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Post-Exposure Management of Multidrug-Resistant Tuberculosis Contacts: Evidence-Based Recommendations

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SUMMARY

On 12-13 April 2015, a global panel of 51 tuberculosis practitioners from 33 cities in 19 countries gathered at the Harvard Medical School Center for Global Health Delivery in Dubai to synthesize evidence and produce practical guidance for the management of children and adults exposed to multidrug-resistant tuberculosis (MDR-TB; i.e. resistance to at least rifampin and isoniazid, the most commonly used first-line anti-TB drugs). After review of published and unpublished evidence, this panel arrived at a set of seven principles to guide the management and treatment of MDR-TB exposure and infection. We summarize these recommendations along with the process employed to produce them.

THE SPECTRE OF DRUG-RESISTANT INFECTIONS

Infections caused by drug-resistant organisms are increasing: a recent report suggested that, by 2050, drug-resistant organisms will kill over 10 million individuals each year, more than are predicted to die from cancer. From an economic perspective, the cost to the global economy could be as much as USD 100 trillion.[1] Nine million people develop tuberculosis (TB) each year, of which at least half a million have MDR-TB. The control of TB will require the identification and treatment of both individuals who are sick with TB disease as well as the treatment of asymptomatic contacts who have been exposed to TB and are likely to have been infected.[2] This is as true for MDR-TB as it is for drug-susceptible (DS)-TB. However, to date, the investigation and treatment of individuals exposed to MDR-TB is rarely carried out.

HOW TO STOP AN OUTBREAK OF MULTIDRUG-RESISTANT TUBERCULOSIS

In June 2007, on the Island state of Chuuk in the Federated States of Micronesia, an adult was diagnosed with pulmonary TB. Treatment with standard first-line drugs was initiated but no clinical improvement was seen. In November 2007, drug susceptibility test (DST) results identified the strain of *M. tuberculosis* from the patient as MDR.[3] Second-line drugs were not available and the patient died. Subsequently four others were diagnosed with MDR-TB and, without access to appropriate treatment, three died, including a two year-old child. The majority of these patients had been infectious for prolonged periods and had a large number of close family contacts. In July 2008, at the request of the Micronesian government, a team from the U.S. Centers for Disease Control and Prevention (CDC), together with representatives from the World Health Organization (WHO), arrived to investigate the outbreak.[4] Through contact investigation, 232 contacts were identified; 15 were diagnosed with MDR-TB disease. These patients were started on appropriate treatment with second-line drugs with good response. Of the remainder, 119 were found to be infected and were offered treatment with a fluoroquinolone-based regimen.[5] None of the contacts given treatment for TB infection developed TB disease and the treatment of TB infection was found to be safe and well tolerated. Among the 15 who refused to take treatment, 3 (20%) developed MDR-TB disease over the subsequent three years. The combination of active case-finding and treatment of those with MDR-TB disease, together with the identification and treatment of close contacts with MDR-TB infection, contained and halted this outbreak.

DEVELOPING EVIDENCE-BASED GUIDANCE

Today MDR-TB exposure and infection is treated in only a small number of settings. One reason for this is the dearth of clear guidance.[6-16] With the lessons learned from Micronesia, together with more than two decades of observational evidence for the safety and efficacy of treatment for presumed MDR-TB infection, many front-line healthcare providers think that more should be done for close contacts of MDR-TB patients. A lack of evidence for the efficacy of any drug to treat MDR-TB infection has been cited frequently as the reason not to provide guidance about how to treat infection before disease develops. The WHO currently advises no treatment for MDR-TB contacts as the GRADE process used by WHO to derive recommendations would likely find insufficient evidence to confirm efficacy.[7,8,14] However, given the severe consequences of developing MDR-TB disease, many providers are increasingly uncomfortable with a 'watch and wait' approach to vulnerable contacts. More evidence is badly needed and although three clinical trials are due to start within the next year with the aim of evaluating different treatment regimens for MDR-TB infection, the results from these studies will not be available for several years. In the interim many thousands of individuals will develop MDR-TB disease. For over 20 years, guidance in the United States has advised treatment for the contacts of MDR-TB patients, using drugs to which the strain from the source case is susceptible.[16] Many experts feel that enough evidence currently exists to recommend treatment.

