screening of high-risk populations, including household contacts of MDR-TB cases and those exposed in congregate settings such as hospitals and prisons, is likely to play an important role [22]. Current WHO guidelines advocate screening of all close contacts of infectious MDR and extensively drug-resistant TB (XDR-TB; i.e. MDR plus resistance to the fluoroquinolones and a second-line injectable agent) cases [26, 27]. Preventing disease or identifying disease at an early stage in these populations will benefit individuals and reduce ongoing transmission within their communities [28]. Regular symptom-based screening of other high-risk populations such as people living with HIV would also be beneficial. The roll-out of GeneXpert MTB/RIF® to 122 countries illustrates the potential for new technologies to bypass the limitations of weak laboratory infrastructure in resource-limited settings [23]. However, sustainability of funding for rapid genotypic tests is an ongoing concern in many countries, where donor funds have driven the scale-up. In addition, access to DST for second-line drugs remains an important priority in order to avoid delayed diagnosis and inappropriate treatment of XDR-TB with standardised MDR-TB regimens [29, 30].

Timely commencement of effective treatment

The delivery of effective treatment is critical to achieve optimal patient and public health benefits, since the disease is curable and effective treatment rapidly renders affected patients non-infectious. A South African study found that patients on effective MDR-TB treatment became non-infectious, to guinea pigs in adjacent wards exposed to exhaust air from these patients, within 2 days [31]. Only those on ineffective treatment (undiagnosed XDR-TB)

contributed to ongoing transmission to exposed guinea pigs. The study also showed that transmission varied substantially between patients, with a minority of patients being responsible for the bulk of transmission. Although patients ceased to be infectious within days of initiating effective treatment in this study, expert opinion recommends at least two weeks of effective TB therapy before transmission risk is considered to have reduced [31].

Since effective therapy limits the transmission risk, closely supervised MDR-TB therapy can be delivered to patients in the community without the resource implications of a prolonged inpatient stay [32, 33]. Home-based treatment also improves patient wellbeing [34] and treatment outcome [35, 36]. Studies of DS-TB found that home-based treatment did not increase infection or disease among household contacts [37]. This approach should also apply to effective MDR-TB treatment. In light of the available evidence, current WHO policies support decentralised MDR-TB care [1], with home confinement during the initial stages of therapy to minimise the transmission risk [38]. Not only is timely treatment commencement vital, but ongoing patient support for the full treatment duration is essential to avert treatment failure, disease relapse or amplification of drug resistance. Patient support includes methods of ensuring treatment adherence measures, such as direct observation of therapy, accompanied by social and psychological support [39]. Furthermore, monitoring bacteriological evidence of MDR-TB treatment response is important in settings where second-line drug resistance is unavailable, and more advanced drug resistance possible.

Enhanced infection control measures

Transmission of DR-TB within healthcare facilities and other congregate settings is a major concern, especially in resource limited settings. The well-documented XDR-TB outbreak in KwaZulu-Natal, South Africa, highlighted the dire consequences of poor infection control practices in healthcare settings [6]. Both hospitalised patients and healthcare workers were affected. Subsequent molecular strain typing and social network analyses demonstrated that 82% of patients may have acquired their infection in hospital. Studies in the surrounding community showed no increased XDR-TB prevalence [40], reinforcing the role of hospitals and clinics as important sites of potential TB transmission. The outbreak also highlighted the

risk of transmission and poor outcomes seen for people living with HIV exposed to drug resistant disease. This indicates the critical importance of prevention strategies among populations with high rates of HIV infection.

Institutional measures to control TB transmission form a critical part of an adequate health system response. The F-A-S-T strategy provides a valuable programmatic framework for reducing MDR/XDR-TB in high-prevalence settings [41]. Rapid diagnosis and effective treatment strategies act synergistically with the hierarchy of TB infection control measures; consisting of administrative, engineering or environmental and personal respiratory protection measures [42]. Facility-based administrative controls include cough triage systems and management of patient flows to separate possible TB or MDR/XDR-TB patients. There is limited evidence to quantify the impact of standardized administrative measures, but common-sense approaches are likely to be cost-effective. Engineering and environmental controls may include improved ventilation, directed airflow and use of ultraviolet light for germicidal irradiation [43].

