## Paediatric chemoprophylaxis for child contacts of patients with drug-resistant tuberculosis: Are current guidelines effective in preventing disease?

**To the Editor:** The World Health Organization (WHO) estimates that there were 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB) in 2013.[1] Alarmingly, 40% of MDR-TB cases for which second-line drug susceptibility test results were reported originated in South Africa (SA).[1] This has important implications in vulnerable populations, such as children, where infection with drug-resistant strains of TB are usually attributable to transmission rather than acquisition of resistance.[2] In high-burden settings, it is estimated that there are at least two child contacts who are either HIV-infected or younger than 5 years of age for every MDR-TB source case.[3,4] The growing spread of MDR-TB, the protracted and toxic nature of current treatment regimens and the associated morbidity and mortality all emphasise the need for effective preventive therapy. There is limited evidence on optimal paediatric chemoprophylaxis to prevent disease in child contacts of MDR-TB cases, and the subject remains controversial. We have examined recently adapted paediatric chemoprophylactic guidelines and evaluated their effectiveness in the context of drug-resistant TB. We highlight a critical gap in research that is urgently needed to guide policy.

The 2013 *South African Guidelines for the Management of Tuberculosis in Children* make the following recommendations, following exclusion of TB disease: (*i*) isoniazid preventive therapy (IPT; 10 - 15 mg/kg/day for 6 months) in all child contacts that are HIV infected or <5 years of age; (*ii*) rifampicin (15 mg/kg/day for 4 months) in isoniazid mono-resistant index cases; and (*iii*) high-dose isoniazid (15 - 20 mg/kg for 6 months) for neonates born to mothers with infectious drug-resistant TB.[5] While IPT significantly reduces the risk of drug-susceptible TB disease, and possibly TB strains with low-level isoniazid resistance, its applicability in the prevention of MDR-TB disease is questionable. Indeed, Kritski *et al.*[6] found that isoniazid had no protective effect in adult and child contacts of MDR-TB patients. In addition, Sneag *et al.*[7] described the failure of chemoprophylaxis with standard antituberculosis agents in five child contacts of MDR-TB patients.

There are no randomised chemoprophylaxis clinical trials for child contacts of MDR-TB patients. A prospective study in the Federal States of Micronesia found that of 110 adult and child MDR-TB contacts, administered a tailored (based on the susceptibility pattern of the source case) 12-month, multidrug prophylactic regimen, none developed TB disease.[8] Two studies conducted in SA report similar findings. Schaaf *et al.* [3] prospectively followed up 105 child contacts of adult MDR-TB patients for 30 months. Only 5% (2/41) of children who received an individualised, multidrug prophylactic regimen developed TB disease compared with 20% (13/64) of children who were monitored without preventive therapy. Most recently, Seddon *et al.*[9] demonstrated that a three-drug prophylactic regimen consisting of high-dose isoniazid, ofloxacin and ethambutol for 6 months was both effective and well tolerated in child contacts of MDR-TB; only 3.2% of children (6/186) developed incident TB.

Although there is a growing number of observational studies suggesting that MDR-TB chemoprophylaxis may be beneficial in MDR-TB-exposed children, there is still a lack of international consensus on the management of child contacts of MDR-TB patients. The WHO does not advocate the use of second-line agents as chemoprophylaxis for contacts of MDR-TB patients.[5] Likewise, the UK National Institute for Health and Clinical Excellence recommends close follow-up rather than intervention.[4] In contrast, several US institutions support the use of a regimen containing two drugs to which the source case is susceptible.[4] Such discordance is largely attributable to the potential adverse effects associated with anti-MDR-TB drugs. Both Bamrah *et al.*[8] and Seddon *et al.*[9] have reported good drug tolerability, however, with only 0 - 5.5% of patients experiencing adverse effects necessitating treatment interruption.

The lifetime risk of progression to active TB disease is 5 - 15% in people with latent infection.[10] Given that this figure rises sharply to 50% in children younger than 12 months,[11] and that inadequate chemotherapy may result in significant morbidity, the management of children with latent TB (including MDR-TB) is fundamental to TB control. In the absence of a randomised clinical trial, observational studies strongly indicate that appropriate MDR-TB chemoprophylaxis should be considered when TB disease has been excluded, there is significant exposure to a close drug-resistant TB contact and the risk of disease progression is high. More research is urgently required to conclusively guide policy.

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