To address this gap in guidance, in early 2015 a group of TB clinicians and researchers (MCB, JAS, JJF, SK, JRS, SS) supported by the Harvard Medical School Center for Global Health Delivery -Dubai, convened a global consultation on how to best manage household contacts of MDR-TB patients. Through literature review and evaluation of personal networks, experts were identified and invited to participate in a two-day meeting in Dubai on 12-13 April 2015. Over the two-day consultation, both published and unpublished evidence was presented from studies and TB programs, as well as available relevant guidance.[6-16] There were formal presentations and small-group break-out discussions during which the experts were asked for their opinions on a series of structured questions, which were then discussed by the larger group. An independent rapporteur recorded all presentations and discussion and synthesized these into a formal report of proceedings.[17]

A writing group was assembled to draft a guidance document providing evidence-based recommendations to assist front-line providers, based on a summary of the evidence presented and the views of the assembled experts. JAS and MCB prepared a draft, which was refined and edited over multiple iterations and conference calls by the writing group. The draft document was sent to the entire group who attended the meeting in Dubai for endorsement, as well as to other experts in the field. Those endorsing these recommendations are listed at the end of this brief.

EVIDENCE CONSIDERED

Treatment with fluoroquinolone-based therapy

The treatment of DS-TB infection with isoniazid or a rifamycin-based regimen to prevent the progression to DS-TB disease is highly effective in both HIV- negative[18,19] and HIV-positive contacts.[20] The use of these regimens to treat TB infection in contacts of MDR-TB cases is, however, questionable.[21-23] In contrast, the fluoroquinolones have good efficacy in the laboratory against *M. tuberculosis* have good early bactericidal activity, and improve treatment outcomes in adults with MDR-TB disease, suggesting effectiveness.[24]

While there have been concerns about the safety of fluoroquinolones in children, originating from a study in juvenile beagles in 1977,[25] a significant body of evidence has demonstrated drugs of this class to be safe in children, even for long-term use. This includes a number of studies describing the treatment of MDR-TB in children.[26-31] An expert panel of the American Academy of Pediatrics concluded that fluoroquinolone use in children is justified when clinically indicated and, in 2011, an Essential Medicines Committee of the WHO supported the use of fluoroquinolones in infants and children with TB.[32,33]

Efficacy and safety

The group acknowledged that further evidence was urgently needed and the findings from the planned clinical trials will be crucial to improving our confidence in the efficacy and safety of regimens for the treatment of MDR-TB infection. However, the current evidence base now includes at least ten observational studies, including over six hundred contacts treated for presumed MDR-TB infection. In addition to the experience in Micronesia, other studies have described outbreaks or cohorts in a number of different contexts (Table 1). The largest of these are two studies from Cape Town and two from New York. The first describes the management and follow-up of 105 children exposed to MDR-TB. Two (5%) of 41 children given six months of treatment for TB infection (using combinations of drugs to which the strain from the source case was susceptible) developed TB, whereas 13 (20%) of 64 children not given treatment progressed to disease.[34] In the second Cape Town study, 186 children were given six months of ofloxacin, ethambutol and high-dose isoniazid. Only two children who took the medications developed TB disease during 219 patient-years of observation time.[26] In the late 1990s, 51 children in New York were treated for MDR-TB infection. Treatment was tailored to the DST of the source case. Children received an average of three drugs, most commonly including a fluoroquinolone, and were treated for an average of ten months. None developed TB disease. The other study from New York describes contact investigations and management following the diagnosis of MDR-TB in two HIV-positive individuals. Fifty mainly HIV-positive adults were treated for TB infection with either moxifloxacin alone or moxifloxacin and pyrazinamide; 30 completed 12 months of treatment and none developed TB. In all four of these studies, as well as in Micronesia, treatment was well tolerated and few adverse events were noted. The unpublished results from several treated cohorts of individuals exposed to MDR-TB are consistent with the published cohorts in terms of both effectiveness and safety.[17]

Concordance

The likelihood of concordance between the drug susceptibility of the strain from a putative source case and the strain in an identified contact is determined by several factors. These include the infectiousness of the source case, the intensity of exposure, the duration of exposure and the presence of other TB patients who might have infected the contact recently or in the past.[35] In household contact investigations concordance is high, as the intensity and duration of exposure is significant.[36-39] In addition, concordance is likely to be higher in young children than in either older children or adults, as young children interact primarily with a small circle of caregivers. It is acknowledged that for non-household or older contacts, concordance may be lower, but even if the contact is infected with a DS-TB strain, a fluoroquinolone-based regimen is likely to be effective.

