levofloxacin, or moxifloxacin. These drugs—unlike the other key drugs recommended for the treatment of multidrug-resistant tuberculosis—are also supported by evidence from randomised trials,[8] as is the drug delamanid, which was not included in this meta-analysis because it was only used in a small number of people living with multidrug-resistant tuberculosis.[9]

In July, 2018, the WHO Guidelines Development Group reviewed the evidence from this meta-analysis, which forms the basis for WHO's updated multidrug-resistant tuberculosis treatment guidelines; the top-line recommendations were released on Aug 17, in a welcome and unprecedented move.[10] These recommendations for more effective, all-oral treatment with novel and repurposed drugs are applicable to most people diagnosed with multidrug-resistant tuberculosis, and stand to radically alter the treatment experience for those affected by the disease.

These recommendations must now be rapidly implemented on a global level, with support provided by technical partners and donors so that optimal outcomes can be achieved. A core value in medical practice is to do no harm. Yet each year, tens of thousands of people experience permanent damage from the widespread use of injectable drugs,[4] and there is now evidence that for many people these drugs are not only very toxic but could also be associated with worse treatment outcomes. Delays in providing access to the life-saving drugs bedaquiline, linezolid, and the later-generation fluoroquinolones cannot be tolerated, including for children, pregnant women, and other susceptible populations. The recent activities undertaken by the National Department of Health of South Africa—to replace injectable drugs with bedaquiline in the routine treatment for multidrug-resistant tuberculosis[11]—should serve as a model to improve treatment outcomes, and to spare people with the disease from debilitating adverse events. The data and the WHO recommendations are clear: rapid and concerted action must follow to translate these into treatment changes on the ground to show the men, women, and children who have already lost (or who are at risk of losing) their hearing that although their worlds might have become silent their voices have been heard.

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Better and safer treatment for multidrug-resistant tuberculosis

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From a patient's point of view, treatment of multidrug-resistant tuberculosis has advanced very little in the past 40 years. A long and difficult course of treatment, even when successful, usually means episodes of serious or life-threatening side-effects or disease complications. Patients who push through are not guaranteed a cure. Some who do survive are left with permanent disability.

Throughout the 1990s, clinicians from Partners in Health encountered patients with multidrug-resistant tuberculosis, from Haiti and Peru to Lesotho and Siberia,

who had endured multiple unsuccessful treatments with first-line tuberculosis drugs. Again and again, we met families who spent their savings and then sold their possessions to buy expensive second-line tuberculosis drugs in the private sector. Many of these drugs were developed decades ago and discarded because of toxic side-effects, difficulty of administration, poor activity against *Mycobacterium tuberculosis*, and, often, all of these issues combined. It was the same story across Russia, India, and South Africa. Sick with highly resistant tuberculosis—this was before the term extensively drug-resistant (known as XDR) came into use, but many cases were retroactively classed as such—these patients trusted clinicians to do the best they could.

At that time, there was little scientific evidence about how to treat such extensively resistant strains. To do so, clinicians grouped drugs into a regimen: usually, a fluoroquinolone, a second-line injectable (kanamycin or capreomycin), ethionamide, cycloserine, para-amino-salicylic acid, and clofazimine.[1] The side-effects were often horrible. Patients regularly had nausea, some became floridly psychotic, and others had hearing loss. Renal and liver damage were far from rare, and neither was hypothyroidism. Parenteral drugs were administered by painful intramuscular injections, often for longer than a year. That said, these patients, mostly young, chose to pursue this potentially curative treatment in the majority of cases. To help them through this arduous treatment, physicians and nurses trained community health workers, provided nutritional, economic, and psychosocial support, and invested in medications to ease these side-effects.[2]

These approaches resulted in outcomes that were far better than predicted, and helped change the dogma that, among people of low socioeconomic status, multidrug-resistant tuberculosis need be a death sentence.[3] Some of those cured, even after enduring severe toxicities, became praiseworthy advocates for those facing the same grim prospects. But the treatment regimens themselves do not merit praise. Although physicians have, for years, recommended these multidrug regimens for patients sick from highly drug-resistant strains of *M tuberculosis*, we did so as an alternative to repeated courses of first-line drugs, or no therapy at all. Advocates and clinicians alike hoped these regimens would be shelved as soon as better and safer drugs were developed. Several years ago, they were. Yet these painful and outmoded regimens are still the most commonly used to treat multidrug-resistant tuberculosis, for those lucky enough to receive any potentially curative therapy at all. This regimen, previously spurned as neither cost-effective nor tolerable, became the standard of care when it was included in the first WHO guidelines on treatment of multidrug-resistant tuberculosis. It is still included as the control group of several clinical trials to develop new multidrug-resistant tuberculosis regimens.[4] And far too many patients not cured by empirical second-line therapy still end up receiving another round of therapy based on these drugs.


