BTS MDR-TB Clinical Advice Service
Annual Report 2020

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This work forms part of the BTS Respiratory Quality Improvement activities. We work with our members, healthcare professionals from other specialties, and patients and carers to improve standards of care for people with respiratory diseases, and to support those who provide that care.

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EXECUTIVE SUMMARY

The BTS MDR-TB Clinical Advice Service was launched in January 2018 with the intention of fulfilling three key objectives: facilitating the provision of expert advice on the treatment and monitoring of multidrug-resistant tuberculosis (MDR-TB), increasing the understanding of drug toxicity patterns across the UK, and providing a formal gatekeeping function for the use of specially commissioned and novel drugs.

Impact of the Clinical Advice Service

Expert clinical advice on the treatment and monitoring of cases of MDR-TB (and similar infections) has a direct and immediate impact on patient care. These cases are rare and complex, and the importance of expert clinical, microbiological and public health advice cannot be overstated.

Education is essential, with clinicians gaining experience in treating MDR-TB. We have recorded 30 person-hours of clinician involvement in MDTs over 18 months (for their own cases). However, we have not quantified the time many clinicians remain in the MDT after their own case has been discussed. Anecdotal feedback is that the MDTs provide a valuable learning opportunity for clinicians and expert advisers alike.

Specialist trainee involvement in MDTs also has a wider implication for the future of the workforce. Following an initial trial period where four person-hours of trainee involvement were recorded in virtual MDTs (from April to June 2020) trainee involvement has been expanded. We are actively exploring ways to improve the educational impact of the Service in the future.

It is also anticipated that the Service will facilitate research through the BTS Data Access Request Process, launched in January 2020. This allows researchers to request access to pseudonymised data for research (from patients who have specifically consented to this use) which would ultimately help improve patient care.

Provision of advice to clinicians

See Overview 1: Service Activity in Numbers

The Service facilitates the provision of advice on a case by case basis. From January 2018 to June 2020 our panel of expert Clinical Service Advisers (CSAs) had advised on 242 cases, of which 57% were known or suspected MDR/XDR-TB. Many other cases involved sensitive TB that was functionally MDR due to toxicity.

Over 1,250 written advice messages were sent to clinicians, often within hours of a case being posted. Monthly virtual multidisciplinary team (MDT) meetings were also used to discuss 90% of cases, with treating clinicians often dialling in to provide extra detail and ask additional questions. These virtual MDT meetings were originally held by telephone, but these are now held using videoconferencing facilities.

Drug toxicity patterns in the UK

See Overview 2: Drug Toxicities

Clinicians using the Service provide details of the reasons for ceasing treatment with each drug. Reported toxicities are published in our annual report, forming a resource which may be referenced by clinicians.

Gatekeeping function – specialised commissioned and novel drugs

See Overview 3: Specialised Commissioned and Novel Drugs

Finally, the Service provides an independent review and consensus on supporting Blueteq applications for the use of bedaquiline and delamanid. Overall 53% of cases involving XDR, MDR or suspected MDR-TB have had one or more of these drugs recommended. This important gatekeeping function is likely to expand as bedaquiline use increases and with the introduction of other novel therapies such as pretomanid.

The BTS MDR-TB Clinical Advice Service forms a valuable resource supporting the care of patients both directly and indirectly. Wider implications of the Service include facilitating ongoing training and development of the respiratory workforce. As the important work of this Service continues it is anticipated that further benefit will also be realised through research activities.

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FOREWORD

The Multidrug Resistant Tuberculosis Clinical Advice Service (MDR-TB CAS), which launched in January 2018, is unique in its function within BTS as a direct clinical advice service. This Service focuses on the most complex tuberculosis cases across the UK, addressing not only MDR and XDR-TB, but also complex TB and NTM cases.

Through this Service clinicians receive advice on drug regimens, toxicity management and public health measures, as well as the impact of microbiological reports (including whole genome sequencing). This is provided through both a monthly virtual interactive MDT meeting and a rapid web-based advice service.

This multi-disciplinary service is provided by a national panel of expert volunteer Clinical Service Advisers. This expert panel comprises respiratory and infectious diseases physicians, paediatricians, public health specialists, TB nurses, pharmacists and microbiologists.

In recognition of this service, the MDR-TB Clinical Advice Service is recommended within the National TB Plan and now receives NHSE funding. This report describes the volume and breadth of the work carried between January 2018 and June 2020, and highlights the achievements of this Service which continues to provide a valuable and important resource to support clinicians and their patients.

Professor Onn Min Kon
Chair, BTS MDR-TB Clinical Advice Service Steering Group

This first annual report from the BTS MDR-TB Clinical Advice Service showcases the important role of this formal UK MDR-TB consilium in ensuring expertise and experience in the treatment of patients with MDR-TB are coordinated and shared across the UK.

The provision of advice to clinicians – often as little as hours after the case is posted – is essential in ensuring appropriate regimens are started as early in treatment as possible. Work to improve the understanding of drug toxicity patterns in the UK will help form a valuable resource for clinicians busy balancing effective antibiotic treatment with overall patient wellbeing in these highly complex cases.

The BTS MDR-TB Clinical Advice Service represents a crucial new and innovative practice within BTS, and it is hoped that this valuable work will continue for many years to come.