Resistance propagation

A large systematic review and meta-analysis found no statistically significant risk of increased isoniazid resistance in contacts developing TB disease following isoniazid monotherapy.[40] If a contact is not adequately screened for TB disease prior to the initiation of monotherapy for TB infection, it is possible that resistance will emerge to that single agent. However, if disease is excluded, the low number of organisms present in TB infection is unlikely to allow the development of resistance. Spontaneous mutations that give rise to isoniazid resistance occur once every $10^{5\text{-}6}$ divisions[41] whereas mutations causing resistance to the fluoroquinolones arise every $10^{6\text{-}8}$ divisions.[42] This, in theory, suggests that there is a smaller chance of developing resistance to the fluoroquinolones compared with isoniazid. Recent modeling suggests that the treatment of MDR-TB infection may, in fact, lead to less resistance.[43]

Concerns have been raised that the use of fluoroquinolones for the treatment of TB infection will lead to resistance in other bacteria. This is a possibility, particularly over the long durations of therapy that are used for TB treatment; a study from South Africa seems to support this concept.[44] However, given the extensive use of fluoroquinolone monotherapy in many parts of the world for gastrointestinal infections, urinary tract infections, otitis media, and pneumonia, among other indications, the proportion of individuals receiving this drug class for treatment of TB infection will be low.

Consequences of developing multidrug-resistant tuberculosis disease

Should an exposed child or adult develop MDR-TB disease, the consequences are profound. Treatment is long, and frequently requires admission to a hospital away from family and community. The second-line drugs used to treat MDR-TB disease are toxic; a quarter of children develop hearing loss on treatment[45] and half have thyroid dysfunction.[46] A lack of tolerability can also compromise adherence and potentially lead to resistance amplification. Successful treatment outcomes are seen in only 62% of adults.[47] Outcomes for children are better when treated by experts in specialist centres[48] but, under operational conditions they are similar to those for adults.[31] MDR-TB disease is expensive to treat once it has developed, consuming a large proportion of most countries' TB budgets.[49-52] It should be acknowledged, however, that earlier diagnosis and treatment initiation should be associated with better outcomes, underscoring the importance of screening contacts and close follow-up.

EVIDENCE-BASED GUIDANCE: SEVEN PRINCIPLES

The group decided that the highest priority was to carry out post-exposure management in the context of a household contact investigation. Five to ten percent of household contacts have MDR-TB disease at the time the source case is diagnosed and half have evidence of TB infection.[53] This provides a far higher yield than other forms of contact investigation. Definitions of 'household' vary in different settings[54] and programs will need to define a context-specific definition prior to carrying out this activity. Some programs may decide to expand screening and treatment of contacts beyond the household. We identified seven principles to guide the management of households exposed to MDR-TB.

1. DEFINE COMMON TERMS.

'Prophylaxis' and 'preventive' therapy can suggest that treatment is unimportant. 'Latent' suggests that an established immunological equilibrium has occurred and the mycobacteria are in a state of dormancy; this is unlikely to be true in recently infected adults and even less likely in children. We suggest adopting the term 'treatment of TB infection.' We further propose the term "post-exposure management" of MDR-TB household contacts, which encompasses the investigation and treatment of either disease or infection (or exposure if infection cannot be ascertained). These terms underscore urgency and the practical task of delivering drug treatment (among other interventions).

2. IDENTIFY ALL HOUSEHOLD CONTACTS.

Following the diagnosis of MDR-TB in an infectious individual, all others in the home (adults and children) should be identified, reported and recorded (Figure 1). This can happen through discussion with the patient in the clinic, but consideration should be given to carrying out a home visit. Frequently contacts are identified at a home visit who had not been revealed by history-taking. Teams need to be creative about how to conduct home visits as this can be a stigmatizing activity and it may not be appropriate or desired for healthcare teams to arrive at a patient's home. Consideration also needs to be given to the best time to carry out the home visit. School-age children and those with jobs are rarely at home in the hours that healthcare workers call. Multiple visits may be necessary to identify all contacts. A registry of household contacts will not only allow appropriate case management, but it will also permit an assessment of workload for healthcare workers and serves as a basis for programs to set and monitor household care targets.[55] Standardized data collection tools are being developed.

