



# The epidemiology, transmission, diagnosis, and management of drug-resistant tuberculosis—lessons from the South African experience

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Drug-resistant tuberculosis (DR-TB) threatens to derail tuberculosis control efforts, particularly in Africa where the disease remains out of control. The dogma that DR-TB epidemics are fueled by unchecked rates of acquired resistance in inadequately treated or non-adherent individuals is no longer valid in most high DR-TB burden settings, where community transmission is now widespread. A large burden of DR-TB in Africa remains undiagnosed due to inadequate access to diagnostic tools that simultaneously detect tuberculosis and screen for resistance. Furthermore, acquisition of drug resistance to new and repurposed drugs, for which diagnostic solutions are not yet available, presents a major challenge for the implementation of novel, all-oral, shortened (6–9 months) treatment. Structural challenges including poverty, stigma, and social distress disrupt engagement in care, promote poor treatment outcomes, and reduce the quality of life for people with DR-TB. We reflect on the lessons learnt from the South African experience in implementing state-of-the-art advances in diagnostic solutions, deploying recent innovations in pharmacotherapeutic approaches for rapid cure, understanding local transmission dynamics and implementing interventions to curtail DR-TB transmission, and in mitigating the catastrophic socioeconomic costs of DR-TB. We also highlight globally relevant and locally responsive research priorities for achieving DR-TB control in South Africa.

## Introduction

Tuberculosis is a leading cause of death from an infectious disease and remains a global public health threat. Although the estimated global incidence of tuberculosis was declining from 2001 until 2020, these declines were reversed by the COVID-19 pandemic.<sup>1</sup> Encouragingly, the declining trend in tuberculosis incidence across the WHO African region has been maintained.<sup>1</sup> However, these achievements in tuberculosis control are threatened by the continued high incidence of drug-resistant tuberculosis (DR-TB), with an estimated 410 000 individuals developing multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis (RR-TB) globally in 2022.<sup>1</sup> Despite increased access to novel, oral, shorter (6–9 months) treatment regimens, approximately 20% of patients with MDR-TB died despite being initiated on treatment, and treatment success rates among patients with DR-TB remain persistently sub-optimal at less than 65%.<sup>1,2</sup> Factors that continue to undermine the therapeutic success in DR-TB include diagnostic delays, the high burden of comorbidities including diabetes and HIV, poor linkage of patients with a positive microbiological result for DR-TB to treatment services, and high rates of loss-to-follow-up and disease relapse.<sup>3,4</sup> It has been estimated that low-income countries could lose 2–5% of their gross domestic product by the year 2050 due to MDR-TB and RR-TB, ultimately costing the global economy \$US17·5 trillion.<sup>5</sup> Despite only accounting for 3% of all notified tuberculosis cases in South Africa, DR-TB consumes over 33% of the total financial resources available for tuberculosis control.<sup>1,6</sup> Addressing the challenges of delivering effective DR-TB treatment, achieving long-term relapse-free cure, and halting the emergence and transmission of drug resistance requires

sustained effort to develop and implement high-impact interventions for DR-TB prevention and management. Herein, we reflect on the lessons learnt from the South African experience in implementing state-of-the-art advances in diagnostic solutions, recent innovations in pharmacotherapeutic approaches for rapid cure, and interventions to curtail DR-TB transmission guided by an

## Key messages

- Drug-resistant tuberculosis (DR-TB) threatens to derail tuberculosis control programmes globally and poses unique social, biomedical, and economic challenges in the African region
- Uncontrolled transmission of DR-TB, underdiagnosis of all forms of tuberculosis, and high levels of attrition from care are key targetable drivers of the South African epidemic
- Structural challenges including poverty, stigma, and social distress disrupt engagement in care, promote poor treatment outcomes, and reduce the quality of life in people with DR-TB
- Locally responsive innovations—leveraging technological tools, programmatic data, and multisectoral partnerships—are emerging in DR-TB programmes in South Africa
- Major innovation, beyond diagnostic and therapeutic solutions, are needed to advance a patient-centred, human-rights-based, multisectoral approach to DR-TB
- Ongoing high levels of political will, advocacy, community engagement, and higher levels of resource investment and funding are needed to materialise the goal of eliminating the threat of DR-TB

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understanding of local transmission dynamics. We also highlight the efforts toward mitigating the catastrophic socioeconomic costs of DR-TB and propose globally relevant and locally responsive research priorities for achieving DR-TB control in South Africa.

### Epidemiology of DR-TB in sub-Saharan Africa

Among the approximate 410 000 individuals who develop MDR-TB or RR-TB globally each year, 62 000 (15%) reside in the African region.<sup>2</sup> However, both the global and African region estimates are associated with wide CIs (global: 370 000–450 000; and Africa: 52 000–72 000), reflecting considerable uncertainty arising from an insufficient capacity to conduct routine surveillance or costly national surveys, and sparse access to tuberculosis drug resistance testing in many countries. Scarce active case-finding efforts, incomplete and inaccurate country data submissions to WHO, a paucity of post-mortem examination services, and the large-scale dependence on verbal autopsy data are additional contributors to the uncertainty around estimates of tuberculosis incidence and mortality in Africa.<sup>7–12</sup> South Africa, Mozambique, and Zambia are the only African countries with high MDR-TB or RR-TB burden that tested more than 80% of individuals with bacteriologically-confirmed tuberculosis for rifampicin resistance.<sup>13</sup>

MDR-TB and RR-TB burden can be described in terms of overall estimated numbers, the proportion of all individuals with tuberculosis who have MDR-TB or RR-TB, and by population level MDR-TB and RR-TB incidence (table 1<sup>14</sup>). These indices each highlight unique epidemiological contexts and are essential in designing and implementing tailored strategies for specific settings.

Absolute numbers are necessary for informing health service planning and budgeting. The proportion of MDR-TB and RR-TB among individuals who have not received previous tuberculosis treatment and the population-level MDR-TB and RR-TB incidence reflect the current and future risks of community-level transmission. Across all three indices, South Africa, Angola, Mozambique, and Somalia feature in the top ten (table 1), with an estimated combined total of 23 500 people developing MDR-TB or RR-TB in 2022.<sup>1</sup> A modelling study estimated that each episode of RR-TB in Africa results in 23 disability-adjusted life years, and that a total of 1·72 million disability-adjusted life years were generated by RR-TB in the African region in 2020.<sup>15</sup>

A large proportion of the MDR-TB and RR-TB burden in Africa remains undiagnosed and untreated due to inadequate access to rapid molecular diagnostic solutions for detecting tuberculosis and screening for drug resistance. In 2022, only 67% of the total 1·75 million individuals with tuberculosis in Africa had a bacteriologically-confirmed diagnosis. Additionally, among these, only 67% were tested for rifampicin resistance.<sup>1</sup> As a result, approximately 65% of the estimated number of individuals with MDR-TB or RR-TB were either not diagnosed with tuberculosis at all or were erroneously diagnosed as drug-susceptible tuberculosis. The failure to diagnose and treat a significant proportion of Africa's MDR-TB and RR-TB burden likely contributed to the high total estimated numbers observed between 2015 and 2022 in most WHO-defined high tuberculosis burden countries (appendix p 1). It is important to note that the declining trend for Africa overall has been principally driven by the significant decline in the incidence of tuberculosis in South Africa.<sup>2,16</sup> The declining trend in South Africa is encouraging and suggests several worthy priorities for intervention across the continent. These include the provision of rapid diagnostics for all individuals under investigation for tuberculosis, with drug resistance testing for both rifampicin and isoniazid as a minimum. Notably, across Africa in 2020, only 23% of the estimated people with MDR-TB or RR-TB were placed on treatment, with less than 1000 children among these.<sup>13</sup>

South Africa, through its National Strategic Plan for HIV, Tuberculosis, and Sexually Transmitted Infections 2023–2028, implemented several innovative measures to recover the national tuberculosis programme from the impact of the COVID-19 pandemic and to chart a bold new path towards tuberculosis eradication.<sup>14</sup> The National Strategic Plan places people and communities at the centre of interventions, espouses an inclusive and multisectoral national response, and leverages evidence-based innovations in the services and solutions advocated for implementation. This includes plans to integrate traditional health practitioners in detecting and delivering community-led tuberculosis services. The South African Tuberculosis Recovery Plan is

See Online for appendix

|                | Highest number of people with MDR-TB and RR-TB |         | Highest percentage of MDR-TB and RR-TB among new tuberculosis cases |     | Highest population incidence of MDR-TB and RR-TB (per 100 000) |           |
|----------------|------------------------------------------------|---------|---------------------------------------------------------------------|-----|----------------------------------------------------------------|-----------|
|                | Country                                        | Number  | Country                                                             | %   | Country                                                        | Incidence |
| First          | Nigeria                                        | 12 000  | Botswana                                                            | 5·7 | Lesotho                                                        | 26        |
| Second         | South Africa                                   | 11 000  | Somalia                                                             | 4·6 | Namibia                                                        | 21        |
| Third          | DR Congo                                       | 6300    | Namibia                                                             | 4·4 | Gabon                                                          | 20        |
| Fourth         | Angola                                         | 6100    | Eswatini                                                            | 4·4 | Eswatini                                                       | 19        |
| Fifth          | Mozambique                                     | 4300    | Angola                                                              | 4·0 | South Africa                                                   | 18        |
| Sixth          | Somalia                                        | 2100    | Lesotho                                                             | 3·5 | Angola                                                         | 17        |
| Seventh        | Ethiopia                                       | 2000    | South Africa                                                        | 2·9 | Botswana                                                       | 14        |
| Eighth         | Zambia                                         | 1900    | Mozambique                                                          | 2·9 | Mozambique                                                     | 13        |
| Ninth          | Tanzania                                       | 1700    | Gabon                                                               | 2·6 | Somalia                                                        | 11        |
| Tenth          | Uganda                                         | 1400    | Malawi                                                              | 2·3 | Zambia                                                         | 10        |
| African region | African region                                 | 62 000  | African region                                                      | 2·3 | African region                                                 | 5·2       |
| Global         | Global                                         | 410 000 | Global                                                              | 3·3 | Global                                                         | 5·2       |

MDR-TB=multidrug-resistant tuberculosis. RR-TB=rifampicin-resistant tuberculosis.

