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MDR-TB

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## What will it take to eliminate drug-resistant tuberculosis?

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### SUMMARY

Drug-resistant tuberculosis (DR-TB) is challenging to diagnose, treat, and prevent, but this situation is slowly changing. If the world is to drastically reduce the incidence of DR-TB, we must stop creating new DR-TB as an essential first step. The DR-TB epidemic that is ongoing should also be directly addressed. First-line drug resistance must be rapidly detected using universal molecular testing for resistance to at least rifampin and, preferably, other key drugs at initial TB diagnosis. DR-TB treatment outcomes must also improve dramatically. Effective use of currently available, new, and repurposed drugs, combined with patient-centered treatment that aids adherence and reduces catastrophic costs, are essential. Innovations within sight, such as short, highly effective, broadly indicated regimens, paired with point-of-care drug susceptibility testing, could accelerate progress in treatment outcomes. Preventing or containing

resistance to second-line and novel drugs is also critical and will require high-quality systems for diagnosis, regimen selection, and treatment monitoring. Finally, earlier detection and/or prevention of DR-TB is necessary, with particular attention to airborne infection control, case finding, and preventive therapy for contacts of patients with DR-TB. Implementing these strategies can overcome the barrier that DR-TB represents for global TB elimination efforts, and could ultimately make global elimination of DR-TB (fewer than one annual case per million population worldwide) attainable. There is a strong cost-effectiveness case to support pursuing DR-TB elimination; however, achieving this goal will require substantial global investment plus political and societal commitment at national and local levels.

**KEY WORDS:** drug resistance; elimination; incidence reduction; prevention; cost effectiveness

THE WORLD HEALTH ORGANIZATION (WHO) End TB Strategy and the United Nations Sustainable Development Goals set a vision for drastically reducing tuberculosis (TB) incidence by 2030 and for ultimately eliminating TB as a public health problem.<sup>1,2</sup> Drug resistance presents an obstacle to achieving those goals. The global burden of drug-

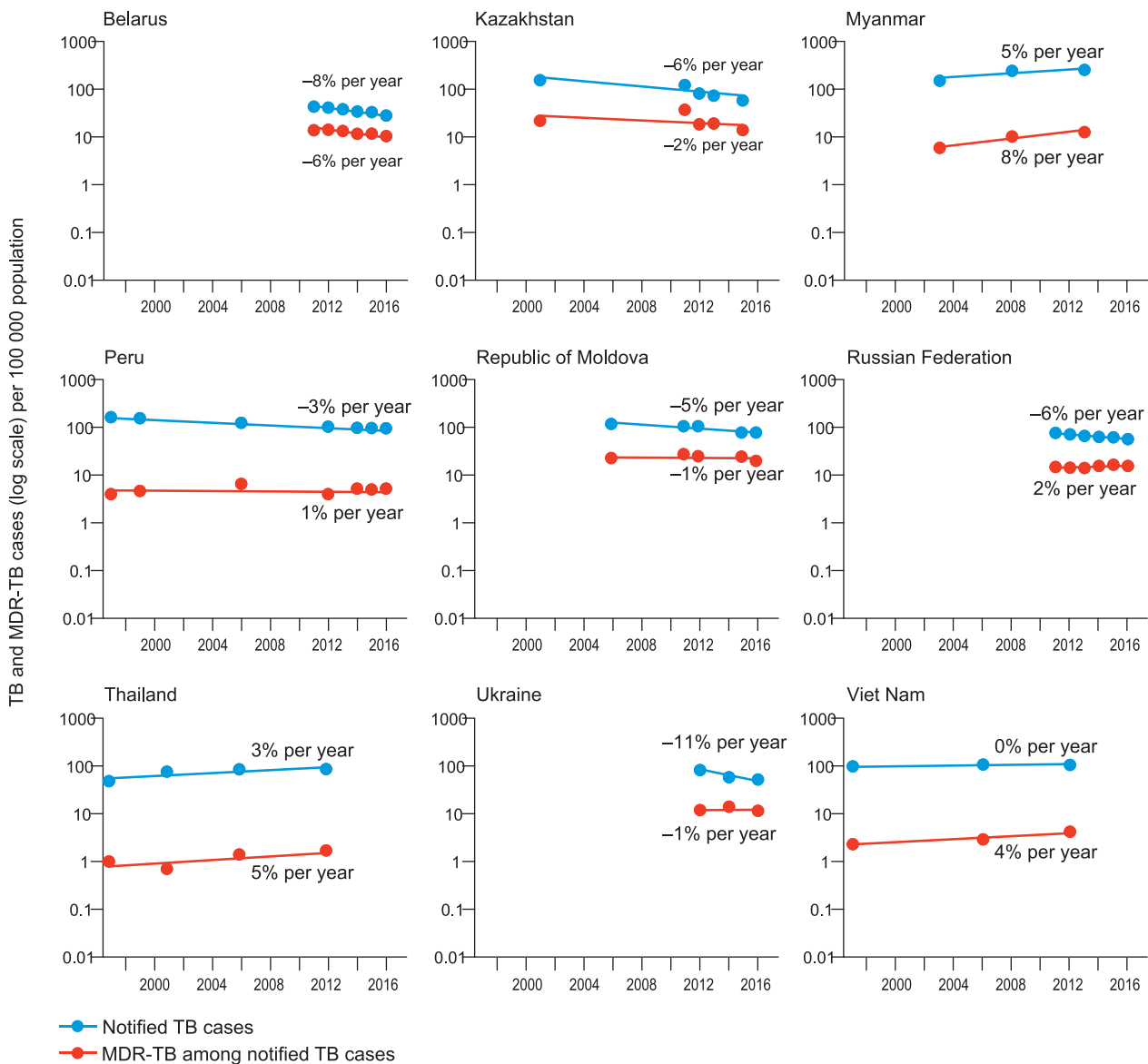
resistant TB (DR-TB) is imprecisely known and heterogeneous but, worldwide, an estimated 558 000 people developed multidrug-resistant TB (MDR-TB; TB resistant to at least isoniazid [INH] and rifampin [RMP]) or RMP-resistant TB (RR-TB, all RMP resistance irrespective of INH resistance) in 2017.<sup>3</sup> MDR and RR-TB were also responsible for >25% of all deaths from drug-resistant infections.<sup>4</sup> Across high-burden settings with known trends, the incidence of MDR-TB is declining more slowly or increasing more quickly than that of TB overall (Figure 1).<sup>5</sup>

