Applying new tools to control tuberculosis

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In this Tuberculosis Updates 2018 series, experts from various parts of the world review important innovations and developments in a global effort to end the tuberculosis (TB) epidemic. Major gaps remain in reaching, diagnosing and effectively managing TB patients in many parts of the world. Social inequities continue to hamper TB control, especially in resource-limited settings. Universal health coverage and social protection are necessary to remove the barriers to the access to quality TB care.

Antimicrobial resistance represents a growing threat to public health and economic growth worldwide. Standardized treatment regimens, while having facilitated large-scale programmatic implementation, could have inadvertently accelerated the development of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB through drug-specific resistance amplification. Although the End-TB Strategy advocates universal access to drug susceptibility testing (DST), this is not widely available. The slow growth of Mycobacterium tuberculosis complicates phenotypic DST, and the long turn round time severely limits its clinical utility in guiding the initial choice of drugs. Unlike the regular reporting of minimal inhibitory concentration (MIC) for other bacterial infections, the use of a single critical concentration that inhibits the growth of 99% of phenotypically wild-type strains to classify phenotypical susceptibility or resistance to TB drugs may not bear a direct relationship with either achievable serum drug level or clinical response of a mutant strain. Clinical breakpoint, or MIC at or below which the relevant strain is likely to respond to treatment, may be useful for drugs that can be used at higher doses, such as isoniazid, rifampicin and fluoroquinolones. However, with the intrinsic difficulty in delineating the effect of individual drugs in a combination regimen, suggested values for the clinical breakpoint are given only for moxifloxacin in the recently published technical report from the World Health Organization (WHO). Commercial rapid molecular tests are now available for direct application to clinical specimens to detect mutations associated with resistance to key first- and second-line drugs, such as rifampicin, isoniazid, pyrazinamide, fluoroquinolones and second-line injectables, but their drug target coverage is still too limited to guide the formulation of individualized treatment regimens. Whole-genome sequencing holds promise for revolutionizing the coverage and predictive power of genotypical DST, but cost, throughput, facility requirement, background noises and replicative errors still remain important hurdles preventing its direct application to clinical specimens.

The preliminary results of the STREAM Stage 1 Trial showed marginally lower favourable outcome (78.1% vs 80.6%) for the standardized 9–12-month shorter MDR-TB regimen as compared to the conventional 18–24-month regimen. The difference could neither demonstrate non-inferiority of the shorter regimen nor superiority of the longer regimen. The trial end-point may not fully reflect the operational advantages of the much shorter regimen. Following an expedited review, the WHO continues to conditionally recommend the shorter regimen for adults and children with pulmonary MDR rifampicin-resistant (RR) TB who were not previously treated with second-line TB drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely. However, no more than 4–50% of patients in some MDR-TB hotspots, such as Eastern Europe, South East Asia, Pakistan and Brazil, are likely to be eligible for the shorter regimen because of the high prevalence of drug resistance to one or more of the drugs used in the regimen, thus raising concern of its longer-term sustainability.

TB drugs used in the longer conventional regimen for MDR-TB have been regrouped into three different categories by the WHO in August 2018. Group A drugs, including levofloxacin/moxifloxacin, bedaquiline and linezolid, are to be prioritized. Group B drugs, including clofazimine and cycloserine/terizidone, are to be added next. Group C drugs (ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin/streptomycin, ethionamide/prothionamide, p-aminosalicylic acid) are included when drugs from Groups A and B cannot be used. Judicious use of repurposed and new drugs is essential to avoid the emergence of resistance to these drugs, which would further set global TB control efforts back, in view of the relatively slow rate of TB drug development. With the reasonably favourable outcomes achievable with an optimized background regimen in both the STREAM Stage 1 Trial and Delamanid Trial 213, there may be a valid question as to whether the relatively toxic drug, linezolid, and the expensive new drug, bedaquiline, with very short and incompletely established safety record, are needed in the treatment of MDR-TB in the absence of fluoroquinolone resistance. Kanamycin and capreomycin are no longer recommended by WHO based on their associated risk of treatment failure and relapse in a recent individual data meta-analysis. However, retrospective observational data on treatment
outcomes are often subject to confounding by indication as well as non-comparability between cases and controls. In that meta-analysis, the overall treatment success rate was only 61% (or 71% after excluding those who died during treatment). Use of kanamycin and capreomycin were associated, respectively, with very good treatment success rates of 2192 of 2523 (86.9%) and 821 of 938 (87.5%) in drug-susceptible cases, even though they still fell short of the exceptionally high success rate of 406 of 455 (89.2%) observed in a possibly non-comparable control group not using injectables. Furthermore, in vitro susceptibility to second-line injectables has been consistently associated with better treatment outcomes in MDR-TB.\textsuperscript{18,19} The disparate effects between amikacin and the other two injectables may not be expected from their shared mechanisms of action. Kanamycin has been successfully used in the shorter MDR-TB regimen for adults.\textsuperscript{2,3} Intermittent dosing of the injectable after a daily phase may also help to reduce side effects and improve tolerance.

