Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis

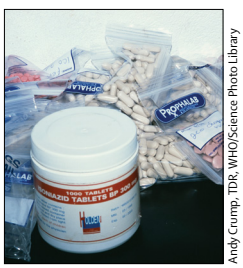
In May, 2016, WHO launched new guidelines for the management of multidrug-resistant tuberculosis,[1] including a conditional recommendation of the so-called shorter regimen. Originally known as the Bangladesh regimen,[2] this 9 month course of treatment is much cheaper (less than US$1000) than the normally used longer regimen (up to 24 months; US$20 000 or more)[3] and potentially more effective. If successful, introduction of the short-course regimen will make a substantial difference to the treatment of multidrug-resistant tuberculosis, which is at present lengthy, difficult (because of common adverse events), and expensive. Only roughly 50–60% of patients will have successful outcomes.[4–6] By contrast, in early observational studies,[1,2] the new short-course regimen achieved a success rate of more than 90% across a range of settings, such as in Bangladesh, Niger, and Cameroon.[4]

The newly recommended regimen includes kanamycin, moxifloxacin (gatifloxacin in the original Bangladesh regimen), protionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol for 4–6 months, followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol for the remaining 5 months. The advantages of an effective and safe regimen that is standardised (therefore easy to administer), costs 20 times less, and lasts less than half the duration of the longer regimen are obvious. However, enthusiasm needs to be balanced with careful assessment of the likely effect of introducing the short-course regimen, taking into account the varying proportions of eligible patients (ie, those who have not been previously treated with second-line drugs and are unlikely to be resistant to them). At present, no evidence exists on the effects of implementing the short-course regimen in the medium and long term.[5]

In *The Lancet Respiratory Medicine*, Emily A Kendall and colleagues[7] describe a sophisticated dynamic transmission model to project the reduction in incidence of multidrug-resistant tuberculosis by 2024. The primary analysis was tailored to a southeast Asian setting and showed a median decline in incidence of 14% (95% uncertainty range [UR] –36 to 39)—from 4·9 [4·2–5·9] per 100 000 population in 2014 to 4·3 [2·9–7·6] per 100 000 population in 2024—if current practices continue. The investigators also attempted to capture, in different scenarios, factors driving future effects of introducing the short-course regimen. These factors included long-term efficacy of the short-course regimen, degree of treatment scale-up, and the likely transmission of drug-resistant *Mycobacterium tuberculosis* strains in the community. At present, information is missing on the regimen's efficacy under programmatic conditions, the durability of its effectiveness (eg, no additional drug resistance generated), and its potential to increase numbers of patients who are ineligible for treatment because of additional resistance.

Kendall and colleagues[7] modelled several scenarios based on different combinations of the factors mentioned above. In the most optimistic scenario in which the short-course regimen would double treatment access and achieve long-term efficacy, the incidence of multidrug-resistant tuberculosis in 2024 (3·3 [95% UR 2·2–5·6] per 100 000 population) would be 23% (10–38) lower compared with the continued use of longer therapy (4·3 [2·9–7·6] per 100 000 population). If treatment access does not expand (ie, only efficacy is improved with the new regimen), the relative decline in incidence would be 14% (4–28), whereas if the new regimen improves only treatment access but not efficacy the relative decline would be 11% (3–24). However, if 30% of patients are ineligible for the short-course regimen because of second-line drug resistance, the relative change in incidence would be –2% (–20 to 28).

Kendall and colleagues[7] provided examples of many possible scenarios, of which two are particularly useful. Assuming a reasonable success rate of the short-course regimen (85%) in programmatic conditions, in a problematic setting with 50% durable cure in patients receiving the longer regimen and 50% of patients who are ineligible for the short-course regimen, the relative change in incidence of multidrug-resistant tuberculosis would be –2% (95% UR –15 to 13). In a less pessimistic scenario in which the longer therapy



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has a success rate of 77% and 30% of patients would be ineligible for the short-course treatment, the relative reduction in incidence would 18% (8–32).[7] These two scenarios are likely to represent the extremes, so the real decline will probably lie between the values in these two examples.[8,9]

We hope the excellent results achieved by the short-course regimen will be consistent when scaled up across a range of settings. It will be crucial to correctly apply the WHO guidance[1,10] and ensure rapid molecular testing (complemented by drug susceptibility testing when necessary) to prevent prescription of the short-course regimen to patients who are resistant to one or more drugs in the regimen and thus the development of super-resistance.

Although some evidence shows that the pessimistic scenario (in which 50% of patients are ineligible for short-course regimen) can be real in certain settings (such as Pakistan and Europe[8,9]), we need to focus on the potential of the short-course regimen to benefit individual patients and reduce the burden of multidrug-resistant tuberculosis worldwide.[10,11]

More information is also needed on the potential effect of other concomitant epidemics, such as HIV and diabetes. For example, in Latin America, particularly Mexico, up to 40% of patients with multidrug-resistant tuberculosis also have diabetes.[12]

As clinicians and public health experts, we welcome the important opportunity offered by the short-course regimen to treat eligible patients. The careful and detailed modelling described by Kendall and colleagues is particularly helpful in predicting the likely effects on the overall epidemic in different scenarios worldwide.

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