However, there is cause for optimism about the potential to alter the trajectory of DR-TB. Historical

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**Figure 1** Observed TB and MDR-TB trends. The limited number of high-burden settings which have serially collected data on MDR-TB burden all report that MDR-TB cases are declining more slowly or increasing more rapidly than DS-TB incidence, and thus MDR-TB is growing as a proportion of overall TB. Several such countries are observing steady declines, however, in the absolute incidence of MDR-TB. Reprinted with permission from <sup>5</sup> p 48. TB = tuberculosis; MDR-TB = multidrug-resistant TB; DS-TB = drug-susceptible TB.

factors contributing to today's DR-TB epidemic can now be overcome by scaling up existing diagnostic and therapeutic strategies. Improved diagnosis, drugs, and care delivery for DR-TB could help lower the intensity of DR-TB transmission. Simultaneous reduction of the number of drug-susceptible TB (DS-TB) cases could shrink the pool from which drug resistance develops. These developments present opportunities to change course now and to reflect on the steps required to achieve DR-TB elimination.

Elimination of DR-TB can be understood both as a component of overall TB elimination and as a goal in its own right. DS- and DR-TB epidemics are intrinsically linked. DR-TB is both an already entrenched part of the global TB epidemic and a

renewed risk each time TB is treated.<sup>6</sup> Yet most cases of MDR-TB today result from MDR-TB transmission events.<sup>7,8</sup> Targeted efforts are therefore required even to just keep DR-TB in check. However, a more proactive and ambitious reframing of goals for combating DR-TB is conceivable. Global TB efforts have begun to focus upon elimination, defined as one incident case per million people per year.<sup>9</sup> Extending this target to MDR- and RR-TB—which currently number around 75 cases per million per year worldwide<sup>3</sup>—sets an ambitious but achievable target that could unify and drive both the global DR-TB response and TB elimination efforts.

It should be noted that although our current discussion is framed around MDR- and RR-TB, drug

resistance is an evolving concept. Foreseeable advances in drug development are likely to reduce the specific importance of resistance to RMP and INH, as reliance on newer drugs expands. Nevertheless, TB drug resistance will remain an important risk that should be monitored and minimized. Even as the evolving treatment landscape leads to changes in the most relevant definition of ‘drug-resistant’ TB,<sup>10</sup> the principles outlined here will continue to apply.

### ADDRESSING DRUG-SUSCEPTIBLE TUBERCULOSIS: ESSENTIAL BUT INSUFFICIENT

Combating TB overall (>90% of which is DS-TB) is essential to DR-TB elimination. Treatment of DS-TB can lead to acquired drug resistance by selecting for spontaneously occurring, resistance-conferring mutations, and effective treatment limits this risk. Programs should treat DS-TB with proven drug regimens, recognize risk factors for poor outcomes (including host characteristics)<sup>11</sup> and non-RR/MDR-TB drug resistance<sup>12</sup> when selecting these regimens, ensure reliable supplies of quality-assured drugs, support patient adherence, implement TB infection control, and make quality improvement a key component of national TB programs.<sup>13</sup> Research towards a shorter duration of DS-TB treatment should likewise be reinforced. Preventive interventions, which lower the number of DS-TB patients requiring treatment, also prevent DR-TB by shrinking the reservoir from which acquired resistance can develop. Finally, programmatic efforts to improve case detection can reduce transmission of all forms of TB, including DR-TB.

### NEXT STEP: IMPLEMENTATION OF CURRENT DRUG-RESISTANT TUBERCULOSIS GUIDELINES

Drug resistance should be considered in all patients diagnosed with TB. The prevalence of MDR- or RR-TB among TB patients with no previous treatment is 3.5% worldwide, and exceeds 1% in nearly all high TB burden countries.<sup>3</sup> WHO guidelines have recommended since 2009—and now strongly recommend—that TB programs perform routine rapid drug susceptibility testing (DST), for RMP resistance at least, among all individuals diagnosed with TB.<sup>14</sup> The End TB Strategy recommends universal DST at the time of diagnosis as a key component of patient-centered care,<sup>1</sup> and the 90-(90)-90 targets include identifying and appropriately treating 90% of MDR- and RR-TB cases.<sup>15</sup> The WHO makes additional recommendations for patient-centered treatment approaches without mandatory hospitalization, a shorter 9–12-month treatment regimen, and the introduction of new drugs under specific conditions.<sup>14</sup> In the area of DR-TB prevention, guidelines

advocate high-quality treatment of DS-TB, evaluation of close contacts for co-prevalent DR-TB and possible preventive therapy,<sup>16</sup> and improved infection control at health facilities and congregate settings.<sup>17</sup>

While a scale-up of these existing policies is unlikely to be sufficient for reaching DR-TB elimination, they represent an important step. Unfortunately, a considerable gap exists between international guidelines and their adoption and implementation at the national level. Tight constraints on financing, infrastructure, technology, and expertise can hinder the implementation of recommendations. Competing health priorities, uncertainty about how to localize global recommendations, and the inertia of established practice can be important barriers to progress.