Small particulate filters, such as N95 masks, protect the wearer from airborne infection, but are expensive, must be tight fitting to prevent air leaks and should be worn during all patient encounters. Washable cloths or single use surgical facemasks do not protect the wearer from becoming infected. If worn by infectious patients, surgical facemasks may reduce aerosol production and offer some protection to people in close proximity. Obligatory wearing of facemasks reduced the rate of infection by 56% (33 to 70.5%) in MDR-TB wards in South Africa [44], indicating the inadequacy of this strategy if used in isolation [45]. However, ensuring that infectious patients wear facemasks is challenging and may offer false reassurance to staff. More broadly, health systems should implement mechanisms for regular monitoring of basic infection control measures [46].

Contact investigation among high-risk groups

Screening of close contacts of infectious patients is an important public health priority, with early detection providing benefits for both individuals and the population. Household contact

investigation is important to screen symptomatic members, especially vulnerable young children and those with immunocompromise [47]. At the community level, routine use of molecular typing and social network analysis should alert public health officials to transmission hotspots and identify additional high-risk groups for whom screening may be required. In addition to screening household contacts, TB control programmes may also identify congregate settings or community locations where MDR-TB transmission is occurring. In some high-income settings, this approach has enabled public health programmes to enhance MDR-TB detection [48].

Strategies to reduce progression to disease

Preventive therapy

Preventive therapy with isoniazid or rifamycin-based regimens has long been the standard of care for infected contacts of patients with DS-TB [49]. However, evidence to inform the appropriate management of MDR-TB contacts is limited. Several observational studies suggest that preventive therapy based on second-line drugs may lower the risk of progression to TB disease. During two MDR-TB outbreaks on the island of Chuuk, Federated States of Micronesia, 104 infected contacts received fluoroquinolone-based preventive therapy. After 36 months of follow-up, none of the treated contacts but three of the 15 contacts who refused preventive therapy developed MDR-TB [50]. The program achieved exceptional (89%) adherence with directly observed therapy (DOT). Tailored regimens included a daily fluoroquinolone (moxifloxacin 400mg or levofloxacin 20 mg/kg), with ethambutol or ethionamide according to the DST of the source case.

A cohort study done in Cape Town, South Africa, provided six months of ofloxacin, ethambutol and high-dose isoniazid to young children (<5 years of age) in household contact with an infectious MDR-TB source case [51]. During 219 patient years of follow-up, only six of 186 (3.2%) infected children who received preventive therapy developed incident TB, which is much less than the number expected from natural history of disease studies. A previous study from the same setting provided tailored chemoprophylaxis to 105 young children (<5 years of age) in household contact with an infectious MDR-TB source case.

Among infected children, 2/41 (5%) that received appropriate MDR preventive therapy developed TB, compared to 13 of 64 (20%) who did not receive preventive therapy (odds ratio 5.0) [52].

Table 1 provides an overview of all published studies where preventive therapy was given to MDR-TB contacts. To date, no randomized controlled trial has assessed the efficacy of a particular preventive therapy regimen. A placebo-controlled randomized trial to treat LTBI in transplant candidates was terminated early on account of high rates of tendinopathy among those receiving levofloxacin [53]. However, this study population was not representative of most MDR-TB contacts, given all participants were taking prednisone – a recognised contributor to tendinopathy with fluoroquinolones. Trial results augur some caution in the use of fluoroquinolones, but similar findings have not been reported in the other prospective studies involving fluoroquinolones.

Current guidelines offer no consistent advice regarding the appropriate management of MDR-TB contacts. WHO recommends a conservative approach with periodic screening of infected contacts for at least two years, given the absence of randomized trial data [49]. However, a recent expert consensus paper suggested that fluoroquinolones should be considered in high-risk contacts, depending on the DST results of the likely source case in conjunction with follow-up [54]. US guidelines offer both preventive therapy and periodic surveillance without therapy as valid options [55]. In response to the need for improved clinical evidence, three randomised controlled trials will soon be underway to evaluate the effectiveness of preventive therapy for infected MDR-TB contacts. These will clarify the roles of levofloxacin alone (VQUIN and TB CHAMP) in the treatment of MDR-TB contacts and delamanid compared to standard dose isoniazid (PHOENix) as a potential universal preventive therapy regimen [56, 57]. Until these data are available, ongoing surveillance of contacts treated with preventive therapy is recommended, given that the effectiveness of these regimens is not yet known. Importantly, individuals with impaired immunity have a particularly high risk of progressing to disease. Consequently, high-risk contacts with reduced immunological function, particularly young children (<5 years of age) and people living with HIV, should be prioritised for follow-up

and/or preventive therapy in consultation with MDR-TB experts, in light of their increased susceptibility to develop TB disease.