Professor Jonathan Bennett
Chair, BTS Board of Trustees

BTS MDR-TB Clinical Advice Service Steering Group Membership 2020:

Professor Onn Min Kon	Chair
Dr Colin Campbell	Public Health England (PHE) TB Surveillance Team
Dr Toby Capstick	Consultant Pharmacist
Dr Martin Dedicoat	British Infection Association (BIA) representative
Professor Marc Lipman	British HIV Association (BHIVA) representative and Chair of the TB Specialist Advisory Group (SAG)
Professor Grace Smith	National Mycobacterial Reference Service (NMRS) representative
Dr Simon Tiberi	Infectious Diseases Consultant
Lynn Altass	NHSE (Corresponding member)
Mrs Sheila Edwards	BTS Chief Executive
Miss Sally Welham	BTS Deputy Chief Executive
Mr Miguel Souto	BTS Head of Clinical Programmes
Miss Maria Loughenbury	BTS Lung Disease Registry Manager

ACKNOWLEDGEMENTS

The BTS MDR-TB Clinical Advice Service received initial funding from Public Health England (PHE) for the year 2017/18. Funding to support the continued operation of the Service was received from NHS England for the years 2018/19 and 2020/21.This support is gratefully acknowledged.

We would also like to acknowledge the Clinical Service Advisers who generously volunteer their time and expertise, without which the Clinical Advice Service would not be able to run. A full list of the Clinical Service Advisers who have supported the Service since 2018 is included on page 35.

If you would like to know more about the BTS MDR-TB Clinical Advice Service please visit the BTS website at:
https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

INTRODUCTION

The management of MDR-TB is more complex and associated with more adverse effects than standard TB treatment. The number of people in the UK with MDR/RR-TB increased to 52 in 2019. Treatment was completed within 24 months in only 60.9% of the 2017 cohort[1]. Furthermore, the complexity of MDR-TB cases is broad and a substantive proportion of patients have health, social or economic circumstances that confound their treatment and contribute to poor outcomes. The cost of treating MDR-TB is extremely high (at least 10 times that of drug sensitive TB), in part due to prolonged isolation in hospital and costly alternative anti-mycobacterial drugs.

MDR-TB cases appear sporadically and in any location across the UK. Therefore, patients may be seen by clinicians with little experience of MDR-TB or the drug regimens required for successful treatment. As a result, there is potential for patient outcomes to vary widely on an individual case basis and across the country. Given the low incidence of MDR-TB and the potential for some TB units seeing none or very few cases routinely, there was felt to be an important case for facilitating access to an experiences national panel. This panel would allow discussion of the most complex and serious TB cases in the setting of a multidisciplinary team including public health, pharmacists and the National Mycobacterial Reference Service. This in the background of increasing use of genomic resistance data, complex novel and toxic drug regimens and more stringent public health considerations.

Consequently, the BTS MDR-TB Clinical Advice Service was launched in January 2018. It is a clinically-orientated service whereby the UK's leading MDR-TB experts provide advice to clinicians on the care of patients on a case by case basis. It was developed with the aim of improving standards of care for patients with MDR-TB (or other complex TB/mycobacterium infections). To this end the Service is used to record and analyse information about the health and treatment of patients, including genotypic and phenotypic drug sensitivity results, drug regimens used, regime changes/toxicities and non-medical complexities that it is hoped may lead to better granularity regarding what actually occurs in these cases and the clinical and social issues that prevent optimal management.

There are three primary routes through which the Service works with to improve patient care:

- **Facilitating the provision of advice to clinicians**
  After patient consent is obtained clinicians can post their case to the Clinical Advice Service. The panel of expert Clinical Service Advisers (CSAs) then reviews the anonymised case details, and advisers are able to provide their advice on treatment and monitoring through the website as soon as the case is posted.

  Virtual multidisciplinary team meetings (MDTs) are also held monthly, where CSAs from a range of disciplines discuss cases in real-time and reach a consensus on the advice to feed back to clinicians. Treating clinicians frequently attend these MDTs, proving valuable extra insight into the cases discussed.

- **Providing an expert opinion on the use of specialised commissioned and novel drugs**
  One role of the panel of CSAs is to consider the appropriateness of the use of specialised commissioned and novel drugs. When clinicians make an Individual Funding Request (IFR) through the Blueteq system, for funding to use bedaquiline or delamanid, they are asked to confirm whether the BTS panel of MDR-TB CSAs has considered the case and supported the use of these drugs.

- **Supporting research**
  All patients whose cases are discussed through the Service must give consent for their data to be processed for the purpose of advice being given on their treatment. They are also, separately, asked if they give consent for their anonymised data to be used for the purpose of research.

  In 2020 BTS launched a data access request process, through which researchers from external organisations may apply to access pseudonymised data. The intention is that the data gathered through the Service may be used to improve care for patients with TB in the future.

  For more details about the BTS Data Access Request Process please visit:
  https://www.brit-thoracic.org.uk/quality-improvement/bts-clinical-data-policy-and-data-access/

This report is intended to provide an overview both of the activities of the Clinical Advice Service and also of the cases which have been discussed through the Service.

Who can participate in the BTS MDR-TB CAS and how many are doing so now?

