The Lancet Respiratory Medicine Commission: 2019 update: Epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis

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***The Lancet Respiratory Medicine* Commission on drug-resistant tuberculosis was published in 2017, which comprehensively reviewed and provided recommendations on various aspects of the disease. Several key new developments regarding drug-resistant tuberculosis are outlined in this Commission Update. The WHO guidelines on treating drug-resistant tuberculosis were updated in 2019 with a reclassification of second line anti-tuberculosis drugs. An injection-free MDR tuberculosis treatment regimen is now recommended. Over the past 3 years, advances in treatment include the recognition of the safety and mortality benefit of bedaquiline, the finding that the 9–11 month injectable-based 'Bangladesh' regimen was non-inferior to longer regimens, and promising interim results of a novel 6 month 3-drug regimen (bedaquiline, pretomanid, and linezolid). Studies of explanted lungs from patients with drug-resistant tuberculosis have shown substantial drug-specific gradients across pulmonary cavities, suggesting that alternative dosing and drug delivery strategies are needed to reduce functional monotherapy at the site of disease. Several controversies are discussed including the optimal route of drug administration, optimal number of drugs constituting a regimen, selection of individual drugs for a regimen, duration of the regimen, and minimal desirable standards of antibiotic stewardship. Newer rapid nucleic acid amplification test platforms, including point-of-care systems that facilitate active case-finding, are discussed. The rapid diagnosis of resistance to other drugs, (notably fluoroquinolones), and detection of resistance by targeted or whole genome sequencing will probably change the diagnostic landscape in the near future.**

Introduction

Addressing the drug-resistant tuberculosis epidemic is crucial to reduce morbidity, mortality, and economic and health-care related costs. Multidrug-resistant (MDR) tuberculosis, and resistance beyond MDR tuberculosis, poses a severe threat to global health security and is the only major airborne drug-resistant epidemic. The number of confirmed MDR cases over the past 5 years has almost doubled globally. Drug-resistant tuberculosis has a high mortality and is responsible for about one third of deaths related to antimicrobial resistance globally. Thus, it underpins the global antimicrobial resistance threat and the disease should be prioritised as a key component of the global antimicrobial resistance response. Drug-resistant tuberculosis is associated with devastating economic consequences and could cost the global economy about US$16·7 trillion between 2015 and 2050.

With the introduction of new drugs and molecular diagnostic technologies in the past 5 years, the field of drug-resistant tuberculosis has become an exciting and rapidly changing landscape. Results from clinical trials and systematic reviews,[1] updated guidance from the WHO,[2] and information about newer technologies prompted us to update *The Lancet Respiratory Medicine* Commission[3] on drug-resistant tuberculosis (appendix pp 2–6).

Key messages

- The WHO has published a new hierarchical classification of second-line anti-tuberculosis drugs broadly based on treatment-related outcomes
- An all-oral treatment regimen for multidrug-resistant (MDR) tuberculosis is now recommended
- Several observational studies have indicated that bedaquiline is relatively safe and associated with a reduction in mortality in patients with drug-resistant tuberculosis
- The optimal treatment duration and number of drugs in a regimen remains to be clarified
- Over the past 2 years, data indicate that a successful all-oral 6–9 month treatment regimen for MDR tuberculosis is a feasible and promising prospect
- Newer genomic approaches including the automated Xpert drug-resistant tuberculosis cartridge, whole genome sequencing, and targeted sequencing are likely to accelerate the time to diagnosis and selection of individualised regimens (impact studies are needed)
- Point-of-care portable battery-operated genomic tools (eg, Xpert Edge and Xpert Omni) will facilitate community-based active case finding of drug-resistant tuberculosis
- Emerging data about pharmacokinetic mismatch due to transcavitary and intralesional drug gradients suggest that optimal dosing and alternative drug delivery methods are needed to prevent resistance amplification and improve outcomes
- Several new approaches, including the evaluation of repurposed drugs and new compounds, hold promise to further improve drug-resistant tuberculosis outcomes in patients

Medical management of MDR tuberculosis

Given that second line injectable drugs are no longer recommended as part of a first-line multidrug-resistant (MDR) tuberculosis regimen for most patients, the current definition of extensively drug-resistant (XDR) tuberculosis has become less clinically relevant.[4] In the future, XDR tuberculosis will probably be defined on the

