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EDITORIAL

Challenges in TB regimen development: preserving evidentiary standards for regulatory decisions and policymaking

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Rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant TB (MDR-TB), defined as infection with *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid, represent a global health emergency, with almost half a million new cases and over 200 000 deaths estimated in 2018 [1]. Drug-resistant strains are increasingly transmitted in the community [2], and particularly so among people previously treated with anti-tuberculosis drugs [3]. Timely and effective treatment of patients with active RR/MDR-TB disease is, therefore, key to preventing unnecessary deaths and further transmission of drug-resistant tuberculosis. While the treatment of fully drug-susceptible TB should have a cure rate of >95%, the global treatment success rate is only 86% due to many factors (availability and quality of drugs, adherence to treatment, etc.). According to the World Health Organization (WHO), however, in 2016, only 56% of people with RR/MDR-TB that started treatment were treated successfully, a proportion dropping to 39% among people with extensively drug-resistant tuberculosis (XDR-TB), defined by additional resistance to any fluoroquinolone and any second-line injectable [1]. Improved treatment regimens for RR/MDR-TB are direly needed.

Randomized controlled trials (RCT) are the universally recognized gold standard for evaluating the efficacy and safety of any intervention, and necessary to establishing – and informing changes to – standards of care. In the field of RR/MDR-TB, however, RCTs to determine the optimal combination and duration of treatment are challenging due to limited resources, complex patient management requirements, operational hurdles, and increasingly rapid and regular changes to the treatment landscape based both on clinical trial and observational data. This editorial discusses some of the challenges research sponsors face in conceiving of, implementing, and completing RCTs for RR/MDR-TB, and the role of regulatory and normative bodies in promoting and preserving high evidentiary standards for the development of new TB medicines and regimens.

The time needed to design, obtain ethical approval for, enroll, and present the results of a phase III RCT is substantial, and on average can take up to more than 4 years [4]. In the case of RR/MDR-TB, the delay between trial initiation and its final results may be even more prolonged, due to the length of treatment (up to 2 years) and the need for a post-treatment follow-up period (at least 6 months) to detect relapses [5]. In parallel, the standard-of-care for RR/MDR-TB treatment is evolving more rapidly than ever before, for multiple reasons: (a) the approval of new drugs, like bedaquiline, delamanid and pretomanid; (b) the re-purposing of drugs used for other infectious diseases, like linezolid and clofazimine; (c) the uptake of new, often observational, evidence in updated recommendations by the WHO [6]; and d) the withdrawal of an effective drug (gatifloxacin) from the market due to toxicity concerns. These changes risk jeopardizing the relevance of large clinical trials, which might become obsolete as they are enrolling and/or by the time results are published. In addition, the control arm of such trials, which often reflect the standard of care at the time, the trial was first designed and/or opened to enrollment, may no longer provide for a relevant comparison. Or, if designed with flexibility to adapt to a changing standard of care, it will vary considerably (both in composition and duration) during the life of the study.

The growing amount of observational evidence available in the field of drug-resistant tuberculosis is good for the field but poses new challenges for study design and analysis, normative guidance, and regulatory oversight. Historically, WHO guidelines for RR/MDR-TB treatment have been based on expert opinion and very few, if any, RCT data [7]. Although this has recently changed with the availability of phase II and III RCT data [8–11], major shifts in the WHO-recommended drugs and regimens for DR-TB have been driven mainly by observational data. A recent example is the replacement of the injectable agent with bedaquiline in the standardized short-course regimen, previously recommended only under the conditions of

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operational research, and still yet to be validated in an RCT. Although this should be considered somewhat exceptional, given the serious safety concerns linked to the use of the injectable agents, there is concern that the trend of observational data driving guidelines changes will continue. If it does, giving an outsized role to observational data has the potential to undermine ongoing research efforts and lower the evidentiary standards required for changes to RR/MDR-TB treatment policies.

Since 2016, WHO guidelines for the treatment of RR/MDR-TB have been based on the rigorous GRADE methodology, which includes the appraisal of the quality of evidence [12]. However, a majority of recommendations provided to date for the treatment of RR/MDR-TB, including the recommendations most recently released by the WHO via rapid communication [13], are based on observational studies which by definition provide evidence of 'low' or 'very low' quality, often leading to conditional recommendations. The analysis of large individual patient data datasets, although increasing the precision and reducing the variance of the estimated effect, does not and cannot prevent selection bias or confounding. The emphasis on the use of 'real-world data,' opposed to clinical trial data, is misleading and does not serve the cause of providing the best guidance to clinicians [14,15]. In addition, the fact that the current standard-of-care has been established based on observational studies, could potentially discourage the conduct of confirmatory phase III RCTs, which are more expensive and require more time to produce results [16].

