EDITORIAL
TUBERCULOSIS

Investing in a novel shorter treatment regimen for multidrug-resistant tuberculosis: to be repeated

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Donor support of innovative interventions such as operational research can reap rapid benefits for TB control http://ow.ly/wcXM3091P9H

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Background

Tuberculosis (TB) patients with multidrug-resistant (resistance to isoniazid and rifampicin) (MDR-TB) or rifampicin-resistant strains (MDR/RR-TB) do not respond to the standardised first-line TB regimen which is highly effective in other TB patients, requiring much longer and toxic second-line treatment [1]. In fact, only about a half of all MDR/RR-TB patients placed on these regimens worldwide complete them successfully, attesting to the difficulties in scaling up such regimens satisfactorily [2]. Even if only about 4% of new TB patients globally have MDR/RR-TB, they account for over half a million new individuals annually, challenging the constrained resources available for TB care in the low- and middle-income countries where most of them live.

Attempts to simplify and shorten MDR-TB treatment started in Bangladesh in the mid-1990s [3]. Treatment of selected patients with shorter regimens yielded success rates exceeding 85%, comparable to the success rates in drug-susceptible TB cohorts. Results from a randomised controlled trial of a standard-composition regimen of 9–11 months' duration which started in 2012 are expected by early 2018 [4]. Meanwhile, similar regimens have been introduced in several African and Asian countries, and promising results have already been reported [5, 6].

Until evidence from these studies emerged, the World Health Organization (WHO) recommendations for MDR-TB treatment focused primarily on regimens lasting at least 20 months, often adapted to the individual resistance patterns of patient strains [1]. This approach represented the most widespread practice in MDR-TB treatment worldwide and for which most experience had accumulated. In the absence of sufficient data on the effectiveness and safety of significant departures from this "convention", WHO advised countries to only introduce shorter MDR-TB regimens as part of operational research.

Funding operational research

The Global Fund to Fight AIDS, Tuberculosis and Malaria is the major external source of financing for the drug-resistant TB response in low- and middle-income countries: between 2002 and 2015 it spent USD730 million in country grants in support of such activities. Among these different activities is operational research, which can generate evidence to improve programme performance. From 2013, several countries received Global Fund money to implement shorter MDR-TB regimens under operational research conditions. This

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support was approved on condition that the national TB programmes developed study protocols for their cohorts and that these plans were approved ahead of start of treatment by the ethics authorities of each country and by the WHO Global TB Programme. Between 2013 and 2015, at least USD6.4 million in Global Fund grants was disbursed across 10 countries to help implement shorter MDR-TB regimens (table 1). This was matched by contributions from other sources, including domestic funds mobilised by national governments, and external technical and financial support from Action Damien, France Expertise Internationale, and The Union (the International Union Against Tuberculosis and Lung Disease).

TABLE 1 Support of the Global Fund to Fight AIDS, Tuberculosis and Malaria for implementation of shorter multidrug-resistant TB (MDR-TB) regimens by country, 2013–2015

Country	Technical agency assisting implementation	Amount disbursed to support components of shorter MDR-TB regimens (USD millions)
Bangladesh	Action Damien	0.42
Benin	The Union	0.12
Burkina Faso	The Union	0.99
Burundi	The Union	0.34
Cameroon	The Union	1.04
Côte d'Ivoire#	The Union	1.77
DR Congo	The Union, Action Damien	1.14
Niger	Action Damien	0.09
Guinea#	Action Damien	0.43
Senegal#	The Union	0.09

Source: Global Fund financial data. The amounts shown include support to different components of the shorter MDR-TB regimens, which varied between countries and at times reflect conservative estimates. Amounts for Niger refer to 2014–2015 and for Senegal to 2015 alone. Other Global Fund support in strengthening tuberculosis programmes and health systems may have indirectly benefited the implementation of the shorter MDR-TB regimens. #: data from these countries were not included in the evidence reviews undertaken for the 2016 update of World Health Organization guidance [7, 8].

In May 2016, based on the evidence which accrued until late 2015 from observational studies of over 1200 patients treated in 10 countries (including seven of those shown in table 1), WHO revised its policy and included a conditional recommendation on the use of a standardised 9–12 month shorter MDR-TB regimen in selected MDR/RR-TB patients [7, 8]. The simultaneous endorsement by WHO of line-probe assays to test for resistance to the two major classes of medicines of second-line regimens facilitates the rapid identification of patients eligible for shorter regimens [9]. While Global Fund support has been critical in enabling studies to be conducted on shorter MDR-TB regimens, it is anticipated that the Fund will favour the continued expansion of these regimens under programmatic conditions. If patient allocation to appropriate treatment improves, overall TB treatment success should increase, while at the same time substantial savings for TB programmes can be made given that the costs of medicines required for the shorter MDR-TB regimen are much lower than those for a longer MDR-TB regimen.

A reproducible model?

This experience shows how investment in operational research can steward the course of new interventions to fruition and also help generate evidence swiftly for policy change. Other "investment cases" modelled on the shorter MDR-TB regimen intervention could help develop methods and technologies which bear the promise of significant impact for TB care but lack the evidence needed for large-scale implementation. Thus, it is critical for countries to work towards the targets of the WHO's End TB Strategy, the Stop TB Partnership's Global Plan to End TB, and the Global Fund Strategy 2017–2022 [10–12]. Other areas could likewise benefit, such as active case finding, digital health interventions and patient-centred care approaches, as well as other novel TB regimens. Donor agencies other than the Global Fund need to assist countries to implement initiatives aligned to Pillar 3 of the End TB Strategy. Countries concentrating the largest MDR/RR-TB caseload need, in particular, to invest more domestic resources in such action. Keeping drug-resistant TB in check will require continued efforts to generate new evidence to inform policies, alongside bold action and creativity to have more MDR/RR-TB patients placed on effective treatment – such as the shorter MDR-TB regimen – and to achieve a lasting cure.

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