TITLE:

Multi-Drug/Extensively Drug Resistant Tuberculosis -Epidemiology, Clinical Features, Management and Treatment

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SUMMARY
Multidrug resistant Tuberculosis (MDR-TB) is a growing global public health threat. Today MDR-TB affects more than half a million people worldwide and is characterised with significant morbidity and mortality. Over the last decade new rapid diagnostic methods like the GeneXpert, and availability of new MDR-TB drug and the shorter treatment regimens hold promise of more patients being diagnosed and put on treatment. Major challenges of lack of adequate resources, poverty and limited access to healthcare remain continue to hamper efforts. This article reviews the Epidemiology, Clinical Features, Management and Treatment, proving new updates and recent changes in guidelines which offer patients better tolerated and shorter regimens for enabling better therapeutic outcomes.

Keywords
Drug-resistant tuberculosis
Multi-drug resistant TB (MDR-TB)
GeneXpert MTB/RIF Assay
Treatment Guidelines
Surgery
Rehabilitation
Workplace safety

Key points

1. Drug resistant TB is currently a threat to global health security, with an estimated 558,000 new MDR/RR-TB infections in 2017 (160,684 notified cases), and 230,000 deaths.

2. Multi-drug-resistant tuberculosis (MDR-TB) is a lethal form of tuberculosis (TB) caused by *Mycobacterium tuberculosis* strains which are resistant to rifampicin and isoniazid. It should be suspected in patients living in high MDR-TB endemic areas or those who have had previous TB treatment. New rapid molecular based diagnostic tests such as the GeneXpert MTB/Rif Assay can provide results operationally within a day.

3. MDR-TB requires treatment with second-line drugs, usually four or more anti-TB drugs for a period extending between 18–24 months. Under ideal program conditions, MDR-TB cure rates can be above 70%. An all oral treatment regimen has been recently approved by WHO.

4. Patients not meeting the criteria for the WHO shorter regimen should receive the longer regimen.

5. Surgery for drug resistant TB remains an option when there is a lesion that is resectable together with poor response, lack of drugs, intolerance to medications.

6. Pulmonary rehabilitation is useful for patients with reduced exercise performance and impaired quality of life.

Definitions

Drug sensitive (susceptible) TB (DST): is defined as TB caused by *Mycobacterium tuberculosis* sensitive to all first line TB drugs.

Rifampicin mono-resistant TB (RR-TB) is now managed as MDR-TB, since the WHO 2016 MDR-TB guidelines update.[1]

Isoniazid mono-resistant TB has been recently reviewed,[2] and guidance updated.[3]

Poly-resistant TB is defined as multiple resistances but not fulfilling the MDR-TB definition i.e. resistance to isoniazid, streptomycin, ethambutol and pyrazinamide.

Multi drug resistant Tuberculosis (MDR-TB): is defined as TB resistant to rifampicin and isoniazid.

Extensively drug resistant TB (XDR-TB): is defined as MDR-TB with additional resistance to a fluoroquinolone and a second line injectable (capreomycin, amikacin, kanamycin).

Acquired drug resistant TB. Acquired drug resistance is the selection of mutant resistant *Mycobacterium tuberculosis* strains due to inadequate, incomplete or poor-quality treatment or sub-optimal patient compliance with quadruple therapy. Simultaneous natural mutations in *Mycobacterium tuberculosis* resulting in resistance to more than one TB drug do occur but are very rare.

Primary drug resistant TB. Patient is infected with a drug resistant strain of *Mycobacterium tuberculosis.* The natural history of infection is similar to that of drug-susceptible TB.
Drug resistant TB was noted after the first clinical trial using streptomycin in monotherapy.[4] The most common cause of drug resistance is through acquired drug resistance and predominantly by adding a single active drug to a failing regimen.[5]

Latent *Mycobacterium tuberculosis* Infection (LTBI): LTBI is defined by the World Health Organization (WHO) as 'a state of persistent immune response to *Mycobacterium tuberculosis* antigens with no evidence of clinically active TB disease'

Introduction, Background and Epidemiology

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium* tuberculosis. Tuberculosis (TB) has plagued humankind for millennia. Today TB it is the most common cause of death from an infectious disease and the 9th cause of death globally.[6] The WHO annual TB report (2018) estimated that 10 million people (3.2 million women and 1 million children) developed TB. Tuberculosis caused 1.3 million deaths in non-HIV infected and an additional 300,000 HIV-positive people.[6] Tuberculosis caused by *Mycobacterium tuberculosis* strains resistant to TB drugs is harder to treat than those infected with drug-susceptible strains.

Tuberculosis frequently affects adults in the prime of their productive life and makes an enormous impact on the poor or socially disadvantaged, costing the global economy 617 billion USD from 2000-2015 with this number set to rise to 983 billion from 2015-30. These figures are even more significant when taking into account that the majority of highest incidence countries are developing economies.[7]

Drug resistant TB is a new threat, globally, 3.8% of all new cases have MDR-TB and it is now estimated that there were 558,000 new MDR/RR-TB infections (160,684 notified cases), and 230,000 deaths. Europe has the highest proportion of drug resistant cases with 17% of all new cases of TB being MDR-/RR-TB. Of concern the number of MDR-TB cases increase year on year.[6] A recent model calculation has estimated that a third of Tuberculosis cases in Russia will be drug resistant by 2040 (ref).[6-8] Drug resistant cases threatens to replace susceptible cases and delay/hamper TB elimination, hence it constitutes a considerable challenge to health programmes.

Clinical presentation

Drug resistant TB presents in the same way as drug susceptible TB, and currently is less likely to occur through primary transmission because of the low prevalence of drug resistant cases. Pulmonary TB is the most common presentation of DR-TB cases and in cases with HIV or other causes of immunosuppression features of extra-pulmonary TB may be present. There are factors which make resistance more probable. Prior TB treatment increases the risk of drug resistant TB, alcoholism, homelessness increases the likelihood of resistance, as well as being a contact with a patient with active drug resistant TB. Drug resistant TB should be suspected in patients who are not responding to treatment and are not smear and culture converting after two months of adhering to standard quadruple TB drugs.

Patients will give a history of chronic cough, and non-specific constitutional symptoms of anorexia, lethargy and fever. Over time the cough becomes productive with purulent sputum, sometimes blood stained (hemoptysis), pleuritic chest pain and breathlessness. As the disease progresses there is worsening breathlessness, night sweats, weight loss, and general wasting such that the patient feels tired, sleepy and unable to perform a day's work.