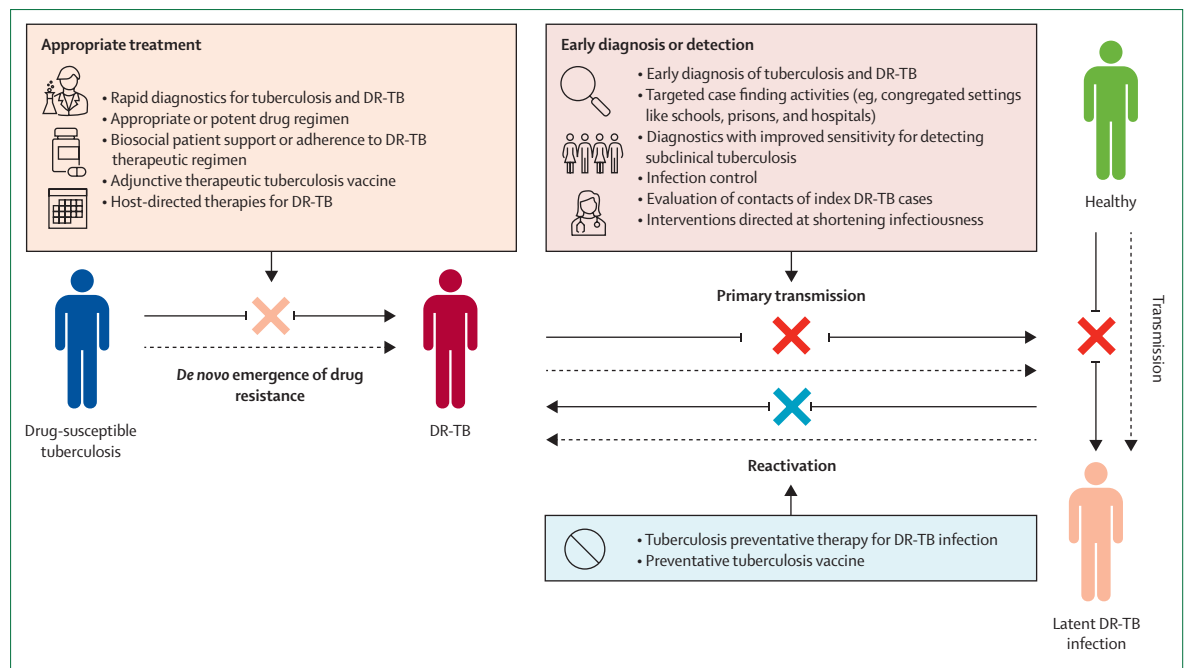
**Table 1:** Estimated total number of people with MDR-TB or RR-TB, percentage MDR-TB or RR-TB among new tuberculosis cases, and population incidence of MDR-TB and RR-TB globally and in the highest tuberculosis burden African countries in 2022<sup>14</sup>

designed to accelerate efforts toward attaining the National Strategic Plan targets and to define crucial interventions for closing the gaps within the tuberculosis care cascade.<sup>17</sup> Specific case-finding interventions include the introduction of a tuberculosis self-screening mobile application (Tuberculosis Health Check App), the introduction of routine annual tuberculosis testing for key populations, the expanded use of mobile digital chest radiographs, and urine lipoarabinomannan testing. To enhance linkage to care, all patients tested for tuberculosis receive their results via SMS notification, with tracer teams and patient navigators in place to strengthen engagement efforts. The combination regimen bedaquiline–pretomanid–linezolid (BPaL)–levofloxacin (BPaL-L) rollout is being scaled up nationally and provides free access to an unprecedentedly short (6 month) all-oral DR-TB regimen. Clinical audits are routinely conducted across the decentralised South African tuberculosis control programme treatment network to inform updates to the treatment algorithm. Rapid detection and surveillance of resistance is a prioritised activity for preventing resistance amplification and improving outcomes. A national pharmacovigilance monitoring system in South Africa ensures that adverse events are identified, managed, and reported accordingly. The National Clinical Advisory Committee and Provincial DR-TB Technical Advisory Groups leverage the country's extensive network of experts to strengthen DR-TB care.

### DR-TB transmission in sub-Saharan Africa

Early in a DR-TB epidemic, resistance arises primarily within individuals and under drug selection pressure (acquired or treatment-emergent resistance). However, the expansion of drug resistance to the broader population occurs from person-to-person transmission of drug-resistant strains. This epidemiological transition from acquired to transmitted resistance has been well documented for older tuberculosis drugs and is further evidenced by studies that demonstrate minimal genetic diversity among prevailing MDR-TB and extensively drug-resistant (XDR)-TB strains in WHO high-burden tuberculosis settings.<sup>18–23</sup> As such, in most high-incidence settings, widespread community transmission of drug-resistant strains is the primary driver of new DR-TB cases and is mainly dependent on population-level factors such as the extent of social mixing, the patterns of migration, and the promptness of diagnosis and treatment.<sup>24,25</sup> Studies combining traditional epidemiological investigation and whole genome sequencing have shown that 70–80% of MDR-TB or XDR-TB cases arose due to transmission rather than through the intra-host acquisition of resistance.<sup>18–21,24,26–29</sup> For this reason, the dogma that DR-TB epidemics are fueled by unchecked rates of acquired resistance in inadequately treated or non-adherent individuals is no longer valid in most high DR-TB burden settings.

The distribution of *Mycobacterium tuberculosis* strains within South Africa is region-specific, in keeping with the strong phylogeographical signals exhibited globally.<sup>30</sup> The predominant strains circulating in the Western Cape of South Africa are lineage 2 (or Beijing genotype), and those in KwaZulu-Natal are primarily members of lineage 4.<sup>24,31–34</sup> Within lineages, the genetic diversity of *M. tuberculosis* tends to decrease steeply from drug-susceptible to increasing forms of DR-TB (ie, from MDR to pre-XDR and XDR),<sup>21,35</sup> whereby the transmission of a limited number of strains characterises ongoing regional DR-TB epidemics. Within DR-TB epidemics, strain distributions are thought to shift partly due to the accumulation of pathoadaptive polymorphisms.<sup>18,19,36,37</sup> However, the underlying mechanisms facilitating DR-TB endemicity are complex and have multiple components (eg, case detection, available diagnostics, treatment, migration and mobility patterns, infection control, and bacterial factors). For example, one of the first major XDR-TB outbreaks was reported in a nosocomial setting in rural KwaZulu-Natal, South Africa, in 2005.<sup>38</sup> Most XDR-TB cases in KwaZulu-Natal are attributable to a signal monomorphic strain, referred to as LAM4/KZN (lineage 4), which can be traced to the original outbreak.<sup>18,20,24</sup> Population genetic analysis suggests that the XDR LAM4/KZN strain emerged in the early 1990s, nearly 12 years before recognition, expanded in parallel with the regional HIV epidemic, and was further propelled by compensatory genetic evolution, with a site of origin located approximately 400 km away from the site of the outbreak in 2005.<sup>18</sup> These strains are now distributed throughout the socio-geographically diverse province, most likely due to rural-urban-rural migration.<sup>39</sup> Moreover, in at least one study, epidemiologically unlinked patients with XDR-TB had low pairwise single nucleotide polymorphism differences with at least one other participant, consistent with transmission—suggesting that significant transmission might result from casual community contact between individuals unknown to one another.<sup>25</sup> Similarly, in the Western Cape, a genomic investigation of over 460 XDR-TB isolates spanning 10 years (2006–2017) found that lineage 2 strains accounted for over 90% of all strains.<sup>34</sup> One strain group (lineage 2.2.2, considered an atypical Beijing genotype<sup>33</sup>) comprised over 70% of lineage 2 members and over 65% of all XDR-TB strains. Lineage 4 strains, highly prevalent throughout South Africa and dominant among XDR-TB strains in KwaZulu-Natal (LAM4/KZN), occurred in only 7% of XDR-TB cases in the Western Cape. Although drug-susceptible lineage 2.2.2 strains are generally present in low frequency, they are enriched among MDR, pre-XDR, and XDR strain populations in the Eastern Cape where they emerged.<sup>31</sup> These highly drug-resistant strains are thought to have made their way to the Western Cape because of high levels of interprovincial migration.<sup>31</sup> In contrast to the LAM4/KZN XDR epidemic in KwaZulu-Natal, the



**Figure 1: Strategies to interrupt DR-TB transmission suitable for high tuberculosis burden settings**

The figure illustrates major types of DR-TB acquisition (including *de novo* emergence, primary transmission, and reactivation of latent DR-TB) and strategies for mitigating the development of DR-TB in each scenario. DR-TB=drug-resistant tuberculosis.

genomic analysis indicates that the rise of XDR-TB in the Western Cape is likely due to the epidemic spread of MDR and pre-XDR lineage 2.2.2 strains with repeated and independent acquisition of fluoroquinolone resistance, a pattern seen elsewhere.<sup>19,34</sup>

The growing recognition that transmission is the key driver of DR-TB in high-burden settings has led to prioritising interventions that interrupt transmission, mainly through early detection and treatment of DR-TB (figure 1). South Africa is a global leader in the implementation of new tuberculosis diagnostics. In 2011, South Africa scaled up universal drug susceptibility testing by using Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) as the initial tuberculosis diagnostic test, replacing acid-fast bacilli smear. Xpert MTB/RIF is a reliable test for diagnosing tuberculosis and polymorphisms within the 81-basepair hotspot region of *rpoB* associated with rifampicin resistance.<sup>22</sup> However, less common resistance-conferring mutations not covered by commercial tests are at risk of being missed by routine services. For instance, in Eswatini, 30% of multidrug-resistant isolates harbour rifampicin resistance-conferring mutations outside the 81-bp region (ie, 1491F), which are missed by commercial assays.<sup>40</sup> The mitigation of further regional expansion of such diagnostic escape strains is an emerging priority, necessitating regional surveillance and high levels of cooperation between national laboratories.<sup>41</sup>

South Africa is leading the world in the implementation of the new WHO-recommended all-oral, six-month

regimen of BPaL for the treatment of DR-TB. Although rapid scale-up of this regimen is expected to improve DR-TB outcomes, the emergence of widespread resistance to these drugs will rapidly undermine any gains. Bedaquiline was only approved in 2012 and bedaquiline-resistant tuberculosis strains are already well documented, with approximately 3–5% of all MDR-TB strains in South Africa presently demonstrating phenotypic resistance to bedaquiline.<sup>42,43</sup> A genomic analysis of ST34 strains from Eswatini and South Africa suggests that these strains harbour three separate mutations in *Rv0678*, a gene implicated in bedaquiline resistance, and the genomic analysis was highly suggestive of transmission of these bedaquiline-resistant strains.<sup>44,45</sup> Large-scale transmission of bedaquiline-resistant strains has yet to be reported; however, genomic clusters of bedaquiline-resistant strains with epidemic potential have been identified.<sup>42,43,45</sup> With the scale-up of DR-TB treatment using bedaquiline-containing regimens, an increase in treatment-emergent bedaquiline-resistant tuberculosis cases is likely, especially as treatment-emergent resistance has been found to occur in approximately 2% of bedaquiline-treated cases under both programmatic and clinical trial conditions.<sup>46–48</sup> The emergence of bedaquiline resistance within a highly transmissible *M tuberculosis* strain could exponentially accelerate the incidence of bedaquiline resistance.

