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Clinical Commissioning Policy Statement

2317: Treatment for defined patients with rifampicin resistant (RR) tuberculosis (TB), multidrug-resistant (MDR) TB, pre-extensively drug-resistant (pre-XDR) TB and extensively drug-resistant (XDR-TB) including bedaquiline and delamanid (All Ages)

Summary

NHS England will commission treatment for defined patients with suspected, functional, or confirmed rifampicin-resistant (RR) tuberculosis (TB), multidrug resistant (MDR) TB, pre-extensively drug resistant (pre-XDR) TB and extensively drug-resistant (XDR) TB including bedaquiline and delamanid in accordance with the criteria outlined in this document.

In creating this policy statement, NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy statement document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

What we have decided

NHS England have reviewed existing evidence and obtained updated clinical consensus to make the following treatment available for defined patients with RR-TB, MDR-TB, pre-XDR and XDR-TB with: the extended (>6 months) and/or sequential and/or concurrent use of bedaquiline and delamanid. We have concluded that there is enough evidence to make the treatment available.

The 2024 update to this clinical commissioning policy statement covering the concurrent use of bedaquiline and delamanid is outside of the scope of the original independent evidence review conducted in 2019 and is based on clinical consensus in conjunction with the updated WHO 2022 guidelines.

Links and updates to other policies

- This document updates 201203P: Clinical commissioning policy statement: Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid
- This document is linked to the following policy: Bedaquiline (B), pretomanid (Pa), linezolid (L) +/- moxifloxacin (M) (BPaLM/BPaL) for patients aged ≥14 years with suspected, functional or confirmed rifampicin resistant (RR) tuberculosis (TB), multidrug-resistant (MDR) TB or pre-extensively drug resistant (pre-XDR) TB [URN: 2310]

Plain language summary

About RR-TB, MDR-TB and XDR-TB

TB is a disease caused by the bacterium Mycobacterium tuberculosis (M.tuberculosis), which mainly affects the lungs, but can cause disease in other areas of the body. Rifampicin-resistant (RR) TB occurs when the TB bacteria is resistant to the antibiotic (anti-TB drug) rifampicin. Multidrug-resistant tuberculosis (MDR-TB) is when the TB bacteria is resistant to rifampicin and isoniazid. Pre-extensively drug-resistant (pre-XDR) TB is a form of TB that is resistant to rifampicin isoniazid, and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant tuberculosis (XDR-TB) is a form of TB that is resistant to at least four of the main anti-TB drugs (rifampicin, isoniazid, at least one fluoroquinolone and at least one other 'Group A' drug) (WHO, 2022). Patients usually acquire drug resistant disease either as a result of spread of a drug resistant strain from another person or as a result of ineffective or incomplete treatment. In addition, functional resistance to antibiotics occurs when patients are unable to take certain medicines for reasons other than microbiological resistance, such as intolerance or drug interactions e.g., patients who do not have evidence of microbiological resistance to rifampicin but are unable to take rifampicin due to potential interaction with other medications they are using. As a result, they have functional RR-TB. This policy is for patients with suspected, functional or confirmed RR-TB, MDR-TB, pre-XDR TB or XDR-TB for whom a WHO-recommended regimen cannot be constructed.

About Current Treatment

The medicines used in the treatment of drug-resistant TB are classified into Groups A, B and C (WHO, 2022). Group A drugs include: levofloxacin or moxifloxacin, bedaquiline and linezolid. Group B drugs include: clofazimine, cycloserine or terizidone. Group C drugs include: ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, ethionamide or protionamide, and P-aminosalicylic acid (PAS). The combination of treatments used is based on the results of drug-susceptibility testing (DST) and the patient's clinical history. Treatment for patients with RR-TB is the same as for patients with MDR-TB. Individualised treatment regimens consist of at least four drugs to which the mycobacterium is likely to be susceptible (WHO, 2022). Where possible, preference is given to treatment regimens where all the medicines used can be taken orally.

There is a smaller subset of patients with RR-TB, MDR-TB, pre-XDR TB or XDR-TB, who are not covered by the above standard treatment options. For these patients, it is not

possible to construct a WHO recommended treatment regimen, either as a result of additional drug resistance (in the case of patients with confirmed, suspected or functional XDR-TB), or as a result of functional resistance. Current treatment options for these patients are limited and consist of individualised treatment regimens with a total treatment duration of 18–20 months suggested for most patients, but this may be modified according to the patient's response to therapy (often continuing for 15–17 months after culture conversion). Bedaquiline and/or delamanid form part of these individualised treatment regimens.

