final efficacy follow-up decreased more substantially for cefiderocol than imipenem-cilastatin. Clinical response was almost identical at test of cure (226 [90%] of 252 patients in the cefiderocol group *vs* 104 [87%] of 119 patients in the imipenem-cilastatin group; treatment difference 2·39%, 95% CI −4·66 to 9·44) and at the final efficacy follow-up, the difference remained non-significant (205 [81%] *vs* 86 [72%]; 9·02%, −0·37 to 18·41).

The effect of cefiderocol on its intended target, multi-resistant pathogens, could not be properly assessed. However, cefiderocol was microbiologically successful in only 44% of infections caused by *P aeruginosa*, an organism against which it has strong in-vitro activity,[4] suggesting that biofilms and other in-vivo factors might pose future challenges, or worse, that efflux pumps or other resistance mechanisms might be more efficient than anticipated.[4] The overall safety profile of cefiderocol was favourable and similar to that of imipenem-cilastatin, with gastrointestinal disorders most frequently reported.

This was a phase 2 trial, and thus by definition the results provided cannot be used to establish conclusions about the clinical efficacy or safety of cefiderocol. Because the trial used old endpoints that favour early outcomes, meaning little to patients and their clinicians (repeat urine cultures have no place in the clinic), we remain vulnerable to that familiar scepticism. Is this drug going to help my patient durably? Or will it manage only clinical improvement and temporary colony-count reduction?

The FDA's new guidance on complicated urinary tract infection endpoints, issued in June 2018, calls for complete clinical resolution and changed the cutoff for microbiological response to bacterial counts of less than 1×10^3 CFU/mL.[7] An accelerated process to get new antibiotics to market was urgently needed, and regulatory bodies responded. But any trial launched more than 4 months ago (including an ongoing phase 3 cefiderocol trial, NCT02714595) will now be adhering to outdated standards and requirements. There is still no guidance on measuring baseline or emerging resistance; this too will fall to post-market development.

Although these results are promising with regard to obtaining approval for cefiderocol and in the context of increasing antimicrobial resistance, scepticism will persist until more evidence is available. Cefiderocol remains on the fast track to approval. This is welcome news, as long as those in post-market clinical medicine understand the deal we have made: it will fall to us to continue the drug's clinical development, while managing its appropriate use and conservation, and thus take its true measure.

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I declare no competing interests.

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Global burden of tuberculosis: where we are and what to do

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Tuberculosis continues to cause ill health and deaths across many populations in the world, 25 years since WHO declared the disease a global emergency.[1,2] In *The Lancet Infectious Diseases*, the Global Burden of Disease (GBD) Tuberculosis Collaborators report the burden of tuberculosis in 2016 and trends since 1990.[3] The details of some of their data differ from the latest estimates issued by WHO.[1] But both reports are in agreement on one point at least: if the decreases in global tuberculosis incidence and mortality continue

at their current, moderate rates, few countries will reach the Sustainable Development Goal (SDG) target of ending the epidemic of tuberculosis by 2030. Over the past two decades, commendable progress has been made in improving tuberculosis control on a global scale.[1,4,5] Nevertheless, some scepticism about the chances of meeting this SGD goal in understandable given the rate at which tuberculosis incidence is decreasing compared with the ambitious targets.[1,6,7]

To stimulate action towards elimination, goals should be ambitious; however, even humble goals currently seem beyond reach. The data presented on the GBD 2016 study should be a wake-up call to further intensify efforts towards reliable data collection. Although the data are detailed and carefully researched, they are estimated and rely on many assumptions—more primary data are needed from all countries to minimise the need for extrapolation. Our question is, how can this coverage be achieved? The scale of the tuberculosis problem has been recognised and political will to optimise control of the disease exists, as shown by the first United Nations high-level meeting on tuberculosis, held in September, 2018.[8]

A wealth of measures have been suggested to control tuberculosis. Some lean towards the idea of a magic bullet, such as increased innovation through investment in better diagnostics, novel drugs, and improved treatment regimens for all forms of tuberculosis developed through increased investment and innovation. Others are closer to what might be considered a magic gun, in which existing tools are used more effectively, through better means of delivery and broader implementation of measures that are already available—eg, task-shifting (re-structuring workforces in reponse to the health-care workforce problem), robust tracing and treatment of patients, full recognition of the magnitude of the burden of tuberculosis in countries with low absolute but high relative incidences of the disease, treating hard-to-reach population in otherwise low-incidence countries,[9] and refinement of individual treatment strategies. In truth, all of these measures will be needed to address the epidemic of tuberculosis—each will have to be intensively implemented and scaled up in the coming years, if not decades.