The BTS MDR-TB Clinical Advice Service is open to all secondary and tertiary care institutions in England, Scotland, Wales and Northern Ireland, as well as the island territories (Crown Dependencies). At the end of June 2020, over 300 clinicians had registered to use the Service and cases had been entered from a total of 75 sites across the UK.

Clinicians may bring cases of patients with confirmed or suspected drug-resistant tuberculosis, or other complex tuberculosis or mycobacterial infections, to the Service for discussion. Patient consent is required before patient data may be entered into the CAS site.

Overall 242 cases had been discussed through the Service from January 2018 to June 2020.

Data Entry

Data entry for individual patient records is divided into three sections:

- Patient demographic information (age, gender, comorbidities, etc.).
- Clinical features at the time the case is first brought to the Service.
- Follow-up information from subsequent clinic visits.

Service Ethics Approval, Information Governance and Data security

Ethical approval for the British Thoracic Society Multidrug Resistant Clinical Advice Service Database (17/LO/1539) was granted by the London – South East Research Ethics Committee in October 2017. Patient consent must be obtained before any patient information is entered into the BTS MDR-TB CAS. Information for patients and copies of the dataset are available on the BTS website at:
https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

All patient identifiable data (e.g. name, date of birth, postcode) are encrypted at the point of entry and visible only to Clinical Advice Service users in the centre responsible for treating the patient. Therefore, identifiable data may only be accessed by the hospital teams directly responsible for caring for the

patient. No patient identifiable data are available to BTS MDR-TB Clinical Advice Service administrators. The British Thoracic Society Information Governance Policy and associated data security policy documents are available on the BTS website at:
https://www.brit-thoracic.org.uk/about-us/governance-documents-and-policies/

Availability of advice through the MDR-TB CAS

The MDR-TB Clinical Advice Service is provided by the British Thoracic Society to facilitate discussion between health care professionals in relation to individual patient cases of confirmed or suspected MDR-TB (or other complex TB/mycobacterium infections).

The British Thoracic Society or the MDR-TB Clinical Advice Service does not in itself provide medical advice. The posting facility and reports provided are intended to support the clinician so they are provided with a variety of experienced opinions and discussion to inform optimal clinical decision making, and this does not constitute medical advice from BTS. It remains the responsibility of the referring healthcare professionals involved in the Service to make decisions appropriate to the circumstances of each patient in consultation with the patient and or their guardian/carer.

Notes on data and percentages/denominators

Throughout this report figures are displayed as percentages and as exact figures (of the format *numerator/denominator*). Where figures are presented in the form *numerator/denominator* the denominator may vary for a number of reasons.

Although the BTS MDR-TB Clinical Advice Service includes 138 demographic records for patients reported by the clinician to have confirmed or suspected XDR/MDR-TB, not all questions are fully completed by centres for every patient. For example, occupational status was recorded for only 130 patients and thus the denominator in this case would change.

When reading this report please be aware that:

- Denominators in this report always exclude cases where no response was entered.
- Unless otherwise stated, denominators in this report exclude cases where the saved response was ‘not known’ or ‘not recorded’.
- Percentage figures are rounded to the nearest whole number throughout this report. This means rounding errors may lead to some total percentages adding up to 99% or to 101%.

PART 1 – The Impact of the BTS MDR-TB CAS

The BTS MDR-TB Clinical Advice Service has a number of real-world benefits, including:

- **Supporting clinicians** by facilitating the provision of consensus expert advice on the treatment and monitoring regimes for their patients, and by providing an independent review and consensus on supporting Blueteq applications for the use of bedaquiline and delamanid.
- **Supporting patients** by providing clinicians with the tools needed to make the best clinical decisions for their patients, as well as working to improve care across the UK by improving understanding (e.g. of drug toxicity patterns and genomic predictions of drug resistance) and facilitating research.
- **Supporting trainees** by providing the opportunity to observe expert national multidisciplinary discussions.
- **Supporting UK MDR-TB experts** by fostering closer ties among the expert community across the UK and by appointing a mix of new and more experienced advisers (succession planning).
- **Supporting researchers** by allowing applications for access to pseudonymised patient data (for those patients who have given specific consent for their data to be used for research).

Expert clinical advice on the treatment and monitoring of cases of MDR-TB (and similar infections) has a direct impact on patient care. When clinicians post cases to the Service they may receive 'rapid response' advice almost immediately. The first responses are typically received within hours of a case being posted. The responsiveness of the Service is essential in improving patient care; promoting appropriate regimens as early in treatment as possible (ideally before treatment commences). Receiving advice through the Service within hours or days is far more rapid than regional MDTs. Where regional MDTs are available it may be weeks or months before a case is discussed.

In addition to providing this immediate advice, the Service also provides a monthly virtual MDT function. Cases which have been discussed through individual posts from advisers are then discussed in real-time, with the treating clinicians invited to attend. At these virtual MDTs a consensus opinion is reached.

Although these virtual MDTs are arranged to facilitate discussion of individual cases, they also have another dimension: education. When treating clinicians dial in to discuss their own cases they often stay on the call to listen to discussions regarding the treatment and monitoring of other cases. Anecdotal feedback from clinicians is that the MDTs provide a valuable learning opportunity.