3. EVALUATE ALL EXPOSED INDIVIDUALS FOR TB DISEASE.

"Exposed individuals" include children and adults, and evaluation can take place in the household or contacts can be brought to the clinic. A comprehensive symptom screen is adequate to rule out MDR-TB disease.[56] When available, chest radiographs can improve clinical confidence, but lack of availability should not be an obstacle to screening. Any contacts with symptoms of TB disease should be referred to TB or other appropriate health services for further

investigation (including specimens for culture and DST) and appropriate treatment. If TB disease is ruled out, the contact can then be considered for treatment of TB infection.

4. OFFER TREATMENT FOR MDR-TB INFECTION.

The majority of the group felt that all infected household contacts, if exposed to a source case with TB not confirmed to have fluoroquinolone resistance, would benefit from treatment of TB infection. In many contexts, tests of infection (tuberculin skin tests [TST] and interferon-γ release assays [IGRAs]) are unavailable; in these situations significant exposure should warrant treatment for TB infection, after TB disease has been ruled out. Due to limitations in the sensitivity of tests of infection in young children (<5 years) and in individuals who are HIV-positive,[57,58] treatment for TB infection can be provided on the basis of significant exposure in these populations, even if tests for infection are negative. If programs decide not to treat all infected household contacts, specific high-risk groups should be prioritized. These should always include children less than five years of age and contacts felt to be immunosuppressed, irrespective of age.

We recommend treatment with a fluoroquinolone-based regimen and, in the absence of data on optimal duration, we suggest that at least six months of treatment would be appropriate given this duration was used in a number of the studies reviewed. Appropriate regimens would include: a fluoroquinolone alone (either moxifloxacin or levofloxacin) or a fluoroquinolone in combination with another agent to which the organism from the source case has been documented to be susceptible (ethambutol or ethionamide). The combination of a fluoroquinolone and pyrazinamide has been shown to be associated with more frequent adverse events and should be avoided.[59-61]

Treatment should be given daily and can be delivered through mechanisms determined by individual programs. Following the programmatic experiences in Micronesia, treatment support workers, directly observed therapy (DOT) supporters or lay supporters should supervise treatment. With appropriate counselling, some programs may enlist individuals or family members/caregivers to take responsibility for treatment. A registry of those treated for TB infection should be implemented, as a sub-set of a registry of all MDR-TB exposed individuals which should be maintained. The number of contacts treated for infection should be reported to national TB authorities.

5. FOLLOW ALL EXPOSED INDIVIDUALS FOR AT LEAST 18 MONTHS.

All exposed household contacts should be followed up irrespective of whether they receive treatment for TB infection. This is to support treatment if given, and also to identify incident TB disease if it occurs early so treatment can be provided to allow the greatest chance of success. The majority of contacts who progress to disease will do so within the first year or two following infection.[34,62,63] If disease does develop, efforts should be made to collect specimens to confirm the diagnosis and to carry out DST. However, once specimens have been obtained, treatment should be started and directed against the DST of the strain from the source case.[64,65] In the absence of data to inform optimal duration or frequency of follow-up, we recommend that contacts should be followed up clinically for at least 18 months from the time of screening. As the risk of developing TB disease is greatest in the first few months, screening should be every 2-3 months for the first 6 months and then 6-monthly thereafter. Outcomes for those treated and not treated should be recorded and reported.

6. BUILD A PROGRAMMATIC STRATEGY TO TREAT MDR-TB INFECTION.

Treatment of MDR-TB infection can be delivered either through existing mechanisms or through complementary systems. In some contexts the best person to carry out the post-exposure management of a household is the health worker who is supporting the treatment of the patient with MDR-TB disease. This worker is likely to be

visiting the patient regularly (or daily if performing DOT) and will know household members. A well-described example is in New York City where the case manager is responsible for both the patient and the household unit, for both DS- and MDR-TB.[66] Implementing this model may require adjustment in the number of cases that each worker manages to reflect an increase in workload.

In other settings, a dedicated team, separate but complementary, may be tasked with the post-exposure management of households. Parallels can be drawn with the HIV community where prevention of mother-to-child transmission (PMTCT) programs are run in parallel to HIV treatment programs. Lay health workers can be trained and enlisted to perform these tasks. Additional resources will be required for staffing as simply adding this role to the long list of tasks already expected of workers may be impractical. In order to procure resources, it will be necessary to dispel the outdated notion that treating TB infection is a 'luxury' that programs cannot afford. On the contrary, treating MDR-TB infection is likely to be a very cost-effective strategy.[43]

7. LEARN FROM THE EXPERIENCES IN TREATING DS-TB INFECTION.

Efficacy and safety are important characteristics in a regimen for treating MDR-TB infection, but there are other significant factors that can affect successful programmatic implementation. The poor global uptake of isoniazid for the treatment of DS-TB infection has demonstrated multiple health system and socioeconomic factors that must be taken into account to ensure successful implementation of a TB infection treatment program. Commentators have suggested possible solutions to these challenges,[67] which need to be understood and addressed in all post-exposure management plans for MDR-TB contacts.