Diagnosis of Drug resistant TB

Early and accurate diagnosis of TB and MDR-TB is important for successful treatment outcomes. The gold standard for making a specific diagnosis of TB is by identifying the presence of *Mycobacterium tuberculosis* from a clinical sample (which can be sputum, pleural fluid, urine, pus, cerebrospinal fluid, bone marrow, biopsies or excised tissue). Imaging can help localize sites of disease and associated pathology and allows for imaging guided aspiration of lesion, abscess or biopsy of tissue for microbiological and molecular examination. The choice of the optimal microbiological or molecular diagnostic method for TB diagnosis is dependent on clinical context, available laboratory capacity and resources.[1]

***Culture-based methods*:** Culture of clinical specimens for *Mtb* is a diagnostic method for the diagnosis of active TB with a sensitivity of 65% and specificity of 100%. Traditionally solid Lowenstein-Jensen culture medium has been replaced by automated liquid culture systems using the (limit of detection of ~10 organisms per ml) based on modified Middlebrook 7H9 Broth with an oxygen-sensitive fluorescent detection technology, the system scans for increased fluorescence (reflecting presence of viable mycobacteria) every 60 minutes. Liquid culture is now recommended by the WHO as the gold standard confirmatory test for TB (WHO 2017),[9,10] however though it is more sensitive than solid media culture, it is more expensive and complex, with contamination being a technical challenge. Once TB is isolated, phenotypic drug susceptibility tests (DSTs) and genotyping for further molecular epidemiology studies can be performed.[11] The disadvantage of culture methods is the time needed for the growth of mycobacteria. Liquid cultures require at least 9-10 days for positive results and six weeks for being considered negative.[9,10]

Molecular based methods: The World Health Organization guidelines,[1] have simplified diagnosing MDR-TB by the programmatic roll out of TB-PCR testing, mainly with the Cepheid GeneXpert MTB/Rif Assay ®,[12,13] and to a lesser extent by Hain line probe assay and other molecular methods.[14] Culture based methods remain the gold standard to determine drug resistance however these may be replaced in the future by whole genome sequencing.[15]

The GeneXpert® MTB/RIF assay: the WHO has recommended the GeneXpert® MTB/RIF assay (Cepheid Inc, Sunnyvale, USA) as a rapid, near-point of care test for detecting *Mtb* and also rifampicin resistance simultaneously for patients with pulmonary TB.[16] This test is a nested PCR assay for amplifying *Mtb* DNA and part of the *rpoB* gene encoding rifampicin resistance.[13] This assay now updated with the RIF/Ultra cartridge can give a result in under 2 hours, and operationally in hospitals and TB clinics within 24 hours. The GeneXpert® MTB/RIF assay and AFB sputum

smear microscopy have the same specificity but sensitivity of GeneXpert is much higher than AFB smear microscopy on sputum. A single Xpert MTB/RIF test directly on sputum detects 99% of smear-positive patients and 80% of patients with smear-negative disease. Mean time to detection is less than 1 day for Xpert MTB/RIF, 1 day for microscopy, 17 days for liquid culture and more than 30 days for solid culture.[16] In HIV-infected individuals, the Xpert increases case detection of TB by 45% compared with microscopy in HIV-infected individuals. It facilitates earlier diagnosis and reduces time-to initiation of TB treatment. The timeliness of detection of rifampicin resistance in adults and children living with HIV using Gene Xpert MTB/RIF may facilitate timely initiation of MDR-TB treatment.

Management of DR-TB

The management of drug resistant TB requires the use of several drugs in combination, the currently available, new and repurposed drugs are shown in Table 1,[18] and discussed separately elsewhere.[19,20] This section will focus on the WHO guidelines for the management of MDR-TB which have been based on a recent individual patient data-metanalysis of 12,030 patients, which demonstrated better outcomes with linezolid, fluoroquinolones, bedaquiline, clofazimine and the B-lactamase inhibitor/carbapenems and worse tolerability and outcomes with prothionamide and second line injectables.[21]

WHO guidelines for MDR-TB management

The current guidance on the management of MDR-TB is embodied in the following WHO publications in 2011, with an update in 2016 and a recent one in 2018 (ref).[1,16,18]

The 2011 WHO MDR-TB guidelines

In 2011 anti-TB drugs were classified into five groups: Group 1 drugs included the first-line oral drugs (rifampicin, isoniazid, ethambutol and pyrazinamide, Group 2 the injectable second-line drugs (amikacin, kanamycin, capreomycin plus streptomycin with the latter considered as first-line but also an injectable and grouped accordingly), Group 3 the fluoroquinolones, Group 4 the second-line old bacteriostatic drugs (ethionamide/prothionamide, PAS, cycloserine/terizidone) and Group 5 the new or repurposed drugs at the time considered of unclear efficacy.[16] Group 5 comprised several drugs like linezolid, carbapenems, clofazimine which were 'promoted' to a higher rank in future adaptations of the WHO guidelines (ref).[18]

The WHO 2011 guidelines were focusing on culture and drug susceptibility testing as well as on rapid molecular diagnostic methods.[16] The recommended regimen included pyrazinamide, one fluoroquinolone, a second-line injectable drug (to be administered for the duration of the intensive phase), ethionamide or prothionamide and either cycloserine or PAS. The total duration was 20 months or more, with an intensive phase of 8 months. They also recommended early initiation of antiretroviral treatment in HIV-positive individuals.[16]

The 2016 WHO MDR-TB guidelines

The 2016 WHO guidelines,[1] re-organized the classification of anti-TB drugs in Group A, B, C and D, based on their safety and efficacy. Group A drugs included the fluoroquinolones, Group B the second-line injectables and the Group C the other core second-line agents (ethionamide/ prothionamide; cycloserine/ terizidone plus linezolid and clofazimine). Group D (the add-on agents) was subdivided in three subgroups: Group D1 included pyrazinamide, ethambutol and high-dose isoniazid (this very important in the shorter regimen); Group D2 bedaquiline and delamanid and Group D3 PAS and the carbapenems (imipenem and meropenem to be used with clavulanic acid to protect from beta-lactamase action).

The new recommendations of these guidelines were, in addition to the reclassification of the anti-TB drugs, included the following: the introduction of the WHO shorter regimen, a new

recommendation for treatment in children based on paediatric individual meta-analytic data and a new recommendation on partial lung resection surgery.
A regimen was recommended to include at least 5 effective medicines during the intensive phase of treatment, including pyrazinamide and four core second-line TB drugs, one from Group A, 1 from Group D2 and- if necessary one or more agents from Group D3 to reach a total of five.

The WHO shorter regimen

This regimen was known previously as the 'Bangladesh regimen'. The original Bangladesh study,[22] (ref) achieved a relapse-free cure of 87.9% among 206 patients with infrequent and manageable adverse events. The regimen recommended by WHO was the same, the only difference being the use of moxifloxacin to replace gatifloxacin (ref).[1]

The 9 to 12 months standardized WHO shorter regimen is composed of 4-6 months of kanamycin or amikacin, moxifloxacin, prothionamide or ethionamide, clofazimine, pyrazinamide, high dose isoniazid and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol.
Importantly, no modifications were considered possible out of the drugs mentioned above due to lack of evidence. The recommendation applied to adults, children, and people living with HIV.
The indication was for patients with rifampicin-resistant TB or MDR-TB, who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or considered highly unlikely.
The guidelines suggested the following check-list to define eligibility. If any of the following questions have a 'yes' answer, the case was not considered eligible for the WHO shorter regimen:
- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)?
- Exposure to >1 second-line medicine in the shorter MDR-TB regimen for >1 month?
- Intolerance to >1 medicine in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)?
- Pregnancy?
- Extrapulmonary disease?
- At least one medicine in the shorter MDR-TB regimen unavailable?