Even so, some simple and easier to implement measures could be taken to accelerate progress towards controlling tuberculosis. The burden and trends of tuberculosis, tuberculosis in people with HIV/AIDS, multidrug-resistant tuberculosis, and extensively drug-resistant tuberculosis should be assessed with caution. Such caution is especially important in low-income and middle-income countries in sub-Saharan Africa where data accuracy and reliability can be poor, and diagnostic capacity can be inadequate, including for the confirmation of extrapulmonary tuberculosis.[1,10] High-quality data is dependent on good surveillance systems, reliable vital registration systems, and quality notification data, but such high-quality data remains difficult to obtain in many parts of the world, including large parts of sub-Saharan Africa. As such, the number of cases of tuberculosis might be over-reported in such areas because of reliance on smear microscopy that can sometimes detect non-tuberculous mycobacteria, or the number of cases might be under-reported because of unreliable sensitivity and specificity of smear microscopy.[11] Investment in novel diagnostics for tuberculosis needs to be intensified to improve global accuracy, and thus, the quality of estimates, and for understanding the actual burden.

To understand the actual global tuberculosis situation, the burden sometimes needs to be determined in terms of incidence per capita rather than by use of absolute numbers to enable comparisons with other regions. This method needs to be used cautiously considering that WHO also uses similar criteria to define some of the high tuberculosis burden countries of the world and so direct comparisons could be conflicting.[12]

All these approaches to directly address the burden of tuberculosis will need to be supported by governments, non-governmental organisations and agencies, and funders. But there are also broader considerations. In the GBD 2016 tuberculosis study, more than three-quarters of incident cases of tuberculosis and deaths due to tuberculosis in 2016 were in HIV-negative individuals. This fact highlights the importance of considering the social determinants that are sustaining the tuberculosis epidemic other than those related to HIV/AIDS, diabetes, and drug-resistance, as highlighted by GBD 2016.[1,3,13] The SDGs are interconnected, and health goals can only be achieved if the other SDGs are met too.

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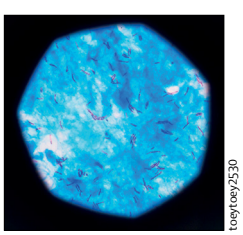
Occult rifampicin-resistant tuberculosis: better assays are needed

Drug-resistant tuberculosis remains an important public health concern. A 2017 meta-analysis[1] of published studies from India suggested that more than 40% of all *Mycobacterium tuberculosis* isolates included in the analysis were multidrug-resistant (MDR). Drug resistance is associated with high mortality despite treatment. Furthermore, prolonged therapy with multiple anti-tuberculosis drugs is onerous both for patients and the health system.

Current WHO-endorsed diagnostic tests for tuberculosis include Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and GenoType MTBDR*plus* (Hain Lifescience, Nehren, Germany);[2] however, these assays do not detect mutations outside of the 81-bp rifampicin-resistance-determining region (RRDR) of the *rpoB* gene of *M tuberculosis,* which contains 95% of known rifampicin-resistance-associated codons.[3] Furthermore, the current standard resistance assay used to validate novel molecular assays is the automated mycobacteria growth indicator tube 960 liquid culture system (BD, Baltimore, MD, USA), which has been reported to miss mutations associated with rifampicin resistance outside of the RRDR.[4]

An important study by Ndivhuho A Makhado and colleagues[5] in *The Lancet Infectious Diseases* reports the prevalence of previously undetected rifampicin-resistant tuberculosis. The group used *M tuberculosis* strains with isoniazid monoresistance, diagnosed by WHO-endorsed assays, and tested these isolates for the Ile491Phe mutation, which confers rifampicin resistance but is not detected by the assays currently endorsed by WHO. The authors randomly selected 277 (15%) of 1823 isoniazid-monoresistant isolates and compared these with strains from a survey in eSwatini (formerly Swaziland) in which 30% of MDR tuberculosis isolates had the Ile491Phe mutation.[6] Using deep sequencing (Deeplex-MycTB) and whole-genome sequencing, the authors were able to genotype, predict drug resistance, and phylogenetically analyse the isolates. The Ile491Phe rifampicin-resistance-associated mutation was detected in 37 (14%) of the South African isolates, thereby reclassifying them as MDR. Additionally, isolates from both eSwatini and South Africa were resistant to all first-line drugs according to Deeplex-MycTB. Ile491Phe was associated with worse prognosis, with five-times increased odds of the mutation being present in cases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