This educational aspect of MDTs is not limited to the treating clinicians. Feedback from Clinical Service Advisers is that the MDTs are a unique opportunity to discuss a range of complex MDR-TB cases, and that there is always a chance to learn something new. Respiratory, infectious disease, paediatric, public health and microbiology trainees may also dial into MDTs to improve their knowledge and understanding of managing MDR-TB. Involving trainees in this way has wider implications for the future of the respiratory workforce. We are actively exploring ways to improve the educational impact of the Clinical Advice Service in the future.

Feedback from clinicians is essential in reviewing and improving the Service. In late 2019 a survey was circulated to seek the views of clinicians across the UK. Overall 100% of the clinicians who used the Service found the advice received to be clinically useful, and 89% described the virtual MDTs as good or excellent. Over 96% found the advice that was used helpful and easy to follow. Of those who had used the drug-o-gram function (a Gantt chart representation of drug treatment history), 83% found it to be useful. Some feedback on various issues (such as the timing of MDTs, automated logout periods, etc.) indicated that improved communication would benefit the Service, and BTS will be working to improve Service communications in the future.

Feedback from the TB community

Since January 2018 the BTS MDR-TB Clinical Advice Service has been an invaluable resource in supporting clinicians in the treatment and monitoring of their patients, and supporting the wider TB workforce. Here you can read quotes explaining the direct impact the Service has had on patients and clinicians at all levels.

Extremely helpful MDT/clinical advice service. For TB clinicians with limited experience with MDR-TB management such as me this service is invaluable as it provides expert advice in the matter of hours to days about all aspects of MDR-TB care. It gives assurance that the care will be based on the most up-to-date evidence and expert opinion for every MDR-TB patient, and the safest possible. The CAS interface is simple to use and MDTs allow direct live discussion. My patients have greatly benefited from the service and I have learned a lot about MDR-TB.

Dr Vjeran Čajić, Infectious Disease Consultant
University Hospital (Coventry)

Despite being an experienced TB physician, I always learn something new during each MDT which enhances my practice. This is a rich source of information sharing and learning for clinicians.

Professor Onn Min Kon, Clinical Service Adviser
St Mary's Hospital (London)

As a respiratory trainee, MDR-TB treatment regimens can be very hard to understand – guidelines are evolving, and the drug regimens used in individual patients are diverse and change frequently. Attending this MDT really helped me to understand how treatment decisions are made. In particular how factors such as patient comorbidities and social contexts, drug side-effects, mechanisms of drug activity, drug sensitivity testing/whole genome sequencing results, and funding challenges shape how these regimens are constructed. The meetings are also really well run, and provide an excellent example of collaborative MDT working across the country to optimise patient care. I have found them to be both educational, and inspiring! A fantastic learning opportunity.

Dr Jamilah Meghji, Respiratory Trainee
Liverpool School of Tropical Medicine (Liverpool)

The BTS MDR-TB CAS across the UK

The BTS MDR-TB Clinical Advice Service was developed with the intention of supporting clinicians in the treatment and monitoring of patients across all four nations of the UK and the island territories (Crown Dependencies).

Figure 1: **Location of submitted cases**
Since the launch of the Service in January 2018 clinicians have submitted cases of MDR-TB (and similar infections) to the BTS MDR-TB Clinical Advice Service from hospitals across England, Scotland, Wales, Northern Ireland and the Isle of Man.

Cases of MDR-TB are more commonly treated in major cities, such as London and Birmingham. The geographical distribution of cases submitted to the CAS highlights the importance of sharing local expertise and experience nationally.

British Thoracic Society

Overview 1: Service Activity in Numbers

When the BTS MDR-TB Clinical Advice Service was launched the intention was to provide an expert service that was responsive to the needs of clinicians. This overview provides a brief summary of the activities of the Service from January 2018 to June 2020.

300 clinicians are registered on the Clinical Advice Service from a total of **75** hospitals across all four nations of the UK, and the Isle of Man

43

Expert Clinical Service Advisers

- Respiratory medicine
- Pharmacy
- Paediatrics
- Thoracic surgery
- Infectious diseases
- TB nursing
- Public health
- Microbiology

242

Cases discussed by our panel of expert advisers

- **15** XDR-TB
- **89** MDR-TB
- **34** Suspected MDR-TB
- **24** Resistant non-MDR-TB

- NTM **32**
- Other **18**
- Other complex TB **11**
- Complex sensitive TB **19**

1,254

Individual messages from expert Clinical Service Advisers to clinicians who have posted cases

Initial responses are often received within hours

Discussion is a key element in identifying the best approach to treatment and monitoring for each individual case

BTS MDR-TB Clinical Advice Service 2020

90%

Of all cases brought to the BTS MDR-TB Clinical Advice Service have been discussed at our monthly virtual MDTs*. The remaining 10% were provided with advice without requiring MDT discussion.

* Excluding 12 new cases with discussion pending at the end of June 2020.

32

Virtual MDTs were held, with 10-12 cases typically discussed per meeting. Cases may be discussed as often as needed.

62

Hours of **MDT discussion.** One two-hour MDT every month, plus two *ad hoc* MDTs for cases which were especially complex

30

Person-hours of **clinician MDT involvement** since this was first recorded in January 2019

550

Person-hours of **adviser MDT involvement**. Our expert advisers gave their time, knowledge and experience voluntarily

4

Person-hours in an initial trial period of **trainee MDT involvement** over three months

We circulated a survey to UK clinicians with an interest in TB. 88% of respondents were aware of the BTS MDR-TB CAS and 63% had used the Service in the preceding 12 months.

