Management of children exposed to multidrug-resistant Mycobacterium tuberculosis

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Children exposed to multidrug-resistant (MDR) Mycobacterium tuberculosis are at risk of developing MDR tuberculosis. Where treatment is available, it is lengthy, expensive, and associated with poor adherence and notable morbidity and mortality. Preventive treatment effectively lowers the risk of disease progression for contacts of individuals with drug-susceptible tuberculosis, but this strategy is poorly studied for contacts of people with MDR tuberculosis. In this Review we discuss the management of child contacts of source cases with MDR tuberculosis. We pay particular attention to assessment, existing international guidelines, possible preventive treatments, rationales for different management strategies, and the interaction with and implications of HIV infection.

Introduction
Nearly half a million new cases of multidrug-resistant (MDR) tuberculosis are estimated to occur each year, including extensively drug-resistant (XDR) tuberculosis. These forms of the disease are associated with high mortality, particularly in people living with HIV infection. MDR tuberculosis is defined as disease caused by Mycobacterium tuberculosis resistant to rifampicin and isoniazid, and XDR as tuberculosis caused by M tuberculosis resistant to both these drugs as well as a fluoroquinolone and an injectable second-line antituberculosis medication.

Tuberculosis control programmes have traditionally focused on case-finding and treatment of infectious patients, most of whom are adults. From a public health perspective, this approach must remain the priority because it will lessen disease transmission and, therefore, the number of new infections. To decrease future disease burden and improve clinical care at an individual level, however, these strategies need to be complemented with the identification and treatment of people who are at a high risk of first becoming infected and then of progressing to disease after contact with infectious individuals. Young children and immunosuppressed people are at the highest risk of progressing to disease after infection. Few studies have investigated the management of children exposed to MDR tuberculosis, and there is no consensus about the use of preventive treatment. In this Review we discuss existing international guidelines for the management of child contacts of individuals with MDR tuberculosis, whether preventive treatment could have a role, and what the possible treatments and rationales might be for different management strategies.

Tuberculosis pathophysiology and immunology
After exposure to aerosolised M tuberculosis, some children will become infected, after which the adaptive immune system might clear the infection, fail to contain it, or reach an equilibrium in which the immune system is unable to eradicate the infection but prevents progression to disease. The definitions and pathophysiological bases of tuberculosis infection are subjects of much debate. The terms latent tuberculosis infection, latent tuberculosis, and tuberculosis latency are all used. In line with our academic work and paediatric practice, in this Review we use the term tuberculosis infection to cover the spectrum from recent infection with M tuberculosis, before an immune response is mounted, to an established state of equilibrium. A proportion of individuals with tuberculosis infection will at some point develop tuberculosis disease. The overall risk of progression is greatest in the first 2 years after infection, and for young children progression occurs within 1 year in 90% of cases. Data collected before the era of chemotherapy show that changes seen on chest radiography spontaneously resolve without treatment in a proportion of children with tuberculosis infection. In this Review, however, as in our clinical practice, we use the term tuberculosis disease to refer to symptomatic illness or any radiographic changes on chest radiography that are consistent with tuberculosis.

Traditionally, the only means of detecting tuberculosis infection was if the patient had a history of exposure and a positive tuberculin skin test (TST) result. The crude antigen mixture used in TSTs, however, does not completely differentiate between BCG, M tuberculosis, and environmental, non-tuberculous mycobacteria. An immune response might take up to 3 months to develop, and the size of induration can be affected by HIV infection, malnutrition, and other causes of immunosuppression (eg, viral infections, neoplastic disorders, or steroid use). Sensitivity and specificity are difficult to measure in the absence of a gold standard, but when sensitivity is measured against confirmed tuberculosis disease, results are variable. Some tests, such as the interferon-γ-release assays (IGRAs), measure the amount of interferon γ released by T cells or the number of T cells that release interferon γ after stimulation by M tuberculosis-specific antigens (eg, ESAT-6, CFP-10, or TB7.7). Large numbers of studies have assessed these in-vitro tests, and in some contexts they seem to show increased sensitivity in confirmed tuberculosis cases or against an exposure gradient. Specificity does not seem to be substantially affected by previous BCG vaccination or exposure to non-tuberculous...
mycobacteria. IGRAs, like the TST, cannot differentiate between tuberculosis infection and disease. Evidence on the role of IGRAs in children is expanding, but data from high-burden settings are limited, especially in children infected with HIV. Few studies have included individuals exposed to MDR tuberculosis, but a meta-analysis suggests that IGRAs offer little additional benefit to TSTs for screening, particularly in low-resource settings. This conclusion is reflected in current international guidelines, which discourage the use of IGRAs in low-income and middle-income countries.