***Panel 1:* 2019 WHO-recommended* grouping of multidrug-resistant tuberculosis drugs and summary of WHO guidance**

Group A
Levofloxacin or moxifloxacin, bedaquiline, linezolid

Group B
Clofazimine, and cycloserine or terizidone

Group C
Ethambutol, delamanid, pyrazinamide, imipenem-cilastin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, p-aminosalicylic acid

Summary of WHO guidance:
The regimen should comprise all three Group A agents and at least one Group B agent, such that at least four likely effective drugs are included at the initiation of treatment. If only one or two Group A agents are used, both Group B agents should be included in the regimen. Group C agents should be used when an effective regimen (four drugs that are likely to be effective) cannot be constituted using group A and B drugs.

A regimen consisting of at least four drugs likely to be effective in the initial phase (bedaquiline used for 6 months) and at least three drugs likely to be effective should be used after the initial phase to make up a total duration of 18–20 months.

An all-oral bedaquiline-based shorter (9–12 month) regimen can be used under operational research conditions.

The standardised shorter MDR-tuberculosis regimen (requiring daily injections for at least 4 months) can be offered to eligible patients (instead of the longer regimen) and to those who agree to a briefer treatment duration of 9–12 months provided they had not been previously treated for more than 1 month with second-line drugs, and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded; this regimen might be less effective than the new longer bedaquiline-based 18–20 month regimen.

*Adapted with permission of World Health Organization.[2]

basis of outcome data, because of resistance to one or more of the WHO group A drugs (panel 1). Until this issue is clarified, we suggest using a term that specifies the group A drug to which the organism is resistant (eg, fluoroquinolone-resistant MDR tuberculosis).

Incorporating the 2019 WHO drug-resistant tuberculosis guidelines[2], and other available evidence, we have outlined our detailed recommendations to clinicians and health-care workers for the medical management of MDR-tuberculosis (and resistance beyond MDR tuberculosis; panel 2). The new WHO drug classification is presented (panel 1) and WHO guidelines regarding management of MDR tuberculosis are summarised (panel 1).

Route of administration (oral *vs* parenteral)

Almost all patients should receive an oral MDR tuberculosis regimen. A meta-analysis study showed that regimens containing kanamycin and capreomycin, but not amikacin, were associated with poorer outcomes than regimens not containing these agents.[1] However, amikacin causes permanent deafness and other serious adverse events[8]—especially in children[9]—and might be associated with reduced adherence.

Optimal number of drugs

The optimal number of proven or effective drugs to be used in a regimen remains unclear. The PETTS study[10] and a patient-level meta-analysis[1] suggested that outcomes were better with five or more effective drugs; however, only a few patients were receiving two or more group A drugs. The WHO recommends at least four drugs when using a regimen including the three group A drugs.[2] However, the optimal number of drugs in a regimen will depend on several factors including the mycobactericidal and sterilising activity of the drugs used, disease extent, and drug susceptibility test profiles (panel 3).

Specific drugs and their optimal duration

On the basis of moderate quality evidence, the WHO has strongly recommended a group A backbone around which an oral MDR tuberculosis regimen should be constructed, as these drugs have been associated with substantial improvements in mortality and treatment outcomes, mainly in observational studies.[13,14] A large South African study showed that bedaquiline substantially reduced mortality, which was an important finding as the phase 2 trial showed an increase in mortality in the bedaquiline arm (probably a chance finding as almost all of the deaths occurred after bedaquiline was stopped). Delamanid has been designated a Group C drug after disappointing results in a phase 3 trial[6] (panel 2). The use of specific drugs will be guided by drug susceptibility testing, drug-specific mycobactericidal and sterilising activity, and risk-benefit ratio. For example, higher doses of linezolid given for longer durations could result in better outcomes than lower doses, but 30 to 40% of patients stop linezolid treatment because of adverse events.[15] The optimal indication, dose, frequency, and duration of linezolid remains unclear. The WHO recommends 600 mg per day for 6 months, but the NIX study[16] successfully used a 6-month regimen that initiated patient treatment on a higher dose of 1200 mg per day. The 2019 WHO guidelines also suggest the use of the Bangladesh-like short course 9–11 month fixed regimen, which was shown to be non-inferior to the longer regimen of 18–20 months in a previous trial.[5] The South African National Tuberculosis Program has replaced the second-line injectable drug with bedaquiline in a 9–11 month

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See **Online** for appendix

regimen, which should improve outcomes,[8] but the efficacy of this regimen has not been defined (panel 1; panel 2).