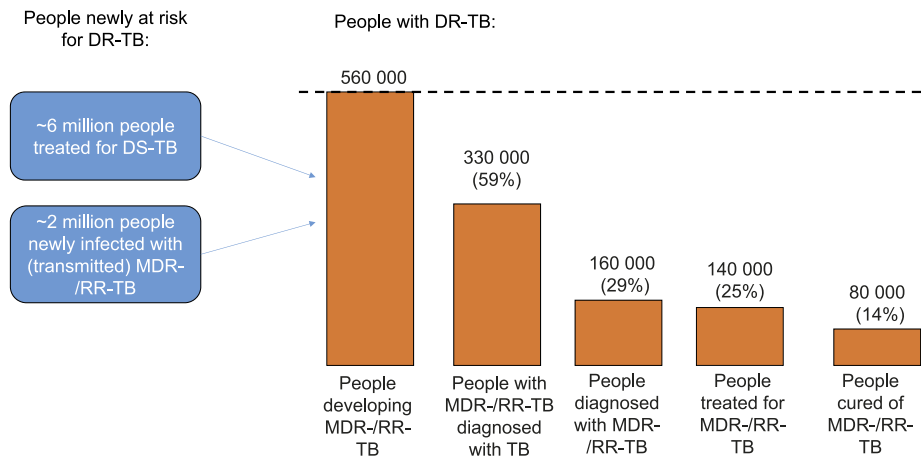
On the diagnostic front, progress toward universal DST has been accelerated by the introduction of Xpert® MTB/RIF testing (Cepheid, Sunnyvale, CA, USA), but remains inadequate.<sup>18</sup> DST coverage remains insufficient among bacteriologically positive TB patients—just 24% of newly diagnosed patients were tested in 2017—and absent among the 44% of TB diagnoses that are bacteriologically unconfirmed.<sup>3</sup> When performed, DST is increasingly limited to RMP alone.<sup>12</sup>

Implementation of newer approaches to DR-TB treatment has been similarly slow. As of 2017, a survey of 29 high TB burden countries found that the use of the 9–12 month treatment regimen, bedaquiline (BDQ), and delamanid (DLM) were included in the policies of respectively 45% ( $n = 13$ ), 79% ( $n = 23$ ), and 62% ( $n = 18$ ) of countries.<sup>19</sup> Compulsory hospitalization at the start of MDR-TB treatment, which can restrict treatment access and delay treatment initiation,<sup>20,21</sup> was still required by nine (31%) surveyed countries.<sup>19</sup> Despite success rates of >80% for standard MDR-TB treatment in recent clinical trials.<sup>22</sup> and some national programs,<sup>23</sup> the latest global treatment success rate for MDR-TB is 55%.<sup>3</sup> Thus, currently fewer than one in four individuals with MDR- or RR-TB worldwide receives corresponding treatment, and only an estimated one in seven are successfully treated (Figure 2).

### ROLE OF IMPROVED DIAGNOSIS

#### *Diagnostic tools*

If MDR- and RR-TB are to be eliminated, they must first be detected in a timely fashion. The quickest way to accomplish this is to scale-up the Xpert rapid molecular diagnostic test and the infrastructure to support it. Xpert, included in the first WHO Essential Diagnostics List, detects RMP resistance with high accuracy and significantly increases programmatic detection of MDR- and RR-TB if used at the time of TB diagnosis.<sup>24</sup> The new-generation Xpert® Ultra (Cepheid) has a higher sensitivity for detecting



**Figure 2** Care cascade for DR-TB worldwide. The boxes to the left show an estimate of the people at risk to develop either transmitted or acquired RR- or MDR-TB. The bar chart shows the people with active MDR- or RR-TB (estimates for 2016, based on aggregation of often-limited country-level data<sup>3</sup>) who are lost at the stages of TB diagnosis, drug resistance diagnosis, initiation of treatment, and completion of curative treatment. DR-TB = drug-resistant tuberculosis; DS-TB = drug-susceptible TB; MDR-TB = multidrug-resistant TB; RR-TB = rifampin-resistant TB.

*Mycobacterium tuberculosis* and promises to further increase TB and RR-TB case detection.<sup>25</sup>

DR-TB elimination will, however, require the expansion of rapid testing for resistance to a growing number of drugs. INH monoresistance is a precursor of MDR-TB and a highly prevalent predictor of first-line treatment failure.<sup>26</sup> Recognition of second-line drug resistance is also important to ensure successful MDR-TB treatment.<sup>27</sup> As scalable rapid molecular DST is needed for additional key drugs besides RMP, the development of such tests for use in a decentralized setting was deemed a priority by a WHO consensus committee.<sup>28</sup> Several next-generation drug susceptibility tests for use in microscopy centers are currently in development; these will include DST for such drugs as INH, and fluoroquinolones.<sup>29,30</sup> As standardized treatment regimens adopt new drug classes, rapid molecular testing for resistance will need to evolve congruently.

In parallel with scale-up of point-of-care tests, expansion of DST at the centralized laboratory level is also important. Techniques for centralized DST include existing molecular tests, such as the Hain GenoType<sup>®</sup> MTBDRs/l line-probe assay (Hain Lifescience, Nehren, Germany) for second-line drug resistance, and phenotypic methods. Eventually, centralized DST will need to incorporate emerging molecular tests, such as the BD Max<sup>™</sup> MDR-TB (BD, Sparks, MD, USA), Hain Fluorotype<sup>®</sup> MTBDR (Hain Lifescience), or Abbott RealTime MTB (Abbott Laboratories, Abbott Park, IL, USA) assays. DST may also increasingly include whole-genome sequencing (WGS), which can theoretically identify all resistance-conferring mutations at once and predict their functional effect. For example, WGS is considered the best approach for diagnosing resistance to