Currently, bedaquiline or delamanid may be used sequentially and for a maximum duration of 24 weeks (six months) in the first instance. Treatment must be reviewed at least every six months and any extension(s) (up to six months at a time) must be agreed with the UK MDR-TB Clinical Advice Service (CAS) in conjunction with the treating MDR-TB Centre and submitted with justification through the prior approval system.

About the new treatment

Antibiotics are medicines that kill bacteria that cause disease. Bedaquiline is a type of antibiotic that is used to treat defined patients with RR-TB, MDR-TB, pre-XDR TB, or XDR-TB. It must always be taken together with other medicines for treating tuberculosis. The combination of drugs is called a regimen. Bedaquiline has been shown to reduce the time to culture conversion which is when samples taken from a patient with tuberculosis do not grow the bacteria that causes tuberculosis in a laboratory. This is an indication of effective treatment.

Delamanid is another antibiotic for the treatment of tuberculosis caused by bacteria that are not killed by the most commonly used antibiotics to treat tuberculosis. It also needs to be given in combination with other drugs to treat defined patients with RR-TB, MDR-TB, pre-XDR TB, or XDR-TB and has also been shown to reduce the time to culture conversion in these patients.

NHS England have made following treatment available for defined patients with confirmed, suspected, or functional RR-TB, MDR-TB, pre-XDR, and XDR-TB: bedaquiline and/or delamanid as part of an appropriate combination regimen. This updated policy statement includes the additional concurrent use of bedaquiline and delamanid in defined patients who meet the below eligibility criteria. These drugs should be given for the necessary time and either concurrently or sequentially, if required, as determined on a case-by-case basis.

This policy statement applies to the use of longer, individualised TB regimens in patients for whom a WHO recommended regimen cannot be constructed. Some of the recommendations sit outside of the current licenses for bedaquiline and delamanid but are supported by a number of studies and clinical consensus.

Epidemiology and needs assessment

TB is a notifiable disease in England. The incidence of TB in England was 7.8 per 100,000 of the population in 2021. In 2021 a total of 4,425 people were notified with TB in England (UKHSA, 2023). Overall, TB incidence has decreased in England since 2011, but the rate of decline is slowing (UKHSA, 2023). MDR TB made up 1.9% of culture-confirmed cases in England in 2021 (Gov.uk, 2021). MDR TB centres are TB treatment centres with established experienced and expertise in managing patients with RR-TB, MDR-TB and XDR TB. As a result of the 2024 update to this policy, it is anticipated that 6 additional patients per year in England, for whom a WHO-recommended treatment regimen cannot be constructed, will be able to access treatment with bedaquiline and/or delamanid.

The National TB Surveillance System (NTBS) collects data on 6 specific social characteristics, referred to as Social Risk Factors (SRFs) that are commonly reported to increase the risk of TB and are associated with barriers in access to healthcare and poor outcomes. These SRFs are: alcohol misuse, drug misuse, homelessness, imprisonment, mental health needs and asylum seeker status. In 2021, the most common SRF was asylum seeker status at 5.4%. Males are 2 and a half times more likely than females to have one or more SRFs (risk ratio (RR) 2.52, 95% CI 2.09 to 3.04). Those recorded as unemployed are also 2 and a half times more likely (RR 2.52, 95% CI 2.15 to 2.95) to have one or more SRFs. Those born in the UK are nearly twice as likely (RR 1.93, 95% CI 1.66 to 2.24) to have an SRF compared with those born outside of the UK (TB Epidemiology Report Gov.uk, 2021).

Implementation

Based on the findings of the original independent evidence review conducted in 2019, and updated clinical consensus, the extended use (>6 months) and/or concurrent and/or sequential use of bedaquiline and/or delamanid as part of a longer, individualised treatment regimen for drug-resistant TB will be commissioned in England in line with the following criteria:

Inclusion criteria

- Laboratory confirmed RR-TB/MDR-TB/pre-XDR/XDR-TB

  OR

- Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely RR-TB/MDR-TB/pre-XDR TB/XDR-TB aetiology (e.g., sputum smear negative active disease in a close contact of a patient with laboratory confirmed RR-TB/MDR-TB/pre-XDR TB/XDR-TB). These will be discussed on a case-by-case basis at the UK BTS MDR-TB CAS and in conjunction with the appropriate specialist MDR-TB centre.