Table 2 provides a brief overview of preventive therapy options for different types of DR-TB. Pyrazinamide is excluded, given the substantial toxicity and high rates of discontinuation reported in observational studies where the drug was used [58-60]. For contacts of MDR-TB plus fluoroquinolone resistance cases with low-level isoniazid resistance, some authors suggest the use of high-dose isoniazid [61], however there is no evidence to support this approach. Use of one or more drugs to which the likely source case is susceptible seems advisable in MDR-TB contacts. Given the potential toxicity and unproven effectiveness of preventive regimens for MDR-TB, clinicians need to weigh the potential toxicities of preventive therapy against the risk of developing TB disease in exposed individuals. In most adults, the risk of disease can be assessed using a test for LTBI, such as TST or IGRA. In young children who are evaluated within the TST/IGRA conversion window, preventive therapy may be commenced without LTBI confirmation [61]. However, it is important to identify uninfected children for whom exposure to potentially toxic preventive therapy has no benefit. Therefore, repeat testing is typically performed eight to 12 weeks after contact has ended, to allow sufficient time for an immunological response to occur.

Immunization

M. bovis BCG was developed as a pre-exposure vaccine and it reduces the risk of disseminated disease in young children. The protection conferred by the vaccine appears to vary substantially between populations, and decline over time [62]. However, the protection provided against adult-type disease is variable and its impact on epidemic transmission is minimal. Newer post-exposure vaccines are in development, but no protective efficacy has yet been established [63].

Future directions and research priorities

TB prevention, including the prevention of MDR/XDR TB, is a cornerstone of the End TB Strategy that defines global ambition for TB control in the coming decades [64]. Each of its

three pillars applies to MDR/XDR-TB prevention, including the importance of intensified research and innovation (Table 3). Research priorities include the development of a strong evidence base for the optimal use of preventive therapy in high-risk populations, determining the protective efficacy of novel vaccines [63], developing sensitive and rapid diagnostic tests for DR-TB (directly from sputum samples), identifying biomarkers to predict future disease risk, identifying pragmatic methods to enhance case detection, testing new models of care to reduce time to effective treatment, developing treatment regimens that are short, safe and durable and improving infection control in all high transmission settings [65].

Conclusion

Preventing the spread of MDR/XDR-TB is a global health priority and requires enhanced efforts to strengthen TB control in resource-limited settings. Given the substantial costs of treating drug resistant TB, targeted prevention strategies among high-risk populations are likely to be cost-effective. Given the substantial flow of migrants from high to low incidence regions around the world, investments in MDR/XDR-TB control in high-incidence countries also benefit countries where TB is less common [66]. Expansion of strategies to prevent MDR/XDR-TB disease and limit ongoing transmission will be critical if the ambitious global goal of TB elimination is to be realised.