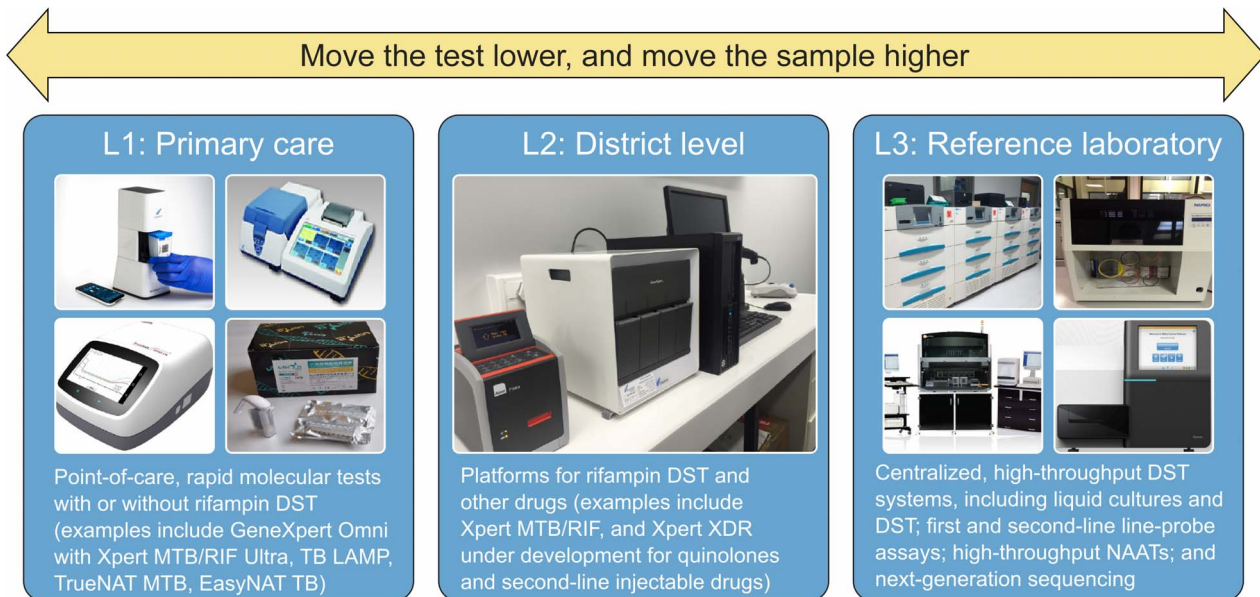
pyrazinamide, a key first-line drug included in several second-line regimens. WGS could become the future of DST, but several obstacles must first be overcome in terms of speed (e.g., reducing turnaround time, direct testing on clinical samples rather than on culture), accuracy of predicting phenotypic resistance (particularly problematic for certain drugs<sup>31</sup>), demonstration of improved clinical outcomes, and resource requirements.<sup>32</sup>

Finally, a diagnostic strategy for DR-TB elimination will require integrated DST solutions across multiple levels of health care provision (Figure 3). Some tests should be optimized for primary care and made readily available at the patients' point of contact within the health system. Other tests are appropriate for centralized settings. Adequate linkages between levels are required, including sample transport and patient referral systems, diagnostic connectivity, and information and communication technologies that can notify patients and physicians of test results and facilitate timely linkages to care.<sup>33</sup> Lack of such integration causes large losses during the care cascade (Figure 2).

#### Case-finding strategies

Early case detection has been recognized as essential for overall TB elimination,<sup>34</sup> and similar principles make enhanced TB case finding vital among people at risk for DR-TB. Many individuals with DR-TB are never diagnosed with TB, or are diagnosed only after a lengthy period of disease. In populations with high DR-TB incidence (including those with an average prevalence of drug resistance but a high incidence of TB overall), active TB case finding and appropriate clinician awareness, combined with rapid DST, have





**Figure 3** Tackling the complexities of DR-TB involves bringing care closer to DR-TB patients, but also developing strong centralized or reference laboratories and ways to link into them when required. This value chain is illustrated here for diagnostic laboratories; however, similar principles apply for treatment (providing care in decentralized ambulatory settings, with strong consultation or referral systems for those who experience complications or require more expert decision-making or specialized treatment). DST = drug susceptibility testing; NAAT = nucleic acid amplification test; DR-TB = drug-resistant tuberculosis.

potential to hasten detection of DR-TB and interrupt transmission.

Systematic screening of populations exposed to DR-TB, such as household contacts, is another important and efficient strategy to enhance DR-TB case-finding. Contacts of patients treated for DR-TB are a readily identifiable population, who bear a considerable risk of infection and disease. A meta-analysis reported a yield of respectively 47% (95% confidence interval [CI] 33–61) and 8% (95%CI 6–10) for latent tuberculous infection (LTBI) and active TB disease at the time of initial contact investigation, although the findings varied considerably between settings.<sup>35</sup> Because infected contacts remain at high risk of incident disease, both screening at the time of identification and ongoing surveillance are recommended.<sup>36</sup> For contacts determined not to have active TB, preventive therapy should increasingly be considered, as discussed below.

### ROLE OF IMPROVED DRUG-RESISTANT TUBERCULOSIS TREATMENT

Beyond MDR- or RR-TB diagnosis, substantial gaps persist in the access to treatment<sup>36</sup> and treatment outcomes. One limitation is current standardized MDR-TB treatment regimens, which—although finally moving away from toxic injectable drugs—remain complex to implement, lengthy, often poorly tolerated, poorly effective, and difficult for patients to complete.<sup>38,39</sup> Other barriers that limit access to MDR- and RR-TB treatment include delays in receiving diagnostic results, the high cost of second-

line drugs, and provision of treatment only at specialized centers. To optimize treatment outcomes for those diagnosed with MDR- or RR-TB, both the drug regimen and care delivery aspects of treatment must improve, as detailed below.

#### *New drugs and regimens*

In terms of drug regimen, MDR- and RR-TB treatment can be improved using drugs that are already available. As recently-revised international guidelines recognize,<sup>40</sup> the inclusion of BDQ,<sup>41,42</sup> DLM,<sup>43</sup> repurposed drugs such as linezolid and clofazimine, or conventional drugs at higher doses<sup>44</sup> can increase regimen efficacy, these agents should be made available to patients for whom they are indicated. However, because individual drugs will not change the lengthy and costly nature of DR-TB treatment that limits its availability and completion, their impact on DR-TB transmission and incidence will be limited. The shorter 9–12-month regimen being adopted in some countries can facilitate management and improve adherence among eligible patients.<sup>14,45</sup> However, weaknesses in this shorter regimen, including eligibility restrictions, injectable components, and preliminary trial results that have not established non-inferiority to the conventional treatment,<sup>46</sup> are likely to make its role temporary while alternative short regimens remain under investigation.

