Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A threat to decentralised care for drug-resistant tuberculosis

Management of drug-resistant tuberculosis has always been a considerable challenge for patients, health-care providers, and the health system. Despite accounting for approximately 5% of all tuberculosis cases globally, in many high burden countries, drug-resistant tuberculosis has historically consumed the majority of national tuberculosis programme budgets. Treatment regimens were often toxic with poor outcomes, and only 56% of patients with drug-resistant tuberculosis commencing treatment in 2016 had a favourable outcome, in comparison with over 80% of patients with drug-sensitive disease.[1] Over the last 10 years, there have been considerable technical and programmatic advances in the management of drug-resistant tuberculosis, and a concomitant increase in frequency of WHO guidelines, with the latest published in June, 2020, becoming the 12th treatment guideline, interim guidance, supplement, or update over this period (panel).[2] A crucial feature of this progress involves new and effective drug options. One consequence of expanded options has been the increasingly complex management algorithms, which could pose a threat to the decentralised and deinstitutionalised care model recommended by WHO, in which non-specialists oversee the care of patients with drug-resistant tuberculosis.

Panel: **WHO drug-resistant tuberculosis treatment guidelines, interim guidance, and supplements 2006–20**

- 2006: Guidelines for programmatic management of drug-resistant tuberculosis
- 2008: Guidelines for programmatic management of drug-resistant tuberculosis: emergency update
- 2011: Guidelines for the programmatic management of drug-resistant tuberculosis: 2nd edition
- 2013: The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance
- 2014: The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance
- 2016: The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance
- 2016: Treatment guidelines for drug-resistant tuberculosis: 3rd edition
- 2018: Guidelines for isoniazid-resistant tuberculosis: supplement
- 2018: Rapid communication: key changes to the treatment of multidrug-resistant and rifampicin-resistant tuberculosis
- 2018: Treatment guidelines for multidrug-resistant and rifampicin-resistant tuberculosis: update
- 2019: Consolidated guidelines on drug-resistant tuberculosis treatment
- 2019: Rapid communication: key changes to the treatment of multidrug-resistant and rifampicin-resistant tuberculosis
- 2020: Consolidated guidelines and operational handbook on tuberculosis: update
- 2020: Operational handbook on tuberculosis: supplement

In 2011, WHO guidance for managing drug-resistant tuberculosis suggested a five-drug regimen, including pyrazinamide, a fluoroquinolone, a parenteral drug, ethionamide (or protionamide), and either cycloserine or para-aminosalicylic acid, for a duration of 20 months. Specific recommendations beyond this regimen were scarce, as was the evidence base. Emerging evidence for novel drugs (ie, bedaquiline, pretomanid, delamanid) and repurposed drugs (ie, linezolid, clofazimine) have upended the previous groupings of drug treatment options because of improved clinical outcomes and reduced toxicity. However, these novel and repurposed drugs have brought new side-effect profiles, drug safety monitoring requirements, and drug–drug interactions—notably with antiretroviral therapy. Simultaneously, an option to reduce treatment duration to 9–12 months from 18–20 months has been rolled out, initially on the basis of observational data and subsequently on global experience, including findings from the STREAM trial (NCT02409290). Based on programmatic data from South Africa, the latest WHO guidelines now endorse further modification of the shorter regimen, replacing the injectable drug with bedaquiline. In addition, a 6-month regimen for fluoroquinolone-resistant tuberculosis using bedaquiline, pretomanid, and linezolid is now recommended under operational research settings, in response to findings from the Nix-TB trial (NCT02333799). Hence, although the removal of the injectable drugs alleviates burdensome patient and programmatic difficulties (eg, daily injection, regular audiology, sharps disposal), most of the other treatment advances have not simplified management.

Historically, drug-resistant tuberculosis was managed in a small number of centralised centres providing individualised, hospital-based, specialist-led care, which was costly and resulted in substantial delays in treatment initiation. Following WHO endorsement in 2011, movement towards a decentralised, deinstitutionalised, programmatic approach increased. In South Africa, the number of drug-resistant tuberculosis initiation sites has risen from 17 in 2011 to 658 in 2019. Expansion of decentralised sites improves access to care, reduces patient and provider costs, and improves

outcomes.[3] Failure to use this approach remains a core barrier to diagnosis and treatment initiation.[4] Although implementation of the decentralised care model varies, in many regions this model is provided within a primary health-care setting, often staffed by junior doctors with an increasing emphasis on nurse-led management. There is already evidence that training, senior support, and provider-to-provider communications are sub-optimal in some of these settings, and this model of care might be further undermined by increasingly complex guidelines.[5,6]

Updates to the management of drug-resistant tuberculosis are likely to be expanded further given the current pipeline of recruitment to phase 2 and 3 studies (SimpliciTB, STREAM Stage 2, TB PRACTECAL, endTB, ZeNix). This growing complexity is also affecting the previously straightforward management of drug-sensitive disease, with multiple ongoing trials assessing the potential for reduced treatment duration or use of additional drugs (TRUNCATE TB, RIFASHORT, PredictTB). Although an eventual aspiration is to develop a simple, highly efficacious, universal regimen, for the next decade, at least, there is likely to be an increasing number of options for subgroups of patients. Although options for, and nuances to, drug-resistant tuberculosis management, with shorter courses and less toxicity, are clearly desirable, the potential effect of increasingly complex treatment initiation algorithms needs to be appropriately considered in light of the value of decentralised care.

