

Accelerating tuberculosis elimination in low-incidence settings: the role of genomics



To the Editor:

In a recent *European Respiratory Journal* article, LÖNNROTH *et al.* [1] proposed a framework to accelerate progress towards tuberculosis (TB) elimination in low-incidence settings. In it, they outline eight priority areas and multiple interventions that align with the World Health Organization's post-2015 global TB strategy [2]. We applaud this framework and the recognition that elimination in low-incidence countries is a unique problem, where infection occurs amongst the most difficult-to-reach individuals. Although "new research and tools" is one of the framework's areas, it overlooks an important new technology that is changing our understanding of TB and our approaches to diagnosis, phenotyping, and treatment – whole genome sequencing (WGS) of *Mycobacterium tuberculosis* (MTB) isolates from cases of active TB [3, 4].

In contrast to genotyping, which interrogates ~0.5% of the MTB genome, WGS reads the entire 4.4 Mbp of sequence; with current sequencing technologies this can be done in under a day at a cost of ~\$50–100 per genome [5]. Many federal public health agencies have invested substantially in genomics and are using it routinely in medical microbiology [6], with TB representing the ideal use case. The MTB genome is uncomplicated (the global population of MTB is clonal and the genome comprises a single chromosome in which variations arise through point mutations) facilitating downstream bioinformatics analyses, such as prediction of antimicrobial resistance phenotypes. Additionally, most TB diagnostic work is performed in well-equipped reference laboratories, where centralisation permits integrating WGS data with the data streams necessary for diagnosis, surveillance, outbreak management and research, and where the need for accredited operating procedures is accelerating the standardisation of TB genomics protocols; Public Health England is already using WGS routinely alongside its traditional mycobacteriology laboratory pipeline in its Birmingham Public Health laboratory [6].

There are many areas of the framework in which WGS is poised to support efforts in TB elimination. First, WGS is able to resolve TB transmission dynamics, including individual transmission events, to a degree not possible with traditional genotyping. This genomic epidemiology approach has been used to reconstruct single transmission events, local outbreaks and regional epidemics [4], and is providing insights into both patterns of spread and characteristics of transmitters. Genomic epidemiology speaks to several priority-action areas. Unlike genotyping, which simply clusters active cases, WGS can elucidate the order and direction of transmission, revealing common trends in TB outbreaks and identifying those individuals who are transmitting disease and those who aren't. This directly informs the framework's goals of describing local patterns of transmission amongst vulnerable populations and identifying individuals most at risk for transmitting disease (areas 2 and 3); it also enables us to prioritise contacts of these key transmitters for screening (area 4). Additionally, real-time WGS of specimens from new TB cases provides a core indicator of ongoing transmission for surveillance (area 6).

Another priority area is the prevention and care of drug-resistant TB (area 5), for which phenotypic methods are the current gold standard. These methods are culture dependent and have turnaround times (TATs) of weeks to months; even rapid molecular methods with TATs of hours, such as the Cepheid GeneXpert (Sunnyvale, CA, USA) and line probe assays, are limited to detecting only a handful of known resistance mutations. As much as one third of isoniazid resistance cannot be explained by these canonical mutations [7], and no commercially available test can probe resistance to all anti-tuberculous drugs. WGS, in contrast, interrogates the entire genome, identifying resistance-associated mutations within hours to days [8], and optimising the prescription of appropriate treatment and supporting rational drug use (area 1). Although this requires a comprehensive database of well-described resistance-associated mutations, several such efforts are underway and more mutations are likely to be described as ever increasing numbers of isolates are sequenced.

There are other, less obvious, benefits to incorporating WGS into the routine diagnosis, management and surveillance of TB in low-incidence settings. Chief amongst these is that just as early MTB genomic efforts led to new molecular diagnostic tools based on a handful of sequenced genomes [9], the generation and sharing of thousands of MTB genomes will likely lead to new molecular tools for use in higher-incidence settings. Genomics is stimulating TB research and reinvigorating a community that has experienced de-prioritisation (area 1), potentially leading to renewed political interest in TB control and the specialised training and creation of central repositories. In addition collaborative efforts, necessary to deploy WGS in

the clinical laboratory, will act to build capacity at national and international levels, which is essential for the elimination of TB in low- and high-incidence settings.

In conclusion, genomics stands to significantly enhance TB elimination efforts through direct and indirect routes. When combined with the framework's recommended interventions, we believe WGS has the potential to accelerate progress towards TB elimination in low-incidence countries, with the knowledge gained in these settings working to support the final priority action area, thereby informing TB prevention, care, and control in countries with a high burden of disease.



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Genomics can aid TB elimination in low-incidence settings via enhanced epidemiology and rapid resistance prediction <http://ow.ly/TkPWS>

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From the authors:

We read with interest the correspondence by J.L. Guthrie and J.L. Gardy, which discussed the role of whole genome sequencing (WGS) in tuberculosis (TB) elimination based on the recently published World Health Organization (WHO) article [1]. The WHO document [1] focused on the priority interventions that should be applied by countries aiming to achieve TB pre-elimination (*i.e.* TB incidence <10 cases per million inhabitants) and elimination (*i.e.* TB incidence <1 case per million inhabitants) [1, 2]. The TB elimination strategy is expected to be initially adopted by low-TB incidence countries where the circulation of *Mycobacterium tuberculosis* strains is lower when compared to that observed in middle- and high-TB incidence countries.

On this basis, the WGS can represent an important clinical and public health tool, whose effectiveness was preliminarily demonstrated; although more operational research is needed to assess the feasibility and the potential impact of this technique. As pointed out by J.L. Guthrie and J.L. Gardy the WGS might play a crucial role in the identification of genomic strains' similarities and, then, in the true recognition of transmission dynamics in outbreaks. Tracking in-country and cross-border outbreaks by next generation sequencing can improve the identification of unsuspected transmissions allowing proper action to be taken.

The recently issued WHO guidelines on the programmatic management of latent TB infection (LTBI) raised the issue of the current diagnostic gaps for both LTBI and TB diseases, which could be filled by modern, rapid, and easy-to-use molecular- and biomarker-based techniques [3].