Duration of the regimen

The optimal duration of therapy for MDR tuberculosis has not yet been determined and will depend on the presence of one or more prognostic factors (panel 3). Variable regimen durations are used for programmatic management of drug-resistant tuberculosis in different parts of the world (panel 2). How long after culture conversion the regimen should be continued and which biomarkers can inform the optimal duration of treatment in different subgroups of patients, including those with severe and non-severe disease (which includes most cases in children) remains unclear. Ongoing clinical trials—for example, NExT (NCT02454205), end-TB (NCT02754765), STREAM Stage 2 (NCT 02409290), Nix-TB (NCT02333799;

Panel 2: **Recommended principles to be used when designing a regimen for the medical management of multidrug resistant tuberculosis and resistance beyond the condition*†**

Route of administration

Use an all-oral regimen

However, whilst scale-up of newer drugs and diagnostics continues, the WHO has recommended that an RR/multidrug resistant (MDR) tuberculosis short course regimen (9–11 month 2016 WHO regimen containing a second-line injectable drug but not containing bedaquiline or linezolid) can be used. In the STREAM trial,[5] this regimen was found to be non-inferior to the conventional 18-20 month WHO regimen, but bacteriological outcomes were worse with the shorter regimen, and a trend to poorer outcomes in HIV-infected people was identified in both groups.

We suggest that this shorter injectable-based regimen preferably not be used. If used all of the following conditions should be met: no proven or probable resistance to any component of the regimen (except isoniazid); access to baseline and longitudinal monitoring for hearing loss; fluoroquinolone and second-line injectable drug resistance should have been excluded; and patients should have been counselled about the risks of this regimen and agreed to receive it. A clear programmatic plan for transitioning to an all-oral Group A-based regimen should be in place.

Number of drugs

Ideally five drugs (minimum four) should be used, to which the strain has proven or likely susceptibility (drugs previously taken for >1 month are generally avoided; use at least three or preferably four drugs that are likely to be effective in the continuation phase‡)

Individual components of the regimen

- Use a backbone of the three Group A drugs: eg, a later-generation fluoroquinolone such as levofloxacin (less QT prolongation but safety relative to moxifloxacin unclear), linezolid, and bedaquiline. The optimal duration of linezolid and bedaquiline remain unclear but they are generally used for at least 6 months (according to end-points used in clinical trials; in practice, extension of bedaquiline to ≥9 months might be undertaken particularly in late culture converters and those with poor prognostic features; panel 3)
- Add additional group B drugs: eg, cycloserine (terizidone), or clofazimine
- Add additional Group C drugs, if necessary (based on toxicity and resistance profiles), so that five drugs that are likely to be effective make up the regimen. In the meta-analysis[1] P-aminosalicylic acid and ethionamide were associated with poor outcomes compared with regimens without these drugs, and using drugs to which there was known resistance was associated with increased toxicity (observed with pyrazinamide).

Duration of treatment

The optimal duration of the multidrug regimen remains unclear. Current practice when treating MDR-tuberculosis (using a Group A backbone) varies from 9 months to 11 months, to the WHO-recommended 18 to 20 months (eg, in South Africa both the 9–11 month and the 18–20 month regimen are used depending on the clinical context and various factors outlined in panel 3). The optimal duration of treatment will depend on several factors including mycobacterial burden (and time of culture conversion), disease extent, disease site, comorbidities (eg, HIV and diabetes), previous treatment, country setting, local resistance profiles, and patient preference.

Empiric versus individualised treatment

To optimise outcomes and to prevent resistance amplification and accelerated loss of newer drugs, drug susceptibility-guided treatment for individual drugs is preferred over empiric treatment regimens. Sputum-based genotypic testing for second-line resistance (particularly for fluoroquinolones) is recommended to minimise resistance amplification. Regimens should be further optimised on the basis of drug susceptibility results when they become available.

