Pan-tuberculosis regimens: an argument for

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600 000 cases of drug-resistant tuberculosis, causing 240 000 deaths, were estimated by WHO to have occurred worldwide in 2016.[1] Cases are expected to increase over the next two decades, driven by the low likelihood that patients will initiate appropriate treatment and, in those who do, the low probability that treatment will succeed.[2] Experience in Africa has highlighted the scope and complexity of this problem. In South Africa, where the Xpert MTB/RIF test has fully replaced sputum acid-fast bacilli smear for tuberculosis diagnosis, 59% of rifampicin-resistant patients have additional resistance to second-line drugs (eg, kanamycin, ethionamide, and ofloxacin).[3] These drugs are essential for rifampicin-resistant-tuberculosis treatment, yet all three second-line drug susceptibility tests (SL-DST) are performed in only 19% of patients.[3] SL-DST is far less available in other high-burden countries. In neighbouring Mozambique for example, WHO estimated 159 000 total tuberculosis cases and 7600 rifampicin-resistant cases of disease in 2016.[1] However, of the 73 480 notified cases, only half were tested for rifampicin-resistance, and only 868 had SL-DST performed. The resulting 25 cases of confirmed extensively drug-resistant tuberculosis are likely to be just a small fraction of the country's true burden. These grim statistics reflect the intrinsic shortcomings of current diagnostics compounded by the implementation challenges they pose. Drug-resistant tuberculosis patients who receive less than fully effective treatment experience increased mortality and contribute to ongoing transmission of increasingly resistant isolates, thereby fuelling the epidemic.[4]

Perhaps the most direct solution to this dilemma is the development of novel, simple, effective regimens that do not require drug-susceptibility tests. Such standardised pan-tuberculosis regimens would be comprised of new drugs without pre-existing resistance, with a high barrier to new resistance, which have satisfactory efficacy, safety, and tolerability.[5] A glimpse into their transformative potential has been shown by the results of the Nix-TB trial, which indicated preliminary efficacy of combined linezolid, pretomanid, and bedaquiline given for 6 months to patients with pre-extensively drug-resistant and extensively drug-resistant-tuberculosis.[6] Although the regimen was poorly tolerated, the substitution of sutezolid (an experimental oxazolidinone with a superior therapeutic index for tuberculosis[7]) for linezolid could potentially improve the safety and tolerability of the regimen, so as to permit wider use. Compounds in earlier stages of development may also be considered in future pan-tuberculosis regimens.

In a recent study, two of the authors (TC and NAM) adapted an existing transmission dynamic model of tuberculosis epidemiology and control interventions[8] to project possible effects of the introduction of a pan-tuberculosis regimen on health outcomes (unpublished data). We calibrated the model to measures of tuberculosis burden and programme performance in each of four countries (South Africa, India, China, and Mozambique) that account for nearly half the global drug-resistant-tuberculosis burden.[1] We projected outcomes for a base case assuming continuation of current policies and practices, and for an alternative scenario in which a new pan-tuberculosis regimen, with efficacy similar to the Nix-tuberculosis regimen, is introduced in 2022, fully replacing other treatments for all patients in these countries by 2024. No changes in duration of treatment, levels of programme coverage, quality of service provision, or type of laboratory support were assumed. Our preliminary analysis suggests that during the subsequent decade, the new regimen could prevent nearly half a million deaths and 4 million tuberculosis infections.

Development and roll-out of new pan-tuberculosis regimens is most appropriately considered in conjunction with development of new diagnostics and adherence monitoring methods, and strengthening of laboratory and health-care systems. Use of a pan-tuberculosis regimen in South Africa, for example, might first be considered in patients with confirmed rifampicin resistance, until SL-DST results become available. A unique opportunity exists for the pairing of a pan-tuberculosis regimen with a non-sputum-based rapid tuberculosis diagnostic test, such as that recently described using hydrogel nanocages to capture and detect picogram concentrations of urinary *M tuberculosis* lipoarabinomannan.[9] The resulting new tuberculosis strategy, appropriately pairing a new diagnostic with a new regimen, could indeed be transformative.

All antimicrobials, including those in future pan-tuberculosis regimens, have finite lifespans limited by

emergence of resistance. Prudent use of new drugs in specific fixed combinations can help protect their period of utility; experience with standardised regimens for initial HIV treatment stands as a testament to this strategy. Our present jumbled approach to tuberculosis treatment, which is neither standardised nor adequately personalised, is already hastening the demise of promising new drugs. Standard short-course therapy (HRZE) as introduced in the 1980s would fail to meet current criteria for a pan-tuberculosis regimen due to substantial levels of isoniazid resistance that arose during three decades of previous use. HRZE was further compromised by delayed recognition of the importance of daily rifampicin throughout treatment. Nonetheless, the regimen served well for over 15 years. It is reasonable to anticipate that an effective and well tolerated regimen comprised of new drugs, if introduced and rationally used exclusively in combination from the start, could exceed that historical experience. We should do our utmost to take advantage of this unique opportunity.

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Pan-tuberculosis regimens: an argument against

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In 1986, after publication of a seminal paper about the use of short-course regimens for tuberculosis treatment, there was great optimism that a universal regimen for tuberculosis had been discovered.[1] Pierre Chaulet described the short-course regimens as "highly effective and reliable with the minimum of constraints either for patients or for health personnel."[2] Unfortunately, the emergence of rifampicin-resistant *Mycobacterium tuberculosis* strains soon rendered these short-course regimens ineffective for many individuals. Estimates by the WHO suggest that, in 2016 alone, more than 600 000 people developed rifampicin-resistant tuberculosis.[3]

The quest for a universal tuberculosis treatment regimen has become a Holy Grail for many working in the field of tuberculosis. It is argued that such a regimen, likely comprising three drugs (bedaquiline, an oxazolidinone-like sutezolid, and a nitroimidazole-like pretomanid or delamanid), would eliminate the need for drug-susceptibility testing, and have the biggest effect on reducing disease burden and mortality. It is certainly true that such a regimen could have real benefit for many people living with tuberculosis and the programmes that serve them. However, focusing on a universal regimen as the answer to the world's tuberculosis woes is a flawed approach for several reasons.

First, rapid resistance amplification will occur, with loss of effective drugs: a universal regimen will only be universal for a short period of time. As was the case with rifampicin—and as is the case with all antimicrobial agents—the major driving forces of antimicrobial resistance are strain variation and selection of drug-resistant strains. Thus, resistance will undoubtedly develop, even with careful attention to adherence. Indeed, resistance to quinolones or aminoglycosides develops in about 10–15% of patients with multidrug-resistant tuberculosis after roughly 4 to 5 months of combination therapy,[4] and many controlled trials have suggested that directly observed therapy short-course does not prevent acquired resistance.[5] Consequently, resistance will emerge, driven by pharmacokinetic variability (modulated by