Table 1: MDR-TB preventive therapy provided and outcomes achieved

Study (ref); Country (year)	Exposed group	Preventive therapy provided	Outcome achieved
Adler-Sohet [58] India (2014)	26 children (<5 years) Household contact TST ≥ 5mm	9 months LFX and PZA	57.7% completed at least 9 months of therapy. No TB after 24 months 46.2% experienced AEs
Attamna [67] Israel (2009)	12 contacts (all ages) Household contact TST positive	CIP and PZA (duration not reported)	No cases of TB
Bamrah [50] Federated States of Micronesia (2014)	104 contacts (all ages) Household or health facility contact TST ≥ 5mm	12 months Adults: MFX and EMB or ETH Children ≤12 years: LFX and EMB or ETH	89% completed therapy None developed TB after 36 months.
Denholm [68] Australia (2012)	18 contacts > 8 hours exposure TST positive	Between 2 and 9 months Various drugs [†]	No cases of TB [#]
Feja [69] USA (2008)	51 contacts (<15 years) TST positive	4.8-18.3 months Various drugs ^{**}	No cases of TB after 2 years.
Garcia-Prats [70] South Africa (2014)	23 children (<5 years) Day-care center contact TST positive or negative	6 months INH ⁺⁺ , EMB, OFX	No cases of TB after 12 months.
Horn [71] USA (1994)	16 health workers	6 months OFX and PZA	14 (88%) discontinued after less than 3 months ^{***} . Incident TB not reported
Kritski [72] Brazil (1996)	45 contacts (all ages) Close contact TST positive	Duration INH (dose not stated)	4% receiving high dose INH developed TB; 9% who did not
Lou [59] Singapore (2002)	48 solid organ transplant recipients Health facility contact TST status not reported	12 months LFX and PZA	27.1% completed; 66.7% discontinued due to AEs (mostly gastrointestinal) Incident TB not reported
Papastavros [73]	17 contacts	6-12 months	14 (82%) developed AEs

Canada (2002)	TST ≥ 5mm	LFX and PZA	Incident TB not reported
Ridzon [60] USA (1997)	22 contacts (21 with recent conversions)	12 months OFX and PZA	59% stopped within 6 months; no TB
Schaaf (52) South Africa (2002)	41 children (<5 years) Household contact TST positive	6 months INH++, PZA, ETH, OFX (3-4 drugs) individualised	5% developed TB during 30 months follow-up; 13/64 (20%) who elected not to receive therapy
Seddon [51] South Africa (2013)	186 children (<5 or HIV+ <15 years) Regardless of TST status	6 months INH++, ETH, OFX	3.2% developed TB during 219 patient-years of observation. Adherence 75.8%
Sneag [74] South Africa (2007)	5 children developed TB on “preventive therapy”	2 -14 months INH, RIF, PZA combinations	All 5 had index cases with MDR-TB
Tochon [75] France (2011)	6 children (<2 years) Household contact contacts (MDR or poly-drug resistant TB)	Up to 3 months INH and RIF. One child CIP and PZA.	1 (16%) developed TB
Trieu [76] USA (2015)	50 contacts (all ages) Two MDR-TB outbreaks	MFX or MFX + PZA Duration of therapy not reported	60% completed therapy; None developed MDR-TB [@]
Williams [77] United Kingdom (2013)	8 children (ages) Household or close social contact TST positive	6-12 months 2 drugs individualized	No TB after at least 2 years follow-up

Ref – reference; MDR - multidrug-resistant; TB - tuberculosis; TST - tuberculin skin test; DOT - directly observed therapy; DST - drug susceptibility test; AEs – Adverse effects; HIV – human immune deficiency virus; USA - United States of America

INH – isoniazid; INH++ - high-dose INH (see Table 2); EMB – ethambutol; ETH – ethionamide; CIP – ciprofloxacin; OFX – ofloxacin; LFX – levofloxacin; MFX – moxifloxacin; PZA – pyrazinamide

+One child was lost to follow-up; no outcome recorded

*Regimens included: MFX; RMP/PZA/EMB; CIP/PZA; INH/PZA; EMB/PZA; MFX/EMB; CIP

**Regimens included: an average of 3 drugs, including: quinolone agents (69%), cycloserine (67%), ethionamide (49%), pyrazinamide (53%), and ethambutol (39%).

***arthralgia (7 workers), gastrointestinal distress (6), hepatitis with alanine aminotransferase levels of 491 to 1776 U per liter (4), pruritus (4), fatigue (4), generalized maculopapular skin rash (3), insomnia (3), and vertigo (2).

Median follow-up period of contacts with LTBI was 54 months.

@One contact who took a month of MOX and PZA in 2006 developed TB due to a different drug susceptible strain than the initial index patient in 2009.

