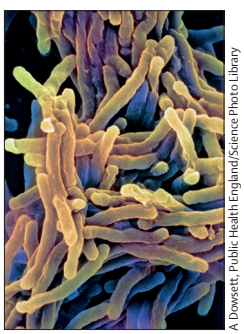
The burden of latent multidrug-resistant tuberculosis



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In the past 10 years, there has been renewed interest in the early phases of the natural history of tuberculosis.[1] Estimates suggest that around 25% of the world's population could have latent tuberculosis infection,[2] 5–10% of whom will develop active disease during their lifetime[3] (10% annually among people with HIV).[4] Failure to implement effective tuberculosis control measures to manage latent infection threatens elimination goals.

Groups at high risk of active tuberculosis are the focus of programmatic management of latent tuberculosis infection.[5] Once active disease is ruled out, tuberculosis preventive therapy can be offered. However, such therapy is thought to be ineffective against multidrug-resistant (MDR) strains (ie, those resistant to isoniazid or rifampicin, or both), and is thus rarely used to treat contacts of people with MDR tuberculosis.

In *The Lancet Infectious Diseases*, Gwenan Knight and colleagues[6] investigated the global burden of latent tuberculosis to provide the first estimates of the prevalence of latent MDR disease. They used surveillance and survey data, estimated annual risks of infection, and informative priors for patterns of increase to develop and validate a novel cohort method to calculate this burden. Knight and colleagues estimated that around 19 million people could be latently infected with MDR tuberculosis (10% of whom were infected in 2013 and 2014—ie, the most recent 2 years included in the model), representing around 1·2% of the total burden of latent infection. Children younger than 15 years, who progress to active disease more quickly than adults and therefore are a sentinel event suggesting recent local transmission, had more than double the risk of latent MDR tuberculosis infection that adults had. These data show that transmission of MDR strains of tuberculosis is worryingly high and probably increasing, and should be urgently addressed. Knight and colleagues also estimated that, even if all tuberculosis transmission was halted, reactivation of latent disease would mean that the future burden of MDR disease would still be substantial.[6] Their work thus clearly emphasises the need for interventions to limit both transmission of MDR tuberculosis and reactivation of latent MDR disease.

Knight and colleagues' findings have important implications at the individual and population level and for policy. Given that the prevalence of latent MDR tuberculosis infection will continue to rise if MDR transmission rates persist, an increasing proportion of people—and children especially—with latent infections[7] might not benefit from recommended tuberculosis preventive therapy regimens, and thus will be at increased risk of developing active MDR tuberculosis.[8] At the population level, as the prevalence of latent tuberculosis infection decreases, the partial protective effect against reinfection or reactivation that latent infection with drug-susceptible tuberculosis provides[9] against MDR strains will also diminish, thus increasing the risk of latent infection with MDR strains. In the meantime, Knight and colleagues' study emphasises the need to strengthen epidemiological surveillance of MDR tuberculosis and programmatic management of active and latent infections to reduce transmission of MDR disease (and thus the number of people with latent MDR tuberculosis). Only 25% of people with active MDR tuberculosis are detected (compared with 64% of people with all types of tuberculosis in 2017).[10] Early identification of cases, prompt initation of highly effective treatment, and close treatment follow-up will help to shorten the infectious period, and MDR tuberculosis preventive therapies will clear infections or prevent disease progression.

Further research priorities for diagnosis and treatment of latent MDR tuberculosis have been identified by Knight and colleagues. First, there is an urgent need to accelerate research into preventive therapy regimens for household contacts of people with confirmed MDR tuberculosis. Observational studies suggest that the contacts of people with MDR tuberculosis might benefit from tuberculosis preventive therapy, but no results from clinical trials have been published yet.[11] Second, novel diagnostics or biosignatures that can identify the people in whom latent infection will progress to active tuberculosis—and thus who are likely to benefit from tuberculosis preventive therapy—are needed.[12] Tools that can identify the resistance pattern of the infecting *Mycobacterium tuberculosis* strain are unlikely to be developed soon. However, given that contacts of cases with MDR tuberculosis might develop drug-susceptible or MDR tuberculosis,[13] there is a clear need for universal tuberculosis preventive therapy (ie, treatment that is effective irrespective of the drug resistance pattern).

Universal tuberculosis preventive therapy would be of great relevance in settings with a high prevalence of MDR tuberculosis, such as eastern Europe, where MDR strains account for more than 25% of tuberculosis transmission in several countries.

Although Knight and colleagues' study advances approaches to and assumptions in modelling of latent tuberculosis infection, gaps remain. Most models of the latent tuberculosis burden assume lifelong infections[2,6]—a contentious assumption given that some infections clear naturally or after treatment with sterilising tuberculosis preventive therapy. The definition of latent tuberculosis infection used did not account for mixed infections, and future models could examine the effect of mixed infections on susceptibility to reinfection or reactivation.[9] Similarly, the reactivation rate could differ between recently infected and remotely infected individuals,[14] and thus could affect the estimated burden of latent infection. It would be valuable to forecast the burden of latent MDR tuberculosis depending on different scenarios of progression and interventions towards the End TB targets at different timepoints, especially in children and young people. Additionally, sensitivity analysis with different MDR tuberculosis fitness cost rates and progression to active MDR disease would help to further clarify the magnitude and threat of the MDR tuberculosis epidemic.

There is a need to strengthen surveillance systems for detection of MDR tuberculosis and adequate patient management for early initiation of second-line treatment and treatment follow-up. The tuberculosis epidemic will not be ended without tackling people who are latently infected, and thus an increasing focus on the left side of the curve of the natural history of tuberculosis should be considered in countries with the highest burden of infection, so that the criteria for recommending preventive therapies can be progressively expanded.

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We declare no competing interests.

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