  AND

- Inability to construct a WHO recommended MDR-TB regimen EITHER through phenotypic or genomic defined resistance pattern OR because of intolerance/ drug interactions (functional RR-TB, functional MDR-TB, functional pre-XDR-TB, or functional XDR-TB). These will be discussed on a case-by-case basis at the UK BTS MDR-TB CAS and in conjunction with the appropriate specialist MDR-TB centre.

Starting criteria

In order to receive treatment with bedaquiline or delamanid for longer than 6 months and/or concurrently and/or sequentially**, ALL** of the following criteria must also be satisfied:

- The case must be discussed, and treatment agreed with the UK BTS MDR-TB CAS (see patient pathway below) and in conjunction with the appropriate MDR-TB centre.
- The patient must be managed effectively with close supervision and follow up, and where appropriate offered directly observed therapy (DOT) or video observed therapy (VOT) or equivalent.

- Bedaquiline and/or delamanid should be used as part of combination therapy in line with WHO guidelines taking into consideration:
    - in vitro resistance to a drug OR
    - known adverse drug reactions, poor tolerance OR
    - contraindication to any component of the combination regimen

Stopping criteria

Treatment will be stopped if the patient meets **ANY** of the following stopping criteria:

- A patient is cured (as defined in the treatment guidance, WHO 2022).
- Maximum duration of treatment of up to 24 months is reached.
- Unacceptable toxicity or side effects caused by bedaquiline or delamanid occur.
- Significant QT interval prolongation ≥500ms or the development of a significant arrhythmia.
- Patients are persistently non-adherent with supervision of treatment.

Monitoring

The following monitoring requirements and considerations should be adhered to in order to receive treatment with bedaquiline and/or delamanid for longer than 6 months and/or concurrently and/or sequentially:

- An obligatory framework must be in place for monitoring QT interval prolongation or development of arrhythmia with pre-treatment ECG to determine baseline QT interval and monitoring at two weeks then monthly throughout treatment; repeat if symptomatic or after the addition of any new medication known to prolong QT (TB Drug Monographs, 2023)
- Caution is required if concurrent administration of drugs recognised to prolong cardiac QT interval (e.g., clofazimine, moxifloxacin, neuroleptics, methadone and some anti-emetics); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment.

The baseline and ongoing monitoring recommendations of the TB drug monograph, (http://www.tbdrugmonographs.co.uk) must be followed.

In addition to those criteria listed above, the following safety criteria must be adhered to in any regime containing bedaquiline:

- Concurrent administration of bedaquiline with CYP3A4 inducers (such as the rifamycins, efavirenz and carbamazepine) is contraindicated in view of its metabolism via this route.
- Bedaquiline should be used with caution when given together with drugs that inhibit liver enzyme function (e.g., ketoconazole or lopinavir/ritonavir effect on CYP3A4) as this could increase bedaquiline concentration and toxicity.

In addition to those criteria listed above, the following safety criteria must be adhered to in any regime containing delamanid:

- Do not administer delamanid if serum albumin is <2.8g/dL.

- Increase ECG monitoring frequency for the full delamanid treatment period in patients who start delamanid with serum albumin 2.8g/dl to 3.4 g/dl or fall into this range.
- Concurrent administration of strong CYP3A inducers (e.g. carbamazepine or rifampicin) is contraindicated in view of delamanid's metabolism via this route.
- Caution is required in patients with known cardiac risk factors for QT interval prolongation (e.g. known congenital QTc-interval prolongation or any condition known to prolong QTc interval or QTc > 500 ms; history of symptomatic cardiac arrhythmias or clinically relevant bradycardia; any predisposing cardiac conditions for arrhythmia; electrolyte disturbances; medicinal products known to prolong QTc interval).