Table 2: Overview of drugs used in DR-TB preventive therapy; dose, potential application and adverse events to consider

Drugs	Daily dose (adult)	Daily dose (child)	Potential application	Common adverse events to consider	Evidence of efficacy
Isoniazid (INH)	Standard 5mg/kg; max 300mg High 10mg/kg; max 450mg	Standard 10 (7-15) mg/kg; max 300mg High 15-20mg/kg; max 450mg	Source case RIF mono-resistant TB and confirmed INH susceptible (not GeneXpert RIF resistance alone), consider INH at standard dose; If source case has low-level INH resistance, consider high-dose INH*	Rash, hepatotoxicity, peripheral neuropathy	n/a
Rifampicin (RIF)	10mg/kg; max 600mg	15 (10-20) mg/kg; max 600mg	INH-mono or polydrug resistant TB with source case RIF susceptible TB	Rash, flu-like illness, hepatitis, cytopaenia, drug-drug interactions (induced liver enzymes)	n/a
Ethambutol (EMB)	15mg/kg#; max 600mg	20mg/kg#; max 600mg	Companion agent if source case EMB susceptible (or likely susceptible) TB	Rash, visual impairment (decreased acuity, colour vision or visual fields)**	May be effective as a part of multi-drug regimen [50]
O/Levofloxacin (O/LFX)	OFX: 800mg LFX: 500-750mg#	OFX: 20mg/kg; max 800mg LFX 15-20mg/kg#; max 750mg	Main drug for preventive therapy following MDR-TB exposure/infection without fluoroquinolone resistance	Rash, tendinitis, tendon rupture, QT prolongation.	[50, 51]
Moxifloxacin	400mg	10mg/kg; max 400mg	Main drug for preventive therapy following MDR-TB exposure/infection without fluoroquinolone resistance	Rash, tendinitis, tendon rupture, QT prolongation.	n/a
Delamanid	100mg twice daily##	n/a	Consider for highly vulnerable close contact of MDR plus FQN and XDR-TB source case	QT prolongation	n/a

MDR – Multidrug resistance, resistance to isoniazid and rifampicin; XDR- extensively drug resistant, MDR with additional resistance to fluoroquinolones and second line injectable antibiotics

n/a – not available, but expected to be efficacious given evidence of adequate activity in comparable situations

*Low level INH resistance defined as resistance at 0.1ug/mL and susceptibility at 0.4ug/mL on liquid culture.

**More common with renal impairment.

#Dose reduction recommended if creatinine clearance <30%.

##Fewer patients taking delamanid had side effects when treated with 100mg twice daily compared to 200mg twice daily [78]

Table 3: Strategies to prevent M/XDR-TB within the End TB Strategy framework

Pillar	M/XDR-TB prevention strategies
1. Integrated patient-centred care and prevention	<ul style="list-style-type: none"> • Early diagnosis with universal drug susceptibility testing • Screening of close contacts • Preventive therapy for infected high-risk contacts • Early and effective therapy for drug-resistant disease
2. Bold policies and supportive systems	<ul style="list-style-type: none"> • Effective infection control policies; scale-up of implementation • Optimised MDR/XDR-TB treatment models, including decentralized support systems and social protection • Active case finding in high-risk populations
3. Intensified research and innovation	<ul style="list-style-type: none"> • Overcome local barriers to improve infection control • Identify optimal preventive therapy strategies • Expedite the diagnosis of drug resistant TB • Improve treatment outcome; short duration treatment with minimal adverse effects

Transparency declaration

No conflicts of interest were declared. G.J. Fox was supported from a CJ Martin Post-Doctoral Fellowship (Australian National Health and Medical Research Council, APP 1054107).

References

- 1 World Health Organization. Global tuberculosis report 2015. In: WHO, ed. 2015.
- 2 Lonnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: An action framework for low-incidence countries. *Eur Respir J*. 2015; **45**: 928-952.
- 3 Seung KJ, Gelmanova IE, Peremitin GG, et al. The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. *Clin Infect Dis*. 2004; **39**: 1321-1328.
- 4 Borrell S, Gagneux S. Infectiousness, reproductive fitness and evolution of drug-resistant *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis*. 2009; **13**: 1456-1466.
- 5 Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: A transmission modelling analysis. *Lancet Respir Med*. 2015; **3**: 963-972.
- 6 Gandhi NR, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in south africa. *J Infect Dis*. 2013; **207**: 9-17.
- 7 Zhao M, Li X, Xu P, et al. Transmission of mdr and xdr tuberculosis in shanghai, china. *PloS one*. 2009; **4**: e4370.
- 8 Gelmanova IY, Keshavjee S, Golubchikova VT, et al. Barriers to successful tuberculosis treatment in tomsk, russian federation: Non-adherence, default and the acquisition of multidrug resistance. *Bull World Health Organ*. 2007; **85**: 703-711.