Achieving a dramatic reduction in DR-TB incidence through enhanced treatment will require—in addition to filling the huge diagnostic gap—a dramatic improvement to existing DR-TB treatment

regimens. Consistent with the current trend, treatment needs to continue to become shorter, simpler to dose, all-oral, more effective, and less toxic, according to already described principles.<sup>47</sup> Existing health systems are treating DS-TB at a global treatment success rate of 85%. A similarly efficacious, 6-month, all-oral regimen could make similar success rates feasible for MDR- and RR-TB. For the near future, hope lies in the 6–12-month all-oral regimens being developed specifically for MDR- and RR-TB; such regimens are currently under evaluation in clinical trials—TBPRACTECAL (clinicaltrials.gov NCT02589782), endTB (NCT02754765), MDR-END (NCT02619994), ZeNiX (NCT03086486), SimpliTB (NCT03338621).<sup>48</sup> Although preliminary, results of a combination of BDQ, pretomanid, and linezolid in extensively drug-resistant TB are encouraging.<sup>49</sup> Less-toxic alternatives to linezolid could enhance the usefulness of this regimen. On a more distant horizon, a highly effective, short-course ‘universal’ TB regimen indicated for all DS- and DR-TB could represent a major step toward TB and DR-TB elimination,<sup>50</sup> although such regimens still carry several uncertainties and would likely remain universal for a limited time only.<sup>51,52</sup> Ultimately, a healthy drug development pipeline will be key to eliminating DR-TB.

#### *Access to quality care*

While the world waits for better and more affordable treatment regimens, improved treatment access and treatment completion can still allow more people with DR-TB to be cured. Many people with MDR- or RR-TB never initiate treatment, and among those who do, loss to follow-up (typically affecting 15–20% of patients) is the greatest barrier to higher success rates.<sup>3</sup> Scale-up of treatment provision in many high-burden settings will require adapting models of care to provide ambulatory treatment at lower (e.g., district and subdistrict) levels of the health system. Decentralizing treatment and removing reliance on in-patient admission can improve access, reduce delays, and make treatment more patient-centered;<sup>20,53,54</sup> this has proven feasible across different contexts and countries.<sup>20,53,55,56</sup> To enable this approach, TB programs will need to routinely implement quality improvement strategies.

When selecting DR-TB treatment regimens, there is currently tension between ensuring that all patients receive effective regimens (which often requires additional DST and evidence-based treatment individualization for patients with second-line drug resistance) and choosing well-designed standardized approaches that facilitate larger-volume, simplified approaches to treatment. Until regimen and DST development allow treatment to be easily tailored at the point of care, programs that seek to expand treatment coverage should balance individualization

and access.<sup>51</sup> The ‘ideal’ balance is setting-specific (depending, for example, on the epidemiology of second-line drug resistance), and is likely to change over time. Enhanced training and decision-making support, possibly including broadly applicable regimen-selection algorithms, must be provided to clinicians who make DR-TB treatment decisions. Regardless of regimen, all DR-TB patients should be monitored for treatment response, with efficient and timely systems for referring patients to more specialized care if required.

In the short term, an unfortunate consequence of enhanced detection of DR-TB will be increased workload for TB treatment programs, particularly in resource-limited settings.<sup>57</sup> Efforts to enhance case detection should therefore be accompanied by simultaneous strengthening of TB programs. Efforts to reorient TB programs toward a patient-centered approach will be an important part of this renewed effort. Patient support services within programs, including adherence counseling, treatment literacy, and socio-economic support,<sup>58</sup> need to be continually emphasized and funded. This is likely to both improve treatment outcomes through improved retention in care, and reduce the negative impacts of treatment upon patients. Fully involving patients in decisions about their treatment is another important aspect of patient-centered care that may increase engagement. Expanded provision of treatment must be accompanied by the capacity to effectively monitor treatment for both treatment response and adverse events. New digital adherence technologies, such as mobile telephone and electronic reminder systems, are likely to play increasing roles in efficient adherence support in high- and low-income settings.<sup>59</sup>

#### *Minimizing and managing second-line drug resistance*

Drug resistance may be acquired even under good treatment conditions with efficacious first-line drugs,<sup>60</sup> but resistance acquisition is particularly problematic for second-line drugs due to limited drug efficacy and varied baseline drug resistance phenotypes.<sup>61</sup> Globally, 6% of MDR- or RR-TB TB are also resistant to both fluoroquinolones and second-line injectable drugs,<sup>3</sup> with much higher rates in some settings where these drugs have been widely used.<sup>62,63</sup> Novel drugs are subject to the same evolutionary pressures.<sup>64</sup> The antimicrobial pressure of DR-TB treatment scale-up could make incident DR-TB increasingly drug-resistant and difficult to treat. Deliberate steps must be taken to minimize acquisition of second-line drug resistance and prevent its spread.

In the multinational Preserving Effective TB Treatment Study (PETTS) on drug resistance acquisition during MDR-TB treatment,<sup>27,61</sup> two dominant predictors largely determined successful MDR-TB treatment outcomes: the number of DST-proven

effective drugs used for treatment and the extent of drug resistance before treatment. The importance of the number of effective drugs is an unsurprising finding, but it highlights the benefits of performing second-line DST and tailoring treatment, if necessary, to ensure effective regimens.<sup>65</sup> Regimens that contain ineffective drugs, even if successful, also expose patients to toxicity risk without benefits. The finding that drug resistance, even after accounting for the number of effective drugs prescribed, is associated with worse outcomes, has an additional critical implication. Prompt and effective treatment for DR-TB today, before strains acquire additional resistance or highly resistant strains spread, will improve DR-TB outcomes in the future and ultimately make elimination more attainable.

PETTS also found that a TB program's participation in the Green Light Committee Initiative was associated with substantially better treatment outcomes and less acquired resistance.<sup>61</sup> This effect could best be explained by many program criteria working together, including 1) government commitment, 2) highly functioning management systems, 3) expert clinicians with peer review, 4) quality-assured drugs, 5) a highly functioning laboratory, 6) adequate in-patient and out-patient care facilities, 7) sound diagnostic and treatment protocols, 8) adequate treatment delivery, 9) management of adverse events, and 10) information systems with standardized periodic reporting.<sup>66</sup> Unfortunately, stringent requirements can adversely limit access to treatment.<sup>67</sup> Programs pursuing DR-TB elimination should aim for similar high standards while also expanding access.