The Eswatini ST34 strain, harbouring rifampicin and bedaquiline resistance in the absence of fluoroquinolone resistance, does not meet WHO definitions for either

pre-XDR or XDR-TB, raising a new challenge for classification, surveillance, and reporting. Indeed, the global implementation of a bedaquiline-containing regimen for DR-TB will likely see a new profile of fluoroquinolone-susceptible, bedaquiline-resistant DR-TB, for which no WHO classification currently exists. In the interim, we propose the term complex resistance

to describe any isolate bearing resistance to bedaquiline, pretomanid, delamanid, or linezolid.

### Diagnosis of DR-TB: challenges and opportunities within the South African context

The WHO End Tuberculosis Strategy calls for not only early tuberculosis diagnosis but also universal drug

|                                                                       | Detection (gene target)*                                                                                                                                                                                                                          | Approximate limit of detection for tuberculosis† | Diagnostic performance for detection in sputum‡                                                                                                                                                                                                                                                                                                                                                                              | Time to result                                                                                                                                                                                | WHO recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Low complexity automated nucleic acid amplification tests</b>      |                                                                                                                                                                                                                                                   |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Cepheid Xpert MTB/RIF                                                 | Tuberculosis ( <i>rpoB</i> ); rifampicin ( <i>rpoB</i> )                                                                                                                                                                                          | 113 cfu/mL                                       | Tuberculosis ( <i>rpoB</i> ): Sens 85%, Spec 98%; rifampicin ( <i>rpoB</i> ): Sens 96%, Spec 98%                                                                                                                                                                                                                                                                                                                             | <2 h                                                                                                                                                                                          | Initial diagnostic test for tuberculosis and rifampicin, replacing smear/culture and phenotypic drug susceptibility testing for pulmonary tuberculosis and extrapulmonary tuberculosis                                                                                                                                                                                                                                                                                                            |
| Cepheid Xpert MTB/RIF Ultra                                           | Tuberculosis ( <i>IS6110</i> , <i>IS1081</i> ); rifampicin ( <i>rpoB</i> )                                                                                                                                                                        | 16 cfu/mL                                        | Tuberculosis ( <i>IS6110</i> , <i>IS1081</i> ): Sens 90%, Spec 96%; rifampicin ( <i>rpoB</i> ): Sens 94%, Spec 99%                                                                                                                                                                                                                                                                                                           | <80 mins                                                                                                                                                                                      | Initial diagnostic test for tuberculosis and rifampicin, replacing smear/culture and phenotypic drug susceptibility testing for pulmonary tuberculosis and extrapulmonary tuberculosis                                                                                                                                                                                                                                                                                                            |
| Cepheid Xpert MTB/XDR                                                 | Tuberculosis ( <i>inhA</i> ); isoniazid ( <i>katG</i> , <i>inhA</i> promoter, <i>oxyR-ahpC</i> , <i>fabG1</i> ); ethionamide ( <i>inhA</i> promoter); fluoroquinolone ( <i>gyrA</i> , <i>gyrB</i> ); amikacin ( <i>rrs</i> , <i>eis</i> promoter) | 136 cfu/mL                                       | Tuberculosis ( <i>inhA</i> ): Sens 98–99%, Spec 22–100%; isoniazid ( <i>katG</i> , <i>inhA</i> promoter, <i>oxyR-ahpC</i> , <i>fabG1</i> ): Sens 94%, Spec 98%; ethionamide ( <i>inhA</i> promoter): Sens 98%, Spec 100% (vs <i>inhA</i> sequencing); fluoroquinolone ( <i>gyrA</i> , <i>gyrB</i> ): Sens 93%, Spec 98%; amikacin ( <i>rrs</i> , <i>eis</i> promoter): Sens 86%, Spec 99% (in rifampicin-resistant patients) | <90 mins                                                                                                                                                                                      | In those with bacteriologically confirmed pulmonary tuberculosis, test for isoniazid and fluoroquinolone, replacing phenotypic drug susceptibility testing. In those with bacteriologically confirmed rifampicin-resistant pulmonary tuberculosis, test for ethionamide, replacing DNA sequence of <i>inhA</i> promoter. In those with bacteriologically confirmed rifampicin-resistant pulmonary tuberculosis, test for amikacin, replacing phenotypic drug susceptibility testing (conditional) |
| Molbio Truenat MTB or MTB Plus and MTB-RIF Dx                         | Tuberculosis (MTB Plus: <i>nrnz</i> , <i>IS6110</i> ; MTB: <i>nrnz</i> ); rifampicin (MTB-RIF Dx: <i>rpoB</i> )                                                                                                                                   | 100 cfu/mL                                       | Tuberculosis (MTB Plus: <i>nrnz</i> , <i>IS6110</i> ; MTB: <i>nrnz</i> ): Sens 73% (MTB assay)/80% (MTB Plus assay), Spec 98% (MTB assay)/96% (MTB Plus assay) rifampicin (MTB-RIF Dx) ( <i>rpoB</i> ): Sens 84%, Spec 97%                                                                                                                                                                                                   | Tuberculosis (MTB Plus: <i>nrnz</i> , <i>IS6110</i> ) (MTB: <i>nrnz</i> ): 35 mins; rifampicin (MTB-RIF Dx) ( <i>rpoB</i> ): ~1 h                                                             | Initial diagnostic test for tuberculosis and rifampicin, replacing smear/culture and phenotypic drug susceptibility testing for pulmonary tuberculosis (conditional)                                                                                                                                                                                                                                                                                                                              |
| <b>Moderate complexity automated nucleic acid amplification tests</b> |                                                                                                                                                                                                                                                   |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Roche cobas MTB or MTB-RIF/INH                                        | Tuberculosis (MTB) (16S rRNA, 5 <i>esx</i> genes); rifampicin (MTB-RIF/INH, <i>rpoB</i> ); isoniazid (MTB-RIF/INH, <i>inhA</i> promoter, <i>katG</i> )                                                                                            | 8.8 cfu/mL                                       | Tuberculosis (MTB, 16S rRNA, 5 <i>esx</i> genes): Sens 93% (MTB assay), Spec 97% (MTB assay); rifampicin (MTB-RIF/INH, <i>rpoB</i> ): Sens 91–100%, Spec 96–100%; isoniazid (MTB-RIF/INH, <i>inhA</i> promoter, <i>katG</i> ): Sens 80–97%, Spec 97–98%;                                                                                                                                                                     | Tuberculosis (MTB, 16S rRNA, 5 <i>esx</i> genes): <3.5 h for first 96 samples; rifampicin (MTB-RIF/INH: <i>rpoB</i> ) and isoniazid (MTB-RIF/INH: <i>inhA</i> promoter, <i>katG</i> ): <3.5 h | Initial diagnostic test for tuberculosis and rifampicin, isoniazid, replacing culture and phenotypic drug susceptibility testing for pulmonary tuberculosis (conditional)                                                                                                                                                                                                                                                                                                                         |
| Becton Dickinson MAX MDR-TB                                           | Tuberculosis ( <i>IS6110</i> , <i>IS1081</i> , <i>devR</i> ); rifampicin ( <i>rpoB</i> ); isoniazid ( <i>inhA</i> promoter, <i>katG</i> )                                                                                                         | 0.5 cfu/mL                                       | Tuberculosis ( <i>IS6110</i> , <i>IS1081</i> , <i>devR</i> ): Sens 93%, Spec 95%; rifampicin ( <i>rpoB</i> ): Sens 99%, Spec 98%; isoniazid ( <i>inhA</i> promoter, <i>katG</i> ): Sens 90%, Spec 100%                                                                                                                                                                                                                       | <4 h                                                                                                                                                                                          | Initial diagnostic test for tuberculosis and rifampicin, isoniazid, replacing culture and phenotypic drug susceptibility testing for pulmonary tuberculosis (conditional)                                                                                                                                                                                                                                                                                                                         |
| Bruker-Hain Diagnostics FluoroType MTB or MTBDR                       | Tuberculosis (MTB: <i>IS6110</i> ; MTBDR: <i>rpoB</i> ); rifampicin (MTBDR) ( <i>rpoB</i> ); isoniazid (MTBDR: <i>inhA</i> promoter, <i>katG</i> )                                                                                                | 15 cfu/mL (MTB)<br>20 cfu/mL (MTBDR)             | Sens 91% (MTB assay)/92% (MTBDR assay), Spec 98% (MTB assay)/99% (MTBDR assay) rifampicin (MTBDR, <i>rpoB</i> ): Sens 97–100%, Spec 95–100%; isoniazid (MTBDR, <i>inhA</i> promoter, <i>katG</i> ): Sens 70–92%, Spec 99–100%                                                                                                                                                                                                | <3 h                                                                                                                                                                                          | Initial diagnostic test for tuberculosis and rifampicin, isoniazid, replacing culture and phenotypic drug susceptibility testing for pulmonary tuberculosis (conditional)                                                                                                                                                                                                                                                                                                                         |
| Abbott RealTime MTB and MTB RIF/INH                                   | Tuberculosis (MTB: <i>IS6110</i> , <i>pab</i> ); rifampicin (MTB RIF/INH: <i>rpoB</i> ); isoniazid (MTB RIF/INH: <i>inhA</i> promoter, <i>katG</i> )                                                                                              | 17 cfu/mL                                        | Tuberculosis (MTB: <i>IS6110</i> , <i>pab</i> ): Sens 96%, Spec 98%; rifampicin (MTB RIF/INH: <i>rpoB</i> ): Sens 94%, Spec 99%; isoniazid (MTB RIF/INH: <i>inhA</i> promoter, <i>katG</i> ): Sens 89%, Spec 98%                                                                                                                                                                                                             | <8 h for 48 samples; <10 h for 96 samples                                                                                                                                                     | Initial diagnostic test for tuberculosis and rifampicin, isoniazid, replacing culture and phenotypic drug susceptibility testing for pulmonary tuberculosis (conditional)                                                                                                                                                                                                                                                                                                                         |

