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Clinical Commissioning Policy

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]

Summary

Bedaquiline (B), Pretomanid (Pa), Linezolid (L) +/- Moxifloxacin (M) (BPaLM/BPaL) is recommended to be available as a routine commissioning treatment option in patients aged ≥14 years old for suspected, functional or confirmed rifampicin resistant (RR) tuberculosis (TB), multidrug-resistant (MDR) TB and pre-extensively drug resistant (pre-XDR) TB within the criteria set out in this document.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended through the licence authorisation process to be used in those age groups not included in the policy. The use of bedaquiline for extra-pulmonary TB as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label. The use of linezolid as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is offlabel. The use of moxifloxacin as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label. The use of pretomanid as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

Committee discussion

Please see the Clinical Panel report for full details of Clinical Panel's discussion. Access the Clinical Priorities Advisory Group committee papers.

What we have decided

NHS England has carefully reviewed the evidence to treat suspected, functional, or confirmed rifampicin resistant, multidrug-resistant and pre-extensively drug resistant TB with BPaLM/BPaL. We have concluded that there is enough evidence to make the treatment available at this time.

Access the evidence review which informs this commissioning position.

Links and updates to other policies

NHS England has an existing clinical commissioning policy statement for the treatment of defined patients with MDR-TB and extensively drug-resistant (XDR) TB. BPaLM/BPaL will be the preferred treatment option for all eligible patients with suspected, functional, or confirmed RR-TB, MDR-TB or pre-XDR TB. BPaLM/BPaL is not suitable for patients with XDR-TB. The existing clinical commissioning policy statement (referenced below) will apply to patients for whom the BPaL/BPaLM treatment regimen is unsuitable.

This document relates to:

NHS England Clinical Commissioning Policy Statement 201203P: Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid

The following advice from the Medicines and Healthcare products Regulatory Agency (MHRA) advice regarding the use of fluroquinolones should be taken into consideration:

- MHRA January 2024
- MHRA August 2023

Plain language summary

About rifampicin resistant TB, multidrug resistant TB and preextensively drug resistant TB

Tuberculosis (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 bacterium is resistant to the antibiotic (anti-TB drug) rifampicin. Multidrug-resistant (MDR) TB is when the TB bacterium is resistant to rifampicin and isoniazid. Pre-extensively drug-resistant (pre-XDR) TB is a form of TB that is resistant to rifampicin and isoniazid, and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant (XDR) TB, which is not covered in this poli, occurs when the TB bacterium is resistant to rifampicin, isoniazid, at least one fluroquinolone and at least one other ‘Group A’ drug (bedaquiline or linezolid) (WHO, 2022). Patients usually acquire drug resistant disease either as a result of the spread of a drug resistant strain from another person or as a result of ineffective or incomplete treatment. 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 or pre-XDR TB.

About Current Standard Treatment

The medicines used in the treatment of RR-TB, MDR-TB and pre-XDR-TB are classified into Groups A, B and C (WHO, 2022). 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.

Current standard treatment options for patients in whom fluroquinolone resistance has been excluded include an all-oral regimen for MDR/RR-TB comprising the combined use of seven agents, most of which will be continued for at least 9 months. Other treatment options include 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).

Group A includes anti-TB medicines known as fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline and linezolid. All three medicines from Group A are generally used as part of the standard drug-resistant TB treatment regimens. In addition to the three medicines in Group A, one or two further medicines from Group B (clofazimine, cycloserine or terizidone) are added. If any medicines from Group A or B cannot be used or are not sufficient, further medicines from Group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, ethionamide, prothionamide, para-aminosalicylic acid (PAS)) may be added. Treatment success is broadly defined as completed treatment in a clinically well patient with consistently culture negative specimens.