100%

Of clinicians found the advice to be clinically useful when they responded to our survey in late 2019

- 83% said that 80-100% of their MDR cases were discussed through the Service
- 96% of clinicians would use the Service again
- 89% of clinicians described the MDTs as good or excellent

PART 2 – Multi and Extensively Drug-Resistant Tuberculosis (MDR AND XDR-TB)

Each case which is entered into the BTS MDR-TB Clinical Advice Service is assigned a 'disease category' by the treating clinician. This section of the report deals with cases initially categorised by the clinician as being either XDR-TB, MDR-TB or suspected MDR-TB.

Available data to 30th June 2020

From January 2018 to June 2020, 48 centres have contributed cases classified by the treating clinician as either XDR, MDR or suspected MDR-TB to the BTS MDR-TB Clinical Advice Service:

138 patient demographic records

138 complete clinical/diagnosis records

80 follow-up records representing 49 unique patients.

2.1 THE MDR/XDR-TB PATIENT COHORT

Patient demographic details are collected at the first clinic visit.

Gender

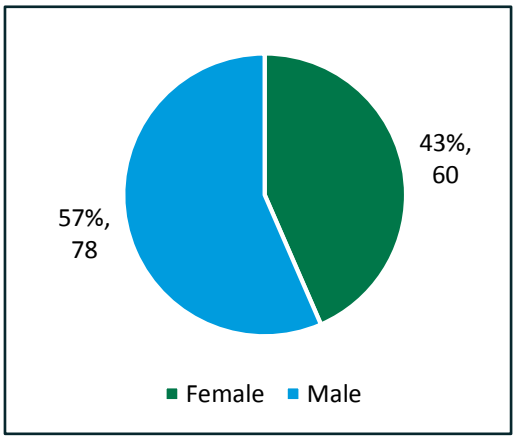


Figure 2: **Gender of patients**
From January 2018 to June 2020 over half (57%, 78/138) of patients reported by the clinician to have XDR, MDR or suspected MDR-TB were female.

Ethnicity

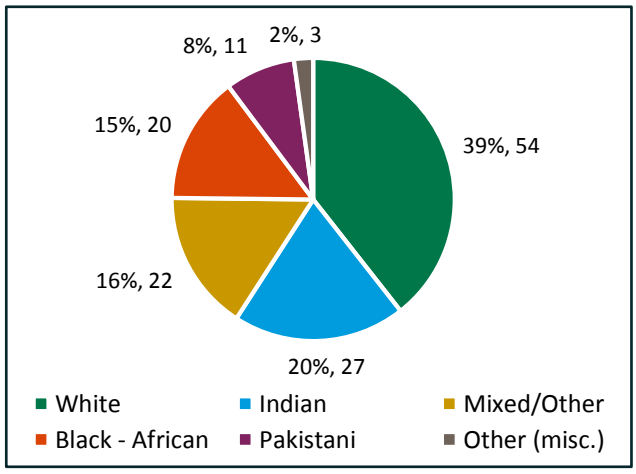


Figure 3: Ethnicity of patients
The majority of patients whose cases were discussed since January 2018 were of either White (39%), South Asian (28%) or Black African (15%) ethnicity.

Age

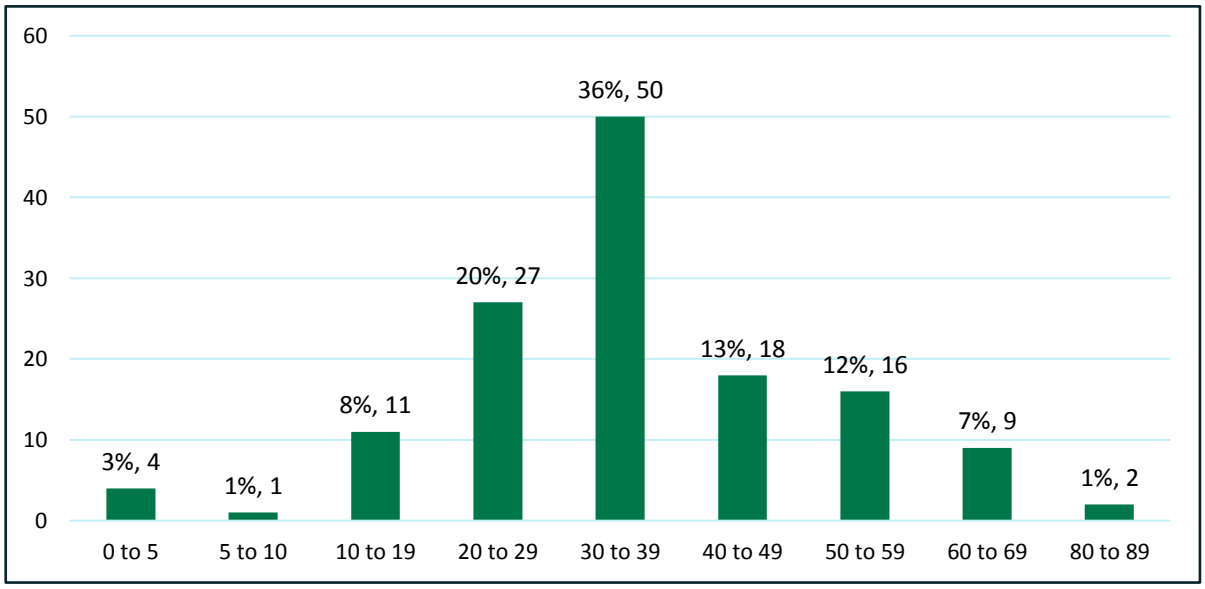


Figure 4: **Age of patients when first discussed in the Clinical Advice Service**
From January 2018 to June 2020 the mean age of patients at the time their case was first discussed on the CAS was 35.8 (± *15.3*, range 1 – 87). Over half of patients (56%, 77/138) were aged 20 – 39.

