Drug-resistant tuberculosis: latest advances

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At the start of 2012, a report from Mumbai, India, that described patients with strains of tuberculosis deemed resistant to all antituberculosis drugs set in motion an eventful year for this disease.[1] What was referred to as totally drug-resistant tuberculosis attracted intense media attention and much debate among health professionals worldwide. Experts convened in March, 2012, by WHO to discuss the global implications of this situation agreed that such cases pose a formidable challenge to public health and point to widespread weaknesses in tuberculosis care.[2] However, revisions of definitions were not recommended in view of an absence of standardised methods to test for susceptibility to several of the existing antituberculosis drugs. Furthermore, the paucity of data for optimum treatment regimens in patients with such advanced patterns of drug resistance precluded revisions to current approaches to treatment. Improvements in the accuracy of drug susceptibility testing and the imminent release of new antituberculosis drugs should allow changes in the near future. In response to the identification of this event, the Indian Government has taken a number of bold steps to strengthen laboratory and hospital facilities, improve contact tracing, and tighten regulations on private sales of antituberculosis drugs and unreliable serological diagnostics. A web-based system was created to enable the nationwide collection of notification data on tuberculosis, which, in May, 2012, became mandatorily notifiable.

In early 2012, WHO released its latest global roundup on multidrug-resistant tuberculosis (defined as resistance to, at least, rifampicin and isoniazid).[3] The highest frequencies of multidrug-resistant tuberculosis ever reported were documented in recent years. Worldwide, about 3% of new and 20% of previously treated patients with tuberculosis have multidrug-resistant tuberculosis, with much higher levels in eastern Europe and central Asia than in other regions (appendix).[4] In Belarus, for instance, 35% of new patients with tuberculosis in the capital Minsk have multidrug-resistant tuberculosis.[5] About 9% of patients with multidrug-resistant tuberculosis have strains resistant to a fluoroquinolone and a second-line injectable drug as well (defined as extensively drug-resistant tuberculosis). 84 countries have now reported at least one extensively drug-resistant tuberculosis case.

Molecular technology has finally emerged to improve approaches to tuberculosis diagnosis, which had stagnated during much of the past century. The extent and speed with which one of these molecular assays—Xpert MTB/RIF—has been implemented in low-resource settings is impressive. Within 2 years of its endorsement for use by WHO, this test is now making a difference in more than 70 low-income or middle-income countries in the diagnosis of patients with tuberculosis and in the detection of mutations known to confer rifampicin resistance. Results from an updated meta-analysis of 18 studies including 9166 specimens from patients with tuberculosis supported its diagnostic accuracy,[6] including for rifampicin resistance (pooled sensitivity and specificity in patients with pulmonary tuberculosis in seven studies were 94·1% [95% CI 91·6–96·0] and 97·0% [96·0–97·7], respectively).

If these encouraging advances in diagnostics are to make a difference to patients with multidrug-resistant tuberculosis, curative treatment needs to be accessible. Treatment for multidrug-resistant tuberculosis is at best long, toxic, and expensive, and is ultimately less effective than regimens used to treat drug-susceptible tuberculosis. The largest individual patient data meta-analysis for outcomes of multidrug-resistant tuberculosis, including results from 9153 patients in 23 countries, showed that treatment was successful in an average of 54% of patients overall, whereas 15% of patients died.[7] This article informed the latest WHO guidelines on multidrug-resistant tuberculosis regimens,[8] which recommend the inclusion of pyrazinamide, a later-generation fluoroquinolone, an injectable agent (amikacin, kanamycin, or capreomycin), ethionamide (or protionamide), and cycloserine or, if cycloserine cannot be used, aminosalicylic acid. An intensive phase lasting 8 months and—for newly diagnosed patients with multidrug-resistant tuberculosis—a total duration of 20 months is suggested in most cases, and modified according to response to therapy. However, only observational data were available for the review and randomised trials are still needed to optimise treatment regimens.

See Online for appendix

The chances of a lasting cure for patients with drug-resistant tuberculosis will not improve dramatically with the medications available. New drugs that can be given

for a shorter period and that cause less severe adverse reactions than current drugs are necessary. Results from randomised trials on the efficacy of two compounds currently in phase 2b (bedaquiline)[9] and phase 3 (delamanid)[10] of clinical development were published in 2012. The first trial showed a significant reduction in time to culture conversion over 24 weeks when bedaquiline was added to a background regimen with standard second-line drugs in patients with multidrug-resistant tuberculosis compared with when it was not (hazard ratio 2·25, 95% CI 1·08–4·71).[9] In the second study,[10] 45% of patients with multidrug-resistant tuberculosis who received delamanid with a WHO-recommended second-line regimen had a sputum culture conversion at 2 months compared with 29·6% in those who did not receive delamanid ($p<0·05$).[10] These results, alongside those showing promising early bactericidal activity of another phase 2 drug (PA-824) when used with moxifloxacin and pyrazinamide in patients with drug-susceptible tuberculosis, are very encouraging.[11] Another trial testing linezolid as a salvage drug in patients with treatment-refractory extensively drug-resistant tuberculosis resulted in culture conversion in 34 (89%) of 38 patients by 6 months.[12] However, adverse events occurred in 31 (82%) and resistance developed in 4 (11%) patients treated for more than 6 months.

In conclusion, drug-resistant tuberculosis still poses a serious challenge to tuberculosis care and prevention. Nevertheless, the advent of new diagnostics, including rapid molecular tests that can detect resistance to second-line drugs, and promising new drugs are positive developments. Ensuring rapid transfer of such technologies and innovations in the most affected countries will be key. Rational access to new drugs for patients who need them should be applied with great care so that these drugs benefit patients now and remain effective for future generations.

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