Rolling out new anti-tuberculosis drugs without diagnostic capacity

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Tuberculosis (TB) remains one of the deadliest infectious diseases of humankind. The roll-out of new treatment regimens must be paired with proper diagnostic capability to prevent future drug resistance and sustain the effect of anti-TB chemotherapy. https://bit.ly/42pQWYD

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Abstract

Deaths from tuberculosis (TB) reached over 1.6 million in 2021 with 10.6 million people becoming ill. Multidrug-resistant TB, defined as the *Mycobacterium tuberculosis* organism having resistance to at least isoniazid and rifampicin, represented 3.9% of new TB cases and 18% of previously treated cases. While new drug regimens continue to be developed and introduced to improve treatment of drug-resistant forms of TB, diagnostic capability to identify drug resistance lags woefully behind. While significant mortality benefits exist for these newer drug regimens, implementing them without proper drug resistance diagnostic capacity could lead to development of more drug resistances and exhaust these new therapeutic tools. Moving forward, the roll-out of new TB drugs and regimens must be paired with implementation of diagnostics to ensure judicious use of resources and the best chance for improving TB worldwide.

Introduction

While the number of tuberculosis (TB) attributed deaths and cases had been improving steadily up until 2019, the years 2020 and 2021 showed an unfortunate increase in the incidence and mortality of TB in large part due to the coronavirus disease 2019 (COVID-19) pandemic. In 2021, ∼10.6 million people (95% uncertainty interval: 9.9–11 million) became ill with TB and this caused 1.4 million deaths among HIV-negative people (95% uncertainty interval: 1.3–1.5 million) and 187 000 (95% uncertainty interval: 158 000–218 000) among HIV-positive people [1]. Multidrug-resistant (MDR)-TB is defined as resistance of *Mycobacterium tuberculosis* against rifampicin and isoniazid. In clinical practice rifampicin-resistant TB (RR-TB) is considered an approximation for MDR-TB. In pre-extensively drug-resistant TB (pre-XDR-TB) there is additional resistance to a later class fluoroquinolone (levofloxacin or moxifloxacin) and in extensively drug-resistant TB (XDR-TB) there is additional resistance to at least one Group A drug (bedaquiline and/or linezolid) [2]. In 2021, ∼3.6% of new TB cases and 18% of previously treated cases were identified as MDR-TB/RR-TB [1]. MDR-TB/RR-TB and XDR-TB are coming to the forefront of public health concerns as newer diagnostic testing is allowing us to detect more drug resistance accurately. Until recently, the treatment of drug-resistant TB required longer and more toxic regimens with much lower success rates than drug-susceptible TB.

Newer anti-TB drug regimens

Efforts are continually made to develop and make available new anti-TB drugs that allow shorter and safer treatment regimens which can be taken orally. While shorter treatment regimens may be easier for patients to take, they also require effective drugs. Recently, the World Health Organization (WHO) updated its recommendations for the management of children and adolescents between 3 months and 16 years of age with non-severe drug-susceptible TB be treated with 4-month regimens, with 2 months of isoniazid (H), rifampicin (R) and pyrazinamide (Z) with or without ethambutol (E), followed by a continuation phase of 2 months of isoniazid and rifampicin (2HRZ(E)/2HR) [3].

Based on the results of the US National Institutes of Health sponsored ACTG study 31/A5349, the US Centers of Disease Control and Prevention has issued an interim recommendation for use of a 4-month treatment regimen consisting of 8 weeks of daily treatment with rifapentine, isoniazid, pyrazinamide, and moxifloxacin followed by 9-weeks of daily treatment with rifapentine, isoniazid and moxifloxacin in patients aged 12 years or older with drug-susceptible TB [4]. Based on the results of recent trials [5, 6], the WHO has recently suggested that patients aged 14 years or older with MDR-/RR-TB or pre-XDR-TB should be treated with a 6-month regimen consisting of bedaquiline (B) pretomanid (Pa) and linezolid (L) with or without moxifloxacin (M) (BPaL(M)) regardless of HIV status [7]. This recommendation applies to patients with <1 month of previous exposure to bedaquiline, linezolid, pretomanid or delamanid; however, when exposure was >1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out. This recommendation does not apply to pregnant and breastfeeding women owing to the limited evidence on the safety of pretomanid.

To utilise anti-TB drugs in an appropriate manner, rapid tests have been developed including nucleic acid amplification tests (NAATs), line probe assays (LPAs) and next generation sequencing (NGS). While these diagnostic tools are imperative to correctly apply newer drug treatment regimens, they require variable amounts of equipment and infrastructure which have not been made readily available in all areas that use these drug regimens [8]. Today, drug susceptibility testing (DST) for fluoroquinolones is encouraged but not required prior to treatment initiation.