Further information

- Delamanid (Group C) can be used together with bedaquiline, if required, to make up the five-drug regimen (monitor QT interval). However, evidence about the efficacy of delamanid for the treatment of MDR-tuberculosis is scarce[6]
- Meropenem (or combination of imipenem and cilastatin) should be administered with clavulanic acid (generally given as oral Augmentin)

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- A second-line injectable drug (amikacin or streptomycin; group C drugs) can be used if an appropriate regimen of four to five oral drugs cannot be constructed, provided baseline and follow-up screening for hearing loss and renal toxicity is accessible. We recommend that an indwelling intravenous catheter be used for administration of amikacin or a carbapenem. If inaccessible, we recommend that amikacin be given intramuscularly together with a local anaesthetic agent.
- Psychosocial, adherence, and financial support are crucial elements of the treatment package.
- Patients should be actively monitored for adverse drug reactions, which are common.
- A single drug alone should not be added to an ineffective regimen.
- The HIV status should be determined and antiretroviral therapy initiated in all HIV-infected patients (within 8 weeks; 2 weeks for advanced HIV). Dolutegravir is safe when used together with the new MDR regimen containing a group A backbone.
- A surgical intervention can be offered to appropriate patients with previous history of ineffective treatment or who are at high risk of relapse.

Children

- All previously described principles should be applied to children, including an all-oral regimen[7]
- Bedaquiline can be used from age 6 years
- Delamanid is safe and effective from age 3 years and prioritised for use in children (data regarding use in children younger than age 3 years will be available soon). Absence of optimal diagnostics and child-friendly formulations remain a major challenge. In children younger than age 6 years, if delamanid is unavailable, P-aminosalicylic acid (or a child-friendly linezolid formulation) can be given instead of the second-line injectable drug.

MDR=multi-drug resistant. *These principles can also be applied to patients with pulmonary tuberculosis, extra-pulmonary tuberculosis, and in children. †Reproduced from reference 3, by permission of Dheda and colleagues. ‡Continuation phase: some group A drugs like bedaquiline or linezolid, or both, can only be given for a short period (eg, about 6 months) and thus the period beyond this point might only contain a small number of drugs. Depending on the length of the regimen and how long each drug is used, in specific instances, there might not be a continuation phase.

Panel 3: Factors that could affect prognosis, outcomes, and the risk-to-benefit ratio of treatment*†

Mycobacterial factors

- Mycobacterial load
- Drug-specific resistance profile
- The number and relative efficacy of mycobactericidal and sterilising drugs
- Strain type

Comments

Time to positivity (sputum culture), smear status, and Xpert Ultra (Cepheid; Sunnyvale,CA, USA) cycle threshold values are useful surrogate markers of mycobacterial load

Host factors

- HIV coinfection
- Diabetes mellitus
- Weight less than 50 kg or low BMI
- History of prior tuberculosis
- Radiological disease burden or disease extent (including disseminated tuberculosis)
- Genetic factors
- Substance and alcohol abuse

Comments

- Chest radiography (and sometimes CT or PET-CT) might be used to quantify disease burden (bilateral involvement, presence of cavitary disease, number and severity of zones affected could be associated with poor outcome)[11]
- Drugs do not penetrate well into thick walled cavities and sputum drug susceptibility testing correlates poorly with samples that are obtained directly from the cavity[12]
- HIV co-infection (especially in the context of unsuppressed viral load), diabetes mellitus (especially if uncontrolled) and weight less than 50kg are all associated with poor outcomes
- Genetics might affect several variables that determine pharmacokinetic profiles including absorption, metabolism, excretion, adaptive immunity, and immunopathology
- Substance abuse is associated with a poorer prognosis

Programme-related and other factors

- Access to effective drugs‡
- Adherence-promoting measures
- Pill burden (HIV and tuberculosis drugs)
- Drug-related adverse events and toxicity
- Social support, including food security, access to shelter, and access to gainful employment

Comments

- Programmatic measures to support adherence, social support, and detection and management of adverse events might affect outcomes and prognosis
- Support should be provided to ensure all patients have access to the best possible care, which could reduce long-term costs associated with poor treatment outcomes

CT=computed tomography. PET-CT=positron emission tomography-computed tomography. *These factors should be considered when deciding the duration of treatment, minimum number of drugs that are likely to be effective, and which individual drugs should be used in regimens for MDR-tuberculosis. †Treatment with five drugs that are likely to be effective, and prolonged duration of treatment (of the regimen or individual drugs) might be justifiable in patients with one or more of these risk factors or descriptors (the same principles would apply to drug-sensitive tuberculosis). ‡Programmes must have access to newer group A and C drugs and use them as outlined in the new guidelines. If they are unavailable, a clear pathway and plan should be conceived to obtain them.