Assessment of MDR tuberculosis child contacts

Process

When presented with a child contact of an MDR tuberculosis source case, several processes need to be undertaken. The first step is to establish whether the child has tuberculosis disease by assessment of history, findings on physical examination, and chest radiography (figure). This decision is not always straightforward, but to give a preventive regimen to a patient with tuberculosis disease yields poor results and increases the risk of resistance. Once tuberculosis disease is excluded, the child should be assessed for tuberculosis infection. When making this assessment, what is meant by the terms source case and exposure need to be clearly understood. In this Review we refer to a source case as any adult likely to have infected the child. This term is in contrast to index case, which refers to the first case identified by the health services in a household or outbreak. Exposure should be viewed as a gradient of risk that must be quantified according to whether a child could have inhaled mycobacteria from a source case and, if so, in what proximity, how frequently, and for how long (the degree of exposure). The findings for extent of exposure should be combined with those for TST or IGRA to determine the probability of infection. If the probability is high, the risk of disease progression must be assessed. If the chance of disease progression is high, the drug susceptibility of the infecting strain of *M. tuberculosis* needs to be established. Only after assessment of all these factors should preventive treatment be considered.

Infection

Infection, rather than merely exposure, is required for disease to develop. Exposed children with a positive TST result are five times more likely to progress to tuberculosis disease than are those with an indeterminate or negative result and, therefore, are more likely to have been infected. Whether the pattern is similar for IGRAs is so far unclear. Owing to the limitations of TSTs and IGRAs, as well as a time delay in conversion to hypersensitivity, clinical assessment and appraisal of the infectiousness of and risk of transmission from the source case should also be done. Although initial animal models implied that isoniazid-resistant mycobacteria were less infectious and pathogenic than drug-susceptible organisms, the findings in human beings are less clear. Specific strains are associated with drug resistance, and virulence differs between strains. The overall picture of infectiousness, however, remains uncertain.

Contacts of patients with sputum-smear-positive drug-susceptible tuberculosis are two to three times more likely to be infected than are contacts of patients with sputum-smear-negative, culture-positive disease. The risk of infection increases with increasing bacterial load in the source case. Although HIV-infected individuals with culture-confirmed tuberculosis more frequently have sputum-smear-negative disease than do those without HIV infection, little evidence suggests that they are less infectious. Extensive pulmonary disease that affects multiple zones on chest radiography is associated with increased infectiousness, independent of mycobacterial load. Assessment of contacts must, therefore, take into account the extent of lung involvement in the source case.

The risk of a contact becoming infected is affected by the physical proximity of the source case during exposure, the duration of interaction per day, environmental factors, and the overall duration of exposure. First-degree relatives are up to five times more likely to cause infection

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**Figure: Decision algorithm for assessing child contacts of source cases with MDR tuberculosis**

MDR=multidrug-resistant. TST=tuberculin skin test. IGRA=interferon-γ-release assay.
in contacts than are more distant relatives, especially when the relative is female.\textsuperscript{49} Contacts sleeping in the same room as a source case are up to three times more likely to become infected than are those who sleep in different rooms,\textsuperscript{33,35,36,44} and proximity of sleeping shows a graded risk.\textsuperscript{33,36} The odds ratio of infection is raised by up to four times in contacts who live with families that include smokers,\textsuperscript{29,41} and the risk is increased if rooms are crowded or poorly ventilated.\textsuperscript{32} The duration and frequency of cough in the source case both affect the risk of infection in contacts,\textsuperscript{43} especially for MDR tuberculosis, when the relative is female.\textsuperscript{31} Contacts sleeping in the same room as a source case are up to three times more likely to become infected than are those who live with families that include smokers,\textsuperscript{29,41} and the risk is increased if rooms are crowded or poorly ventilated.\textsuperscript{32} The duration and frequency of cough in the source case both affect the risk of infection in contacts,\textsuperscript{43} especially for MDR tuberculosis, because many source cases have been previously treated with ineffective first-line regimens and diagnosis has been delayed, which contribute to lengthened exposure time.\textsuperscript{44,45}