The clear advantages of the WHO shorter regimen included lower costs (<US$1,000 in drug costs per patient) and improved adherence due to the shorter duration.
WHO strongly recommended monitoring for effectiveness, relapse, and harms through the active TB drug safety monitoring and management (aDSM) project.
Although initial observational studies achieved better outcomes in patients treated with the shorter regimen in comparison with the longer regimen (e.g. the regimen designed as per WHO guidelines in force) and treatment success rates exceeding 90% in Bangladesh, Cameroon and Niger (ref),[23] a controlled clinical trial (STREAM trial) was conducted to assess comparatively efficacy and safety of the two regimens.
The preliminary and final results of the STREAM trial (ref),[24,25] showed a success rate of 78.1% with the shorter regimen and 80.6% with the longer one. Moreover, the short regimen used in STREAM was noninferior to the WHO long regimen at primary efficacy outcome and similar to the long regimen in terms of safety even though the shorter regimen yielded more severe adverse events (grade 3-5), mortality (particularly among HIV co-infected patients) and QT prolongation exceeding 500 msec.[25]

Considerations on the WHO shorter regimen

Using rapid molecular line probe tests, it is possible to identify, as discussed in a specific paragraph of this review, the genes usually associated with resistance to isoniazid. In the presence of *inhA* alone isoniazid is considered effective at normal doses, but resistance to ethionamide and prothionamide is usually present. In the presence of *katG* alone high dose isoniazid usually is

effective against the majority of *M. tuberculosis* strains (2 out of 99 strains had 'intermediate resistance to isoniazid) (ref).[26] In case both inhA and katG are present high-dose isoniazid is considered ineffective (ref).[27,28] As also resistance to ethionamide and protionamide will be present, the shorter regimen cannot be used (ref). [27,28]
A scientific debate took place on the interpretation of the WHO recommendations, the more controversial points being the eligibility (or not) in settings where MDR-TB is common and the eligibility of the cases harbouring strains of *M. tuberculosis* resistant to ethambutol (and pyrazinamide), considering the unreliability of drug susceptibility testing for these drugs. In Europe, where drug susceptibility testing to ethambutol is considered reliable, ECDC recommended to consider this and exclusion criterion for the shorter regimen (ref).[27,29-33]
The recently published European Union Standards for TB care confirmed this position (ref).[34]
As resistance to fluoroquinolones and or injectables is a clear contra-indication, in settings like former Soviet Union countries where the prevalence of resistance to these drugs ranges between 30 and 45% the proportion of patients able to benefit from this regimen is very small (10 to 30%) (ref).[27,31]
Based on these arguments, a recent modelling study estimated that the impact of the shorter regimen on the MDR-TB epidemic will be minor (ref).[35,36]
As we shall see, the 2018 new WHO MDR-TB guideline have recently recommended a shift towards oral MDR-TB regimens, thus adding an element of uncertainty to the future of the shorter regimen. Furthermore, the future possibility of the use of a 'universal regimen' will eventually open additional perspectives (ref).[37]

The 2018 WHO MDR-TB guideline
At the moment of writing the present document only the pre-final version of this guideline was published by WHO (ref).
The new guideline, based on the evidence from the second global MDR-TB individual data meta-analysis published in 2018 (ref),14 made the historical shift towards a full-oral treatment of MDR-TB.
In the new classification Group A drugs include fluoroquinolones, bedaquiline and linezolid, while Group B drugs (add-on) clofazimine and cycloserine or terizidone. Group C drugs include the remaining drugs (ethambutol, delamanid, pyrazinamide, carbapenems, amikacin, ethionamide/prothionamide and PAS). Importantly, while bedaquiline, linezolid and clofazimine have been further promoted, the injectables have been downgraded because of their toxicity, possible lack of efficacy and worse outcomes, only amikacin is still recommended as it was found to have moderate activity (ref).[21]
The new approach is to use, if possible, all Group A drugs and then from Group B (and if necessary, from Group C) so as to include a sufficient number of active drugs, >4 active drugs.
The recommended regimen would include at least four agents likely to be effective in the first 6 months and three drugs in the continuation phase of treatment for a total duration of about 18-20 months, depending on the patient's response.
The recommendations for the shorter regimen's eligibility has been slightly modified: 'in MDR/RR-TB patients who have not been previously treated for more than one month with second-line medicines used in the shorter MDR regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens'.
The main differences in comparison with the previous guidelines are the clear need for testing and excluding resistance to fluoroquinolones and injectables (the previous wording was 'resistance…considered highly unlikely') and the less evident priority assigned to the shorter regimen in view of the STREAM Trial results (ref).[18,25]

Other management considerations:

Diabetes

We are currently living in an era of a diabetic epidemic, and there has some overlap between diabetes and tuberculosis, with diabetic patients having a 2-3 times higher risk of developing tuberculosis (ref).[38] Diabetic TB patients have been found to generally have greater symptom severity and delayed sputum culture conversion (ref) [39] and a recent meta-analysis demonstrated an association also with MDR-TB (ref).[40,41] Diabetic patients should therefore be screened for TB and should be offered preventive therapy, they should also be risk assessed for MDR-TB. Given delays in gastric emptying absorption of TB drugs may be affected, therapeutic drug monitoring may help ensure adequate levels (ref).[42]

Elderly

Elderly patients with multidrug resistant TB tend to have more extensive disease and higher rates of adverse events to therapy, accompanied with worse outcomes and a higher mortality rate, this is perhaps due to a senescent immune system, presence of comorbidities and drug-drug interactions, a higher suspicion in this cohort is required to avoid transmission of TB in health facilities, elderly care homes and to anticipate the time of diagnosis in order to reduce transmission and improve outcomes (ref).[43-45]

LTBI prophylaxis and MDR-TB

To date only observational evidence around the effectiveness of treatment in programmatic settings are available, a recent meta-analysis of 5 studies suggests that treatment of MDR LTBI is effective. We however are impatiently awaiting results of the first three Randomised Control Trials for preventive therapy in contacts of MDR-TB patients for definitive answers regarding composition of regimen and duration (ref).[46]

Surgery and MDR-TB

MDR and XDR-TB patients despite the new drugs remains challenging, thoracic surgery though controversial, similar to the pre-antibiotic era, continues to remain an option where few options exist. Surgery can act as a therapeutic tool in improving outcomes and obtaining cure especially when indicated (localised disease) and when there are few available drugs, especially in the continuation phase (ref).[47,48]

Pulmonary rehabilitation

Patients undergoing surgery will most certainly need pulmonary rehabilitation (ref).48

Recent evidence suggests that MDR-TB patients, due to extensive disease and long treatment frequently are left with pulmonary sequelae such as obstruction and/or restriction, resulting in reduced oxygen saturation, reduced exercise performance and impairment of quality of life (ref).[49,50] Pulmonary rehabilitation seems to be effective in these cases (ref).[49,51]

Drug toxicities: Delamanid and Bedaquiline in combination

Combination of delamanid and bedaquiline did not appear to potentiate cardiotoxicity in a pooled analysis of 87 patients, (ref)[49,52] however clinical trials will need to demonstrate the long-term safety of this pairing, and their unlicensed combined use at present time can only be considered (with adequate monitoring) in patients with no other option (ref).[53]

Central Nervous System MDR-TB

Multidrug resistant central nervous system TB is extremely challenging to treat and is faced with a higher risk of chronic sequelae and poor clinical outcomes (ref).[54] Unfortunately, the blood barrier penetration of the TB drugs overall is not very good, the drugs which have demonstrated the best brain penetration are pyrazinamide, moxifloxacin, levofloxacin, linezolid, prothionamide and cycloserine (ref).[54] The new drugs delamanid and bedaquiline being highly protein bound are unlikely to be very efficacious against CNS disease, a recent case report has demonstrated that no bedaquiline was found in a patient's cerebrospinal fluid (ref).[55]

Programmatic management of multidrug-resistant tuberculosis (MDR-TB)

The End TB Strategy includes management of MDR-TB as one of the core clinical and public health priorities (ref).[6,56,57] Furthermore, MDR-TB prevention and control is one of the core activities recommended by WHO to pursue TB Elimination (ref).[58]
In a 2016 review, (ref) [56] priority actions have been recommended to impact the MDR-/XDR-TB epidemic, including as follows:

1. *Prevent development of MDR-TB thorough high-quality treatment of drug- susceptible TB;*
2. *Expand rapid testing and detection of drug-resistant TB;*
3. *Provide immediate access to effective treatment and proper care;*
4. *Prevent transmission through infection control;*
5. *Increase political commitment and financing. Ensuring adequate diagnosis, treatment, and management for drug-susceptible TB.*