(Table 2 continues on next page)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Detection (gene target)*                                                                                                                                                                                                                                                                                                                                                                                                        | Approximate limit of detection for tuberculosis† | Diagnostic performance for detection in sputum‡                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Time to result | WHO recommendation                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (Continued from previous page)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                                                                                                                                                                                                                                          |
| High complexity reverse hybridization-based nucleic acid amplification tests                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                                                                                                                                                                                                                                          |
| Hain Lifescience/ Bruker MTBDRplus v1 and v2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Tuberculosis (undefined); rifampicin ( <i>rpoB</i> ); isoniazid ( <i>inhA</i> promoter, <i>katG</i> )                                                                                                                                                                                                                                                                                                                           | 160 cfu/mL                                       | Tuberculosis (undefined): NA; rifampicin ( <i>rpoB</i> ): Sens 96–97%, Spec 98%; isoniazid ( <i>inhA</i> promoter, <i>katG</i> ): Sens 88–95%, Spec 98–99%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ≥5 h           | Initial diagnostic test for rifampicin, isoniazid, replacing phenotypic drug susceptibility testing for smear-positive sputum specimens or cultured tuberculosis isolates (conditional)                                                  |
| Hain Lifescience/ Bruker MTBDRsl v1 and v2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Tuberculosis (undefined); fluoroquinolone (v1: <i>gyrA</i> ; v2: <i>gyrA</i> , <i>gyrB</i> ); amikacin (v1: <i>rrs</i> ; v2: <i>rrs</i> , <i>eis</i> promoter)                                                                                                                                                                                                                                                                  | 150 cfu/mL                                       | Tuberculosis (undefined): NA; fluoroquinolone (v1: <i>gyrA</i> ; v2: <i>gyrA</i> , <i>gyrB</i> ): Sens 86%, Spec 99%; amikacin (v1: <i>rrs</i> ; v2: <i>rrs</i> , <i>eis</i> promoter): Sens 87%, Spec 100%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ≥5 h           | In those with bacteriologically confirmed rifampicin-resistant pulmonary tuberculosis, test for fluoroquinolone and amikacin, replacing phenotypic drug susceptibility testing (conditional)                                             |
| Nipro Genoscholar NTM and MDRTB II                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nontuberculous mycobacteria (various); tuberculosis (undefined); rifampicin ( <i>rpoB</i> ); isoniazid ( <i>inhA</i> promoter, <i>katG</i> )                                                                                                                                                                                                                                                                                    | Undefined                                        | Nontuberculous mycobacteria (various) and tuberculosis (undefined): NA; rifampicin ( <i>rpoB</i> ): Sens 75–100%, Spec 97–100%; isoniazid ( <i>inhA</i> promoter, <i>katG</i> ): Sens 50–95%, Spec 97–98%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | ≥5 h           | Initial diagnostic test for rifampicin, isoniazid, replacing phenotypic drug susceptibility testing for smear-positive sputum specimens or cultured tuberculosis isolates (conditional)                                                  |
| Nipro Genoscholar PZA-TB II                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Pyrazinamide ( <i>pncA</i> , <i>pncA</i> promoter)                                                                                                                                                                                                                                                                                                                                                                              | Undefined                                        | Insufficient data for sputum (Sens 81%, Spec 98% for isolates)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | ≥5 h           | Use on tuberculosis culture isolates for detection of pyrazinamide resistance, replacing phenotypic drug susceptibility testing (conditional)                                                                                            |
| Targeted next-generation sequencing solutions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                                                                                                                                                                                                                                          |
| Genoscreen Deeplex Myc-TB; Oxford Nanopore Technologies NanoTB; ShengTing Biotech Tbseq                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Rifampicin ( <i>rpoB</i> ); isoniazid ( <i>inhA</i> promoter, <i>katG</i> , <i>ahpC</i> , <i>fabG1</i> ); ethambutol ( <i>embB</i> ); pyrazinamide ( <i>pncA</i> , <i>pncA</i> promoter); fluoroquinolone ( <i>gyrA</i> , <i>gyrB</i> ); bedaquiline ( <i>Rv0678</i> ); linezolid ( <i>rrl</i> , <i>rplC</i> ); clofazimine ( <i>Rv0678</i> ); amikacin ( <i>rrs</i> ); streptomycin ( <i>gidB</i> , <i>rrs</i> , <i>rpsL</i> ) | Undefined                                        | Rifampicin ( <i>rpoB</i> ) and isoniazid ( <i>inhA</i> promoter, <i>katG</i> , <i>ahpC</i> , <i>fabG1</i> ) and ethambutol ( <i>embB</i> ): Sens ≥95%, Spec ≥96%; pyrazinamide ( <i>pncA</i> , <i>pncA</i> promoter): Sens 88%, Spec ≥96%; fluoroquinolone ( <i>gyrA</i> , <i>gyrB</i> ): Sens 94 to ≥95%, Spec ≥96%; bedaquiline ( <i>Rv0678</i> ): Sens 68%, Spec ≥95% (in rifampicin-resistant patients); linezolid ( <i>rrl</i> , <i>rplC</i> ): Sens 69%, Spec ≥95% (in rifampicin-resistant patients); clofazimine ( <i>Rv0678</i> ): Sens 70%, Spec ≥95% (in rifampicin-resistant patients); amikacin ( <i>rrs</i> ): Sens 87%, Spec ≥95% (in rifampicin-resistant patients); streptomycin ( <i>gidB</i> , <i>rrs</i> , <i>rpsL</i> ): undefined | 1–3 days       | Use to detect drug resistance after tuberculosis diagnosis to guide DR-TB treatment regimen selection, but does not replace current WHO recommended diagnostics, and phenotypic drug susceptibility testing still required (conditional) |
| DR-TB=drug-resistant tuberculosis. NA=not applicable. Sens=sensitivity. Spec=sensitivity. *Only gene targets for Genoscreen Deeplex Myc-TB kit are listed, as other targeted next-generation sequencing solutions have undefined gene targets. †The limit of detection of each assay for <i>Mycobacterium tuberculosis</i> is only included for reference, as these estimates are not directly comparable across assays unless the same materials and methods are used for all assays to determine the limit of detection (eg, the limit of detection of the Xpert MTB/RIF and Xpert MTB/RIF Ultra assays were determined in the same experiment, increasing confidence in the comparison of these limit of detections). The limit of detection for resistance determination for each assay was not included as these estimates vary not only based upon materials and methods used, but also the genetic sequence and mutations present, although in general these limit of detections are higher for resistance analytes than for <i>M tuberculosis</i> detection analytes as they are generally based upon a single <i>M tuberculosis</i> genetic target (eg, <i>rpoB</i> ) as opposed to multicopy targets (eg, <i>IS6110</i> ). ‡Performance metrics were taken from the WHO consolidated guidelines on tuberculosis (Module 3: Diagnosis), <sup>49</sup> unless otherwise stated; microbiological reference standards were used for all evaluations. |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                                                                                                                                                                                                                                          |
| Table 2: Summary performance characteristics of WHO-recommend molecular diagnostics for DR-TB detection by class and assay                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                                                                                                                                                                                                                                          |

Table 2: Summary performance characteristics of WHO-recommend molecular diagnostics for DR-TB detection by class and assay

susceptibility testing for all tuberculosis patients.<sup>4</sup> To date, WHO has reviewed and recommended three classes of rapid molecular technologies for diagnosing resistance to tuberculosis drugs, including low-complexity and moderate-complexity automated nucleic acid amplification tests and high-complexity reverse hybridisation-based nucleic acid amplification tests.<sup>49</sup> These rapid molecular assays all improve upon the time-to-result of growth-based drug susceptibility testing methods and demonstrate high diagnostic performance for included drug compounds, offering an array of options for tuberculosis and resistance detection suitable for various clinical settings (table 2).<sup>49–58</sup> When selecting

appropriate DR-TB diagnostics for implementation, national tuberculosis programmes must consider not only assay performance characteristics such as diagnostic sensitivity, specificity, and turnaround time, but also epidemiological variables that could impact assay performance, including patient population characteristics, drug resistance prevalence, and current regimens in use. South Africa, for example, is considered a high-burden country for not only DR-TB but also HIV-associated tuberculosis.<sup>2</sup> Populations co-infected with HIV and tuberculosis present a specific diagnostic challenge given that concurrent HIV infection is associated with sputum smear-negative disease and a

high proportion of extrapulmonary tuberculosis.<sup>59</sup> In these settings, platforms accepting both sputum and non-sputum sample types (eg, Xpert stool) for *M tuberculosis* detection and resistance profiling are preferred.<sup>60</sup> Although the scale-up of urine liparabinomannan testing in HIV-endemic settings such as South Africa has narrowed the diagnostic gap for extrapulmonary tuberculosis, it has undermined efforts to enhance tuberculosis drug resistance detection.