Risk of disease progression
The data from studies of the natural history of tuberculosis that were done before the chemotherapy era show that infected infants (ie, age <12 months) have a 50% life-time risk of progression to disease. Risk in children aged 1–2 years is 20–30%, in those aged 3–5 years it is 5%, in those aged 5–10 years it is 2%, and in adolescents it is 5–10%, which is similar to that in adults.\textsuperscript{46,47} In adults with concomitant HIV and tuberculosis infections, the annual risk of developing tuberculosis disease is 7–10%,\textsuperscript{48} although the effect is modulated by antiretroviral therapy and immune status. Infants with HIV infection are at least 20 times more likely to develop tuberculosis disease than those without HIV infection.\textsuperscript{49} Malnourished children have increased vulnerability to development of tuberculosis disease compared with adequately nourished children.\textsuperscript{29}

Drug susceptibility of infecting strain
The origin of tuberculosis infection in child contacts is dependent on background tuberculosis prevalence. Several studies have shown that the \textit{M tuberculosis} strain in contacts who subsequently develop disease is generally the same as that identified in the source case.\textsuperscript{7,23,50,51} In low-prevalence regions the identified source case is likely to be the origin of the infection.\textsuperscript{7} In high-prevalence regions, however, the strains in many contacts differ from those in the purported source cases,\textsuperscript{15,16} and children frequently have evidence of infection without a known household source case.\textsuperscript{17,18} Multiple household members might be infected with different \textit{M tuberculosis} strains, and individual source cases may be infected with multiple strains.\textsuperscript{30,32} The nature of the interaction between the source case and the contact is important: the more intense the interaction, the more likely it is that the strains will be concordant. The likelihood of infection with the same strain as that identified in the known source case is, therefore, higher in young children than in older children, since the latter interact more with the community. Preventive treatment strategies in areas with multiple possible strains should take into account the balance between the most likely and the most dangerous outcomes.

Management of child contacts
Rationale for preventive treatment
Preventive treatment regimens have been used since 1951.\textsuperscript{44} Prophylaxis is the term given to treatment after exposure, whereas treatment of tuberculosis infection implies that infection has been determined. Preventive treatment includes both these situations.\textsuperscript{51} WHO advises that children younger than 5 years or those infected with HIV who are living in close contact with an individual who has tuberculosis disease are at a high risk of infection and progression to tuberculosis disease. Thus, after tuberculosis disease is ruled out, they should be given 10 mg/kg isoniazid daily for up to 6 months with follow-up every 2 months during preventive treatment.\textsuperscript{42,43}

Alternative preventive treatment options for drug-susceptible tuberculosis disease that have been proposed include rifampicin or combinations of rifampicin, isoniazid, and pyrazinamide.\textsuperscript{45-48} In several studies the likelihood of progression to tuberculosis disease has been reduced by 60% for children without HIV infection,\textsuperscript{49-51} and by up to 90% in analysis restricted to patients with good adherence.\textsuperscript{72} In the era before antiretroviral therapy, preventive treatment in children with HIV infection led to a 72% reduction in progression to tuberculosis disease.\textsuperscript{73} A placebo-controlled trial of children with and without HIV infection (infected children were treated with antiretroviral therapy) and no known exposure to a tuberculosis source case, however, showed that 96 weeks of isoniazid did not reduce incidence of tuberculosis disease.\textsuperscript{74} WHO has made a conditional recommendation that all HIV-infected patients in areas with high prevalence of tuberculosis should be given preventive treatment for up to 36 months, irrespective of age, contact with a tuberculosis source case, degree of immunosuppression, or evidence of infection.\textsuperscript{75}