The current COVID-19 pandemic will have consequences for health care globally for several years and is most likely to have the greatest effect in vulnerable populations and settings with fragile health-care systems. Although the interaction with tuberculosis remains to be fully defined, modelling suggests a surge in tuberculosis cases in the coming years, which, coupled with a range of other potential issues, including staffing, transport, and infection control practices, makes COVID-19 a conceivably substantial threat to the decentralised management of drug-resistant tuberculosis.[7]

A solution might lie in another policy increasingly promoted by WHO—health system strengthening through digital health. Although the expansion of digital health has been part of the END TB Strategy for several years, the main focus of the strategy has been on improving adherence. Clinical decision support systems for health-care workers, accessed via smartphones, can provide case-specific advice following the input of minimal patient data and have been used successfully in various settings.[8–10] Given increasing penetrance of appropriate devices and connectivity, there is ample room for this system to grow. Such tools are particularly useful for conditions requiring navigation of complex algorithms and guidelines, which are frequently updated. In the context of drug-resistant tuberculosis, these tools could aid initiation of the correct regimen with correct doses, ensure appropriate drug safety monitoring, support treatment modification decisions in response to adverse events or stock outs, and navigate drug–drug interactions, such as with antiretroviral therapy. These tools could potentially improve patient care and indirectly train health-care workers in decentralised settings. However, it is important that such strategies are centrally coordinated and implemented to prevent so-called pilotitis (ie, the proliferation of pilots without progression to widespread use), and evaluated appropriately to show the effect on patient outcomes.

Providing patient-centred care with a decentralised model, with staff able to navigate the increasingly complex range of therapeutic options, presents a challenge to national tuberculosis programmes globally. We make a recommendation to guideline writers to incorporate digital health into their development plans to mitigate these challenges.

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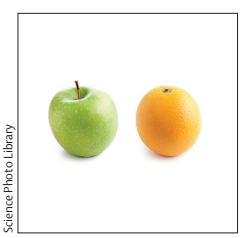
Apples and oranges: international comparisons of COVID-19 observational studies in ICUs



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Multiple observational cohorts describing the outcome of patients with COVID-19 from across the world have been published.[1-3] Typically, these studies have reported regional or national cohorts and no two countries have had the same experience. The reasons for these differences are complex and difficult to quantify. Nonetheless, to be able to draw meaningful inferences from these data we must tackle the issues associated with international comparison.

Initial reports of outcomes in COVID-19, which emerged from China early in the pandemic, reported a range of mortality rates from intensive care units (ICUs) (0–78%).[3] Case series from North America and Europe have been equally variable (with ICU mortality ranging 0–85%).[3] A major issue has been the large number of patients in these series who had incomplete outcomes at the time of reporting, a factor that has commonly resulted in mortality being overestimated or underestimated. For example, in UK Intensive Care National Audit and Research Centre (ICNARC) data, early reports from March, 2020, estimated ICU mortality for COVID-19 to be 79 (48%) of 165 patients admitted, when 610 (79%) of 775 patients had an incomplete outcome (ie, were still in the ICU). In the latest report, from July 31, 2020, ICU mortality had decreased to 40% in 10 341 patients with complete outcomes.[4] In the appendix (pp 1–2), we have summarised European data on COVID-19 mortality, as of Aug 8, 2020, highlighting the range of outcome measures reported. Another key difference is the status of the health systems in which these patients have been managed, in particular the degree of so-called stress that those systems were under.[5] This factor is more difficult to adjust for. Variations in clinical decision making between health-care systems, reflected in the characteristics of patients admitted to ICUs and in the methods of ventilation used, also confound direct comparison. This confounding is potentially evident when comparing ICU admissions between the UK and Germany, where the median age of patients receiving invasive mechanical ventilation was 72 years in a large German series[2] versus 60 years in the latest ICNARC report.[4] However, ICU mortality was similar, emphasising the role of admission criteria. Regardless, the wide variation observed suggests the possibility that some factors are modifiable. Therefore, making comparisons between countries and systems is important.

Beyond careful epidemiological analysis, we could improve comparisons in several ways. The most obvious way to improve comparisons is via a multinational collaboration. Indeed, it is difficult to see how we can mount an effective response to a global pandemic without such collaboration. The fight against COVID-19 has already produced some commendable examples, including the work of the Coalition for Epidemic Preparedness Innovations, the Global Alliance for Vaccines and Immunizations, and the International Severe Acute Respiratory and Emerging Infection Consortium. However, global comparative data on the outcomes from COVID-19 are lacking because a single observational study of global data, with consistent outcomes and definitions used in all sites, has not yet

See **Online** for appendix

For the **Coalition for Epidemic Preparedness Innovations** see https://cepi.net

For the **Global Alliance for Vaccines and Immunizations website** see https://www.gavi.org/

For more on the **Coronavirus Clinical Characterisation Consortium** see https://isaric4c.net/