1. *Prevent development of MDR-TB thorough high-quality treatment of drug- susceptible TB.*

The strategic approach
An important modelling study, (ref) [56,59] suggested that cure rates of drug susceptible cases exceeding 80% can control the MDR-TB epidemic given that rapid diagnosis of new cases is ensured, thus supporting the priority of adequately treating new cases over focusing on failures' management.
The easy principle, in theory, is to limit the 'creation' of new MDR-TB strains of *Mycobacterium tuberculosis* by ensuring high cure rate of new cases, when they are drug-susceptible (see Table 2: Interventions to prevent drug-resistant TB). The standard regimen for new cases (including 2 months with isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 months with isoniazid and rifampicin) if administered with adequate treatment supervision can achieve a success rate exceeding 95% at the programmatic level (ref).[28] The positive effect of this approach is also to break the chain of transmission, thus contributing to a decline of the overall TB incidence. This approach needs to be complemented with the sterilisation of the existing pool of MDR-/XDR-TB cases, to alleviate individual suffering as well as to prevent further transmission of resistant strains (ref).[28,59] This is possible by improving case detection and cure rates, according to the principles of the Ed TB Strategy (ref).[60]

Outcome of MDR- and XDR-TB cases
However, managing MDR and XDR-TB is difficult, particularly when the *M. tuberculosis* strain has a pattern of resistance beyond rifampicin and isoniazid, the drugs defining MDR-TB (ref).[21,58,61,62]

Globally, according to the WHO report, the treatment success of RR/MDR-TB cases increased from 50% in the 2012 cohort to 55% in the 2015 one (ref).[6] A sub-analysis of the first large individual-data meta-analysis coordinated by the McGill University found that while treatment success was higher in MDR-TB cases (65%), in XDR-TB cases it was as low as 40%, and in patients harbouring strains of *M. tuberculosis* with resistances beyond XDR it was below 20% (a result worse than that observed in the pre-antibiotic era) (ref).[63,64,65]
Interestingly, the treatment success rates described in the second individual-data meta-analysis for MDR-TB cases was higher (ref),[21] reflecting the more consistent use of linezolid and of new or repurposed drugs in recent cohorts.
This second large study included 12,030 patients from 50 cohorts enrolled in 25 countries. It reported that 7,346 achieved treatment success (61%), 1,017 failed or relapsed (8%) and 1,729 (14%) died. Treatment success was, in fact associated with prescription of linezolid, new generation fluoroquinolones (moxifloxacin, levofloxacin), carbapenems, clofazimine and bedaquiline. In the same study reduced mortality was associated with the use of linezolid, new fluoroquinolones and bedaquiline (ref).[21]

Evidence from South Africa confirmed improved outcomes and reduced mortality when bedaquiline was used (ref),[66,67] thus accelerating the movement towards the use full-oral regimens (ref).[18]

How to improve the clinical management of MDR- and XDR-TB cases?
The clinical management of these cases is really complex, often requiring a multi-disciplinary approach (ref).[68,69] According to WHO an important proportion of cases reports severe adverse events, 17.2% attributed to linezolid. 14.3% to PAS, 10.3% to amikacin, 9.5% to ethionamide/ prothionamide and 7.8% to cycloserine/ terizidone, just mentioning some of the drugs recommended by WHO (ref).[18]
Therefore, a multi-disciplinary team approach has been recommended to manage these cases, in several countries known as TB Consilium (ref).[69] The idea is that a team including differing and complementary expertise (adult physicians and paediatricians; public health specialists; microbiologists; pharmacologists; surgeons, etc) has better chances to identify the best possible regimen and ensure adequate clinical monitoring and management of adverse events than a single clinician alone (ref).[69] A recent publication described, for some of the known examples of TB Consilia, including pro- and contras of different approaches and experiences. While some of them are internet-based and provide real time answers, others still rely on physical meetings or periodic tele- or video-conferences (ref).69 From a programmatic perspective, each national programme needs ideally to develop a system, tailored to the country-specific needs, able to ensure that at least the more complicated cases (e.g. XDR-TB, cases with severe co-morbidities, adverse events and/or needing bedaquiline and delamanid) are discussed in a TB Consilium-like body.
For cases which have particular problems, for which specific expertise is not available in the country/centre or in cases for whom a second opinion can be beneficial, a supra-national TB Consilium may be useful. In 2018 a clinical advisory service, promoted by the Global TB Network (GTN) called Global TB Consilium has been implemented hosted by WAidid, the World Association for Infectious Diseases and Immunological Disorders (see WAidid website –Global TB Consilium page: http://www.waidid.org/site/clinicalIntro).
In short, the new service provides free clinical advice within 48 hours, through a team of global renown experts recently selected based on very strict criteria (ref).[69] The service currently operates in English, Russian, Spanish and Portuguese (ref).[69]

2. *Expanding rapid testing and detection of drug-resistant TB*

Under the first Pillar of the End TB Strategy the principle that early diagnosis and universal DST (drug susceptibility testing) are necessary is clearly underlined. Resistance to isoniazid and rifampicin can be detected using phenotypic methods on solid culture or liquid-based culture techniques. The main limitation of this approach is that they require long time (2 to 3 weeks minimum) as well as technical capacity and adequate infection control measures (ref).56,70-74

Fortunately, today new rapid molecular methods based on automated nucleic acid amplification are available to detect *Mycobacterium tuberculosis* and the mutations usually determining rifampicin-resistance. These techniques have several advantages, including rapid turn-around time and lower needs for biosafety/infection control and technical skills of laboratory staff, thus representing a step ahead towards the use of a point-of care test.

Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and its new evolution, the Xpert MTB/RIF Ultra assay, both recommended by the WHO, allow rapid diagnosis of rifampicin-resistance (<2 hours), considered a reliable proxy of MDR.

The test, operating in a closed system (the cartridge) is safe, automated, prevents further contamination of the sample and is easy to manage.

Another group of rapid tests (also recommended by WHO) have been developed to detect genetic mutations associated with resistance to fluoroquinolones and injectables, the drugs presently defining XDR-TB.

Although enormous progress has been achieved in scaling-up the use of new rapid diagnostic methods,[75] still an important proportion of MDR-TB cases have no access to these services (ref),[6] ideally tests should be tiered at point of care, this can then be confirmed at a dedicated centre, if confirmed samples are sent to a reference laboratory for drug susceptibility testing.

3. Provide immediate access to effective treatment and proper care

Furthermore, an important proportion of diagnosed cases has no access to adequate treatment, or the access is delayed due to the difficult to procure, distribute and manage new drugs (ref).[6]
Finally, after more than 40 years of silence two new drugs, bedaquiline and delamanid have been approved by the USA and the European regulatory authorities for the treatment of multidrug resistant Tuberculosis in 2012 and 2013, respectively, (ref).[56,76,77]
Fortunately, evidence is accumulating on the efficacy and safety of these drugs (ref).[78] Although caution (justifying ECG monitoring) is necessary, new evidence is accumulating showing the 2 drugs are, in general, well tolerated (ref)[79-81] and even their co-administration seems to be safer than previously thought (ref).[79,82-85] New evidence is also accumulating on some of the re-purposed drugs like linezolid (now largely used and 'promoted' in Group A by WHO)(ref),[18,86,87] clofazimine (ref)[88] and carbapenems (ref).[89-91]
Importantly, adequate surveillance of adverse events needs to be in place, particularly for the new and re-purposed drugs. The WHO, in fact, advocates for the aDSM approach (active Drug Surveillance Monitoring) (ref).[92]
The new challenges are represented by the possibility to offer universal access and social protection to the patients in needs, while ensuring free of charge availability of quality drugs to the highest proportion of cases possible, as well as optimising the clinical capacity to offer rapid diagnosis and quality treatment.