Preventive treatment in MDR tuberculosis child contacts
Few studies have assessed the management of MDR tuberculosis child contacts and none is a randomised controlled trial. Only three studies have investigated the role of preventive treatment in contacts.\textsuperscript{7} One study in Cape Town, South Africa, followed up 105 children, of whom 41 had received a multidrug preventive regimen tailored to the drug-susceptibility pattern of the strain in the source case.\textsuperscript{7} Only two (5%) of these 41 children developed tuberculosis disease, compared with 13 (20%) of the 64 who had been observed without intervention. The second study, done in Rio de Janeiro, Brazil, retrospectively assessed 218 adult and child contacts of MDR tuberculosis source cases.\textsuperscript{29} In the 45 who had been given prophylactic isoniazid, a non-significant trend was seen towards a protective effect. Finally, 110 infected adult and child contacts of 19 MDR tuberculosis source cases in Chuk,
Federated States of Micronesia, were given multidrug preventive treatment for 12 months in a directly observed therapy programme.69 No patients given preventive treatment developed tuberculosis disease. Although no definitive conclusions can be drawn from these studies, the findings suggest that preventive treatment of MDR tuberculosis child contacts is beneficial.

International guidelines for the management of MDR tuberculosis contacts vary. The UK National Institute for Health and Clinical Excellence and WHO advocate that after screening for tuberculosis disease all contacts of patients with infectious MDR tuberculosis should be followed up without medication, because the data supporting the use of drugs other than isoniazid and rifampicin are limited.44,70 The WHO guideline does imply that contacts of MDR tuberculosis source cases might also have been exposed to drug-susceptible source cases and, therefore, could be infected with a strain susceptible to isoniazid.41 The National Department of Health of South Africa suggests giving high-dose isoniazid (15 mg/kg) to asymptomatic children aged 5 years and younger who are contacts of MDR tuberculosis source cases.48 A Delphi survey supported the use of preventive treatment but did not reach consensus on the most appropriate preventive regimen.41 A regimen of 1500 mg pyrazinamide daily plus ciprofloxacin 750 mg twice daily for 4 months was suggested for adult contacts, but the researchers concluded that the attending physician should make the decision and advocated further study. The US Centers for Disease Control and Prevention, the American Thoracic Society, and the Infectious Diseases Society of America have issued a joint statement which indicates that high-risk contacts of MDR tuberculosis source cases should receive a regimen that includes two drugs to which the source case’s tuberculosis strain is susceptible.81 The American Academy of Pediatrics suggests specialist referral.44 Other expert opinions vary,86–88 as do reported practices.86–92 Although use of medications to which the source case’s isolate is susceptible is intuitively convincing and biologically plausible, data that indicate success in the prevention of infection or progression from infection to disease are limited. The adverse effects of such treatments have also not been explored, and the costs to patients and the health system have not been assessed.

### Available medications for use as preventive treatments

Clinicians must become familiar with all the available drugs and issues related to dose, mechanisms of action, and possible adverse effects.89 The drugs in the table have been suggested for use in preventive treatment regimens for MDR tuberculosis.

Delivery of the correct amount of drugs to children is problematic in terms of confidence in ingestion and achievement of the correct dose. Traditionally, paediatric dosing has been extrapolated from adult pharmacokinetic studies, but children generally metabolise medications more rapidly than adults, which leads to lower drug concentrations by weight.90–92 In 2009, WHO revised the first-line tuberculosis drug dosing recommendations.93 Of note is that neonates and very young infants, who have immature liver and enzyme development, seem to metabolise drugs less rapidly than older children. Care must be taken when prescribing for this subpopulation.93,94 Most of the second-line drugs have been minimally studied in children with tuberculosis. Additionally, few drugs are available in paediatric formulations, and adult-sized preparations are frequently inappropriate for small children. Tablets, for instance, must frequently be broken and segments crushed before delivery. This approach, however, is associated with dosing errors that could lead to lowered effectiveness or toxic effects.