in the follow-up phase), ZeNix (NCT03086486), and SimpliciTB (NCT03338621), and SmART Kids (IMPAACT 2020) will help to answer these questions.[17]

Drug susceptibility testing and the minimal standard of antibiotic stewardship

Ideally, the diagnostic standard for management of MDR tuberculosis should include confirmation of resistance to rifampicin, isoniazid, and fluoroquinolones. Diagnostic testing for susceptibility to bedaquiline, linezolid, pyrazinamide, and ethambutol is neither widely available nor validated, and urgently needed. Until then, clinicians in most high-burden settings will continue, in the interests of a patient-centred approach, to use standardised or quasi-individualised regimens. The regimen can then be further individualised on the basis of the results of the available second-line drug susceptibility testing.

Another suggested approach is to use a pan-tuberculosis regimen to treat all forms of rifampicin-resistant tuberculosis with one regimen without preceding comprehensive drug susceptibility testing. The merits and drawbacks of this approach—including rapid and improved access to treatment with a potential benefit on mortality and disease burden versus the risk of resistance amplification,[18] and generating a large population with untreatable tuberculosis in the long term, and the ethics of prioritising the rights of individuals over communities—have been extensively debated.[19,20]

Diagnosis of drug-resistant tuberculosis

Substantially reducing the burden of MDR tuberculosis will necessitate active case finding because 95% or more of transmission cases have already occurred before diagnosis by passive case finding.[3] In addition to targeted screening (eg, of close contacts), a study has confirmed the feasibility of using new portable battery-operated devices for nucleic acid amplification tests for targeted community-based active case finding[10] for MDR tuberculosis (NCT03168945, submitted for publication; figure). Xpert Ultra (Cepheid; Sunnyvale, CA, USA), a version of Xpert that is about 5% more sensitive (expected to pick up more cases of tuberculosis and hence rifampicin-resistant tuberculosis at population level) but less specific than the Generation 4 Xpert cartridge is now the frontline diagnostic being used for tuberculosis in many endemic countries.[21] Drawbacks of Xpert Ultra include limited positive predictive value for rifampicin resistance (when the prevalence of resistance is under 10%) and the lack of clarity on how to handle trace results. The GeneXpert drug-resistant tuberculosis cartridge will be released shortly, which will detect resistance to isoniazid, fluoroquinolones, and second line injectable drugs.[22] Susceptibility to other drugs will be added as new prototypes and new assays emerge. Next generation whole genome sequencing, now routinely used in England for the detection of tuberculosis-specific drug resistance and strain typing[23] can provide comprehensive mutational analysis allowing drug susceptibility profiles

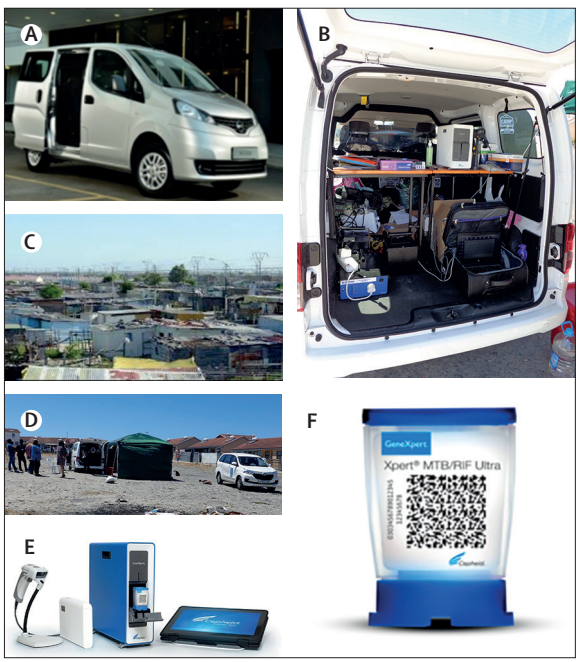

Figure: **An active case finding model for drug-sensitive and drug-resistant tuberculosis in peri-urban informal settlements using a portable battery-operated genomic tool within a low-cost lab-in-a-cab mobile clinic**
(A) The XACT model uses a low-cost panel van (less than US$ 14 000), which is manned by two minimally trained health-care workers for community-based screening and contact tracing. (B) Typical set up of the mobile lab-in-a-cab showing the set up used for XACT. (C) A typical high density peri-urban informal settlement where active case finding or contact tracing for drug-resistant tuberculosis can be done. (D) Community-based active case finding in demonstration mode with adjacent shelter (with portable sputum induction tent) and screening set-up in an informal settlement of Cape town, South Africa. (E) Cepheid GeneXpert Edge used in the XACT model including barcode scanner, Xpert Ultra cartridges, external battery pack and tablet. (F) GeneXpert MTB/RIF Ultra cartridge used on the platform, which also detects rifampicin resistance. XACT=Xpert for active case finding. (E, F) Reproduced by permission of Cepheid.