4. Prevention of transmission through infection control

The importance of infection control within the vision of breaking the chain of transmission is clearly stressed by the WHO End TB Strategy (and by the WHO Policy on Infection Control (ref).[58,93]
In Europe a survey conducted in 5 references centres and aimed at evaluating how MDR-TB cases were managed, found some drawbacks in the area of infection control (lack of negative pressure ventilation rooms and drawbacks in availability of infection control plans) (ref).[94-96] A new audit performed in 2017 found improvement on this aspect (ref).[97]
Recently the WHO, Regional Office for Europe, published a policy document useful to improve infection control in Europe (ref).[98,99]
Although focused on the traditional managerial activities, administrative controls, and environmental controls, the new policy document supports the FAST approach, defined as 'Find cases Actively by cough surveillance and rapid molecular sputum testing, separate safely and Treat effectively based on rapid DST), which gave excellent results in several countries including the Russian Federation. The document also reviews the available evidence on: 1) how TB infectiousness evolves in response to effective treatment (and which factors can lower or boost infectiousness); 2) presents policy options on the infectiousness of TB patients relevant to the WHO European Region; 3) defines the limitations in the available evidence and 4) provides recommendations for further research.

5. Increase political commitment and financing. Ensuring adequate diagnosis, treatment, and management for drug-susceptible TB.

The relationship between socio-economic conditions and TB is well known (ref).[56]
Recently, in evaluating the potential impact of the End TB Strategy, a modelling study has shown that reducing extreme poverty and expanding social protection can reduce the TB incidence by 84.3% (ref).[100-102]
An important aspect of political commitment deserving further discussion is the legal framework, and in particular its effect on TB control. Although WHO recommend reduction of unnecessary hospital admission and a shift towards home-care management in view of the economic, patient-related and infection control implications, this cannot be done if the health system refunds is based on hospital-bed occupancy (as common if former Soviet Union countries).
In several of these countries, for example, the hospital stay is a standard of care for the intensive phase of treatment (in MDR-TB case it can be higher than 200 days) with associated costs ranging from US$ 2935 (Uzbekistan) to US$ 64,250 (Latvia) (ref).[56]
Clearly such an approach prevents these recommendations to be applied.[103,104]
Armenia recently piloted a change in the refund approach, opening the door to an out-patient driven approach (ref).[105]
Clearly political commitment is necessary to support all the above-mentioned actions, from adoption of updated guidelines to implementation of adequate infection control measures as well as quality diagnosis and treatment.

The need for updated definitions

Given the recent change in MDR/RR-TB treatment classification, with rifampicin resistant TB being treated as MDR-TB and the significant removal of second line injectables promoting a preferred all oral regimen, the current definitions for MDR-TB and XDR-TB may require updating (ref).[37]

Conclusion

Notwithstanding the gradual declines in TB incidence worldwide, MDR-/XDR TB is a growing threat to global health security.

Recent advances in basic and operational research has led to the development and implementation of rapid diagnostic methods for MDR-TB, allowing for increased detection and treatment. New WHO recommendations for use of an all oral, less toxic treatment regimen provides hope for more patients being enrolled on treatment. Several new drug trials experimenting multiple combinations of regimens to determine more effective and shorter regimens are ongoing.
Several new technologies are being rolled out and an upscaling of efforts are being made to meet the programmatic challenges of MDR-TB. Achieving control of MDR-TB will require increased political commitment, resources, reducing poverty, improving the quality of housing and sanitation, resolution of conflicts as well as providing minimum levels of free healthcare to all.

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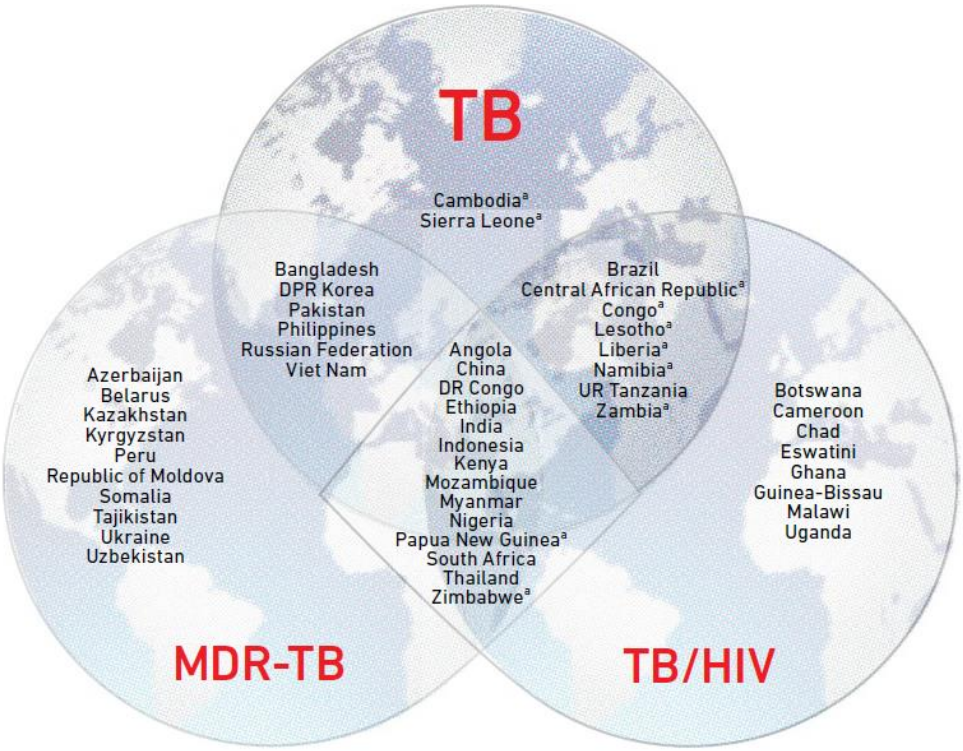
Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

Table 1: New WHO drug classification for MDR-TB regimens. WHO MDR-TB guidelines 2019.[18]

Table 2: Interventions to prevent drug-resistant TB (Ref: WHO Companion handbook for programmatic management of DR-TB)

There are five principal ways to prevent drug-resistant TB: 1. Early detection and high-quality treatment of drug-susceptible TB. 2. Early detection and high-quality treatment of drug-resistant TB. 3. Effective implementation of infection control measures. 4. Strengthening and regulation of health systems. 5. Addressing underlying risk factors and social determinants



[a] Indicates countries that are included in the list of 30 high TB burden countries on the basis of the severity of their TB burden (i.e. TB incident cases per 100 000 population per year), as opposed to the top 20, which are included on the basis of their absolute number of incident cases per year. Also see Table 2.4.