Isoniazid is effective when used alone as preventive treatment for drug-susceptible tuberculosis infection because it is highly bactericidal and leads to rapid bacterial clearance.95 Resistance does not develop if monotherapy is used in patients with tuberculosis infection but in whom tuberculosis disease has been excluded before treatment.96 In contacts of patients with MDR tuberculosis disease, the use of this drug is questionable owing to the high likelihood that the strain in the contact is resistant. Most isoniazid resistance, however, is encoded by the katG gene or the inhA promoter region. Resistance can, therefore, be detected by genetic tests and can be classified as high level or low level, respectively.97

Pyrazinamide effectively kills M tuberculosis but only in the acidic environment created by active inflammation seen in response to rapidly replicating mycobacteria. Such conditions are not generally seen in people with tuberculosis infection and, therefore, the usefulness of this drug as a preventive treatment is uncertain.98 Regimens containing pyrazinamide are associated with severe adverse effects in adults and adherence can be poor.105–107 In children with tuberculosis disease, though, pyrazinamide seems to be well tolerated and adverse effects are rare.108,109 Resistance to pyrazinamide is complicated to test, since conditions of very low pH are required that are difficult to replicate in vitro. Direct resistance testing and surrogate and genetic techniques have shown that levels of resistance can be high in strains already resistant to isoniazid and rifampicin.110

Fluoroquinolones have good activity against M tuberculosis,112 but concerns related to adverse effects on cartilage growth in immature beagles had previously prevented use of these drugs in children.113 Studies in children, however, have yielded no evidence to support these concerns.114 Fluoroquinolones have good bactericidal activity and seem to be well tolerated. Ciprofloxacin has poor early bactericidal activity, despite effectiveness in vitro, but other fluoroquinolones are likely to be more effective.115 Of the tested fluoroquinolones, moxifloxacin has the best in-vitro activity against M tuberculosis in the
exponential growth phase and levofloxacin is the most effective in the latent phase, which might make it effective as a preventive treatment.116

Ethambutol is effective, but concerns about its effect on the optic nerve restricted its use in patients in whom colour vision and visual acuity could not be tested, including young children. Changes to dosing schedules have made optic neuritis rare,117 but resistance seems to be high in MDR strains of M tuberculosis. A rationale exists to use this drug alone at low doses because it is well tolerated, adverse effects are minimal, and optic neuritis is rare.117,118

Isoniazid is similar to isoniazid, since it inhibits the synthesis of mycolic acid and consequently impairs the formation of the cell wall. A mutation in the mycobacterial inhA promoter region generally leads to low-level isoniazid and ethionamide resistance.119 If the mutation is in the katG gene, no increased risk of resistance to ethionamide is seen, despite high-level resistance to isoniazid. Adverse effects, including nausea and vomiting, are common but generally lessen with time and can be reduced by initially splitting the daily dose or starting treatment with a reduced dose that is increased to the full dose over a couple of weeks.

Preventive treatment strategies
Possible strategies are to give children monotherapy, a standard multidrug regimen (all patients are given the same combination irrespective of susceptibility), or an individualised multidrug regimen determined from the results of drug-susceptibility testing in the source case.

In child contacts of tuberculosis source cases with isolates only resistant to either rifampicin or isoniazid, the other agent alone can generally be used as preventive treatment. Of note, the increasing use of line-probe assay genotypic tests to diagnose MDR tuberculosis has led to an increase in the proportion of source cases classified as having rifampicin-monoresistance tuberculosis who might, in fact, have MDR tuberculosis. Because these assays only detect the katG and inhA mutations, they could miss a small but important proportion of isoniazid resistance. Contacts of individuals with XDR tuberculosis might be infected with a strain that is resistant to even more drugs than contacts of patients with MDR tuberculosis. Few treatment options are available and until new agents become available close follow-up remains the key component of management.

Although good evidence exists for the efficacy of isoniazid in preventing progression from drug-susceptible infection to tuberculosis disease, limited data support its use alone in individuals exposed to MDR tuberculosis. A rationale exists to use this drug alone at high doses because it is well tolerated, adverse effects are rare, and it would treat drug-susceptible strains as well as strains with low-level resistance.119,120 Some
children exposed to MDR tuberculosis have, however, progressed to tuberculosis disease while taking 5 mg/kg isoniazid as preventive treatment.\textsuperscript{133} Use of a fluoroquinolone on its own might be effective, since these drugs are well tolerated and have bactericidal and sterilising activities. Fluoroquinolones are, however, used widely to treat non-tuberculosis bacterial infections, and there is concern that increases in the breadth and duration of use could promote resistance. Several drugs are in the research and development pipeline that might be suitable for preventive treatment against MDR tuberculosis: TMC207 (previously known as R207910), OPC-67683, and PA-824.\textsuperscript{122}