Diagnostics for drug resistance

Rapid TB diagnosis and accurate drug resistance diagnosis are crucial to improve treatment outcomes for TB patients. Drug resistance occurs when *M. tuberculosis* has the capacity to survive under the effect of anti-TB drug(s). Identification of drug resistance can be divided into phenotypic and genotypic DST. Phenotypic DST requires inoculation of positive samples in drug containing media and is time-consuming, even with the use of liquid-based culture systems such as the BACTEC MGIT 960 system (Becton, Dickinson and Company) [9]. Genotypic DST predicts drug resistance by identifying mutation(s) in drug-regulated gene(s), which can be performed by sequencing and non-sequencing methods. NAATs can detect the components of *M. tuberculosis* genes in a timely manner and are therefore used to diagnose TB and drug resistance simultaneously. These methods are used on a variety of patient specimens, including direct sputum, sputum culture growth, and stool. GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra (Cepheid) are routinely used to not only diagnose TB but also identify *rpoB* gene mutations associated with resistance to rifampicin [10, 11]. Xpert MTB/XDR (Cepheid) is now able to detect resistance to isoniazid, fluoroquinolones, ethionamide and amikacin [12].

Targeted NGS or high throughput sequencing is a swiftly evolving area in TB diagnostics, as it has the ability to provide rapid information regarding mutations associated with drug resistance on multiple targets from a patient sample [13]. Using these tools, molecular surveillance may be possible to identify emerging drug resistance in a population to allow a proactive rather than reactionary approach to evolving drug resistance epidemiology. Diagnostics for identifying drug resistance are often most lacking in the areas that need them the most. As newer diagnostic tools require infrastructure and money, they are first rolled out in countries with existing sophisticated laboratory infrastructure and highly skilled personnel. This trend continues and widens the inequality gap that exists in diagnostic capacity and therefore mortality outcomes [8].

Epidemiology of drug resistance

Drug resistance is driven by a number of mechanisms including exposure to sub-therapeutic drug levels, increasing drug tolerance, and spontaneous mutations when targets are nonessential genes. The WHO estimated 450 000 incident MDR-/RR-TB cases in 2021 (95% uncertainty interval: 399 000–501 000). Bedaquiline, part of all the WHO's oral MDR-/XDR-TB treatment recommendations, already has treatment resistance developing and this can subsequently cause treatment failure [14–16] with cross-resistance to clofazimine (CFZ) associated with the *Rv0678* mutation [14, 17]. A recent systematic review identified an overall rate of 2–4% drug resistance to bedaquiline with rates as high as 15% in eastern Europe [18]. This

increased drug resistance has been linked to clinical failure [19] and will continue to worsen as this drug is used more without proper diagnostics [20]. Unpublished data have indicated rates of drug resistance vary by geographic region, which may be based on the TB lineages and strains or human behaviour and living environment in these settings, and it would be unreasonable to expect that *M. tuberculosis* does not develop resistance to novel anti-TB medicines. The first patient with pretomanid-resistant TB has already been described [21]. The human body itself may assist in drug resistance *via* the phenomenon that drugs are delivered at different concentration gradients in tissues and create a "reservoir" of drug, with drugs like bedaquiline modelled to persist in tissue for months as a monotherapy [22], which may lead to selection of drug-resistant mutants.

Conclusion

New drug treatment options must be paired with proper diagnostic capability to ensure a sustainable step forward for TB patient outcomes [23]. Newer drug options have shortened treatment duration as well as improved accessibility; however, these benefits might not be sustainable if they are misused without proper application in clinical scenarios [20]. The increase in drug resistance, especially with regards to bedaquiline, is of particular concern and can be ameliorated with proper diagnostics. Rapid molecular tests to predict DST for BPaLM regimens are currently only available for moxifloxacin (M), highlighting the need for NGS technologies to identify resistance to all medicines in the regimens as early as possible to provide appropriate therapies for all patients affected by TB. Mandatory molecular surveillance monitoring for drug resistance as well as targeted NGS which can provide a wider breadth of information on drug resistance rapidly may assist in these endeavours. Without full DST, unrecognised resistance to even one drug in these short regimens may increase risk of failure/relapse and acquired drug resistance. Drug developers, in particular, should contribute to diagnostic development as they pursue the development of new drugs. While diagnostic capacity should not delay treatment initiation in patients diagnosed with TB, efforts must be made to link diagnostics and drug supply in an equitable manner to ensure continued progress in the treatment of TB and drug-resistant TB.

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