Aiming for zero tuberculosis transmission in low-burden countries

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The End TB Strategy, approved by the World Health Assembly in May 2014, proposes ambitious targets to reduce the global burden of tuberculosis (TB).[1] The strategy calls for all governments to show high-level political commitment, including those of high-income countries with a low burden of disease. The framework for TB elimination in low-incidence countries, launched at the World TB Conference in 2015, challenged low-burden countries to aim for TB elimination (defined as <1 incident case of TB per million population) by 2035 or earlier.[2] In low-incidence settings, most cases of TB occur among foreign-born individuals; thus, to achieve a substantial reduction in case numbers, meticulous premigration screening and an emphasis on the identification of active cases among often hard-to-reach populations, with treatment of both active and latent TB infection, is necessary.[3] Consideration will need to be given to risk–benefit analyses and the cost-effectiveness of these approaches, which might not always be feasible or ethically acceptable.

Despite these efforts, it seems unlikely that low-incidence countries will achieve TB elimination according to the current definition. As long as uncontrolled *Mycobacterium tuberculosis* transmission persists in large parts of the world, cross-border importation of infection and disease is an inevitable result of high population mobility. In addition to unprecedented levels of migration, frequent international travel (eg, for business and leisure) provides opportunities for new infections or reinfections to occur, which will hamper efforts to eliminate TB, and could lead to political fatigue caused by chasing a seemingly unrealistic public health target. An alternative means to achieve and sustain high-level political commitment in low-incidence countries is to introduce zero TB transmission as an interim and measurable target, and credit countries with TB transmission-free status, akin to WHO's Roll Back Polio campaign.[4] Zero TB transmission could be defined as no more than one bacteriologically confirmed case of locally acquired TB among people born in the country of interest per million population.

Whole genome sequencing (WGS) is the biggest advance in diagnostic microbiology since culture techniques enabled pathogen identification and Robert Koch showed the cause of TB to be *M tuberculosis*. WGS allows locally transmitted TB to be monitored with accuracy unattainable with previous molecular methods.[5,6] For all incident cases to be traced with WGS, all bacteriologically confirmed cases of TB would need to be routinely submitted for WGS to allow genome comparisons with previously sequenced strains, with reconstruction of probable transmission pathways. WGS data can also assist in individual patient management by predicting drug resistance with minimal lag time and at no additional cost.[7–9] The detection of laboratory cross-contamination using WGS—a problem that occurs in all settings, but is rarely discussed—provides important patient and programmatic benefit because it limits false-positive diagnoses with unnecessary treatment, and improves the accuracy of laboratory results.[9] The introduction of routine WGS to track TB transmission and drug-resistance profiles in settings in which incidence of TB is low would make TB control services leaders in the exciting public health revolution facilitated by advances in genomics.

Some might argue that the implementation of routine WGS for accurate tracking of TB transmission in countries with a low incidence of TB could detract from efforts to improve TB control in high-incidence settings by diverting financial and academic resources away from the everyday challenges faced in resource-limited settings. However, such implementation of routine WGS might instead ensure the sustained engagement of low-incidence countries in global TB control challenges, with more support provided to resource-limited settings. The refinement of novel technological advances will also provide crucial insight for and direct benefit to high-incidence settings, once these technologies are sufficiently mature and cost-efficient. Additionally, constant vigilance will be required for countries to maintain their TB transmission-free status, if all low-incidence countries are requested to report the number of locally transmitted TB cases to WHO on an annual basis and if TB transmission-free status can be revoked when set criteria are no longer met. This will discourage disinvestment in TB control services as the incidence of TB declines, which is a constant challenge

that has fuelled previous epidemic resurgences in low-incidence settings.

Although several countries have piloted WGS to explore the dynamics of local TB transmission and assist better targeted public health responses,[6–10] the first routine WGS-based diagnostic service for mycobacterial infection was launched by Public Health England in March, 2017. The benefits of WGS are likely to differ according to each country's disease burden. Whereas verification of the status of zero TB transmission is relevant in low-incidence countries, high-incidence countries are more likely to benefit from comprehensive drug susceptibility prediction. In England, routine WGS data used for TB surveillance and clinical management have incentivised research into cataloguing all molecular determinants of drug resistance, which provides accurate WGS-based predictions of drug susceptibility. Collaboration between high-incidence and low-incidence countries to develop quality assurance standards for WGS, shared databases and common workflows for data analysis, and ethical guidance on how these data should be shared and used by clinicians and public health officials is essential to unlock the full potential of the WGS revolution. Given the rapid rate of technological progress and reduction in the unit cost of WGS, countries with the necessary technical resources should be encouraged to transition to routine WGS, and jointly develop the processes and systems required to facilitate future deployment in high-incidence settings. These advances will accelerate progress towards precision medicine by guiding individualised TB treatment and targeted public health responses, and will ultimately provide better solutions to end TB.

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We declare no competing interests.

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