About BPaLM/BPaL

In 2022, the World Health Organization (WHO) recommended the use of a 6–9-month, alloral treatment regimen for patients with RR-TB, MDR-TB and pre-XDR TB (WHO, 2022). The regimen is known as the BPaLM regimen and comprises the following medicines: bedaquiline (B), pretomanid (Pa), linezolid (L) and moxifloxacin (M). The WHO recommendation was that the BPaLM regimen may be used programmatically for 6 months (26 weeks) in place of the longer, individualised treatment regimens, in patients aged ≥14 years with MDR/RR-TB. This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). The BPaLM/BPaL regimen can be extended to a total duration of 9 months (39 weeks). If resistance to bedaquiline, linezolid or pretomanid is confirmed or suspected, the BPaL/BPaLM regimen should be stopped, and patients should be referred for a longer individualized regimen.

Whole genome sequencing (WGS) is performed as standard in England for all cases of culture confirmed TB. If mutations coding for resistance are detected, phenotypic drug susceptibility testing (DST) is performed. WGS, and subsequent DST, should not delay initiation of BPaLM; however, the WGS and DST results should guide the decision on whether moxifloxacin can be retained. In cases of documented resistance to fluoroquinolones, BPaL (without moxifloxacin) would be initiated or continued.

The use of bedaquiline for extra-pulmonary TB as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label. The use of linezolid as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label. The use of moxifloxacin as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

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 designated TB treatment centres with established experienced and expertise in managing patients with RR-TB, MDR-TB and pre-XDR TB. Across England there is an annual case load of approximately 50-60 patients per year with suspected, functional, or confirmed RR-TB, MDR-TB or pre-XDR TB who may be eligible for treatment with BPaLM/BPaL.

Implementation

Inclusion criteria

Patients aged 14 years and older are eligible for treatment with bedaquiline, pretomanid, linezolid (BPaL) with or without moxifloxacin (BPaLM) if they meet the following criteria:

- Pulmonary TB or any form of extrapulmonary TB (except those listed in the exclusion criteria)

  AND

- Laboratory confirmed RR-TB, MDR-TB or pre-XDR TB OR

- Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely RR-TB, MDR-TB or pre-XDR TB aetiology (e.g., sputum smear negative active disease in a close contact of a patient with a laboratory confirmed RR-TB, MDR-TB or pre-XDR-TB)

  OR

- Where intolerance or drug interactions leads to the development of functional resistance (functional RR-TB, functional MDR-TB or functional pre-XDR TB)

Exclusion criteria

Patients are excluded from the BPaL/BPaLM regimen if they meet ANY of the following criteria:

- Evidence of, or suspected resistance to, bedaquiline, linezolid or pretomanid
- Known allergy to any of the BPaL/BPaLM component drugs
- A diagnosis of XDR-TB as defined by the 2021 WHO definitions
- Pregnant, breastfeeding, or if the patient is of childbearing potential is unwilling to use appropriate contraception[1]
- TB involving the central nervous system (CNS), osteoarticular TB or disseminated (miliary TB) at initiation of treatment.

Starting criteria

- Each case must be discussed, and treatment agreed at the UK BTS MDR-TB Clinical Advice Service (CAS) in conjunction with the appropriate MDR-TB treatment centre.

- Whole genome sequencing (WGS) and drug susceptibility testing (DST) should be performed in all cases of culture confirmed TB. Although this should not delay the initiation of BPaLM, the results of WGS/DST should inform the decision of whether moxifloxacin can be retained (BPaLM) or dropped (BPaL) from the regimen.

- Patients must be offered appropriate supervision, including, where appropriate, management with directly observed therapy (DOT) or video observed therapy (VOT).

[1] Patients who become pregnant during the course of treatment must be switched to an alternative treatment regimen as clinically appropriate.

Stopping criteria

- Treatment discontinuation for all patients on the BPaLM/BPaL regimen should be discussed and agreed at the UK BTS MDR-TB CAS in conjunction with the appropriate MDR-TB treatment centre. The following treatment durations are considered standard for programmatic implementation:
    - For programmatic implementation the treatment duration of BPaLM/BPaL is standardised to 6 months (26 weeks) However, an extension to a total of 9 months (39 weeks)[2] should be considered if sputum cultures are positive between months 4 and 9 or if there is inadequate clinical response.