In 2021, WHO introduced a new pre-XDR-TB definition and an updated XDR-TB definition.<sup>61</sup> These changes have important implications for diagnostic strategies and algorithms, primarily driven by a recommendation that all individuals with MDR-TB or RR-TB undergo drug resistance testing for fluoroquinolones. However, in 2022, only 46% of MDR-TB and RR-TB cases were tested for fluoroquinolone resistance globally, and 36% in Africa.<sup>2</sup> When fluoroquinolone resistance is identified, further testing for resistance to other Group A (appendix p 12) drugs like bedaquiline and linezolid is necessary. Globally, including in most African countries, the adoption of this practice was below 20%, highlighting the significant diagnostic gap resulting from the absence of an upfront comprehensive resistance profiling tool.<sup>2</sup> The 2023 WHO recommendation of the BPaL, bedaquiline–pretomanid–linezolid–moxifloxacin (BPaL-M), or BPaL-L regimen as first-line treatment of MDR-TB and RR-TB underscored the urgency to bridge these diagnostic gaps. This therapeutic shift will likely require upfront reflex bedaquiline drug susceptibility testing in all newly diagnosed MDR-TB and RR-TB cases. Enhancing access to these diagnostic services and ensuring timely results for informing clinical decisions is essential.

South Africa has the longest-running molecular diagnostic programme using the Xpert MTB/RIF platform for tuberculosis diagnosis and detection of rifampicin resistance, and the line probe assays for further reflex resistance characterisation of other drugs including isoniazid, fluoroquinolones, and second-line injectables. Several advances have since been made, including implementation of the Xpert MTB/XDR test, a low-complexity assay for rapid isoniazid, fluoroquinolone, and amikacin resistance detection. This assay detects isoniazid mono-resistant tuberculosis and provides fluoroquinolone susceptibility, informing BPaL-M (or BPaL-L) treatment eligibility. The Xpert MTB/XDR offers similar operational characteristics as the Xpert MTB/RIF assay, with the potential to be run on the same reagent-treated sputum sample from the upfront Xpert MTB/RIF or Ultra assay if tested within 4 h, and has 93% sensitivity for fluoroquinolone resistance detection.<sup>62</sup> The revised South African DR-TB management guideline supports the collection of a second sputum sample following RIF-resistance detection by upfront low complexity (ie, Xpert) or moderate complexity (ie, Cobas [Roche Diagnostics, Rotkreuz, Switzerland] or BD Max [Becton Dickinson, NJ, USA]) automated nucleic acid amplification tests at

peripheral healthcare centres or central laboratories, respectively. Xpert MTB/XDR is then performed on this second sample, favouring an indirect reflex use case of the Xpert MTB/XDR assay over direct reflex testing.<sup>63</sup> Impact data for implementing the Xpert MTB/XDR assay in these different diagnostic algorithms, including direct reflex testing, is forthcoming.

The treatment of MDR-TB and RR-TB has been progressively transformed by the introduction of bedaquiline, which has significantly improved outcomes and reduced mortality.<sup>64</sup> Hence, resistance to bedaquiline could threaten the high levels of efficacy associated with bedaquiline-containing regimens and might precipitate the return to the high rates of drug toxicity, drug discontinuation, and attrition from care seen in the pre-bedaquiline era.<sup>42,65,66</sup> Published literature shows pre-treatment prevalence rates of bedaquiline resistance varying from 2% in fluoroquinolone-susceptible isolates, 7% in fluoroquinolone-resistant isolates, and up to 21% in patients with linezolid resistance or a history of previous bedaquiline or clofazimine exposure.<sup>42,67</sup> Alarming, emergent bedaquiline resistance is found in approximately 40% of patients in whom a bedaquiline-containing regimen has failed, making it crucial to minimise the risk of treatment failure during programmatic implementation of bedaquiline-based therapy.<sup>65</sup> Current methods for detecting resistance to the BPaL drugs are limited to phenotypic drug susceptibility testing, as genetic targets often span multiple genes without a clear genetic hotspot.<sup>68</sup> Nevertheless, genetic hotspots for bedaquiline and linezolid are emerging, suggesting that sequencing technologies might be the only viable rapid drug susceptibility testing solution for the near future.<sup>69–71</sup> However, sequencing is computationally intense, has not yet been evaluated for real-time application, excludes repeat regions of the genome, misses genome deletions, and has suboptimal performance on paucibacillary direct patient samples. In 2023, WHO recommended targeted next-generation sequencing as a diagnostic solution for three of the four BPaL-M drugs (fluoroquinolones, bedaquiline, and linezolid).<sup>64</sup> South Africa, like most African countries, currently relies on phenotypic methods for bedaquiline, pretomanid, and linezolid, making timely pre-treatment drug susceptibility testing impossible and necessitating the initiation of treatment without drug susceptibility testing data. Although targeted next-generation sequencing showed excellent turnaround time and performance for fluoroquinolones (sensitivity and specificity ≥95%), its sensitivity was lower for bedaquiline (68%) and linezolid (69%).<sup>50</sup> Specificity was excellent for linezolid (100%) but lower for bedaquiline (97%),<sup>50</sup> necessitating careful consideration of pre-test resistance probability. If targeted next-generation sequencing performed at centralised facilities can provide results within a week, conducting targeted next-generation sequencing on concentrated sputum pellets would be a

suitable option, removing the need for the Xpert MTB/XDR test and allowing for follow-up phenotypic drug susceptibility testing when necessary. Phenotypic drug susceptibility testing remains essential for detecting resistance to pretomanid and delamanid, and when targeted next-generation sequencing fails—a scenario that could occur in approximately 10% of cases, primarily in low bacterial load samples. Moreover, as new drugs are discovered and added to tuberculosis treatment, phenotypic drug susceptibility testing will continue to be invaluable for defining resistance and understanding the genetic basis of resistance, particularly when combined with whole-genome sequencing. The WHO catalogue of mutations utilises this combination and serves as a reference source to facilitate new drug resistance diagnostic developments and interpretation of mutation data.<sup>72</sup> The most recent version includes resistance-associated variants for bedaquiline (19), linezolid (eight), and pretomanid (six).<sup>71,72</sup> This signifies major progress towards identifying high-confidence *M. tuberculosis* genetic markers of phenotypic resistance, which could be used to accelerate the development of new and improved molecular assays for comprehensive detection of resistance to tuberculosis drugs.<sup>72</sup> Although whole-genome sequencing remains an important reference test, the requirement of a culture isolate remains a significant limitation; hence, targeted next generation sequencing performed on direct patient samples represents an attractive diagnostic solution. Finally, the full value of these technologies can only be realised if all individuals with bacteriologically confirmed tuberculosis are tested for rifampicin resistance; currently, a significant proportion remains untested, with figures at 30% globally and 35% in Africa. Uptake of WHO-recommended rapid diagnostics is expected in the coming years following the release of the WHO standards on universal access to diagnostics, the reduction in pricing of some tests, the increase in the number of manufacturers competing in this space, and the current pace of innovation in diagnostic tests.<sup>73–75</sup>

## Treatment of DR-TB

### Novel, all-oral regimens for DR-TB

New drugs such as bedaquiline, delamanid, and pretomanid have made it possible to develop all-oral short-course regimens for DR-TB.<sup>76</sup> However, managing DR-TB remains complex due to factors such as HIV co-infection, diabetes, low BMI, extensive lung disease, and substance abuse. Additionally, complex resistance patterns limit the available options of active DR-TB drugs for constructing effective treatment regimens (appendix pp 6–13).

Several studies evaluating novel DR-TB regimens showed substantially improved DR-TB treatment outcomes with reduced toxicity compared with historical regimens. The NiX-TB trial (NCT02333799) assessed the efficacy of bedaquiline, linezolid, and pretomanid in

patients with pulmonary XDR-TB and non-responsive MDR-TB, and showed favourable outcomes in 90% of patients following 6 months of treatment, with durable relapse-free survival over 24 months.<sup>77</sup> Sputum culture conversion occurred within 2 months of treatment initiation; however, high rates of adverse events, including peripheral neuropathy in 81% and myelosuppression in 48%, were observed. Given that linezolid was the primary contributor to these adverse events, the ZeNix trial (NCT03086486) evaluated various dose and duration strategies for linezolid and found that a daily 600 mg dose for 26 weeks was as effective as 1200 mg for 26 weeks but with fewer adverse events, dose modifications, and treatment discontinuations.<sup>78</sup> The TB-PRACTECAL study (NCT02589782) compared unfavourable outcomes among patients receiving 6 months of BPAL versus BPAL plus clofazimine (BPAL-C) versus BPAL-M, and showed unfavourable outcomes in 11.3% for BPAL-M, 18.8% for BPAL-C, 23.3% for BPAL, and 48.5% in the control group who received the locally accepted standard of care.<sup>79</sup> Furthermore, significant toxicity was more common in the control group (58.9%), compared with the BPAL-C group (31.9%), the BPAL group (21.7%), and the BPAL-M group (19.4%). The dose of bedaquiline used in these pivotal trials varied. Patients in the TB-PRACTECAL trial received 400 mg daily for 2 weeks, followed by 200 mg three times per week for 22 weeks, and patients in the ZeNix trial received a simplified regimen of 200 mg daily for 8 weeks, followed by 100 mg daily for 18 weeks. Importantly, the TB-PRACTECAL study also suggests that linezolid exposure could be reduced further without compromising efficacy, using a dose of 600 mg daily for 16 weeks and 300 mg daily for 8 weeks. The SimpliciTB trial (NCT03338621) performed an exploratory, non-comparative evaluation of the safety and efficacy of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in patients with DR-TB.<sup>80</sup> The study found that 17% of patients with DR-TB had unfavourable outcomes, mainly due to high rates of hepatotoxicity and drug discontinuation caused by the combination of pretomanid and pyrazinamide. A complete list of clinical trials that have evaluated or are currently evaluating all-oral, short-course regimens for DR-TB is provided in table 3.