for many second-line drugs to be simultaneously determined.[24–27] However, major limitations include the poor predictive value for some drugs (eg, clofazimine and cycloserine), the poor sensitivity when using sputum rather than a culture isolate as a sample (meaning that results from a culture isolate are generally only available after 4-8 weeks of empiric treatment), infrastructure requirements, and availability and cost (still not accessible and beyond the affordability of most health-care systems in endemic countries). Some mutations have a good association with minimum inhibitory drug concentrations,[3] and development of a standardised platform for phenotypic drug susceptibility testing, and minimum inhibitory concentration determination of 14 drugs (including bedaquiline and delamanid) is encouraging.[28] Critical concentration cutoff points for second-line drugs have recently been updated by the WHO.[29] The clinical effect of targeted and whole genome sequencing technology, and the clinical benefit over more limited molecular readouts (such as in the Xpert drug-resistant tuberculosis cartridge) requires clarification.

Search strategy and selection criteria

A literature search in PubMed and Google Scholar was done using the following search terms: "tuberculosis", "drug-resistant", "MDR-TB", and "XDR-TB". We also identified relevant articles through searches of the authors' personal files, review articles, and landmark papers, and selected publications were included from Jan 31, 2017, to April 1, 2019 (a full reading list is provided in appendix pp 2–6). Only important new developments and additional information absent from the 2017 Commission are included in this update.

Pharmacokinetic and pharmacodynamic aspects, and newer drug regimens and agents

Studies analysing tissue sections from lung lesions using mass spectrometry have shown differential drug penetration into solid nodules including areas of caseous necrosis.[30] Over the past 12 months, studies creating transcriptomic[12] and pharmacokinetic cavity maps (using explanted human lungs from patients with drug-resistant tuberculosis in whom treatment was ineffective) have confirmed the existence of drug-specific gradients across the walls of pulmonary cavities (with very low levels of some drugs, but not others, in the cavity centre where there is a high mycobacterial burden) and their association with resistance amplification.[31] Collectively, these data suggest that alternative dosing and drug delivery strategies are needed to reduce functional monotherapy at the site of disease, and prevent amplification of resistance. Studies on the effect of therapeutic drug monitoring of second-line drugs are needed. Newly available pharmcokinetic and safety data from children allow us to use bedaquiline in children age 6 years and older and delamanid in children age 3 years or older. An FDA advisory panel has approved the use of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of pulmonary XDR tuberculosis, and treatment-intolerant or non-responsive MDR tuberculosis,[32] with regulatory approval expected. Publications using the hollow fibre and other models have suggested that certain repurposed drugs including ceftazidime avibactam, tedizolid, once a week tigecycline, and minocycline, might hold promise for the treatment of drug-resistant tuberculosis.[33,34] Promising new agents that have partially or fully completed testing, or are in phase 1 clinical trials, include mycobacterial respiratory chain inhibitors such as Q203 (imidazopyridine),[35] the cell wall biosynthesis inhibitor OPC167832,[36] and DprE1 inhibitors such as benzothiazole.[37,38]

Conclusion

Although drug-resistant tuberculosis threatens to derail already fragile tuberculosis control programmes across the world, emerging new public health strategies, diagnostic technologies, drugs, and interventions to prevent resistance amplification, are exciting and encouraging. Together with poverty alleviation and political will, exemplified by the 2018 UN General Assembly High Level meeting on ending tuberculosis, these advances signal the ability to curtail and eventually solve the problem of drug-resistant tuberculosis.

Contributors

KD developed the preliminary update document. GM, TG, JF, and RMW provided major edits to the document. All the co-authors reviewed and further contributed to the document. KD, TG, GM, KED, MM, JF, EAN, and RMW were all equal contributors to the work.

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Declaration of interests

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