Figure 1: In 2015 WHO defined three High burden country (HBC) lists for the period 2016–2020: one for TB, one for MDR-TB and one for TB/HIV, the figure above demonstrates overlap of these lists. Courtesy of WHO TB Report 2018.[1]

Figure 2: WHO map with the estimated incidence of MR/RR TB in 2017. Courtesy of WHO TB Report 2018.[1]

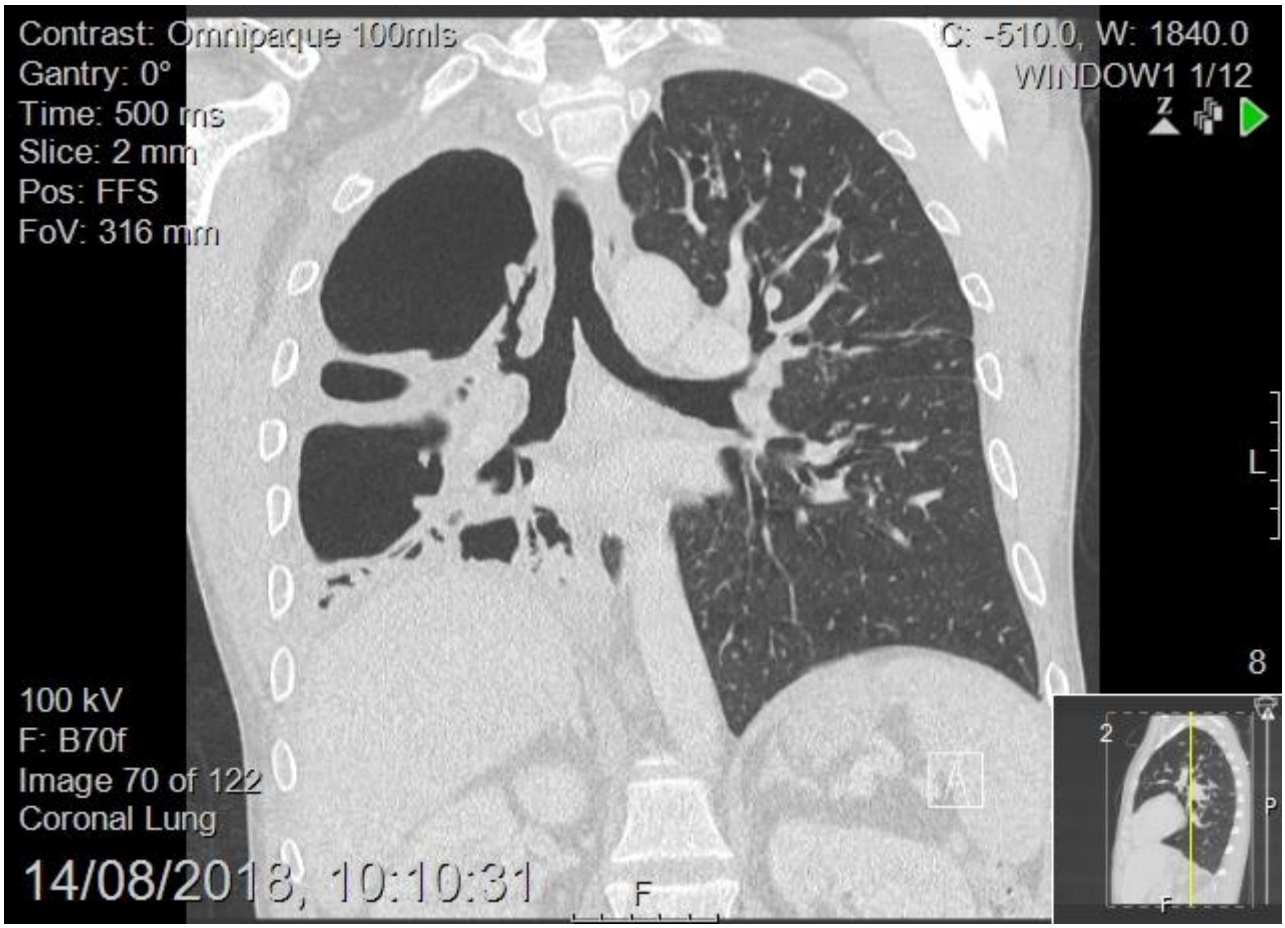


Figure 3: Computer Tomography scan of a 35-year-old man with a destroyed right lung from Tuberculosis.

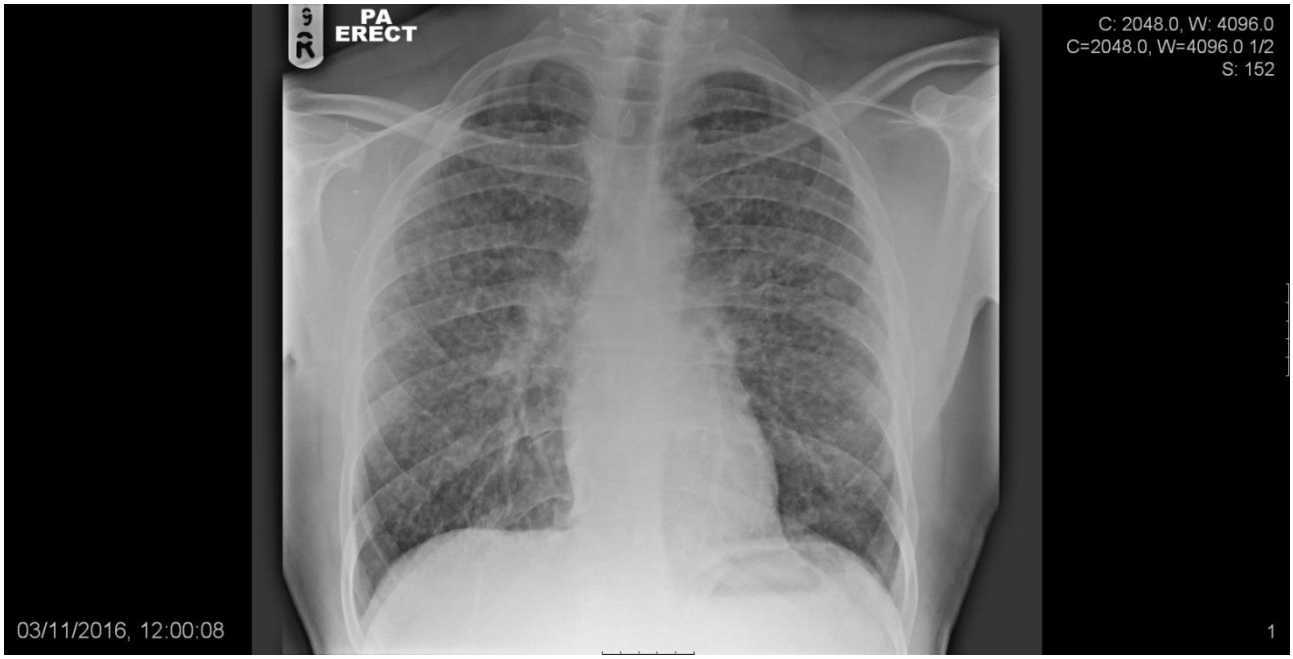


Figure 4: Chest x-ray of a 20-year-old man living with HIV presenting with miliary changes, mycobacterial blood cultures isolated *Mycobacterium tuberculosis*.