- 9 Royce S, Falzon D, van Weezenbeek C, et al. Multidrug resistance in new tuberculosis patients: Burden and implications. *Int J Tuberc Lung Dis.* 2013; **17**: 511-513.
- 10 Clark TG, Mallard K, Coll F, et al. Elucidating emergence and transmission of multidrug-resistant tuberculosis in treatment experienced patients by whole genome sequencing. *PloS one.* 2013; **8**: e83012.
- 11 Trauer JM, Moyo N, Tay EL, et al. Risk of active tuberculosis in the five years following infection . . . 15%? *Chest.* 2016; **149**: 516-525.
- 12 Lin PL, Rodgers M, Smith L, et al. Quantitative comparison of active and latent tuberculosis in the cynomolgus macaque model. *Infect Immun.* 2009; **77**: 4631-4642.
- 13 Barry C, Boshoff H, Dartoise V, et al. The spectrum of latent tuberculosis: Rethinking the biology of intervention strategies. *Nat Rev Microbiol.* 2009; **7**: 845-855.
- 14 Seddon JA, Godfrey-Faussett P, Hesselning AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*. *Lancet Infect Dis.* 2012; **12**: 469-479.
- 15 Pai M, Zwerling A, Menzies D, Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: An update. *Ann Intern Med.* 2008; **149**: 177-184.
- 16 Marks GB, Bai J, Simpson SE, Stewart GJ, Sullivan EA. The incidence of tuberculosis in a cohort of south-east asian refugees arriving in australia 1984-94. *Respirology.* 2001; **6**: 71-74.

- 17 Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood rna signature for tuberculosis disease risk: A prospective cohort study. *Lancet*. 2016; **387**: 2312-2322.
- 18 Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: Systematic review and meta-analysis. *Clin Infect Dis*. 2014; **58**: 381-391.
- 19 O'Donnell MR, Jarand J, Loveday M, et al. High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among south african health care workers. *Ann Intern Med*. 2010; **153**: 516-522.
- 20 Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and hiv in a rural area of south africa. *Lancet*. 2006; **368**: 1575-1580.
- 21 Becerra M, Appleton S, Franke M, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: A retrospective cohort study. *Lancet*. 2011; **377**: 147-152.
- 22 Grandjean L, Gilman RH, Martin L, et al. Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: A prospective cohort study. *PLoS Med*. 2015; **12**: e1001843; discussion e1001843.
- 23 Albert H, Nathavitharana RR, Isaacs C, Pai M, Denkinger C, Boehme CC. Development, roll-out and impact of Xpert MTB-RIF for

- tuberculosis: What lessons have we learnt and how can we do better?
Eur Respir J. 2016; **In press**.
- 24 World Health Organization. Who treatment guidelines for drug-resistant tuberculosis - 2016 update. In: WHO, ed. Geneva: WHO 2016.
- 25 Barrera E, Livchits V, Nardell E. F-a-s-t: A refocused, intensified, administrative tuberculosis transmission control strategy. *Int J Tuberc Lung Dis.* 2015; **19**: 381-384.
- 26 World Health Organization. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva. 2012.
http://www.who.int/tb/publications/2012/contact_investigation2012/en/
(Accessed 1/1/2014).
- 27 World health Organization. Systematic screening for active tuberculosis: Principles and recommendations. In: Organization WH, ed. Geneva: WHO 2013.
- 28 Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. *Am J Respir Crit Care Med.* 2013; **187**: 543-551.
- 29 Lacombe A, Garcia-Sierra N, Prat C, et al. Genotype MTBDRsl for molecular detection of second-line-drug and ethambutol resistance in *Mycobacterium tuberculosis* strains and clinical samples. *J Clin Micro.* 2012; **50**: 30-36.
- 30 Van't Hoog AH, Bergval I, Tukvadze N, et al. The potential of a multiplex high-throughput molecular assay for early detection of first and second line tuberculosis drug resistance mutations to improve