The 6 month BPAL and BPAL-M regimens are not approved for use in the following patient groups: DR-TB involving the CNS, osteoarticular tuberculosis or disseminated tuberculosis, women who are pregnant or breastfeeding, and patients with more than 1 month of previous exposure to bedaquiline, linezolid, pretomanid, or delamanid. Therapeutic strategies for these groups are urgently required, especially for patients with severe forms of extrapulmonary tuberculosis, which are associated with poorer outcomes.<sup>81</sup> Instead of the more extended 18 month regimen, WHO also supports the use of a 9-month all-oral regimen consisting of bedaquiline,

levofloxacin or moxifloxacin, and linezolid combined with other drugs (ie, ethambutol, pyrazinamide, high-dose isoniazid, and clofazimine) for treating fluoroquinolone-susceptible DR-TB in adults with non-severe forms of tuberculosis and who have not had previous exposure to the component drugs. Switching to an individualised 18 month regimen, based on the WHO drugs groups, is recommended by the South African treatment guidelines in the following circumstances: identification of resistance

to bedaquiline (most common reason), pretomanid, or linezolid; a positive culture at month 4 whether due to delayed culture conversion or reversion; premature and permanent discontinuation of bedaquiline, linezolid, or pretomanid due to toxicity; or if a patient deteriorates clinically or does not improve on a shorter regimen. Comprehensive drug susceptibility testing data and discussion with local experts should closely guide the composition of such a regimen.

|                   | Regimen                                                                                                                                                                                                                                                                                                                              | Focus                                                                                                                                                                     | Phase | Location                                                                           | Status                       | Clinical trial number |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|------------------------------------------------------------------------------------|------------------------------|-----------------------|
| Nix-TB            | BPaL                                                                                                                                                                                                                                                                                                                                 | Safety and efficacy of BPaL in pulmonary DR-TB                                                                                                                            | 3     | South Africa                                                                       | Completed                    | NCT02333799           |
| ZeNix             | BPaL regimen but lower dose and shorter duration of linezolid                                                                                                                                                                                                                                                                        | Various doses and durations of BPaL in DR-TB                                                                                                                              | 3     | Georgia, Moldova, Russia, and South Africa                                         | Completed                    | NCT03086486           |
| mBPAL             | BPaL regimen based on Nix-TB and ZeNix; modification in linezolid doses                                                                                                                                                                                                                                                              | Modified BPaL regimen for managing pre-extensively drug-resistant tuberculosis and MDR-TB                                                                                 | 3     | India                                                                              | Recruiting                   | NCT05040126           |
| TB Practecal      | Bedaquiline, clofazimine, linezolid, moxifloxacin, and pretomanid                                                                                                                                                                                                                                                                    | Pragmatic clinical trial for a more effective concise and less toxic MDR-tuberculosis treatment regimen                                                                   | 2–3   | Belarus, South Africa, and Uzbekistan                                              | Completed                    | NCT02589782           |
| SimpliciTB        | Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide                                                                                                                                                                                                                                                                              | Efficacy, safety, and tolerability of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in DS-TB and DR-TB                                                          | 2–3   | Brazil, Georgia, Malaysia, Russia, South Africa, Tanzania, Philippines, and Uganda | Completed                    | NCT03338621           |
| MDR-END           | Delamanid, levofloxacin, linezolid, and pyrazinamide                                                                                                                                                                                                                                                                                 | Treatment shortening of MDR-TB using existing and new drugs                                                                                                               | 2     | South Korea                                                                        | Unknown status               | NCT02619994           |
| TB TRUST          | Cycloserine, levofloxacin, linezolid, and pyrazinamide (or clofazimine if resistant to the latter)                                                                                                                                                                                                                                   | Refining MDR-TB treatment regimens for ultra short therapy                                                                                                                | 4     | China                                                                              | Active, not recruiting       | NCT03867136           |
| BEAT-tuberculosis | Bedaquiline, delamanid, linezolid plus clofazimine or levofloxacin                                                                                                                                                                                                                                                                   | Building evidence for advancing new treatment for rifampicin resistant tuberculosis comparing a short course of treatment with the current South African standard of care | 3     | South Africa                                                                       | Active, not recruiting       | NCT04062201           |
| DRAMATIC          | Bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine                                                                                                                                                                                                                                                                     | Efficacy and tolerability of drugs to treat MDR-TB                                                                                                                        | 2     | Philippines and Viet Nam                                                           | Recruiting                   | NCT03828201           |
| Beat-TB India     | Bedaquiline, delamanid, linezolid, and clofazimine                                                                                                                                                                                                                                                                                   | Efficacy and safety of a combination regimen of bedaquiline, delamanid, linezolid, and clofazimine pre-extensively drug-resistant tuberculosis and extensively DR-TB      | None  | India                                                                              | Fully enrolled               | CTRI/2019/01/017310   |
| STREAM Stage 1    | Kanamycin, clofazimine, moxifloxacin, ethambutol isoniazid, pyrazinamide, and protionamide                                                                                                                                                                                                                                           | Evaluation of standard WHO MDR-TB regimen with 9-month modified Bangladesh regimen                                                                                        | 3     | Ethiopia, Mongolia, South Africa, and Viet Nam                                     | Completed                    | ISRCTN78372190        |
| STREAM Stage 2    | Bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide, isoniazid, and protionamide                                                                                                                                                                                                                                        | Evaluation of a 6 month (containing an injectable) and 9 month (all oral) bedaquiline-containing regimen versus the WHO and Bangladesh regimen                            | 2     | Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda              | Fully enrolled; in follow-up | NCT02409290           |
| InDEX             | Gene-derived individualised DR-TB regimen versus standard tuberculosis regimen                                                                                                                                                                                                                                                       | Individualised MDR-TB treatment strategy to improve treatment outcomes                                                                                                    | 4     | South Africa                                                                       | Terminated                   | NCT03237182           |
| endTB             | Bedaquiline, moxifloxacin, linezolid, and pyrazinamide; or bedaquiline, clofazimine, levofloxacin, linezolid, and pyrazinamide; or bedaquiline, delamanid, levofloxacin linezolid, and pyrazinamide; or delamanid, clofazimine, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, moxifloxacin, and pyrazinamide | Evaluating newly approved drugs for MDR-TB                                                                                                                                | 3     | Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa              | Completed                    | NCT02754765           |
| GRACE-TB          | Individualised regimen dictated by outcomes of rapid molecular drug susceptibility tests                                                                                                                                                                                                                                             | NGS-guided regimens of anti-tuberculosis drugs for the control and eradication of MDR-TB                                                                                  | None  | China                                                                              | Not yet recruiting           | NCT03604848           |
| FS-1 Trial        | Randomised, placebo-controlled study of safety and therapeutic efficacy of the drug FS-1 in the oral dosage form in DR-TB                                                                                                                                                                                                            | Randomised, placebo-controlled study of safety and therapeutic efficacy of the drug FS-1 in the oral dosage form in DR-TB                                                 | 3     | Kazakhstan and Kyrgyzstan                                                          | Enrolling participants       | NCT02607449           |

(Table 3 continues on next page)

| Regimen                                                                                                                                                                                       |                                                                                                                     | Focus                                                                                                                                                                                                                                                | Phase | Location                                                                          | Status                                   | Clinical trial number |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------|------------------------------------------|-----------------------|
| (Continued from previous page)                                                                                                                                                                |                                                                                                                     |                                                                                                                                                                                                                                                      |       |                                                                                   |                                          |                       |
| STAND                                                                                                                                                                                         | Moxifloxacin, pretomanid, and pyrazinamide                                                                          | Evaluating the efficacy, safety, and tolerability of moxifloxacin, pretomanid, and pyrazinamide after 4 and 6 months of DS-TB treatment, and after 6 months of MDR-TB treatment in adults with MDR-TB: shortening treatment by advancing novel drugs | 3     | Georgia, Kenya, South Africa, Tanzania, Uganda, Malaysia, Philippines, and Zambia | Completed                                | NCT02342886           |
| NC-005                                                                                                                                                                                        | Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide                                                             | Evaluate the efficacy, safety, and tolerability of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide in adults with DS-TB or MDR-TB                                                                                                            | 2     | South Africa, Tanzania, and Uganda                                                | Completed                                | NCT02193776           |
| ACTG5343                                                                                                                                                                                      | Bedaquiline, delamanid, and dolutegravir                                                                            | Evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination for DR-TB                                                                                                                           | 2     | Peru and South Africa                                                             | Enrolling participants                   | NCT02583048           |
| Opti-Q                                                                                                                                                                                        | Levofloxacin                                                                                                        | Study of the efficacy and tolerability of levofloxacin in combination with an optimised background regimen in MDR-TB                                                                                                                                 | 2     | Peru and South Africa                                                             | Completed                                | NCT01918397           |
| Janssen Japan Trial                                                                                                                                                                           | Bedaquiline                                                                                                         | Safety, efficacy, and pharmacokinetics of TMC207 in MDR-TB                                                                                                                                                                                           | 2     | Japan                                                                             | Enrolling participants                   | NCT02365623           |
| Otsuka 213                                                                                                                                                                                    | Delamanid and optimised background regimen                                                                          | Evaluate the safety and efficacy of daily oral delamanid for 6 months in MDR-TB                                                                                                                                                                      | 3     | Estonia, Latvia, Lithuania, Moldova, Peru, Philippines, and South Africa          | Recruitment completed; follow-up ongoing | NCT01424670           |
| NeXT                                                                                                                                                                                          | Linezolid, bedaquiline, levofloxacin, pyrazinamide, isoniazid, ethionamide, terizidone, moxifloxacin, and kanamycin | Evaluating a new treatment regimen for MDR-TB                                                                                                                                                                                                        | 2–3   | South Africa                                                                      | Completed                                | NCT02454205           |
| China PZA Trial                                                                                                                                                                               | Pyrazinamide-containing regimen versus no pyrazinamide regimen                                                      | Optimisation of MDR-TB regimen based on the molecular drug susceptibility results of pyrazinamide                                                                                                                                                    | 3     | China                                                                             | Unknown                                  | NCT02120638           |
| BPaL=bedaquiline, pretomanid, and linezolid. DR-TB=drug-resistant tuberculosis. DS-TB=drug-susceptible tuberculosis. MDR-TB=multidrug-resistant tuberculosis. NGS=next-generation sequencing. |                                                                                                                     |                                                                                                                                                                                                                                                      |       |                                                                                   |                                          |                       |
| Table 3: Global clinical trials assessing safety and efficacy of novel DR-TB regimens                                                                                                         |                                                                                                                     |                                                                                                                                                                                                                                                      |       |                                                                                   |                                          |                       |