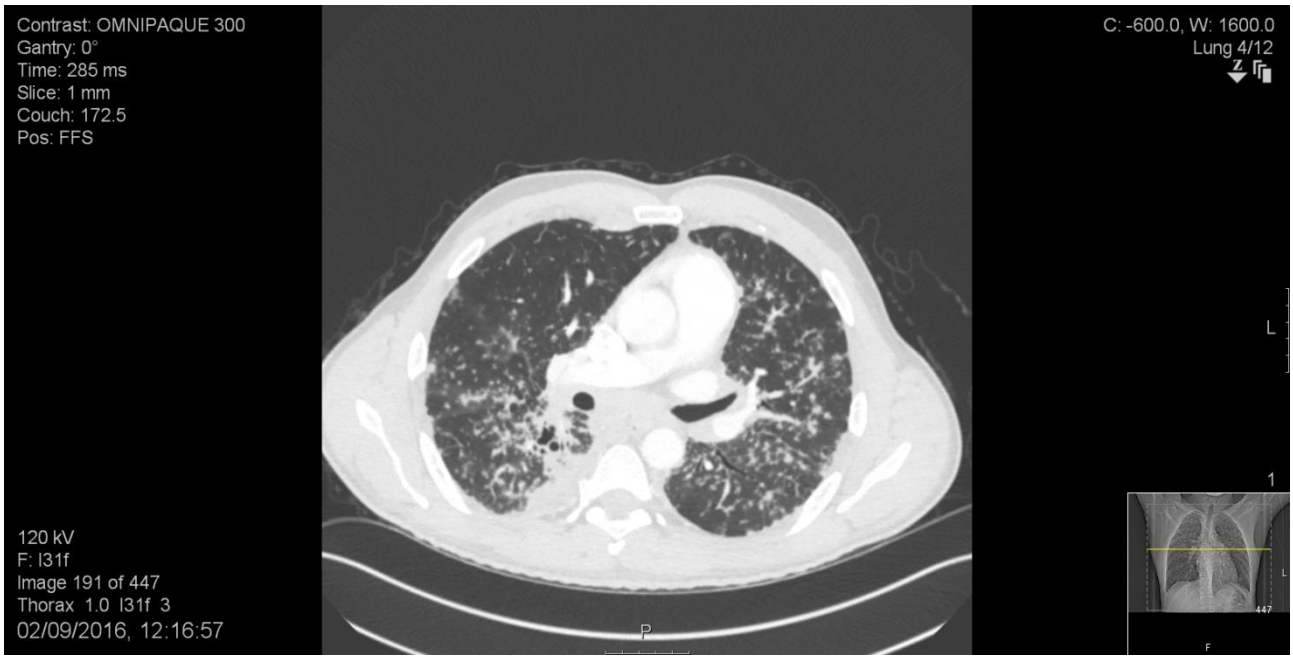


Figure 5: Computer Tomography scan of chest of a 40-year-old man multinodular – tree in bud appearance in both lung fields, the patient was positive for acid fast bacilli on sputum smear microscopy examination.

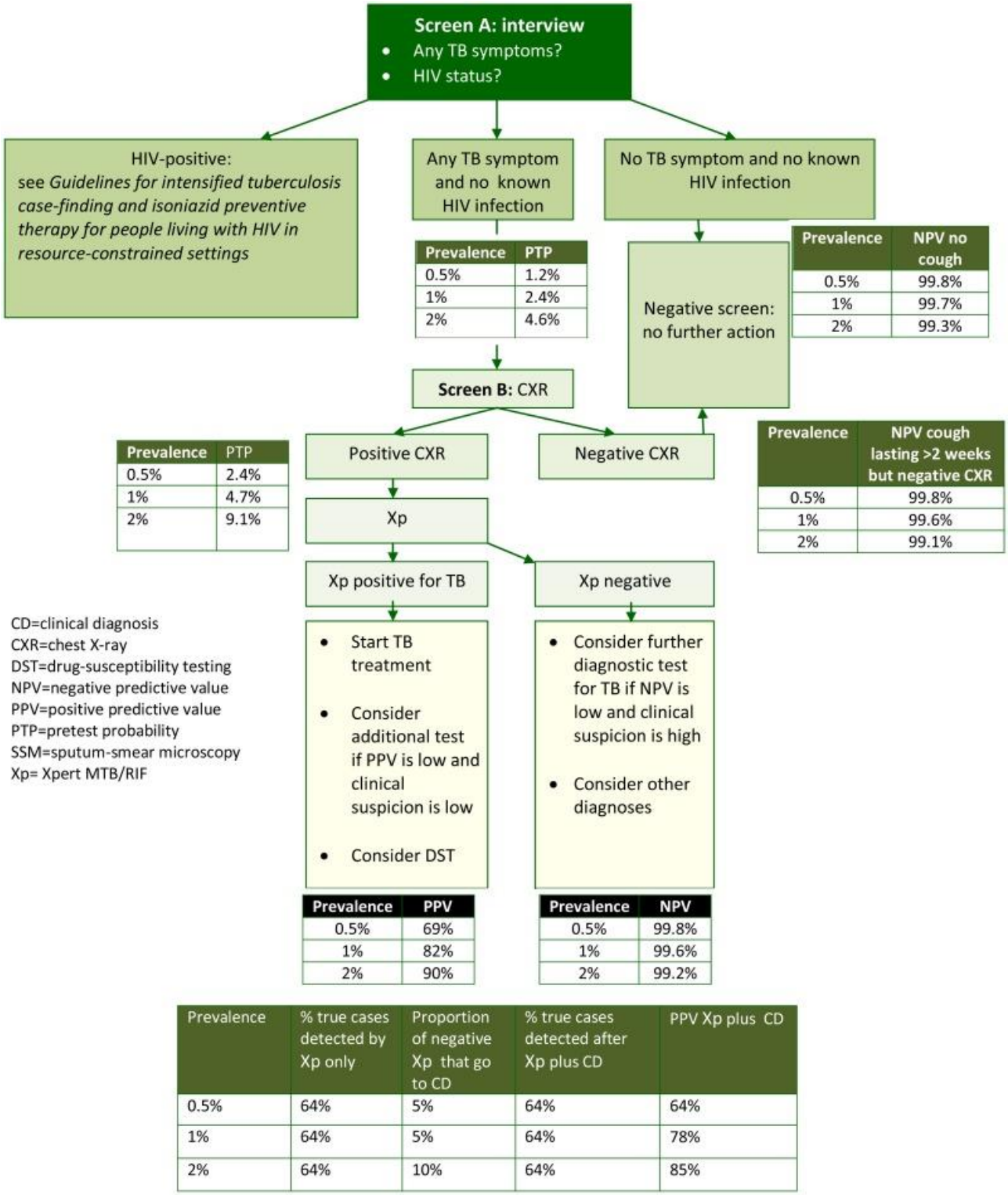


Figure 6: Diagnostic algorithm incorporating use of GeneXpert. Courtesy of Systematic Screening for Active Tuberculosis: Principles and Recommendations. Geneva: World Health Organization; 2013.[17]