## ROLE OF PREVENTION

As has been shown for DS-TB,<sup>34,68</sup> DR-TB will not be eliminated unless the large reservoir of LTBI is reduced. An estimated 23% of the world's population is infected with *M. tuberculosis*, and 3 million individuals worldwide are newly infected with INH-resistant TB each year.<sup>69</sup> While the absolute burden of latent MDR- or RR-TB infection is not known, indirect evidence, such as similar proportions of MDR-TB among adults and children<sup>70</sup> and the high prevalence of MDR-TB among treatment-naïve patients in the moderate-burden countries of Eastern Europe,<sup>71</sup> suggests that reactivation of latent MDR-TB is common. If the annual incidence of MDR- or RR-TB is 8/100 000<sup>3</sup>—and even if only 25% of this incidence (2/100 000) reflects reactivation—then 19 of 20 MDR- or RR-TB reactivation events must be prevented to achieve global elimination. Achieving DR-TB elimination will therefore require 1) improved infection control, 2) preventive therapy for both DR-TB and DS-TB, and 3) improved strategies for the delivery of preventive interventions at the population level.

## Infection control

Hospitals and other congregate settings can be foci of DR-TB outbreaks,<sup>72</sup> and health care workers are also at increased risk for TB, including DR-TB.<sup>73</sup> Frequent delays in effective treatment for DR-TB make measures to prevent nosocomial transmission particularly important.<sup>74</sup> High-income countries established airborne infection control programs and respiratory isolation units in response to health care-associated TB outbreaks in the 1990s, occupational safety legislation, and the severe acute respiratory syndrome epidemic.<sup>75</sup> They must now transfer their experience and technology to the middle- and lower-income countries most affected by TB, and support implementation of protective measures, including environmental ventilation, isolation protocols, and the use of respirator masks. Clinical practices must also facilitate prompt diagnosis of patients with cough who could have unrecognized TB.<sup>76</sup>

## Drug-resistant tuberculosis preventive therapy

Because of their high risk of incident DR-TB, contacts of DR-TB patients may be considered not only for DR-TB case finding but also for antibiotic treatment to prevent latent DR-TB infection from developing into active disease. Effectiveness data are currently limited,<sup>77,78</sup> but the WHO recently proposed a conditional recommendation supporting preventive therapy based on individual risk assessment of contacts of DR-TB patients while trial results are awaited.<sup>16</sup> Clinical trials are underway to evaluate the effectiveness of levofloxacin (TB CHAMP [ISRCTN92634082] and V-QUIN Trials [ACTRN12616000215426]) and delamanid (PHOENIX MDR-TB Trial [A5300B/I2003B]) in treating DR-TB infection. These trials are expected to indicate the steps required to most effectively manage DR-TB contacts and other individuals with likely DR-TB infection.

## Need for new preventive tools

While preventive therapy regimens are likely to play an important role for DR-TB contacts, much TB transmission occurs outside of known close contact pairs.<sup>79</sup> To reduce the reservoir of latent DR-TB to a level sufficient for elimination, we need novel tools, e.g., a well-tolerated, easily administered, highly effective preventive regimen with activity against MDR-TB. Ongoing efforts to identify effective and tolerable preventive regimens for DR-TB—ideally combined with improved diagnostics for identifying those at risk of progression to TB disease—must be prioritized if the goal of eliminating DR-TB is to be attained.

## POLITICAL COMMITMENT TO ELIMINATION

DR-TB elimination will require bold action and sustained commitment on the part of many, including



governments, health systems, investigators, clinicians, and funding bodies. The first ever United Nations High Level Meeting on TB in September 2018 set the stage for increased political commitment, and must be followed by bold actions.

In 1985, the eminent TB clinician Michael Iseman warned that, ‘We are transforming an eminently treatable infection into a life-threatening disease that is exorbitantly expensive to treat’.<sup>80</sup> The potential cost of complacency remains the same today: each time we fail to cure a patient with DR-TB, or miss an opportunity to prevent DR-TB from developing, we increase human suffering and the work required for DR-TB treatment in the future.

If we are to end the DR-TB epidemic, the path to elimination needs to incorporate large-scale prevention, patient-centered care, engagement of affected communities, and strategic innovation. A globally representative sentinel surveillance system could aid strategy and priority setting. To advance diagnostic and therapeutic pipelines, there may be roles for innovative funding mechanisms and regulatory incentives.<sup>81</sup> It is also critical that communities at highest risk for DR-TB be given greatest access to new diagnostic tools and medicines<sup>82</sup>—as well as to broader poverty reduction interventions. Broadly shared social and economic advancement are also likely to reduce all forms of TB<sup>83</sup> and help in DR-TB elimination.

DR-TB takes a considerable toll on affected patients, and patient advocacy has an important place on the path toward DR-TB elimination. The TB community can learn from the example of HIV (human immunodeficiency virus) infection in insisting on health as a human right for patients with DR-TB and in working to make effective interventions available for patients with DR-TB in developing countries.<sup>84</sup> Ultimately, there is a strong case—explored below—that attainment of DR-TB elimination can be cost-effective. Nevertheless, it will require monetary investment by national health systems, with backing from international funding bodies and technology licensees. Aid to lower-income countries should take a long view by transferring technology and expertise and helping to build sustainable TB programs for a decades-long elimination process.

## ECONOMICS OF DRUG-RESISTANT TUBERCULOSIS ELIMINATION

Allocating sufficient resources to fund DR-TB elimination remains a challenge despite the increasing array of interventions available. The cost-effectiveness of DST and MDR-TB long-course treatment was established over a decade ago, in a range of low- and middle-income countries.<sup>85</sup> In many high TB burden countries, <2% of all notified patients are treated for MDR-TB, yet costly DR-TB management consumes 25% of TB budgets.<sup>3</sup> Limited overall TB funding and

low health spending have left many programs with the stark choice of developing DR-TB services or treating more people with DS-TB. Elimination of DR-TB will therefore require a broader policy commitment at the global level to increase TB funding more generally.