Clinical risk factors

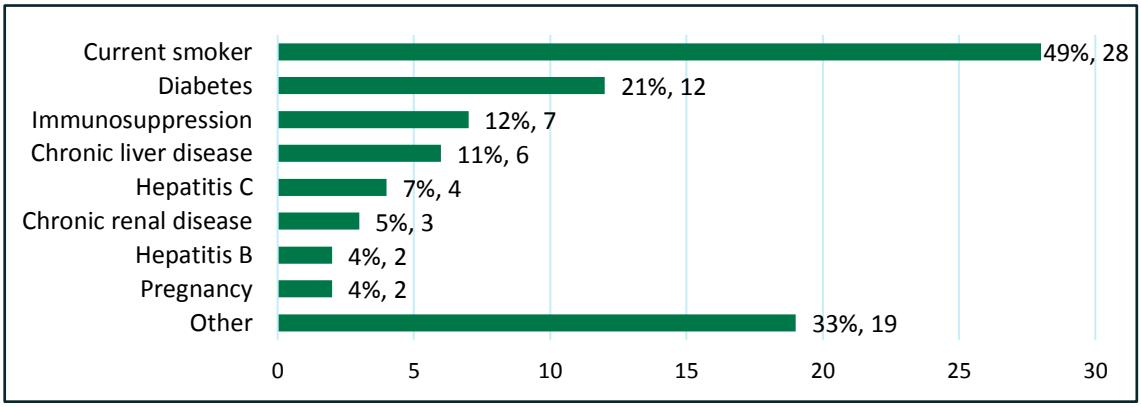


Figure 5: Clinical risk factors at first discussion in the Clinical Advice Service
From January 2018 to June 2020 almost half of all patients (45%, 47/104) had no listed clinical risk factors. Where present the most common were smoking, diabetes, immunosuppression and chronic liver disease. The most common cause of immunosuppression was biological therapy (anti TNFα) (43%, 3/7). Just under 1% of patients were known to be HIV positive (status was unknown in 5% of cases).

Social risk factors

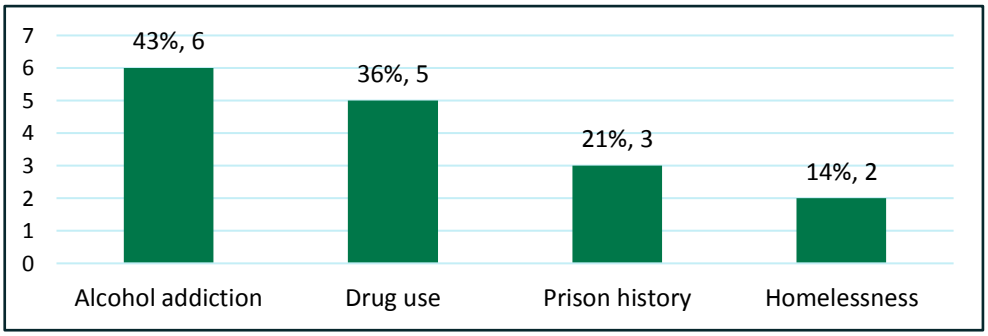


Figure 6: **Social risk factors at first discussion in the Clinical Advice Service**
From January 2018 to June 2020 the majority (88%, 103/117) of patients had no listed social risk factors. Of those who did the most common were alcohol addiction or drug use. Where drug use was a known risk factor the majority of patients (80%, 4/5) were still actively using drugs.

Occupation

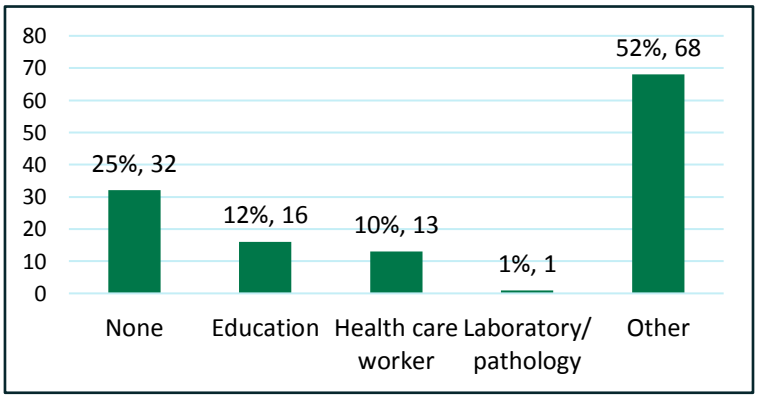


Figure 7: Occupation of patients
Overall 25% (32/130) of the cases discussed between January 2018 and June 2020 involved a patient who was known to be unemployed. Occupation categories where the risk of exposure to TB may be elevated include education (12% of all cases), healthcare (10%) and laboratory/ pathology work (1%).