### Pregnant women with DR-TB

Pregnant and postpartum women, especially those living with HIV, are at increased risk of tuberculosis and DR-TB.<sup>82–84</sup> Effective treatment is crucial as maternal tuberculosis increases the risks of TB-related hospitalisation and death,<sup>85,86</sup> adverse pregnancy outcomes,<sup>85–87</sup> and vertical tuberculosis and HIV transmission to infants.<sup>85,88</sup> Although the recent development of novel, shortened, all-oral DR-TB regimens have improved treatment outcomes and are less toxic, the exclusion of pregnant women from participation in these clinical trials has resulted in insufficient drug safety data for supporting use in this important population.<sup>89</sup> Physiological changes in pregnancy affect tuberculosis drug absorption, distribution, and clearance, elevating the importance of generating data in this population to guide regimen composition, drug dosing, and safety monitoring strategies.<sup>90–93</sup>

In the largest published cohort of pregnant women treated with a bedaquiline-containing regimen for DR-TB in South Africa, 41 (71%) of 58 women had a successful treatment outcome, compared with 31 (62%) of 50 women who received a regimen without bedaquiline. Although low birth weight was reported in a higher proportion of bedaquiline-exposed infants compared with unexposed infants (45% vs 26%;  $p=0.034$ ),<sup>94</sup> by 12 months no significant weight difference was observed.

This study informed WHO guidelines on the treatment of pregnant women with RR-TB.<sup>95</sup> Similarly, a small South African case study found favourable maternal outcomes and birth outcomes in women treated with bedaquiline, delamanid, and linezolid.<sup>96</sup>

Trials such as the BEAT-tuberculosis trial and the TB-PRACTECAL study sought to establish the safety and efficacy of shortened all-oral regimens containing bedaquiline, pretomanid, and linezolid with or without moxifloxacin (BPAL and BPAL-M), and also excluded pregnant women. Nonetheless, 36 women who became pregnant during these studies continued with their pregnancies and achieved favourable maternal treatment and pregnancy outcomes.<sup>97,98</sup> Pregnant women are not presently eligible for BPAL or BPAL-M, but the data from BEAT-TB and TB-PRACTECAL support the use of 6 month all-oral regimens with Group A and B drugs (appendix p 12), together with delamanid.<sup>99</sup> Close monitoring of pregnant women receiving these novel DR-TB treatment regimens, the use of national pregnancy registries, and follow-up of infants will improve confidence in this approach.

### Socioeconomic impact of DR-TB

DR-TB imposes profound socioeconomic impacts on individuals, families, and communities.<sup>100–102</sup> The catastrophic costs and diminished quality of life

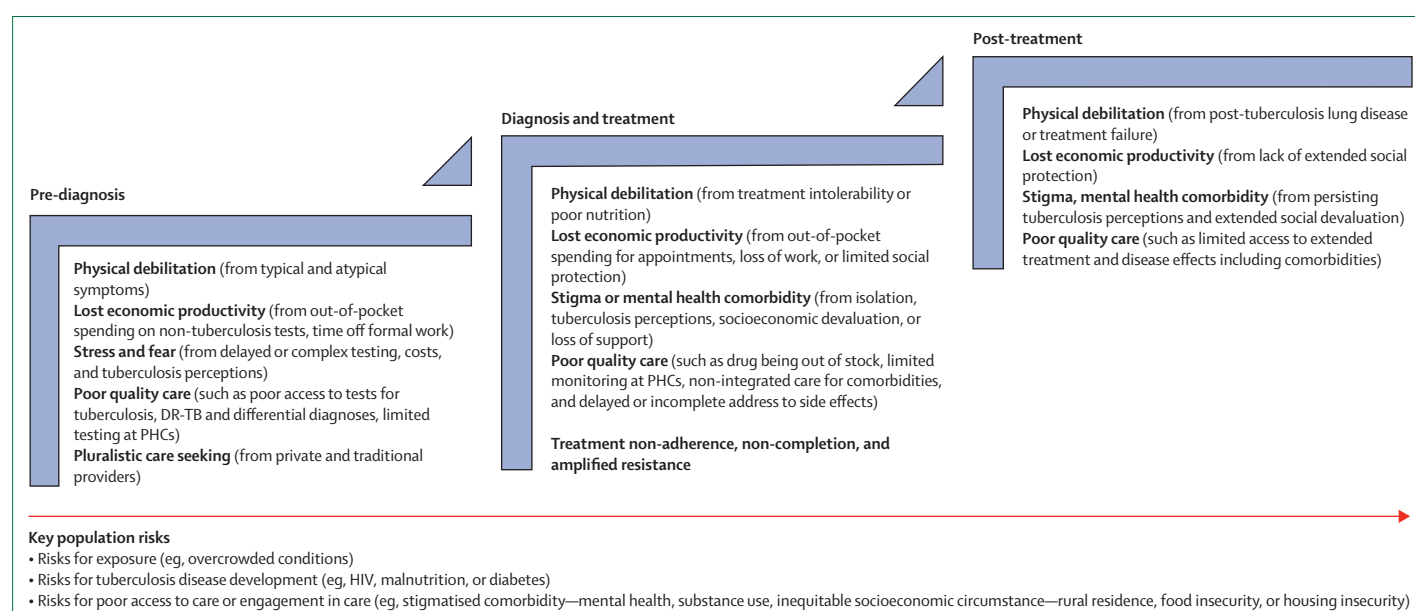
associated with DR-TB are often far greater than those observed in drug-susceptible disease and might persist for years after treatment completion.<sup>1,2,103,104</sup> Globally, 81% of families affected by DR-TB incur costs related to tuberculosis that exceed 20% of their household income.<sup>1,2</sup> In South Africa, these costs are far-reaching, tied to lost income from patients' inability to work and lost household productivity for patients and their caregivers. Out-of-pocket spending is largely incurred on nutritional supplements (including traditional medicine products), private medical and traditional healer consultations, and transport to health-care facilities.<sup>105,106</sup> Disability grants mitigate the effect of these expenses but are terminated during hospitalisation or, conversely, as patients' health improves during treatment, leaving families economically vulnerable in both instances.<sup>102,105,107</sup> Short-course regimens for MDR-TB (eg, BPAL) will probably reduce the burden on patients, their families, and health systems.<sup>107</sup> A patient's journey with DR-TB involves multiple phases, from symptom onset (pre-diagnosis), diagnosis, treatment initiation, adherence to multidrug therapy over a relatively long period, and resultant treatment failure or success. Each phase is laden with socioeconomic challenges for individuals and the health system (figure 2).

### Stigma and mental health comorbidity

People with DR-TB face heightened stigma and discrimination, discouraging positive health-seeking behaviour and leading to delays in diagnosis, reduced uptake of treatment, challenges to adherence, and higher rates of non-disclosure with associated avoidance of

infection control measures.<sup>100,101</sup> Public perceptions about the incurability and mortality of big TB, as it is occasionally referred to by South African patients, in contrast to drug-susceptible or regular tuberculosis, can provoke greater psychological distress, social avoidance and isolation, loss of social support, human rights violations, and gender-based violence.<sup>100,108</sup> Patients' inability to stay productive while still afflicted with convalescing symptoms of DR-TB and side effects of treatment can further diminish perception of their social value and increase their dependence on others. It is in these contexts of inequity that stigma becomes amplified.<sup>102,109</sup> Tuberculosis discrimination has been increasingly documented within the South African health, education, labour, and housing sectors,<sup>110,111</sup> calling for state-level intervention. However, most legal action still centres on involuntary treatment and quarantine to prevent DR-TB transmission, especially of extensively drug-resistant and programmatically incurable forms of the disease, as opposed to strengthening patient protections. There is growing recognition of the association between stigma and mental health in DR-TB.<sup>112</sup> The pooled prevalence of depression in people with DR-TB is estimated to be 52%.<sup>113</sup> Patients with mental illness display lower adherence and decreased rates of treatment completion in DR-TB. They are also more likely to have substance use disorders, leading to syndemic challenges.<sup>114</sup>

Despite an inclusive categorisation, national tuberculosis programmes have historically overlooked the intersectional key tuberculosis populations, particularly in low-resource, high-burden settings such as South Africa.



**Figure 2: Socioeconomic challenges along the journey of patients with multidrug-resistant tuberculosis**

The figure describes the diverse challenges (physical, psycho-emotional, socioeconomic, and structural) experienced at discrete stages (pre-diagnosis, diagnosis and treatment, and post-treatment) of the DR-TB patient journey. DR-TB=drug-resistant tuberculosis. PHC=primary health-care clinic.

