WHO 2019 guidelines on drug-resistant tuberculosis treatment: based on evidence or expert opinion?

To the Editor:

Since 2011, the World Health Organization (WHO) has used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for grading quality of evidence [1, 2] to update guidelines for the management of drug-resistant tuberculosis (DR-TB). This represents an undeniable improvement towards evidence-based recommendations compared to previous guidelines, which were primarily based on expert opinion [3]. However, some aspects of guideline development remain unclear. In our opinion, the WHO 2019 consolidated guidelines on DR-TB treatment [4] have raised some concerns in the way recommendations were drawn from the evidence evaluated to answer specific PICO (Patient, Intervention, Comparator, Outcome) questions.

Firstly, the evidence that was graded to assess the standardised shorter multidrug-resistant tuberculosis regimen (SCR) (PICO 1) used the 2011 [5] or 2016 [6, 7] WHO longer regimens as a comparator. This does not provide conclusive evidence on the performance of the SCR as compared to the new longer regimens that include new core drugs, such as bedaquiline and linezolid, as recommended by the 2019 WHO guideline. Similarly, the phase III trial STREAM, which tested the SCR regimen, did not include these drugs in the control arm [8]. Therefore, the recommendation of the SCR as an equal alternative to the longer regimen designed according to 2019 guidelines is based on no direct evidence.

Secondly, the analyses conducted on patients treated with the 2016 WHO longer regimen do not inform about the optimal number of drugs and the duration of the newly recommended regimen (PICO 3 and PICO 4, 5 and 6). Moreover, assessing treatment duration from retrospective observational studies, as conducted for the individual patient data meta-analysis [9] where, for instance, deaths and patients lost to follow-up were excluded from the analyses, may lead to formulating recommendations that are inherently biased. Any recommendation based on these findings would benefit from being presented as extrapolations and expert opinion. This also applies to the recommendation to routinely stop bedaquiline treatment after 6 months, which is not supported by evidence, in contrast with available observational reports [10, 11], and inconsistent with the recommendation to use other drugs (*e.g.* linezolid) for a longer duration than in their approved labelling.

Thirdly, the 2019 guidelines follow the assumption that the combination of the most effective drugs (three group A and one group B), as identified by the individual patient data meta-analysis (PICO 2), would result in the most effective longer regimen. Conversely, a similar assumption has not been made for the SCR, a regimen that excludes two of the most potent group A drugs (linezolid and bedaquiline). Furthermore, an exception was made to this second assumption with the replacement of kanamycin by amikacin in the SCR, although such a change is not supported by evidence.

We understand that some PICO questions could not be directly answered and that recommendations had to be based on extrapolations from indirect evidence; however, this needs to be made explicit to programmes and clinicians so they may be empowered to make appropriate, informed clinical decisions. As evidence evolves in the complex field of DR-TB, and with the availability of new observational and clinical trial data, it is key that guidelines make a clear distinction between evidence, expert opinion and assumptions, so as to allow appreciation of the uncertainty surrounding the recommendations.

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WHO guidance on multidrug-resistant tuberculosis treatment: using and communicating the evidence

From the authors:
L. Guglielmetti and co-workers acknowledge that methods used by the World Health Organization (WHO) to develop guidance have improved policies on multidrug-resistant tuberculosis (MDR-TB) in recent years. However, they express some concerns about the interpretation and communication of evidence in the 2019 WHO consolidated guidelines for drug-resistant TB treatment [1].

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WHO MDR-TB treatment guidelines detail how evidence and other considerations are used to develop recommendations http://bit.ly/35qSrZT

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WHO guidance on MDR-TB treatment remains in high demand, given the complexity of the intervention, divergent expert views on optimal therapeutic options, rapid recent developments and a shortage of reliable evidence. Since 2010, WHO has used the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) to increase the clarity of its MDR-TB treatment guidance [1, 2], presenting estimates of effect alongside other considerations critical to successful scale-up, such as patient or caregiver preference, acceptability, feasibility, resource implications and impact on equity [3]. GRADE provides for downgrading the certainty of evidence when indirect comparisons and extrapolations are used; to be differentiated from expert opinion provided in the absence of a distinct evidence base [4]. The GRADE evidence-to-decision framework (table 1) allows guidelines expert panels convened by WHO to systematically document their decisions, to communicate uncertainties in the evidence arising from data shortcomings, and to propose research priorities (Annex 8 in [5]).