- infection control and reduce costs: A decision analytical modeling study. *BMC Infect Dis.* 2015; **15**: 473.
- 31 Dharmadhikari AS, Mphahlele M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2014; **18**: 1019-1025.
- 32 NICE. *Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control.* 2011.
<http://guidance.nice.org.uk/CG117>
- 33 Sinanovic E, Ramma L, Vassall A, et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in south africa. *Int J Tuberc Lung Dis.* 2015; **19**: 172-178.
- 34 Horter S, Stringer B, Reynolds L, et al. "Home is where the patient is": A qualitative analysis of a patient-centred model of care for multi-drug resistant tuberculosis. *BMC Health Serv Res.* 2014; **14**: 81.
- 35 Cox H, Hughes J, Daniels J, et al. Community-based treatment of drug-resistant tuberculosis in khayelitsha, south africa. *Int J Tuberc Lung Dis.* 2014; **18**: 441-448.
- 36 Loveday M, Wallengren K, Brust J, et al. Community-based care vs. Centralised hospitalisation for mdr-tb patients, kwazulu-natal, south africa. *Int J Tuberc Lung Dis.* 2015; **19**: 163-171.
- 37 Kamat SR, Dawson JJ, Devadatta S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in south india. *Bull World Health Organ.* 1966; **34**: 517-532.

- 38 National Institute of Health and Care Excellence. Tuberculosis: Nice guideline (ng33). 2016.
- 39 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update. Geneva: WHO 2011.
- 40 Bantubani N, Kabera G, Connolly C, et al. High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (mdr-tb) among hospital inpatients in kwazulu natal, south africa indicate risk of nosocomial transmission. *PloS one*. 2014; **9**: e90868.
- 41 Bates M, O'Grady J, Mwaba P, et al. Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients. *PloS one*. 2012; **7**: e40774.
- 42 World Health Organization. *Who policy on tb infection control in health-care facilities, congregate settings and households*. 2009.
whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf
- 43 Escombe AR, Moore DA, Gilman RH, et al. Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. *PLoS Med*. 2009; **6**: e43.
- 44 Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: Impact on infectivity of air on a hospital ward. *Am J Respir Crit Care Med*. 2012; **185**: 1104-1109.

- 45 Chen SK, Vesley D, Brosseau LM, Vincent JH. Evaluation of single-use masks and respirators for protection of health care workers against mycobacterial aerosols. *Am J Infect Control*. 1994; **22**: 65-74.
- 46 Migliori GB, Sotgiu G, D'Ambrosio L, et al. Tb and mdr/xdr-tb in european union and european economic area countries: Managed or mismanaged? *Eur Respir J*. 2012; **39**: 619-625.
- 47 Arend SM, van Soolingen D. Editorial commentary: Genotyping of *Mycobacterium tuberculosis* in China and missing links in the chain of ongoing transmission of tuberculosis. *Clin Infect Dis*. 2015; **61**: 228-232.
- 48 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in new york city--turning the tide. *New Engl J Med*. 1995; **333**: 229-233.
- 49 World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva: WHO 2014.
- 50 Bamrah S, Brostrom R, Dorina F, et al. Treatment for Itbi in contacts of mdr-tb patients, federated states of micronesia, 2009-2012. *Int J Tuberc Lung Dis*. 2014; **18**: 912-918.
- 51 Seddon JA, Hesselning AC, Finlayson H, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: A prospective cohort study. *Clin Infect Dis*. 2013; **57**: 1676-1684.
- 52 Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesselning PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: A 30-month follow-up. *Pediatrics*. 2002; **109**: 765-771.

- 53 Torre-Cisneros J, San-Juan R, Rosso-Fernandez CM, et al. Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: Safety analysis of a multicenter randomized trial. *Clin Infect Dis*. 2015; **60**: 1642-1649.
- 54 Seddon J, Fred D, Amanullah F, et al. Post-exposure management of multidrug-resistant tuberculosis contacts: Evidence-based recommendations. *Policy Brief No 1*. Dubai, United Arab Emirates: Harvard Medical School Center for Global Health Delivery - Dubai. 2015.
- 55 Curry International Tuberculosis Center and California Department of Public Health. Drug-resistant tuberculosis: A survival guide for clinicians, 3rd edition. 2016.
- 56 V-QUIN MDR Investigators. *The VQUIN MDR trial*. 2016. <https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817> (Accessed 15th July, 2016).
- 57 McKenna L. *Momentum in the pediatric tuberculosis treatment pipeline*. 2015. <http://www.pipelinerreport.org/2015/tb-pediatrics> (Accessed July 15, 2016).
- 58 Adler-Shohet FC, Low J, Carson M, Girma H, Singh J. Management of latent tuberculosis infection in child contacts of multidrug-resistant tuberculosis. *Pediatr Infect Dis J*. 2014; **33**: 664-666.
- 59 Lou HX, Shullo MA, McKaveney TP. Limited tolerability of levofloxacin and pyrazinamide for multidrug-resistant tuberculosis prophylaxis in a solid organ transplant population. *Pharmacotherapy*. 2002; **22**: 701-704.