Another critical issue in the design and conduct of RCTs is the choice of the control [17]. Controlled trials provide the best level of evidence for GRADE-based recommendations, since they prevent bias linked to (a) differences in baseline and on-treatment variables that could influence outcome between the trial participants and the comparator (i.e. rates of HIV co-infection); (b) other unmeasured factors that may impact treatment outcomes (i.e. treatment), which may vary across countries/historical periods but will be constant across experimental and control arms within each site; and (c) differences in methods and frequency for monitoring clinical and safety outcomes (usually stricter in a trial). The comparison of experimental regimens to an individualized, concurrent, internal control is the most meaningful for programs and for policymakers. One recent approach is flexible designs that allow the internal, concurrent control arm to be dynamic and evolve in accordance with global guidelines affecting the standard of care implemented under program conditions [15].

Available alternatives to a flexible internal control capable of evolving with the global standard of care may not be equally satisfactory. For instance, the choice of a static control, i.e. retaining as the control the regimen in place at the time of trial design, may compromise the relevance of the final results of the trial should the standard of care change while the trial is still enrolling (i.e. the STREAM 1 trial) [11]. Uncontrolled studies (i.e. Nix-TB [NCT02333799] and ZeNiX [NCT03086486]) using external, historical comparators may produce misleading results. For instance, both STREAM 1 [11] and the delamanid phase III [10] trials would have likely concluded that the experimental treatment was vastly superior if compared to historical controls. In fact, the experimental regimen in both trials performed similarly to the internal control used in each study. In addition, trials without an internal control greatly increase the risk of 'biocreep' which is intrinsic in non-inferiority trials [18].

Historically, RCTs have played an unparalleled and crucial role in the development of new TB drugs and regimens [19]. Pivotal RCT results usually represent the core of submissions to regulatory agencies which establish that a drug submitted for licensure is safe and effective for the proposed use, while recommending bodies like the WHO define how to use the drug optimally within a regimen. An exception to this process is represented by the recent approval of pretomanid by the United States Food and Drug Administration (FDA). The FDA approved pretomanid as part of a standardized regimen for XDR-TB patients based on the results of a historically controlled phase III clinical trial, Nix-TB. This decision has been criticized on the grounds of both the choice to use historical data as the comparator and its small sample size, which among other factors makes it difficult to clearly establish the contribution of each component of the regimen [20]. Although performing uncontrolled phase III trials may be appropriate under specific conditions, notably in the absence of a reliable 'standard-of-care' treatment, this does not appear to be (anymore) the case for XDR-TB [21]. Worryingly, approvals based on limited evidence have the potential to lower the evidentiary standard regulatory authorities require for new drug approvals. This may be a particular worry for medicines that benefit from orphan disease designation [22] and as a result, are eligible for FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) [23]. LPAD was set up to incentivize the development of medicines for diseases of little commercial interest or with limited or hard-to-enroll patient populations, but has come under scrutiny for accepting lesser proof of efficacy and, in turn, greater uncertainty and higher risks for the populations affected by qualifying diseases and conditions [24].

While there has in recent years been a justifiable focus on the development of new regimens, it is important that research addresses both questions of regimens and of the comparative safety and efficacy of individual drugs, especially those from the same class. In coming years it will, for example, be important for clinicians to know when to use delamanid and when to use pretomanid, as both are nitroimidazooxazoles. The most reliable way to establish the differences between these two drugs is an RCT where two study arms are treated exactly the same apart from randomization to one of these two drugs. One benefit of such head-to-head comparisons is that the interpretation of such study findings is less sensitive to changes in the standard of care than studies in which the only comparison is between an experimental regimen and a standard of care control. Such an RCT would likely require a large sample size to detect what might be an expected small difference between the two regimens – although the use of a combined efficacy/safety composite endpoint may in certain circumstances help parse out important clinical differences with smaller sample sizes [17].