The economic gain from DR-TB elimination is potentially sizable in terms of future health system costs as well as wider economic impact. While the primary motivation for investment is disease and mortality burden, DR-TB can also be a particularly devastating disease from a poverty reduction perspective, with catastrophic economic costs at the household level.<sup>86</sup> Despite these compelling qualitative arguments for the benefits of elimination, quantifying the case for the large upfront investment required is problematic. Data are lacking on the costs and cost-effectiveness of emerging DR-TB technologies, and of the operational and health system costs of expanding DR-TB service coverage to the levels required for elimination.<sup>87</sup>

Nevertheless, the economic understanding of DR-TB is rapidly evolving. Several interventions described above have demonstrated the potential to improve both the costs and cost-effectiveness of the DR-TB response of health systems. Shortened regimens containing new drugs are potentially cost-saving compared with current approaches.<sup>88,89</sup> Likewise, countries such as South Africa that have led the move to decentralize care are now benefiting from large reductions in DR-TB treatment costs.<sup>90</sup> Wider adoption of new service delivery models that reduce hospitalization or allow remote monitoring of treatment may be pivotal in changing the perception of DR-TB treatment as a costly, infeasible endeavor.

A greater challenge lies in making the investment case for the expanded case detection and improved DST required for DR-TB elimination. Rapid molecular DST for at least RMP, if implemented correctly, is a key part of a cost-effective TB strategy in many settings; however, evidence on the costs and cost-effectiveness of scaling up rapid molecular DST is more limited than for new treatment regimens. It also varies considerably between settings,<sup>91</sup> and both the technologies and the evidence base on how to efficiently implement them are rapidly evolving. Increasing use of multipurpose technologies and shared laboratory platforms, and synergy with wider efforts to address antimicrobial resistance, may help to lower the ‘marginal’ costs of scaling up DR-TB treatment services.

There remains a substantial dearth of data on both the costs and cost-effectiveness of the different modalities of case detection. Developing efficient service delivery models to reach undetected cases remains one of the most under-researched (yet important) areas in the economics of TB and DR-TB. Understanding the costs and feasibility of different approaches for reaching individuals with



**Table** Summary table of barriers to DR-TB elimination and action steps for addressing them

Barrier to elimination	Description of the barrier	Solutions
Preventing generation of DR-TB Acquired first-line drug resistance	A proportion of DS-TB patients develop resistance to drugs in their regimen	Improve quality of DS-TB care (optimal dosing, authentic drugs, patient support, programmatic quality improvement, DST) Pursue multifaceted efforts to reduce overall TB incidence
Improving DR-TB diagnosis Late TB diagnosis	Individuals with DR-TB are often diagnosed with TB after significant transmission (or are never diagnosed)	Improve access to TB screening and evaluation and to rapid, sensitive TB diagnostics (e.g., radiography, Xpert® MTB/RIF). Perform active case finding + DST among DR-TB risk groups, including high TB incidence populations and DR-TB contacts
Under-detected first-line drug resistance	Most TB patients are not tested for drug resistance	Perform universal DST, at least for rifampin, in all TB patients before treatment. Increase availability of rapid DST, including laboratory support and infrastructure, including electricity or alternative energy supplies
Under-detected second-line drug resistance	Many MDR-TB patients have additional drug resistance	Strengthen laboratories, sample transport, and results-reporting systems for centralized DST Improve second-line DST options (including both point-of-care molecular assays and whole genome sequencing)
Improving DR-TB treatment Low regimen efficacy	Critical components of short-course anti-tuberculosis treatment are inactive against MDR-TB	Increase access to newer drugs that can increase regimen efficacy Monitor DR-TB patients for treatment non-response, and react promptly Pursue development of shorter, more effective DR-TB and pan-TB regimens
Inadequate treatment completion	Conventional MDR-TB treatment has ≥ 18 months' duration, significant toxicities, and high rates of attrition	Develop more tolerable drugs from existing and new drug classes Use shorter and more tolerable regimens when clinically appropriate Engage patients in decisions and provide treatment literacy and adherence support throughout treatment
Limited treatment access	Logistical and programmatic barriers often prevent or delay DR-TB treatment	Ensure adequate financial and social support for patients Provide DR-TB care in decentralized ambulatory settings Cautiously use standardized regimens to facilitate access, while also strengthening second-line DST access, local clinician training, and specialized referral/consultation systems Pursue development of shorter, all-oral, and more-universal regimens
Acquired second-line drug resistance	Second-line drug resistance is acquired frequently and makes DR-TB more difficult to cure	Invest pre-emptively in better DR-TB treatment now Make quality improvement part of DR-TB treatment programs Monitor for acquired resistance to new anti-tuberculosis drugs
Preventing propagation of DR-TB Transmission in public settings	Hospitals in particular can be hotbeds of transmission of undetected or ineffectively treated DR-TB	Strengthen airborne infection control in hospitals and other settings where transmission is common
Transmission to close contacts	Contacts of DR-TB cases often have latent DR-TB infection and a high risk of reactivation	Monitor close contacts of MDR- and RR-TB patients for development of active TB Consider preventive second-line antibiotic treatment when latent MDR-TB is likely
Latent DR-TB reservoir	Elimination DR-TB will require eliminating most DR-TB reactivation	Pursue more tolerable and easily administered preventive therapies
Supporting and funding DR-TB elimination Complacency	DR-TB moves slowly and affects marginalized populations; political urgency is often lacking	Advocate for investment commensurate with health burden and public health threat Advocate for DR-TB care as part of a fundamental human right to health
High costs of DR-TB care	DR-TB drugs and care delivery consume a disproportionate share of tightly constrained TB budgets	Increase overall TB funding Innovate or adopt lower-cost care models Integrate DR-TB care into broader health system
Poverty and weak health systems	Social disadvantage and poor health contribute to TB and DR-TB risk	Strengthen health and community systems broadly Reduce poverty and improve access to health care
Limited epidemiologic, economic and implementation data	Uncertainty about the burden and distribution of DR-TB, and about the costs and efficiency of DR-TB control modalities, limits strategic planning	Establish globally representative DR-TB surveillance Strengthen and modernize DR-TB information systems for disaggregated real-time reporting Assess feasibility and costs of the above interventions in different settings, to identify the most efficient path to DR-TB elimination

DR-TB = drug-resistant TB; DS-TB = drug-susceptible TB; DST = drug susceptibility testing; TB = tuberculosis; MDR-TB = multidrug-resistant TB; RR-TB = rifampin-resistant TB.