- 60 Ridzon R, Meador J, Maxwell R, Higgins K, Weismuller P, Onorato IM. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. *Clin Infect Dis*. 1997; **24**: 1264-1265.
- 61 Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: A survival guide for paediatricians. *Paediatr Respir Rev*. 2011; **12**: 31-38.
- 62 Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus calmette-guerin vaccination against tuberculosis. *Health Technol Assess*. 2013; **17**: 1-372, v-vi.
- 63 Luabeya AK, Kagina BM, Tameris MD, et al. First-in-human trial of the post-exposure tuberculosis vaccine h56:lc31 in *Mycobacterium tuberculosis* infected and non-infected healthy adults. *Vaccine*. 2015; **33**: 4130-4140.
- 64 Uplekar M, Weil D, Lonroth K, et al. Who's new end tb strategy. *Lancet*. 2015; **385**: 1799-1801.
- 65 Mitnick CD, Rodriguez CA, Hatton ML, et al. Programmatic management of drug-resistant tuberculosis: An updated research agenda. *PloS one*. 2016; **11**: e0155968.
- 66 Schwartzman K. Domestic returns from investment in the control of tuberculosis in other countries. *N Engl J Med*. 2005; **353**: 1008-1020.
- 67 Attamna A, Chemtob D, Attamna S, et al. Risk of tuberculosis in close contacts of patients with multidrug resistant tuberculosis: A nationwide cohort. *Thorax*. 2009; **64**: 271.

- 68 Denholm JT, Leslie DE, Jenkin GA, et al. Long-term follow-up of contacts exposed to multidrug-resistant tuberculosis in victoria, australia, 1995-2010. *Int J Tuberc Lung Dis.* 2012; **16**: 1320-1325.
- 69 Feja K, McNelley E, Tran CS, Burzynski J, Saiman L. Management of pediatric multidrug-resistant tuberculosis and latent tuberculosis infections in new york city from 1995 to 2003. *Pediatr Infect Dis J.* 2008; **27**: 907-912.
- 70 Garcia-Prats AJ, Zimri K, Mramba Z, Schaaf HS, Hesselning AC. Children exposed to multidrug-resistant tuberculosis at a home-based day care centre: A contact investigation. *Int J Tuberc Lung Dis.* 2014; **18**: 1292-1298.
- 71 Horn DL, Hewlett D, Jr., Alfalla C, Peterson S, Opal SM. Limited tolerance of ofloxacin and pyrazinamide prophylaxis against tuberculosis. *New Engl J Med.* 1994; **330**: 1241.
- 72 Kritski AL, Marques MJ, Rabahi MF, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med.* 1996; **153**: 331-335.
- 73 Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. *CMAJ.* 2002; **167**: 131-136.
- 74 Sneag DB, Schaaf HS, Cotton MF, Zar HJ. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. *Pediatr Infect Dis J.* 2007; **26**: 1142-1146.

- 75 Tochon M, Bosdure E, Salles M, et al. Management of young children in contact with an adult with drug-resistant tuberculosis, France, 2004-2008. *Int J Tuberc Lung Dis*. 2011; **15**: 326-330.
- 76 Trieu L, Proops DC, Ahuja SD. Moxifloxacin prophylaxis against multidrug-resistant tuberculosis, New York, New York, USA. *Emerg Infect Dis*. 2015; **21**: 500-503.
- 77 Williams B, Ramroop S, Shah P, et al. Management of pediatric contacts of multidrug-resistant tuberculosis in the United Kingdom. *Pediatr Infect Dis J*. 2013; **32**: 926-927.
- 78 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *New Engl J Med*. 2012; **366**: 2151-2160.