CONCLUSIONS

Further evidence is urgently needed in this field and findings from the planned clinical trials are keenly awaited. However, in the interim, action can be taken. Post-exposure management of household contacts of MDR-TB is effective, feasible and cost-efficient, and could be implemented immediately. We have identified general principles that can be incorporated into local guidance and policies. How these principles are incorporated will vary by context and setting. It is vital, however, that these experiences are reported and shared so that the evidence base continues to grow in support of an improved global strategy for MDR-TB prevention and control.

Figure 1. Algorithm for post-exposure management for households of patients with multidrug-resistant tuberculosis

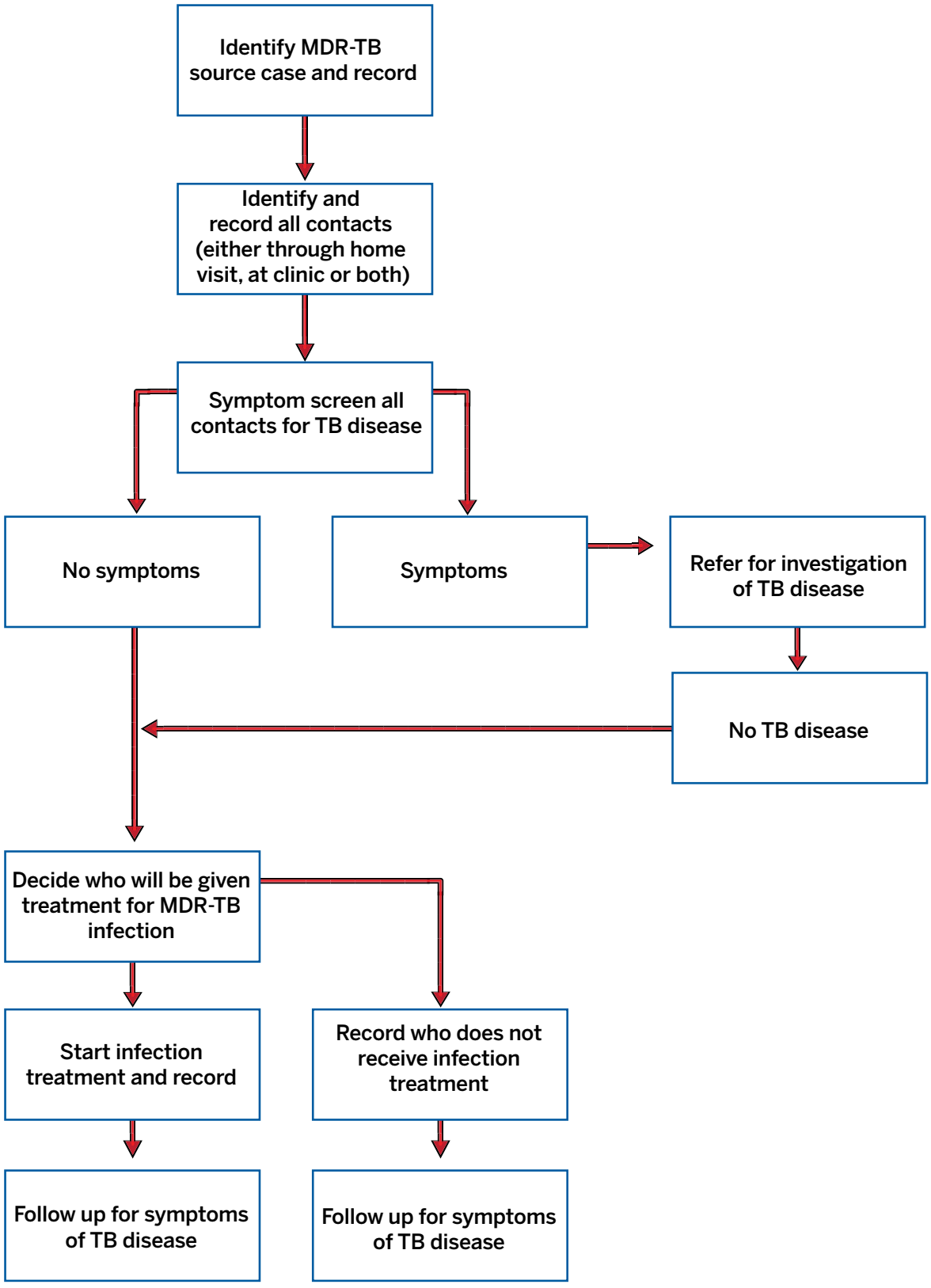

Table 1. Reports of the treatment of presumed multidrug-resistant tuberculosis infection