LTBI will be similarly critical to ensuring that interventions to address latent MDR-TB are cost-effective. A better understanding of these costs at both the global and country levels can help to clarify the economic case and the most cost-effective strategy for achieving DR-TB elimination.

## NEXT STEPS

The Table summarizes the important obstacles faced in pursuing a goal of DR-TB elimination, and proposes a path forward. Efforts to reduce DS-TB can reduce DR-TB both directly and indirectly, but specific actions targeted to DR-TB are also fundamental. Improving DR-TB case detection is essential and requires DST scale-up and targeted case finding, particularly among contacts of DR-TB patients. Once DR-TB patients are in care, providing prompt, high-quality treatment with effective drug regimens in a patient-centered context can improve treatment success. Regimen design should increasingly incorporate new drug options and clinically relevant second-line DST results, although limitations in the drugs or diagnostic assays available should not unduly limit access to DR-TB treatment in the short term. For DR-TB prevention, as with TB prevention in general, infection control is essential, and preventive therapy has an important role.

These actions—supported by political commitment, financial investment, and broader socio-economic and health system development—can considerably reduce MDR- and RR-TB. As MDR-TB epidemics and the available tools evolve, ongoing evaluations of cost, feasibility, and impact should guide efficient elimination strategies. However, only research and development will allow dramatic transformation of the DR-TB landscape, for example, through highly tolerable novel regimens, corresponding point-of-care DST, and preventive therapy with potential for population-wide reach. If the world commits to such a path, then reaching an elimination threshold for DR-TB could become a major global health accomplishment and (with continued attention to DR-TB prevention) an important milestone on the path toward TB elimination overall.

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## R É S U M É

La tuberculose pharmacorésistante (TB-DR) constitue un défi en matière de diagnostic, de traitement et de prévention, mais ceci est en train de changer. Si le monde veut réduire de manière drastique l'incidence de la TB-DR, nous devons en premier lieu arrêter de créer de nouveaux cas de TB-DR. L'épidémie de TB-DR en cours doit également être affrontée directement. La pharmacorésistance aux médicaments de première ligne doit être rapidement détectée grâce à un test moléculaire universel de résistance au moins à la rifampicine et de préférence à d'autres médicaments majeurs lors du diagnostic initial de TB. Les résultats du traitement de la TB-DR doivent également s'améliorer considérablement. Une utilisation efficace des médicaments actuellement disponibles, nouveaux et recyclés, combinés avec un traitement centré sur le patient qui contribue à l'adhérence et réduit les coûts catastrophiques, sont essentiels. Les innovations en vue, comme des protocoles courts, très efficaces, largement indiqués, couplés à des tests de sensibilité aux médicaments faits sur place, pourraient accélérer les

progrès en matière de résultats du traitement. Prévenir ou contenir la résistance aux médicaments de deuxième ligne et aux médicaments nouveaux est également crucial et nécessitera des systèmes de grande qualité pour le diagnostic, le choix du protocole et le suivi du traitement. Enfin, une détection plus précoce et/ou une prévention de la TB-DR est nécessaire, avec une attention particulière à la lutte contre les infections par voie aérienne, à la recherche des cas et au traitement préventif des contacts de patients atteints de TB-DR. La mise en œuvre de ces stratégies peut surmonter l'obstacle que représente la TB-DR pour les activités d'élimination de la TB dans le monde et pourrait finalement permettre d'atteindre l'élimination de la TB-DR dans le monde (moins d'un cas par an par un million d'habitants dans le monde). Il y a de solides arguments de rentabilité pour soutenir la poursuite de l'élimination de la TB-DR, mais atteindre ce but nécessitera un investissement mondial substantiel ainsi qu'un engagement politique et sociétal au niveau national et local.

## R E S U M E N

La tuberculosis farmacorresistente (TB-DR) plantea problemas de diagnóstico, tratamiento y prevención, pero esta situación mejora poco a poco. Con el fin de disminuir de manera drástica la incidencia de TB-DR en el mundo, un primer paso fundamental consiste en interrumpir la aparición de nuevos casos resistentes. Asimismo, es primordial abordar de manera directa la epidemia actual de TB-DR. Es necesario detectar rápidamente la resistencia a los medicamentos de primera línea, con la práctica a todos los pacientes de pruebas moleculares de resistencia como mínimo a rifampicina y, en condiciones ideales, a los demás medicamentos en el momento del diagnóstico inicial. También se debe alcanzar un progreso radical en los desenlaces terapéuticos de los casos de TB-DR. Una utilización eficaz de los medicamentos actualmente disponibles, los nuevos fármacos y los medicamentos reposicionados, aunada al tratamiento centrado en el paciente que favorece la adhesión y disminuye los costos catastróficos son medidas indispensables. Las innovaciones próximas como los esquemas breves muy eficaces con indicaciones amplias, acopladas a las

pruebas de sensibilidad en el lugar de la consulta, acelerarían el progreso de los desenlaces terapéuticos. Asimismo, es imprescindible prevenir o contener la resistencia a los medicamentos de segunda línea y a los nuevos fármacos, lo cual precisará sistemas de gran calidad de diagnóstico, selección de pautas terapéuticas y supervisión del tratamiento. Por último, es necesario lograr una detección más temprana y la prevención de la farmacorresistencia, con una atención especial en el control de las infecciones de transmisión aérea, la búsqueda de casos y el tratamiento preventivo de los contactos de pacientes con TB-DR. La introducción de estas estrategias contribuirá a vencer el obstáculo que representa la farmacorresistencia frente a las iniciativas de eliminación mundial de la TB y en último término haría alcanzable la meta de eliminación mundial de la TB-DR (menos de un caso anual por cada millón de habitantes en todo el mundo). Existe un sólido argumento de costo-efectividad que respalda la búsqueda de este objetivo, pero su cumplimiento necesitará una cuantiosa inversión mundial, además de compromiso político y social a escala nacional y local.