Title:

Programmatic versus personalized approaches to managing the global epidemic of multidrug-resistant tuberculosis

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The push to end TB as a global public health threat received a major boost from the first ever United Nations General Assembly High Level Meeting on Tuberculosis (TB) in 2018[1]. Ending TB as by 2035, however, will need to overcome hurdles in detection and provision of care and treatment of drug resistant TB. In 2018, an estimated 500,000 people had rifampicin resistance (RR-TB), of whom 78% had multi – drug resistant TB (MDR-TB)[2]. Prevalence of RR/MDR-TB is higher in previously treated persons, however, the larger burden of disease is in people who have never been treated for TB[3]. Care cascade analyses demonstrate major gaps in the continuum of care from diagnosis to treatment completion for persons with RR/MDR-TB. Current global RR/MDR-TB treatment success rate is unacceptably low at 56%,[3] with patients in rural areas probably at an increased risk of poorer outcomes[4]. These constraints continue to fuel both ongoing RR/MDR-TB transmission and the emergence of additional drug resistance.

The challenge of providing care to people with RR or MDR tuberculosis is that diagnosis and treatment are often viewed in terms of standardised programmatic responses. These standardised responses aim for simplified approaches that will achieve the best overall outcomes. By contrast, personalised approaches might improve individual management, but with the trade-off of increased complexity and insufficient programmatic resources to deliver care.[5]

Utilisation of the rapid GeneXpert system, recommended by WHO 10 years ago, remains largely suboptimal in most settings with a high burden of RR or MDR tuberculosis, particularly in countries where optimal diagnostic systems are needed most to address the high burden.[6]
In addition, the GeneXpert MTB/RIF assay does not characterise the full drug susceptibility profile to guide clinical management and fails to detect relevant rpoB mutations that fall outside the 81-base pair region that determines rifampicin resistance, with diagnostic selection of these mutations in settings such as eSwatini.[7] Access to phenotypic drug susceptibility testing and genotypic line-probe assays is limited by the requirements for high-level laboratory infrastructure.

As a consequence of these health system complexities, many patients are initiated on second-line treatment without essential diagnostic confirmation. Whole genome sequencing8 offers the potential to more comprehensively characterise the mutations that underlie resistance to some drugs; however, it will remain unavailable in tuberculosis endemic areas for the foreseeable future.

Most national TB programs adopt standardized second line drug regimens to facilitate policy implementation and medicine procurement, with regimen formulation based on knowledge of drug susceptibility profiles in the local setting in addition to other considerations such as drug safety, cost and ease of administration. A complete patient-specific drug-susceptibility results are usually not available to guide treatment. While this approach is understandable and potentially preferable in most resource-limited settings, it has many disadvantages. Major risks of using a regimen with uncertain efficacy include treatment failure, amplification of drug resistance, including development of resistance to new and repurposed drugs and ongoing transmission of even more resistant strains.

Although "standardization" of RR/MDR-TB treatment simplifies programmatic provision of care to these patients, it ignores human genetic diversity, relevant environmental differences and more importantly variability in pathogen susceptibility. Indeed, emerging data reveals that patients receiving individualized treatment regimens have a higher likelihood of treatment succes[9].

New insights in systems biology are increasingly used to explore disease diversity and develop precision medicine approaches. While this is also pursued in TB care[10], it remains a long way off from becoming routine practice in resource-limited settings that carry the bulk of the TB disease burden.

As WHO and national TB programs grapple with the implementation challenges posed by the rapidly changing landscape, it is critical for national TB programs to expand and decentralize molecular diagnosis of TB, capacity to utilize WGS or phenotypic testing of specimens from, for example, DR-TB prevalence surveys, to better understand patterns of drug resistance to guide optimal selection of standardized RR/MDR-TB treatment regimens.

With the upward trajectory of advances in treatment regimens and point of care diagnostics, the reality of personalized RR/MDR-TB therapy should become accessible to more people in lower

resourced countries. Meaningful and sustained improvements in RR/MDR-TB outcomes will require better person-centered care, which moves beyond merely improving our choice and delivery of regimens to empowering people affected by TB.

Given the poor outcomes achieved and risk of amplifying drug resistance, a one-size fits all approach to RR/MDR-TB management is no longer an option in the current era of innovation and technology. Confronting RR/MDR-TB in resource-limited settings will require greatly increased investment in research, including operational and implementation research, and in human resources in addition to enhancing capacity to determine variability of pathogen susceptibility and developing care programs that take into account human diversity.

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