First Author	Year	Location	Regimen	Efficacy	Safety
Adler-Shohet[68]	2014	California, USA	Lfx and PZA given under DOT, aiming for 9 months	26 children treated for TB infection. None developed TB disease.	Only 8 completed therapy with Lfx and PZA due to adverse events. 6 changed to Lfx monotherapy.
Attamna[69]	1998-2006	Israel	Tailored treatment mainly Cfx and PZA	12 contacts treated for TB infection with tailored regimen: 71 given H, 6 other treatments and 387 given nothing. None developed TB disease.	Not stated.
Denholm[70]	1995-2010	Victoria, Australia	A variety of regimens including first-line drugs and fluoroquinolones	Of 49 eligible contacts, 11 treated for TB infection. None developed TB disease.	4 of 11 had adverse events. 2 patients stopped treatment early.
Feja[71]	1995-2003	New York, USA	Regimen tailored to the DST of the source case Mean duration: 9.1 months	51 children treated for TB infection. None developed TB disease.	8 out of 22 with charts available for evaluation experienced adverse events. 2 required cessation of treatment.
Garcia-Prats[72]	2013	Cape Town, South Africa	Ofx, E and high-dose H Duration: 6 months	24 children treated for TB infection. None developed TB disease.	2 children developed adverse events; 1 child stopped treatment early.
Lou[60]	1999	Pittsburgh, USA	Lfx and PZA Duration: 12 months	57 solid organ transplant patients treated for MDR-TB infection. None developed TB disease.	32 stopped treatment early due to adverse events.
Morris[5]	2007-2010	Chuuk, Micronesia	Lfx/Mfx alone or in combination with Eto or E	None of 104 contacts who were treated for TB infection developed TB disease, whereas 3 out of 15 contacts who refused infection treatment progressed to TB disease.	4 out of 119 discontinued due to adverse events.
Papastavros[61]	2000	Hamilton, Canada	Lfx and PZA	17 contacts treated for TB infection. None developed TB disease.	Adverse events seen in 14 patients. Treatment stopped in all.
Ridzon[73]	1997	California, USA	Ofx and PZA Duration: 12 months	22 contacts treated for TB infection. None developed TB disease.	Medications stopped in 13 contacts due to adverse events, serious adverse events in 3.
Sasaki[74]	1998-2002	Japan	Varied combinations of first- and second-line drugs	41 contacts treated for TB infection. 13 developed TB disease.	Not stated.
Schaaf[34]	1994-2000	Cape Town, South Africa	Regimen tailored to DST of source case Duration: 6 months	2 (5%) of 41 children given 6 months of treatment for TB infection developed TB; 13 (20%) of 64 children not given treatment progressed to disease	Some gastrointestinal adverse events due to ethionamide.
Seddon[26]	2010-2012	Cape Town, South Africa	Ofx, E and high-dose H Duration: 6 months	186 children treated for TB infection. Of those with good adherence to treatment, 2 developed TB disease.	7 (3.7%) children developed grade 3 adverse events. No children required cessation of treatment.
Trieu[75]	2005	New York, USA	Mfx and PZA	50, mainly HIV-positive, adult contacts treated for TB infection. 30 (60%) completed treatment. None developed TB disease of the same strain as the source case.	3 discontinued due to adverse events.
Williams[76]	2006-2010	UK	A variety of 2-drug regimens including first-line and second-line drugs Duration: 6-12 months	8 children treated for TB infection. None developed TB disease.	Not stated.

Lfx: levofloxacin; PZA: pyrazinamide; Cfx: ciprofloxacin; H; isoniazid; Mfx: moxifloxacin; Eto: ethionamide; E: ethambutol; DST: drug susceptibility test; Ofx: ofloxacin; TB: tuberculosis; MDR: multidrug-resistant; HIV: human immunodeficiency virus

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