2.2 CLINICAL/DIAGNOSTIC DATA

The majority of the 242 cases discussed on the MDR-TB CAS platform (from January 2018 to June 2020) were reported by the treating clinician to have drugresistant TB of some form (67%, 162/242). Of these, 55% (89/162) were reported to have MDR-TB, 9% (15/162) XDR-TB and a further 21% (34/162) were suspected to have MDR-TB at the time of submission (representing 57% of all 242 cases (*89+15+34*)).

This report gives perspective to the 2020 incidence figures from Public Health England that reported 52 cases of MDR/RR-TB in 2019 (1.8% of the total TB cases), demonstrating not only the impact of length of treatment of approximately 18 months but the complexity of the cases managed[1].

Even though the number of people in the drug-resistant cohort (confirmed or treated as MDR/RR-TB) decreased between 2017 and 2018 (64 versus 50), more of these cases were captured overall on the BTS MDR-TB CAS (especially as the Service includes cases which are functionally MDR-TB).

Symptoms

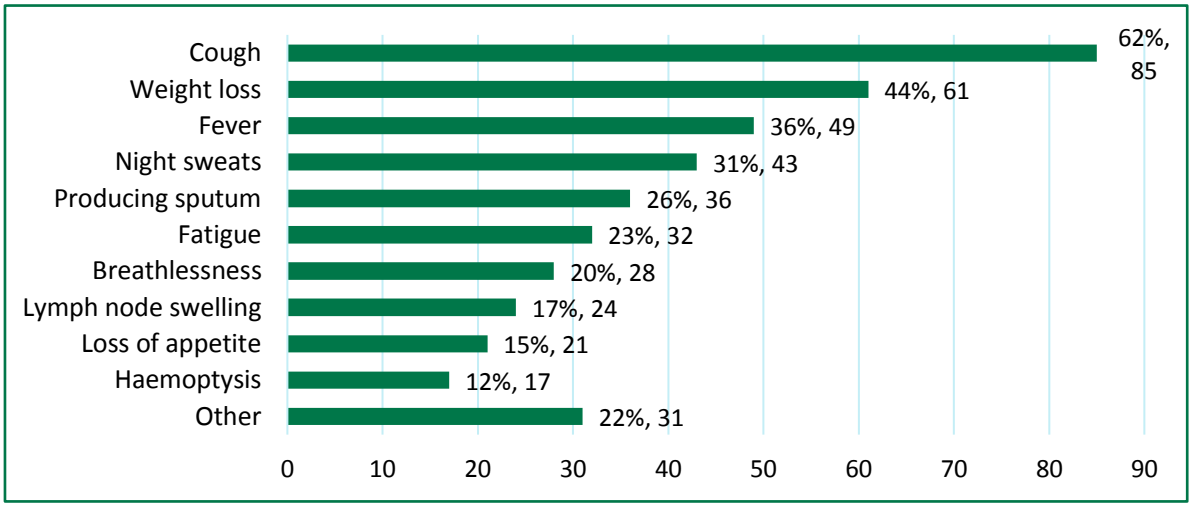


Figure 8: Symptoms at first discussion on the Clinical Advice Service
Unsurprisingly, cough (62%), weight loss (44%), fevers (36%) and night sweats (31%) were the most commonly reported symptoms. Overall 7% (10/138) of patients were reported to be asymptomatic.

Symptom duration

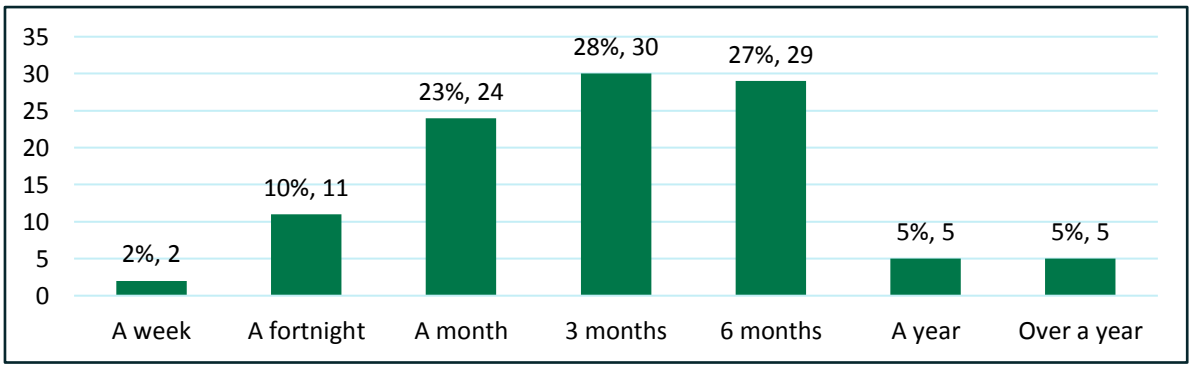


Figure 9: Symptoms at first discussion on the Clinical Advice Service
The majority of patients (73%) experienced symptoms for between one and six months before their case was entered onto the Clinical Advice Service. Symptom duration prior to case entry ranged from a week (2%) to over a year (5%).