In February 2018, the WHO updated the guidelines for programmatic management of latent TB infection (LTBI).\textsuperscript{20} Either tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to diagnose LTBI, but such testing is not a strict requirement for initiating preventive treatment in people living with HIV or child household contacts aged <5 years, particularly in resource-constrained areas with high ongoing risk of TB transmission. IGRA works better than TST among people vaccinated with Bacillus Calmette-Guerin (BCG), particularly when the prevalence of true infection is low relative to BCG-induced cross-reaction.\textsuperscript{5} LTBI tests and biomarkers for predicting TB are subject to a generic limitation imposed on the positive predictive value by the generally low absolute disease risks.\textsuperscript{5,6} A 16-gene host transcription signature has been reported to predict TB in the 12 months in the validation cohort with a sensitivity of 53.7% and a specificity of 82.8%.\textsuperscript{21} However, with an absolute disease risk below 2%, the reported sensitivity and specificity would only translate into a positive predictive value in the region of 5%, still suboptimal for informing clinical decisions on an individual basis. Shorter, better tolerated treatments using rifamycins (weekly rifapentine plus isoniazid for 12 weeks,\textsuperscript{22} daily rifampicin for 4 months,\textsuperscript{23} daily rifampicin and isoniazid for 1 month\textsuperscript{24}) are proving safe and effective alternatives to isoniazid, especially in terms of lower risk of hepatotoxicity. However, the risks of other adverse effects (e.g. hypersensitivity reaction to rifamycins) remain considerable relative to the number of TB averted, thereby necessitating a targeted approach to optimize benefit versus risk ratio, although at the expense of reduced population coverage. In selected high-risk household contacts of MDR-TB, preventive treatment may be considered.\textsuperscript{20} Limited data suggested the protective efficacy of fluoroquinolone-based regimens for contacts of fluoroquinolone—susceptible MDR-TB.\textsuperscript{25}

Most cases of TB in the intermediate burden countries are caused by endogenous reactivation of LTBI among the aging population.\textsuperscript{7} Although the extended family structure is breaking down in many of these Asian cultures, grandparents may still play an important role in caring of young kids, raising a question of whether cross-generation transmission could further sustain the TB epidemic. On the other hand, while family contacts have higher risk of being infected, most TB transmission appears to occur outside the households in ill-characterized community settings.\textsuperscript{8} Before novel tools, such as molecular epidemiology, geospatial analyses and ventilation studies, can be successfully deployed to inform targeted interruption of such transmission in the general community, alternative population-based interventions are desirable to reinforce the current approach of controlling TB at the source through early diagnosis and effective treatment.

Highly predictive correlates of vaccine-induced protection are yet to be identified to de-risk TB vaccine research and development as well as human testing at an early stage.\textsuperscript{6,9} Notwithstanding this current hurdle, various novel TB vaccine candidates are being developed, with at least 12 of them now in clinical trials.\textsuperscript{3} With the high global burden of LTBI, vaccines capable of preventing pulmonary TB in infected individuals will be needed to exert a quick impact on TB incidence. A sub-unit vaccine, M72/AS01E, demonstrated 54% protection against active pulmonary TB in HIV-negative adults with a positive IGRA in a recently published phase IIb trial.\textsuperscript{26} This proof-of-concept study brings fresh hope for new and possibly transformative TB vaccines in the near future.

Heads of state and government, who are meeting on 26 September 2018 at the United Nations General Assembly, have committed to mobilize US$ 13 billion a year by 2022 to implement TB prevention and care and US$ 2 billion for research.\textsuperscript{27} Substantial advances have been made, especially in the diagnostic and treatment tools for drug-resistant TB and LTBI. However, careful planning is required in their field deployment. In particular, screening for TB and LTBI needs to be properly targeted at clearly defined high-risk groups within the specific epidemiological, social and health systems contexts to optimize the potential impact against the opportunity costs.\textsuperscript{28} Further breakthroughs, especially in highly predictive biomarkers for disease development and more effective vaccines for those already infected, are required to maximize the population impact.

**REFERENCES**