The use of standard multidrug regimens has some operational advantages over tailored regimens. They are simpler to implement and health-care workers need to be familiar with smaller numbers of drugs, doses, adverse effects, and interactions. Testing for drug susceptibility is required, but only to determine whether or not the source case has MDR tuberculosis. To make universal recommendations might not be appropriate since, fundamentally, the choices of agents must reflect the susceptibility patterns of prevailing organisms and, therefore, what is suitable for one area might not be so for another. At which level to provide guidance—global, regional, country, district, or hospital—is also difficult to decide. To balance between easy-to-follow unambiguous general policies and provision of the most effective treatments for the target population is a constant public health challenge. Proposed standard regimens have included combinations of pyrazinamide, ethambutol, and a fluoroquinolone, but effectiveness and tolerability in child contacts need to be confirmed.\textsuperscript{82,131}

The advantages of individualised regimens include increased likelihood of success and reduced risk of resistance if tuberculosis disease had been missed when therapy was started. The tailoring of treatment, however, requires extended drug susceptibility testing, routine availability of a variety of first-line and second-line medications, and experienced, expert front-line medical staff. Use of three or more medications to which the bacilli are susceptible in a preventive regimen could be argued to be similar to regimens used to treat tuberculosis disease. In a well child, close observation with rapid identification and treatment if tuberculosis disease develops might, therefore, be a more appropriate strategy.\textsuperscript{135,136}

The Research Excellence to Stop TB Resistance Group met in December, 2009, to discuss research into MDR tuberculosis. They produced three clinical trial protocols, one of which was to compare isoniazid against a new drug alone or against a new drug in combination with existing drugs as preventive treatment in adult and child contacts of people with MDR tuberculosis.\textsuperscript{137} Although the design of the trial is still being discussed, it would need to be large to show a difference between treatments because the endpoint of such a study, tuberculosis disease, would be notably less frequent than tuberculosis infection.

Other factors that affect the choice of regimen are pragmatic considerations, such as regulatory approval, experiences with specific drugs in other diseases, cost, and national programme policies. The optimum duration of different preventive treatment regimens for MDR tuberculosis has not been explored.

**Adherence**

Almost all studies have shown that adherence of individuals to standard isoniazid preventive treatment is poor,\textsuperscript{134,137} and potentially worse if a child is not compliant to the parents’ wishes.\textsuperscript{126,127} In a prospective study in Cape Town, South Africa, 180 child contacts of source cases with drug-susceptible tuberculosis were started on isoniazid as preventive treatment. Only 36 (20%) completed at least 5 months of treatment.\textsuperscript{128} The assessment of adherence, however, was based on monthly clinical attendance to collect the drugs, and no record was made of whether or not they were actually taken. Isoniazid has a good adverse effect profile and, therefore, with more complex regimens adherence might be worse.

Education, counselling, and peer support can lead to good adherence, and tuberculosis programmes must take into account the best methods of promotion for their target populations. Novel techniques are being tried, including directly observed treatment by family members or non-medical supporters, use of mobile-telephone technology, incentives, and decentralised care in the community.\textsuperscript{129–131} The available resources and local prevalence of tuberculosis in the community will affect which model of supervision is used.

**Treatment in patients with HIV infection**

Preventive treatment regimens given to MDR tuberculosis contacts do not contain rifampicin and, therefore, many of the usual drug interactions with antiretroviral therapy are not pronounced. Limited work has been done on the interaction between second-line antituberculosis drugs and antiretroviral therapy.\textsuperscript{131} Whether therapeutic concentrations of antituberculosis drugs are achieved in patients receiving antiretroviral therapy is unclear, especially in children. Additionally, chronic diarrhoea, which is frequently associated with HIV infection, could affect the absorption of MDR tuberculosis preventive treatment and of antiretroviral therapy.\textsuperscript{138}

