Aiming for "Zero TB transmission" in low burden countries

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Keywords: tuberculosis, transmission, whole genome sequencing, TB transmission free

Word Count: 893 words

Conflicts of interests: Authors declare no conflicts of interest

The End TB Strategy, approved by the World Health Assembly in May 2014, proposes ambitious targets to reduce the global tuberculosis (TB) disease burden.(1) It calls on all governments to demonstrate high-level political commitment, including those from high-income countries with a low TB disease burden. The "Framework for TB elimination in low-incidence countries" launched in Barcelona at the World TB Conference in 2015, challenged low burden countries to "lead the way" by aiming for TB elimination, defined as less than 1 incident TB case per million population, by 2035 or earlier.(2) Since most TB cases in low-incidence settings occur among foreign-born individuals, a major reduction in case numbers will require meticulous pre-migration screening and a strong emphasis on active case finding among often hard to reach populations, with treatment of active and latent TB infection.(3) Careful consideration will have to be given to risk-benefit analyses and the cost effectiveness of these approaches, which may not always be feasible or ethically acceptable.

Despite such efforts, it seems unlikely that low-incidence countries will achieve TB elimination as currently defined. 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 for business, leisure and family reunion provide many opportunities for new or re-infections to occur. This will hamper elimination efforts and could lead to political fatigue chasing a public health target that seems unrealistic. An alternative means to achieve and sustain high level political commitment in low-incidence countries is to define "zero TB transmission" as an interim and measurable target, and crediting countries with "TB transmission free" status, akin to the "Roll back Polio" campaign.(4) "Zero TB transmission" could be defined as ≤1 per million bacteriologically confirmed case of locally acquired TB among people born in the country of interest.

Whole genome sequencing (WGS) represents the biggest advance in diagnostic microbiology, since culture techniques enabled pathogen identification and Robert Koch demonstrated that TB is caused by *M. tuberculosis*. WGS provides the opportunity to monitor locally transmitted TB with levels of accuracy that were unattainable with previous molecular methods(5,6) This would require that all bacteriologically-confirmed cases of TB are routinely submitted for WGS, allowing genome comparisons with previously sequenced strains with reconstruction of likely 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, a problem that occurs in all settings but is rarely discussed, also provides important patient and programmatic benefit by limiting false positive diagnoses with unnecessary treatment and improving the accuracy of laboratory results.(9) The introduction of routine WGS to track TB transmission and drug resistance profiles in settings of low TB incidence would identify TB control services as a lead implementer of the exciting public health revolution facilitated by recent advances in pathogen genomics.

Some may argue that the implementation of routine WGS for accurate TB transmission tracking in low-incidence countries could detract from efforts to improve TB control in high-incidence settings, by diverting financial and academic resources away from the every-day challenges faced in resource-limited settings. However, challenging low-incidence countries in this manner could ensure their sustained engagement in global TB control challenges with more support provided to resource-limited settings. The refinement of novel technological advances will also provide critical new insight and directly benefit high-incidence settings once these technologies are sufficiently mature and cost efficient. In addition, 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 the World Health Organization (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 TB incidence declines, which is a constant challenge that has fueled previous epidemic resurgences in low-incidence settings.

Several countries have piloted WGS to explore local TB transmission dynamics and assist better targeted public health responses.(6-10) However, 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 countries’ disease burden. Whereas verification of “Zero TB transmission” is relevant in low-incidence countries, high-incidence countries would mainly 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

92 determinants of drug resistance to provide accurate, WGS-based drug susceptibility prediction.
93 Collaboration between high- and low-incidence countries to develop quality assurance standards for
94 WGS, shared databases and common workflows for data analysis, as well as ethical guidance on
95 how this data should be shared and used by clinicians and public health officials, is essential to
96 unlock the full potential of the WGS revolution. Given the rapid rate of technological progress and
97 reduction in the unit cost of WGS, countries with the necessary technical resources should be
98 encouraged to transition to routine WGS and jointly develop the processes and systems required to
99 facilitate future deployment in high-incidence settings. These advances will accelerate progress
100 towards precision medicine, by guiding optimal individualized tuberculosis treatment and targeted
101 public health responses, and will ultimately provide better contextualized solutions to END TB.
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