- Any decision made by the UK BTS MDR-TB CAS, in conjunction with the appropriate MDR-TB treatment centre, regarding stopping treatment must be discussed with the patient and documented in the patient's notes.

Dosing

The recommended dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM is taken from the WHO operational handbook on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment, 2022 update and is as below:

Drug	Dose
Bedaquiline (100mg tablet)	400mg once daily for 2 weeks, then 200mg 3 times per week afterwards OR 200mg daily for 8 weeks, then 100mg daily[3]
Pretomanid (200mg tablet)	200mg once daily
Linezolid (600mg tablet)	600mg once daily[4]
Moxifloxacin (400mg tablet)	400mg once daily

- If doses are missed as part of the BPaLM/BPaL regimen, any interruption of longer than 7 days should be accounted for by extending the treatment duration for the

[2] If doses are missed, any interruption of longer than 7 days should be made up for by extending the treatment duration (for the number of missed doses); therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

[3] 200mg daily for 8 weeks, then 100mg daily is an off-label dosing regimen for bedaquiline. Trust policy regarding the use of off-label medicines should apply.

[4] It is preferred to continue linezolid at the full dose for the entire duration; however, the dose of linezolid can be reduced to 300mg or can be discontinued (and restarted when possible) if there is significant toxicity. Please refer to the WHO operational handbook on tuberculosis: Module 4: treatment drug-resistant tuberculosis 2022 update for further details.

number of missed doses; therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months respectively.

For further information on suggested dosing please refer to the WHO operational handbook on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment, 2022 update.

Monitoring

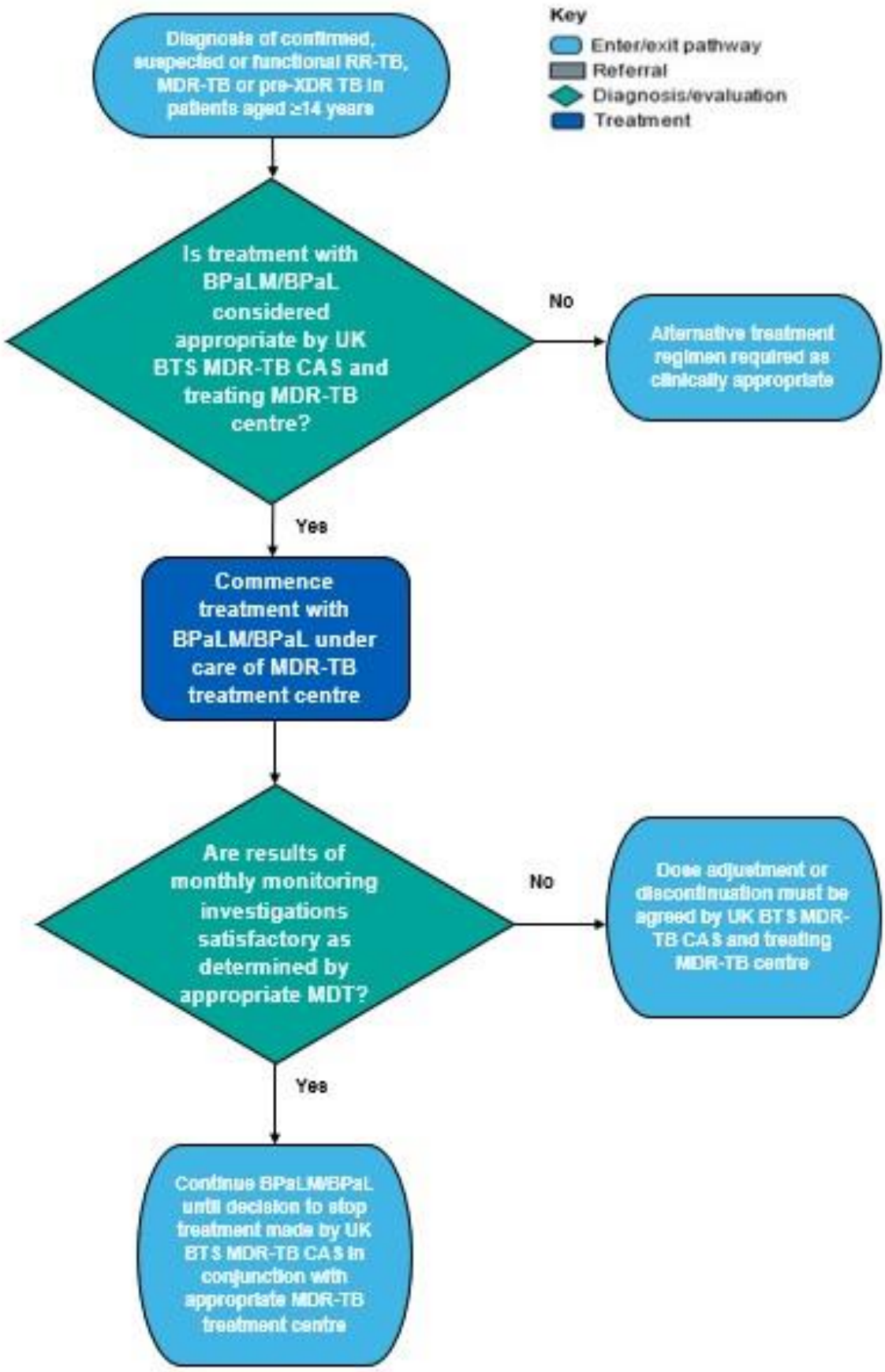
The baseline and ongoing monitoring recommendations of the TB drug monograph, (http://www.tbdrugmonographs.co.uk) must be followed, in addition to the below monitoring requirements:

- 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 1-3 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 and some antiemetics); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment.
- 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).

In addition to those criteria listed above, the following safety criteria must be adhered to in any regimen 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.

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 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 extra-pulmonary TB as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

Pretomanid has a GB Product Licence for use in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis. The use of pretomanid in this policy policy is only permitted as part of the BPaLM/BPaL regimen and in line with the eligibility criteria. The use of pretomanid as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

Linezolid is not licensed for the treatment of drug-resistant TB. The use of linezolid as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

Moxifloxacin is not licensed for the treatment of drug-resistant TB. The use of moxifloxacin as part of BPaLM/BPaL, in line with the eligibility criteria in this policy, is off-label.

Trust policy regarding the use of off-label medicines should apply.

Mechanism for funding

The funding and commissioning of the tariff excluded drugs (bedaquiline and pretomanid) 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. Linezolid and moxifloxacin are both in tariff.

Audit requirements

TB is a notifiable disease in England and standard reporting measures apply.

All cases of RR-TB, MDR-TB or pre-XDR-TB using the BPaLM/BPaL treatment regimen must be registered in the UK BTS MDR-TB CAS registry, along with treatment outcomes and appropriate follow-up data.

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.

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.

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 resistanceconferring 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*
Whole Genome Sequencing (WGS)	Refers to DNA sequencing of the entire *M. tuberculosis* genome, including both coding and non-coding regions. This can be used to identify mutations associated with drug resistance.

References

1. World Health Organization, WHO consolidated guidelines on tuberculosis Module 4: Treatment - drug-resistant tuberculosis treatment, 2022 update. Available at: https://www.who.int/publications-detail-redirect/9789240063129 (Accessed: 12 June 2023).
2. UK Health Security Agency (UKHSA) TB incidence and epidemiology in England, 2021, Research and analysis TB incidence and epidemiology in England, 2021. Available at: https://www.gov.uk/government/publications/tuberculosis-in-england-2022-report-data-upto-end-of-2021/tb-incidence-and-epidemiology-in-england-2021 (Accessed: 18 May 2023).
3. GOV.UK (2021) *TB diagnosis, microbiology and drug resistance in England, 2021*, *GOV.UK*. Available at: https://www.gov.uk/government/publications/tuberculosis-in-england2022-report-data-up-to-end-of-2021/tb-diagnosis-microbiology-and-drug-resistance-inengland-2021 (Accessed: 26 October 2023).