Dosing

The recommended dosing for adults (≥46kg):

- Bedaquiline: 400mg daily for 14 days, followed by 200mg three times per week
- Delamanid: 100mg twice daily

Source: www.tbdrugmonographs.co.uk

Recommended dosing for bedaquiline in children is by a joint weight and age-based approach. Taken from WHO Information Note: Use of bedaquiline in children and adolescents with MDR-TB and RR-TB, 2023:

Weight bands	Age (months)	Dose*
<3kg	-	Consult with Specialist
3-<7kg	0-<3 months	30mg once daily for 14 days, followed by 10mg once daily three times per week (M/W/F)
	≥3 months	60mg once daily for 14 days, followed by 20mg once daily three times per week (M/W/F)
7-<10kg	0-<3 months	30mg once daily for 14 days, followed by 10mg once daily three times per week (M/W/F)
	3-<6 months	60mg once daily for 14 days, followed by 20mg once daily three times per week (M/W/F)
	≥6 months	80mg once daily for 14 days, followed by 40mg once daily three times per week (M/W/F)
10-<16kg	3-<6 months	60mg once daily for 14 days, followed by 20mg once daily three times per week (M/W/F)
	≥6 months	120mg once daily for 14 days, followed by 60mg once daily three times per week (M/W/F)
16-<30kg	-	200mg once daily for 14 days, followed by 100mg once daily three times per week (M/W/F)
30-<46kg	-	400mg once daily for 14 days, followed by 200mg once daily three times per week (M/W/F)

≥46kg	-	400mg once daily for 14 days, followed by 200mg once daily three times per week (M/W/F)

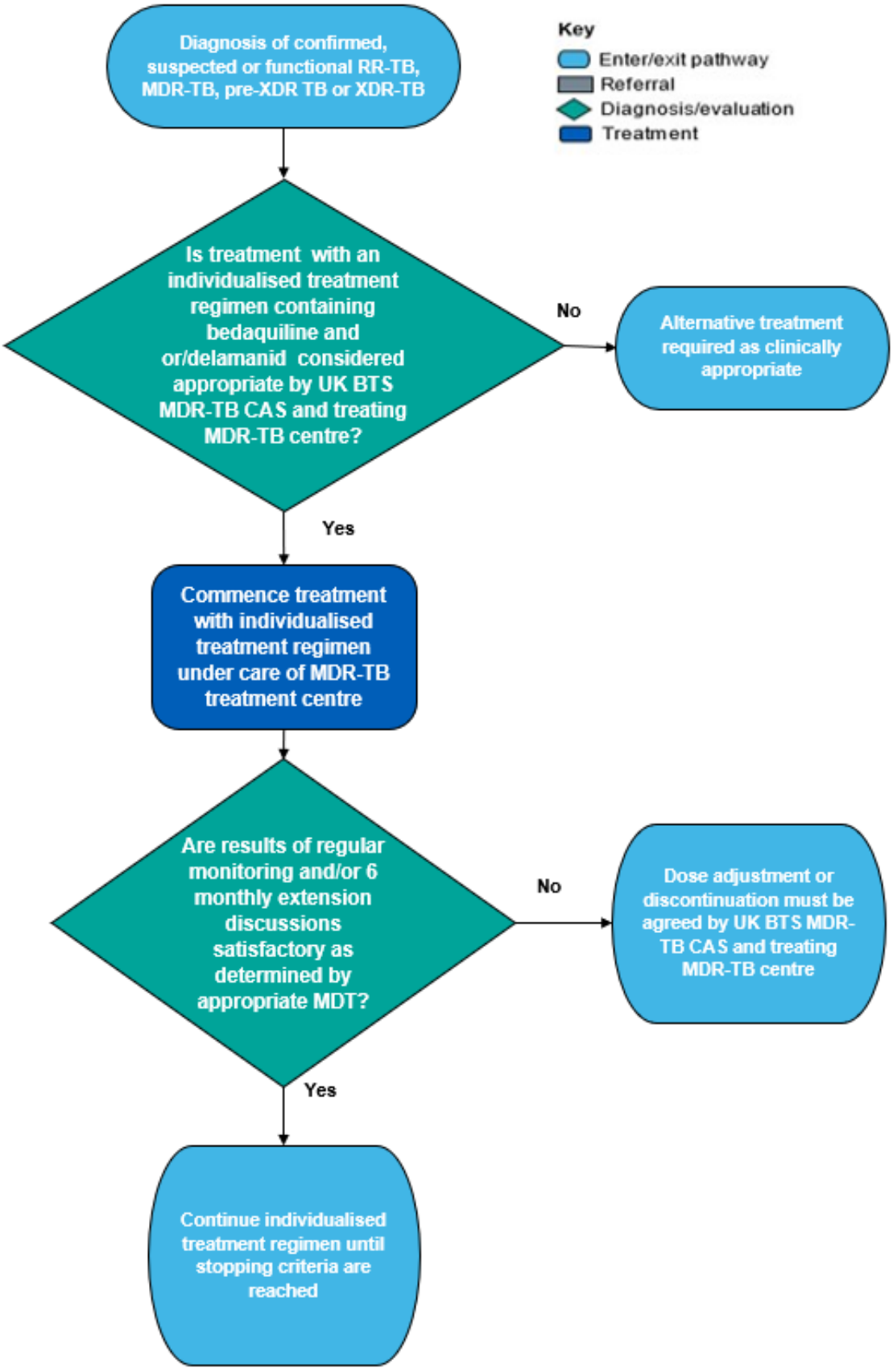
*When available, bedaquiline 20mg dispersible tablets should be prioritised for young children over the adult 100mg formulation. Non-availability of the child-friendly formulation should not be a barrier to treating children with bedaquiline. Bedaquiline 100mg tablets crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