The South African National Strategic Plan 2023–2028, Global Plan to End Tuberculosis 2023–2030, and WHO End Tuberculosis Strategy are now embracing the integration of key tuberculosis populations in programme planning and funding schemes.<sup>14,111,115</sup> Maximising equitable access to tuberculosis services and breaking down barriers such as poverty, stigma, discrimination, gender-based inequalities, and mental health through the promotion of human rights is deeply embedded into South Africa's National Strategic Plan for 2023–2028.<sup>14</sup>

### Improving patient support through DR-TB programmes

DR-TB programmes can play a crucial role in supporting patients throughout their complex journey. Decentralisation, counselling, and drug-susceptibility testing at point-of-care can support early diagnosis and prevent pre-treatment losses to follow-up.<sup>116</sup> Integrated, person-centred strategies encompassing programmatic, psychosocial, and material aids are essential for improving both treatment adherence and quality of life.<sup>117,118</sup> This requires concerted engagement with sectors outside of health, such as social welfare, housing, and transport, as well as traditional and private practitioners, community leaders and organisations, and civil society. Multisectoral engagement is increasingly recognised as crucial to tuberculosis elimination and building accountability within national tuberculosis responses.<sup>119</sup> Furthermore, policy frameworks that enable the integration of traditional medicine into the multisectoral tuberculosis response have been identified as a priority in South Africa.<sup>14</sup>

At the individual level, holistic and motivational approaches to patient education and counselling are shown to build health literacy, dispel misperceptions, counter stigma, and support adherence in DR-TB.<sup>120,121</sup> Incentive-based interventions such as cash transfers have been challenging to implement and garnered mixed levels of community acceptability, resulting in low or non-sustained impacts on patient journeys through care.<sup>122,123</sup> However, there is now clear evidence that the weight gain derived from nutritional interventions among undernourished patients is associated with reduced tuberculosis mortality<sup>124</sup> and that such interventions in households of index patients (people with infectious pulmonary tuberculosis) are associated with reduced tuberculosis incidence.<sup>125</sup>

In parallel, the health workforce must be sensitised to respond to patients' unique needs and vulnerabilities.<sup>110</sup> The constitution of the workforce can also expand; community health workers, peer educators, and traditional health practitioners have helped patients counter psychosocial barriers and navigate complexities throughout their journey in care.<sup>126–128</sup>

The current paradigm of perceiving an episode of tuberculosis as a discrete life event is challenged by estimates suggesting that an average of 3·6 potential years of life are lost after a fully treated episode of tuberculosis and that tuberculosis survivors bear an excess mortality

burden compared with the general population or matched controls.<sup>129,130</sup> Long-term respiratory deficits and reduced physical and mental health have been shown in people previously treated for DR-TB.<sup>131–133</sup> The emerging evidence on this historically neglected health burden suggests that clinical surveillance and psychosocial support beyond treatment completion should be incorporated into programmatic care.

### Differentiated service delivery for DR-TB

Differentiated service delivery models developed in HIV, which tailor services to meet individual patient needs while allocating scarce health system resources, present a feasible and acceptable approach to strengthen DR-TB programmes.<sup>134,135</sup> MDR-TB differentiated service delivery frameworks can intensify support for adherence-challenged subpopulations and relax the intensity of interaction with health-care services for people who require less support.<sup>135,136</sup> For people with less intensive needs, differentiated service delivery can involve home-based care, decentralised treatment centres, and community-based support. For patients with more severe challenges, integrated multimodal support might be beneficial, including counselling, support groups, referrals for mental health or harm reduction strategies, or other forms of social or financial support.<sup>136</sup> Health modalities such as electronic dose monitoring might be useful to assess adherence in real-time, predict treatment response, and empirically triage the intensity of support.<sup>137–139</sup> Differentiated service delivery programmes that offer evaluation and intervention at key stages and are tailored to the needs of adherence-challenged subpopulations could improve treatment outcomes in DR-TB.<sup>135</sup>

### Conclusion

Approximately 7% of deaths attributed to bacterial antimicrobial resistance in the WHO African region in 2019 were due to DR-TB.<sup>140</sup> Since then, the COVID-19 pandemic has severely reversed gains in tuberculosis case finding, treatment, and prevention. Alarming, for the first time in over a decade, there has been an increase in tuberculosis incidence and mortality.<sup>1,2</sup> Furthermore, DR-TB remains a major public health threat, especially to tuberculosis endemic settings, with its high associated mortality, high costs of treatment, occupational risk to health-care workers, and burden on local health-care systems, communities, and economies.

Only one in three patients with DR-TB requiring treatment receive it, highlighting the persistent gaps in DR-TB diagnosis, linkage to care, and therapeutic strategies. The effectiveness of treatment is dependent on access to comprehensive real-time drug susceptibility testing results. Despite advances in the development and availability of low-complexity nucleic acid amplification tests, the inability to generate near-point-of-care comprehensive susceptibility results directly from

sputum still necessitates the application of empiric regimens in most settings, highlighting the desperate need for further innovation in tuberculosis diagnostic technologies to safeguard contemporary therapeutic advances. Sequencing-based solutions, automated phenotypic susceptibility testing, and molecular tests require implementation data to inform context-appropriate diagnostic algorithms. Targeted evaluation of contacts of individuals with DR-TB could prevent future cases and avert DR-TB morbidity and mortality.

Major innovations in the therapeutic landscape have transformed the safety, efficacy, and impact of DR-TB pharmacotherapy. However, emergent resistance and its

amplification must be minimised by comprehensive resistance profiling, vigilance for treatment-emergent resistance, augmented adherence strategies, and strengthening tuberculosis programmes overall.

The socioeconomic impact of DR-TB is substantial and multifaceted, affecting patients, families, communities, and economies. DR-TB programmes must adopt patient-centred approaches, incorporate models, and work towards reducing the catastrophic costs, stigma, and discrimination associated with this disease. Many of the socioeconomic challenges facing patients require multisectoral approaches that extend beyond the walls of health facilities and which counselling and technology

### Panel: Research priorities for DR-TB control in South Africa

#### DR-TB prevention

- Identify interventions (including simple, efficacious, safe, and convenient preventative regimens) for close contacts of individuals with DR-TB, focusing on children aged younger than 5 years and people living with HIV
- Develop comprehensive TB prevention programmes which respond to the prevailing social and economic determinants of DR-TB in South Africa, which include poverty, housing insecurity, food insecurity, substance abuse, and unemployment
- Evaluating efficient decentralised models for contact tracing and active case finding for DR-TB suitable for the South African setting, which include digital chest radiograph screening, school-based screening, and community-based screening
- Measure rates of transmission of DR-TB within households, communities, and congregate settings
- Identify hotspots of DR-TB transmission to inform targeted approaches for screening activities and preventative strategies
- Establish the impact of active case finding, targeted screening, and preventive therapy on tuberculosis transmission in a high tuberculosis or HIV burden setting
- Develop safe and effective vaccines to prevent tuberculosis infection, ameliorate progression to disease, and as adjunct pharmacotherapy for DR-TB treatment shortening

#### DR-TB diagnostics

- Evaluate the feasibility, acceptability, cost-effectiveness, and impact of sequencing-based, molecular, and rapid phenotypic diagnostic solutions for comprehensive resistance profiling in pulmonary and extrapulmonary samples in tuberculosis and HIV endemic settings
- Understand the clinical significance and impact of heteroresistance, and improve the diagnostic and therapeutic capacity to combat heteroresistance
- Improve the understanding of genotypic-phenotypic relationships in TB drug resistance
- Develop a catalogue of locally prevalent high-confidence mutations to guide therapeutic decision-making and understand limitations of currently deployed molecular diagnostic tools

- Regional surveillance to understand the impact of regional migration patterns on the molecular epidemiology of DR-TB in South Africa

#### DR-TB treatment

- Identify and evaluate novel drug delivery systems, novel compounds, and diverse routes of drug delivery to optimise pharmacokinetic-pharmacodynamic relationships at the sites of disease
- Conduct platform trials (including adaptive designs) to improve the efficiency and pace of evaluation of novel drug compounds and regimens
- Evaluate strain-agnostic host-directed therapies, including adjunctive therapeutics, for shortening DR-TB treatment and improving outcomes
- Develop evidence-based treatment strategies for bedaquiline-resistant tuberculosis
- Develop biomarkers to measure bacillary burden and to determine response to DR-TB treatment
- Evaluate the impact of psychosocial, nutritional, and economic interventions on DR-TB treatment adherence and retention in care
- Evaluate the impact of alternate models of differentiated service delivery for DR-TB and HIV care on clinical outcomes
- Investigate novel formulations and regimens to improve the safety, tolerability, and acceptability of DR-TB treatment among children
- Establish the safety and efficacy of novel drugs, including an all-oral, shorter DR-TB regimen in pregnant and breastfeeding women
- Identify and scale-up impactful models for multisectoral engagements with civil society, faith-based organisations, traditional health practitioners, and community-based organisations to prevent the spread of DR-TB and to support the decentralised care of people with DR-TB
- Evaluate scalable models for implementing the WHO's framework for an integrated multisectoral response to tuberculosis, HIV, sexually transmitted infections, and hepatitis in South Africa, suitable for the WHO African Region

DR-TB=drug-resistant tuberculosis.

### Search strategy and selection criteria

Publications related to drug-resistant tuberculosis in Africa were identified by systematically searching Pubmed and Google Scholar from inception to Jan 20, 2024 with terms including (but not limited to) the following combinations: ["Drug-resistant tuberculosis" OR "Multidrug-resistant tuberculosis" OR "Extensively drug-resistant tuberculosis" OR "rifampicin-resistant tuberculosis"] AND ["epidemiology" OR "transmission" OR "diagnosis" OR "treatment" OR "pregnancy" OR "patient-centred" OR "socioeconomic" OR "challenges"]. All primary publications, case reports, and review articles were assessed for relevance and full text papers were obtained where the title and abstract were inconclusive for establishing suitability. Further publications were identified from references cited in relevant articles, reports, and conference proceedings. The search was restricted to English.

alone cannot resolve. There are opportunities to engage other groups more systematically in transforming normative perceptions and practices, including traditional and private practitioners, community leaders, community health workers, and peers. To adequately tackle the root structural barriers in DR-TB, social protections against loss of livelihood and legal recourse against potential human rights violations facing patients and their families are urgently needed.<sup>131</sup> By addressing DR-TB, global health initiatives can make significant progress toward achieving the sustainable development goals and advancing the wellbeing of individuals and societies worldwide.

To fulfil the potential of a tuberculosis-free world, much more progress is needed in developing an effective tuberculosis vaccine, implementing coordinated multi-pronged tuberculosis control interventions, mitigating the socioeconomic drivers of tuberculosis, and sustaining high levels of political will to bring new scientific advances to the field (panel).

### Contributors

All authors contributed equally to the manuscript's conception, writing, and review. The first drafts of each section were prepared as follows: Epidemiology (HC), Transmission (BM), Diagnosis (NI, SVO, and SBG), Treatment (KN, RP, ML, and NN), and Socioeconomic impact (MO and AD). KN and RP coordinated the writing activities of the authors. All authors approved the final version for submission and agree to be accountable for all aspects of the work.

### Declaration of interests

HC is a data and safety monitoring board member for the TRIAD study. AD is a Communities, Gender and Rights consultant for the Stop TB Partnership Secretariat, United Nations Office for Project Services. All other authors declare no competing interests.

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