Regulatory agencies should play a role in ensuring that not only basic safety and efficacy data on new drugs are available, but also that sufficient high-quality research is conducted to inform the best use of these drugs (i.e. regimens, treatment duration). Drug registration, and regulatory requests and requirements for additional evidence (including through conditional approvals) represent potentially the best available leverage with which to compel drug sponsors to ensure that all these critical research questions are answered.

After years of stagnation, the field of drug and regimen development for RR-TB is changing rapidly. With a clinical drug pipeline fuller than it has been in decades, now is the time to double down, not pull back, from investing in RCTs. Single-arm studies and operational research initiatives can help to fill important knowledge gaps and optimize treatment interventions. Ultimately, high-quality evidence to guide regulatory and policy decision-making must come from adequately designed (and funded) RCTs – the highest attainable standard of medical evidence, which we owe to patients affected by drug-resistant tuberculosis to strive for and maintain [25].

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. WHO. Global tuberculosis report 2019. Geneva World Health Organ. 2019;Licence: CC BY-NC-SA 3.0 IGO.
2. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med. 2015;3:963–972.
3. Shah NS, Auld SC, Brust JCM, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Engl J Med. 2017;376(3):243–253. .
4. Hopewell S, Clarke MJ, Stewart L, et al. Time to publication for results of clinical trials. Cochrane methodology review group, editor. Cochrane Database Syst Rev. 2007; Internet]. DOI:10.1002/14651858.MR000011.pub2.
5. Nunn AJ, Phillips P, Mitchison D. Timing of relapse in short-course chemotherapy trials for tuberculosis. Int J Tuberc Lung Dis. 2010;14:241–242.
6. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva world health organ. 2019;Licence: CC BY-NC-SA 3.0 IGO.
7. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis-2008. WHO Geneva Switz 2008;WHO/HTM/TB/2008.402.
8. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009;360:2397–2405.
9. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366:2151–2160.
10. von Groote-bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019;7:249–259.
11. Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380:1201–1213.
12. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–926. .
13. WHO. Rapid communication: key changes to treatment of drug-resistant tuberculosis. Geneva World Health Organ. 2019.
14. Schunemann HJ. All evidence is real world evidence. Blog. 2019. Available from: https://blogs.bmj.com/bmj/2019/03/29/holger-j-schunemann-all-evidence-is-real-world-evidence/
    - **A very interesting blog entry describing on the duality between observational and clinical evidence.**
15. Collins R, Bowman L, Landray M, et al. The magic of randomization versus the myth of real-world evidence. N Engl J Med. 2020;382(7):674–678.
    - **Interesting piece on the misleading concept of "real world" evidence.**
16. Lienhardt C, Vernon AA, Cavaleri M, et al. Development of new TB regimens: harmonizing trial design, product registration requirements, and public health guidance. PLOS Med. 2019;16(9):e1002915. .
17. Phillips PPJ, Mitnick CD, Neaton JD, et al. Keeping phase III tuberculosis trials relevant: adapting to a rapidly changing landscape. PLOS Med. 2019;16:e1002767.
    - **Recommended opinion piece on the landscape and challenges of drug clinical trials in the field of tuberculosis.**
18. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials. 2011;12:106.
19. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British medical research council tuberculosis units, 1946–1986, with relevant subsequent publications. Internaional J Tuberc Lung Dis. 1999;3:S231–S279.
20. McKenna L, Furin J. Are pretomanid-containing regimens for tuberculosis a victory or a victory narrative? Lancet Respir. Med. 2019;7:999–1000.
21. Byar D. Design considerations for AIDS trials. J Acquir Immune Defic Syndr. 1990;3:S16–19.
    - **One of the first papers to define the role and boundaries of uncontrolled trials in therapeutic trials.**
22. Global TB Community Advisory Board. Research, regulatory, and access considerations regarding pretomanid. Cited 2020 Apr 10. http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_consideration
23. FDA. Limited Population Pathway for antibacterial and antifungal drugs – the LPAD Pathway. Cited April 10, 2020. Available fromhttps://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway
24. FDA. Limited population pathway for antibacterial and antifungal drugs; draft guidance for industry. comments. Cited 2020 Apr 10. Available from https://www.regulations.gov/docketBrowser?rpp=25&so=DESC,commentDueDate£0&dct=PS&D=FDA-2018-D-2032
25. Mitnick CD, Castro KG, Harrington M, et al. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. PLoS Med. 2007;4:e292.