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Household contact management and preventive treatment for drug-resistant tuberculosis

Drug-resistant tuberculosis continues to be an urgent global health challenge. Treating multidrug-resistant (MDR) tuberculosis (defined as disease caused by *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin),[1] is associated with worse treatment outcomes, more severe adverse events, and higher costs for both the health system and families than treating drug-susceptible tuberculosis.[2,3] Preventing MDR-tuberculosis is therefore essential. Modelling studies suggest that even with optimised detection and treatment of tuberculosis, efforts to eliminate the disease, including MDR-tuberculosis, as a public health issue will fail unless individuals with *M tuberculosis* infection are identified and treated before they become unwell.[4]

A key strategy to address the global MDR-tuberculosis pandemic is through effective household contact management (HHCM). Following the diagnosis of an individual with tuberculosis, HHCM includes the systematic screening of all household contacts for prevalent tuberculosis, with tuberculosis preventive treatment provided to healthy contacts. Until recently, data to inform the composition of regimens for MDR-tuberculosis preventive treatment were scarce. We previously completed a modelling study that evaluated MDR-tuberculosis HHCM strategies in children,[5] and based assumptions regarding efficacy and safety of MDR-tuberculosis preventive treatment regimens on those for drug-susceptible tuberculosis. Since then, two large phase 3 clinical trials have been completed in South Africa and Viet Nam, evaluating the efficacy and safety of levofloxacin versus placebo to prevent tuberculosis in household contacts of people with MDR-tuberculosis.[6,7] Therefore, we updated our country-level model to evaluate the impact and cost-effectiveness of global implementation of HHCM and levofloxacin tuberculosis preventive treatment to children younger than 15 years with household MDR-tuberculosis exposure (details of methods are in appendix pp 2–4).

See Online for appendix

Globally in 2019, compared with providing no HHCM, HHCM and provision of tuberculosis preventive treatment to all child contacts of patients with MDR-tuberculosis would have resulted in 209 000 courses of levofloxacin (95% uncertainty interval [UI] 189 000–232 000), prevented 5620 incident tuberculosis cases (95% UI 4540–6990), and saved 3600 lives (95% UI 3020–4250), with an incremental cost-effectiveness ratio of US$841 per disability-adjusted life-year saved globally. The impact of other HHCM strategies is shown in the figure and appendix pp 5–9. These results are similar to those of our previous analysis (appendix p 9).

Our results show the potential importance of HHCM and levofloxacin tuberculosis preventive

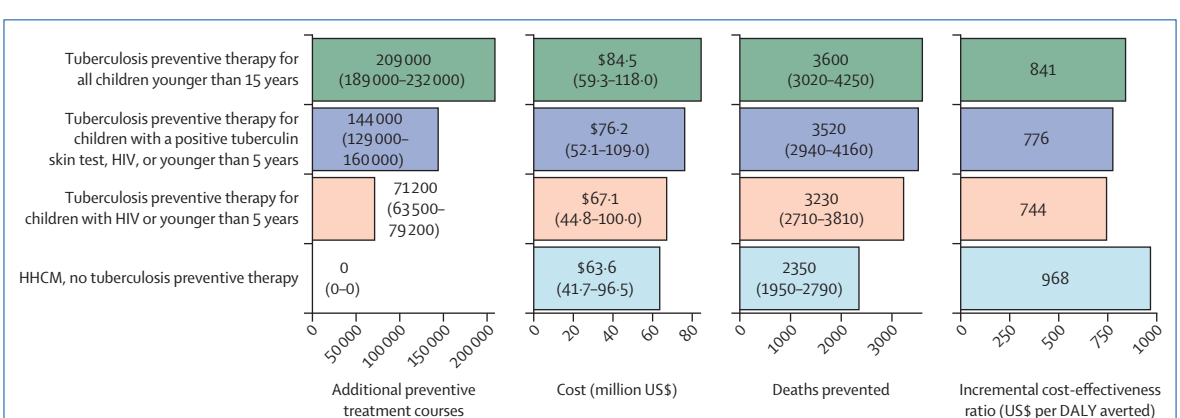

Figure: **Projected intervention changes in tuberculosis preventive treatment courses, costs, deaths and incremental cost-effectiveness ratio globally for 2019**
Values in parentheses are 95% UIs. Corresponding global estimates for the base case of no HHCM were 6110 deaths (95% UI 5230–7090). The total costs associated with the base case of no HHCM were US$50·8 million (95% UI 30·3–84·1). DALY=disability-adjusted life-year. HHCM=household contact management. UI=uncertainty interval.

treatment for children exposed to MDR-tuberculosis. Furthermore, such modelling results allow us to move beyond the within-trial cost-effectiveness in Viet Nam and South Africa to produce estimates of cost-effectiveness at a global level. However, there are limitations in this approach, with substantial country-to-country variation in MDR-tuberculosis epidemiology, important differences in drivers of cost, and fundamental societal variability. These are not full accounted for in the model. Our results are conservative in that they do not consider the importance of costs to the patient and their contacts, but rather to the health system only, or of transmission averted due to the intervention. This makes the case for considering expansion of tuberculosis preventive treatment recipients beyond children, where the high cost of MDR-tuberculosis treatment and the importance of reduced transmission could make the use of tuberculosis preventive treatment cost-effective for adults as well.[8] However, as the age of levofloxacin recipients increases, the drug is less well tolerated and careful risk–benefit analysis will be needed at country level.[6] In addition, the impact on antimicrobial resistance to other non-mycobacterial bacteria and the effect on the host microbiome will need to be considered by policy makers and clinicians, given that levofloxacin is a broad-spectrum antibiotic.

Expanding HHCM and tuberculosis preventive treatment for contacts of patients with MDR-tuberculosis will not be without challenges. Substantial increases in human resource capacity will be required, with more training needed and increased health system costs in the short term to deliver screening for prevalent tuberculosis and the provision of levofloxacin. Decisions will need to be made regarding whom tuberculosis preventive treatment is delivered to and whether tests of *M tuberculosis* sensitisation are used to support decision making. Innovative mechanisms will be required to engage and persuade already over-burdened health workers of the importance of treating individuals who are well and not a current risk to others. Despite these challenges, a failure to act will make achieving the WHO End TB Strategy targets near impossible. Fundamentally, societal engagement will be crucial to create demand for this intervention from those who are likely to benefit the most from it.

After considering the results of these two trials, in Viet Nam and South Africa, WHO issued a Rapid Communication in February, 2024, advising that a regimen of 6 months of levofloxacin should now be used as tuberculosis preventive treatment for contacts of patients with MDR-tuberculosis.[9] A full guideline is expected imminently. However, even with this recommendation, for country implementation, it will be important to consider real-life programmatic contexts and resources. Although our results provide additional evidence to support implementation, substantial in-country work will be required to make this intervention a reality.

We declare no competing interests. JAS, CFM, NM, and PJD conceived the study. PJD and NM carried out the analysis. JAS, CFM, NM, and PJD drafted the manuscript and all authors gave critical input. All authors reviewed the final manuscript.

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