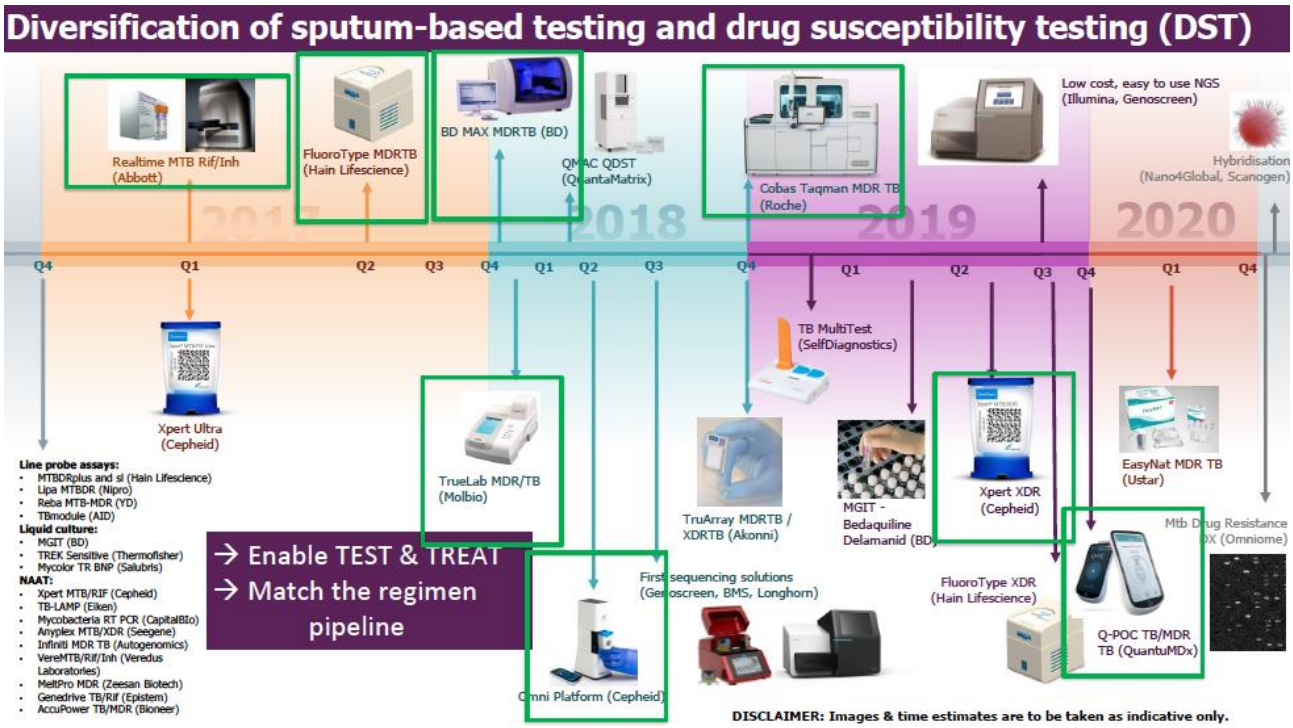


Figure 7: Diagnostic landscape for sputum-based testing methods for Mycobacterium tuberculosis detection and susceptibility determination. Courtesy of FIND Diagnostics Geneva.

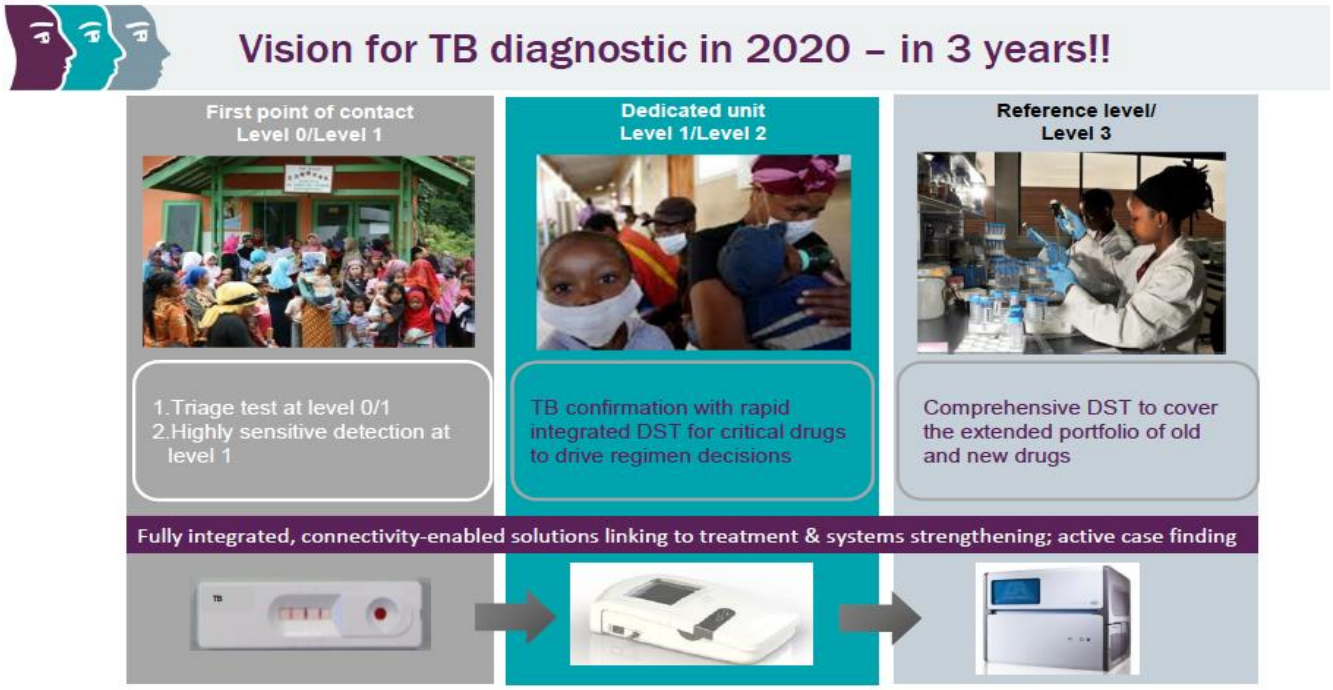
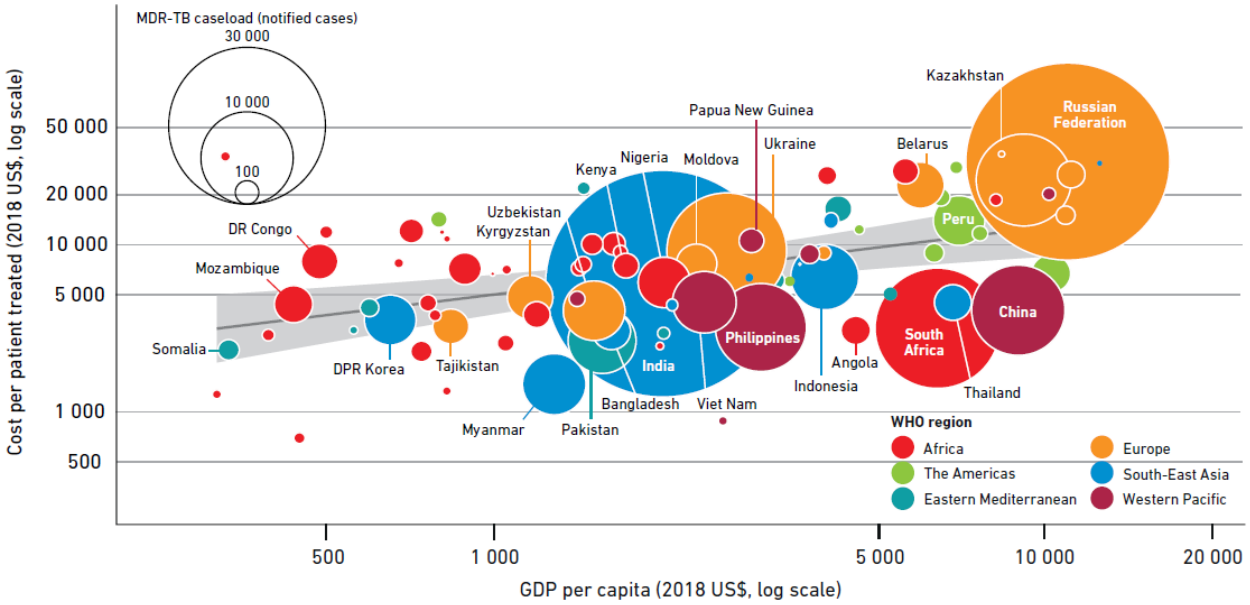


Figure 8: Vision for a diagnostic cascade for Mycobacterium tuberculosis detection and susceptibility determination. Courtesy of FIND Diagnostics Geneva.



[a] Limited to countries with at least 20 patients on second-line treatment in 2017.

Figure 9: Estimated cost per patient to treat MDR-TB in 85 countries. Courtesy of WHO. WHO TB Report 2018.[6]