Atul Loke/Panos Pictures

Such salvage regimens were savage enough in the last decade of the previous century and the first decade of this one. But they are especially noxious now, since new and more effective drugs were at last developed during the past decade. These include three well absorbed and well tolerated oral drugs. In *The Lancet*, The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017[5] presents suggestive evidence about the relative effectiveness of various tuberculosis drugs, not just the older ones included in WHO-endorsed regimens but also newer drugs, such as bedaquiline and linezolid. The authors have combined data from 50 different studies of multidrug-resistant tuberculosis treatment into a large dataset of more than 12 000 patients, allowing them to compare outcomes of treatment with and without specific drugs.

The results confirm what tuberculosis clinicians around the world are seeing with their own eyes. In particular, the use of bedaquiline or linezolid is associated with both treatment success (and thus reduced transmission) and reduced mortality. When considered in context with other data from prospective clinical trials, these results argue strongly for the inclusion of bedaquiline and linezolid in treatment for almost any patient with multidrug-resistant tuberculosis, along with better tolerated later-generation fluoroquinolones such as levofloxacin or moxifloxacin. Injectable and parenteral drugs, which the authors have shown to confer little or no benefit when used with these newer drugs, should be reserved for that minority of patients who are sick with strains resistant to these more effective, less toxic, and far less painfully administered therapies. A recent WHO rapid communication has proposed a new hierarchy of tuberculosis drugs that is consistent with this strategy.[6]

One of the limitations inherent in the meta-analysis is that it assesses regimens made available through publicly financed tuberculosis programmes and by charitable agencies involved in the care of patients affected by these strains. For this reason, no analysis could be done for delamanid, another oral drug shown to be promising in clinical trials. Even though delamanid is commercially available, the high price set by the manufacturer has impeded its inclusion in such programmes; the number of patients in the cohort that used this drug was too small to analyse. This is unfortunate, because decades of research have shown that the best way to cure this chronic and airborne infection is combination chemotherapy with safe and easily administered drugs to which infecting strains are demonstrably susceptible.

Another limitation of this and other studies is the difficulty inherent in comparing the toxicity of individual drugs in multidrug regimens. There has been substantial variation between the 50 studies in how data about adverse events were collected, if such data were collected at all. In recent years, after non-treatment was abandoned as defensible, toxicity of multidrug-resistant tuberculosis drugs was considered to be less important than effectiveness, simply because therapeutic options were so limited. Now, with more drugs to choose from, clinicians need much more information about the relative toxicity of these drugs, how best to screen for and manage adverse events, and optimal dosing.

Finally, although this study can compare the relative effectiveness of specific drug combinations, it remains difficult to infer what might be the safest and most effective ones, and the ideal duration of therapy for incident and chronic cases of extensively drug-resistant tuberculosis. These pressing matters can only be answered by clinical trials or well designed observational studies—precisely the type of studies that have been rare and underfunded over the past 20 years. Patients and survivors of tuberculosis, together with the clinicians who care for them, need to advocate for these studies, and for the funding required to conduct them. Novel combinations of new tuberculosis drugs might well cure multidrug-resistant tuberculosis in 6–9 months, rather than 18–24 months,[7] but the best way to draw such conclusions with confidence is to do these studies while caring for tens of thousands of newly diagnosed patients, and many more who have lived with this disease for years, who remain unable to access these newer drugs.

After 25 years of recommending these toxic regimens as a better alternative to therapies based on drugs to which multidrug-resistant tuberculosis strains are (by definition) resistant, physicians can now turn to new therapies based on safer and better tolerated oral drugs with in-vitro evidence of microbicidal activity against *M tuberculosis*. We are entering a new era in which we do not know how best to treat highly drug-resistant tuberculosis but finally have new tools in hand. But they are in hand for some and not others.[8] If new evidence suggests these drugs are more effective and safer, the financing of these therapies as a public good for public health must be seen as a ranking priority, not in the near future but immediately. The wellbeing of millions of future patients hangs in the balance. So too do the fates of those who will lose not only their hearing but also their lives. Those who do will probably infect family and caregivers in the course of their slow decline. This burden should not rest on their shoulders. Responsibility lies with those who set policies, prices, and priorities for research and clinical care of what is, once again, the world's single leading infectious killer of adults.

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