When to start MDR tuberculosis preventive treatment in patients with HIV infection is an important consideration. If antiretroviral therapy is already well established, continuation and the immediate starting of MDR tuberculosis preventive treatment is probably safe. If the diagnosis of HIV is made in a patient already taking MDR tuberculosis preventive treatment, antiretroviral therapy should be started in accordance with the appropriate guidelines and on the basis of clinical and immunological criteria.\textsuperscript{139} If a child has been exposed to an MDR tuberculosis source case and is found at the same time to be infected with HIV, it might be possible to start preventive
treatment and wait until that is well established or completed before starting antiretroviral therapy, dependent on the clinical and immunological circumstances. Although little evidence is available, clinicians frequently treat HIV infection at an earlier stage than previously, and reduced mortality has been seen, particularly in children. The use of antiretroviral therapy in children with simultaneous diagnoses might even be more effective than MDR tuberculosis preventive treatment. Once HIV infection is confirmed, co-trimoxazole should be started according to the appropriate guidelines, irrespective of whether or not antiretroviral therapy or MDR tuberculosis preventive treatment has been started.

Immune reconstitution inflammatory syndrome is classified as paradoxical or unmasking, and generally manifests in the first few weeks of antiretroviral therapy. The paradoxical form occurs when treated tuberculosis disease becomes worse after antiretroviral therapy is started. Children with tuberculosis infection do not fall into this group, but might be affected by immune reconstitution inflammatory syndrome unmasking as the immune system reconstitutes after the start of antiretroviral therapy. In this case, full treatment for MDR tuberculosis disease should be started. Whether corticosteroids are useful to treat immune reconstitution inflammatory syndrome remains uncertain, but their use might provide some protection in specific reactions.

Conclusions

MDR tuberculosis is emerging as an important challenge to international public health. The disease burden can be reduced by treating contacts at high risk of tuberculosis infection and of progressing from tuberculosis infection to disease. Although the number of contacts varies between populations, conservative estimates suggest that in high-burden regions there are at least two child contacts per MDR tuberculosis source case who are either younger than 5 years or who are infected with HIV. Thus, more than 1 million vulnerable contacts could be considered for preventive treatment each year. These subgroups also account for a substantial proportion of the half a million people who develop MDR tuberculosis disease each year. In some of these cases a source case could have been identified and preventive treatment initiated. A study from Peru has shown that in nearly a quarter of households with a case of MDR or XDR tuberculosis, a contact will develop tuberculosis disease within 4 years of exposure.

Search strategy and selection criteria

We searched CINAHL, Cochrane Library (CENTRAL), Embase, Medline, Web of Science, and Africa NiPAD with the terms ‘MDR’, ‘XDR’, ‘drug-resist*’, ‘multidrug-resist*’, ‘tuberculosis’, ‘TB’, ‘mycobacter*’, ‘prophylaxis’, ‘chemoprophylaxis’, ‘(preventive therapy)’, and ‘(preventive treatment)’ in article titles and abstracts. We reviewed article abstracts and requested full-text versions as appropriate. We also searched the reference lists of these articles to identify further relevant papers and conference abstracts. No language or date restrictions were applied.

Few data are available to guide attending physicians, and there is a strong need for rigorously tested evidence. Numerous calls for further research have been made by working groups, WHO committees, and individual experts. WHO has identified MDR and XDR tuberculosis preventive treatment as an area that merits immediate review. Clinical trials are needed that include existing and novel agents. Meanwhile, physicians must decide whether to monitor carefully or to give some form of preventive treatment. Ideally, the composition of preventive treatment should reflect the prevailing drug-susceptibility patterns of circulating strains, but few options are available. Minimum requirements, therefore, are that regimens should be effective and well tolerated to facilitate adherence and have few adverse effects. By definition, MDR tuberculosis isolates will be resistant to rifampicin and will have low-level or high-level resistance to isoniazid, and strains are also becoming increasingly resistant to pyrazinamide and ethambutol. The other available drugs that satisfy the treatment criteria are fluoroquinolones.

We support the use of high-dose isoniazid and a fluoroquinolone (ideally levofloxacin) for a minimum of 6 months in children younger than 5 years or who have HIV infection who are contacts of MDR tuberculosis sources cases. Children should be closely followed up for a minimum of 1 year, investigated aggressively if they develop clinical or radiological signs of tuberculosis disease, and should be treated early with a regimen selected according to the drug susceptibility results for the child’s isolate or, if unavailable, that of the source case. More research in this field is critically needed.
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