Given the rarity of randomised controlled trials, much of the current WHO MDR-TB treatment guidance relies on analyses of observational studies of standardised 9- to 11-month shorter MDR-TB regimens and individualised longer regimens of 18 months or more in widespread use. Ahead of the 2019 update of the consolidated guidelines, WHO made a call for data in an effort to exploit more contemporary practices and reduce delays incurred when analyses are restricted to published studies recovered by traditional systematic reviews [6]. New recommendations on optimal number of medicines and their duration of use in longer regimens drew upon multi-country experiences since the mid-1990s of combinations of older agents, such as fluoroquinolones and clofazimine used "off-label", as well as new medicines, such as bedaquiline. The dataset used for the guidelines update included many patients on medicines that would be strongly recommended in the new guidelines: nearly 2000 patients were on bedaquiline, 1600 on linezolid and over 3000 on moxifloxacin. The meta-analysis of these data allowed the effects of individual medicines to be compared. Among patients on bedaquiline, only 5% received it for longer than the 6-month period for which its market authorisation had been granted. No recommendation to use bedaquiline beyond the manufacturer's indication could be entertained without clarity about the balance of benefits to harms of doing so. This is nonetheless an area where more research about the efficacy and toxicity of this medicine are expected to influence future guidance.

The limitations of methods used to associate patient outcome with treatment duration in retrospective observational studies have been described repeatedly since the first individual patient data meta-analysis to inform WHO MDR-TB guidelines was conducted [7, 8]. Until direct evidence from regimens of different durations becomes available it is unlikely that this inherent constraint will be solved by different analytical approaches alone.

Since its first release in 2016, the WHO recommendation for the shorter MDR-TB regimen was based upon studies from various settings of standardised treatments whose composition and length were near-identical to those recommended. The recommendation applies primarily to patient inclusion criteria adopted by the studies, for whom evidence of benefit and harms exists. It was not possible to compare the shorter regimen with longer regimens containing linezolid or bedaquiline, given that such regimens have until recently been largely reserved for patients who were ineligible for the shorter regimen (*e.g.* fluoroquinolone-resistant MDR-TB strains). The replacement of kanamycin by amikacin was always a permissible adaptation to the shorter regimen, premised upon the similarity of action of these aminoglycosides and some empirical evidence. When, in 2018, evidence from longer regimens showed

TABLE 1 Main criteria of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) evidence-to-decision framework

Is the problem a priority?
How substantial are the desirable anticipated health effects?
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What is the overall certainty of the evidence of the intervention on health effects?
Is there important uncertainty about or variability in how much people value the main outcomes?
Do the desirable effects outweigh the undesirable health effects?
How large are the resource requirements?
What is the certainty of the evidence of resource requirements?
Are the net benefits worth the incremental cost?
What would be the impact on health equity?
Is the intervention acceptable to key stakeholders?
Is the intervention feasible to implement?

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amikacin to be superior to kanamycin, it was recommended to use only amikacin in shorter regimens. More radical changes, such as replacing the injectable agent with bedaquiline or linezolid, could not be recommended given that no study had tested such radical departures at the time [9, 10]. Results from MDR-TB patients treated with all-oral shorter regimens have only recently become available and are currently being evaluated by WHO.

In conclusion, GRADE frameworks communicate the evidence alongside other considerations used by WHO expert panels to determine the strength, wording and direction of evidence-based MDR-TB treatment recommendations. Analysis of pooled data has allowed the continued consolidation of recent evidence to inform global treatment policy in a context of minimal trial evidence. WHO welcomes more research and better data and commits to keep reviewing new evidence so that its global policies will benefit MDR-TB patients from shorter, safer and more effective treatment options.

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