Recommended dosing for delamanid in children is by a joint weight and age-based approach. Taken from WHO Information Note: Use of delamanid in children and adolescents with MDR-TB and RR-TB, 2023:

Weight bands	Age (months)	Dose*
<3kg	-	Consult with Specialist
3-<5kg	-	25mg once daily
5-<10kg	<3 months	25mg once daily
	≥3 months	25mg twice daily
10-<16kg	-	25mg twice daily
16-<30kg	-	50mg once daily in the morning, followed by 25mg once daily in the evening
30-<46kg	-	50mg twice daily
≥46kg	-	100mg twice daily

*When available, delamanid 25mg dispersible tablets should be prioritised for young children over the 50mg tablet. Non-availability of the child-friendly formulation should not be a barrier to treating children with delamanid. Delamanid 50mg tablets dissolved in water have been shown to be bioequivalent to tablets swallowed whole.

Patient pathway



Governance arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process. Provider organisations must register all patients using software such as Blueteq as the prior approval system and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Bedaquiline is licensed for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The use of bedaquiline for >6 months and for paediatric patients <5 years old and weighing <15kg is off-label.

Delamanid is no longer licensed in the UK. The use of delamanid in line with the eligibility criteria in this policy statement, is off-label.

Mechanism for funding

The funding and commissioning of the tariff excluded drugs (bedaquiline and delamanid) will continue to be managed through the relevant local NHS England Specialised Commissioning Team and in line with the treatment criteria included within this policy.

Audit requirements

Further evidence is needed to assess safety and efficacy. All patients treated with bedaquiline or delamanid for confirmed, suspected or functional RR-TB, MDR-TB, pre-XDR TB or XDR-TB should be recorded and reported using prior approval software. Data should include baseline information on disease severity, treatment history, documented resistance to anti-TB drugs, as well as 29 patients' response to bedaquiline or delamanid (especially for treatment durations >6 months and in children) including culture conversion and monitoring of side effects, in particular QT interval and liver function. MDR-TB centres will be expected to audit the use of bedaquiline and delamanid as outlined in this policy statement.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

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Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Drug susceptibility testing (DST)	In vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.
Extensively drug-resistant TB (XDR-TB)	TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin, isoniazid, at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).
Functional resistance	Resistance to antibiotics that occurs when patients are unable to take certain medicines for reasons other than microbiological resistance, such as intolerance or drug interactions
Multidrug-resistant TB (MDR-TB)	TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.
Pre-extensively drug-resistant TB (pre-XDR-TB)	TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin, isoniazid and at least one fluoroquinolone (either levofloxacin or moxifloxacin).
Rifampicin-resistant TB (RR-TB)	TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e., multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.
Tuberculosis (TB) disease	A disease in humans caused by the M. tuberculosis complex, which comprises eight distinct but closely related organisms: *M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. mungi, M. orygis* and *M. canetti*. The most common and important agent of human disease is *M. tuberculosis*

References

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