Sample types and collection techniques

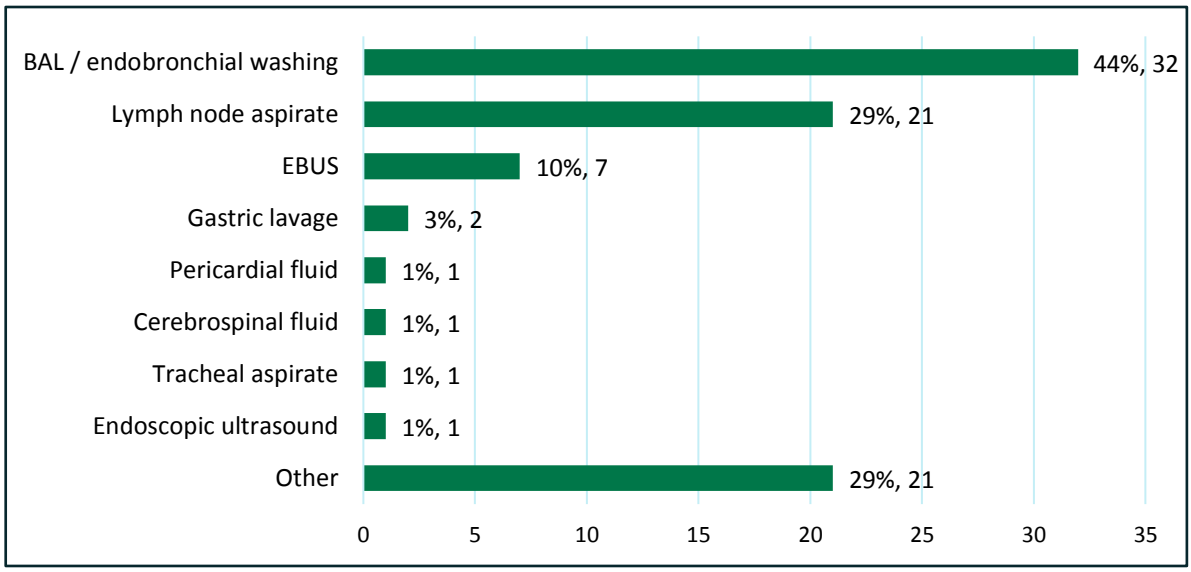


Figure 10: Sample types and collection techniques at the time of first discussion
Excluding sputa, the most common sites and techniques of smear were bronchoalveolar lavage/ endobronchial washing (44%), lymph node aspirate (29%) and endobronchial ultrasound (EBUS, 10%).

Site of disease

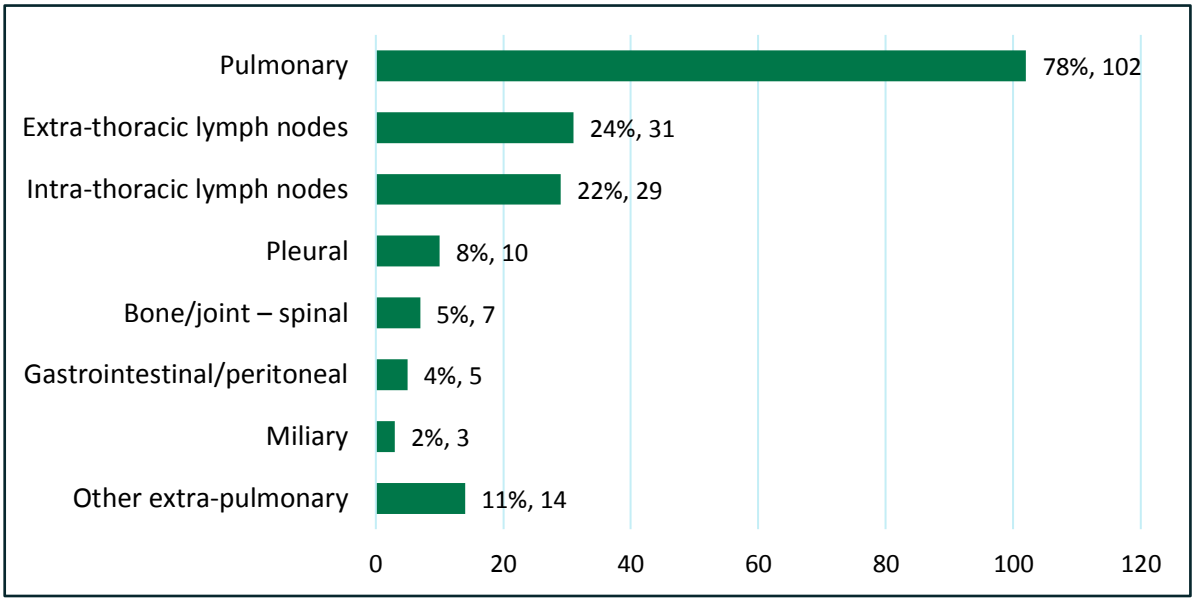


Figure 11: Site of disease
From January 2018 to June 2020 78% (102/130) of cases discussed had pulmonary involvement, with extra-thoracic and intra-thoracic lymph node involvement also frequently reported (24% and 22% of cases respectively). Cases with spinal bone (5%) and gastrointestinal (4%) involvement were less frequently reported. No cases involving solitary CNS disease were discussed.

Previous TB treatment

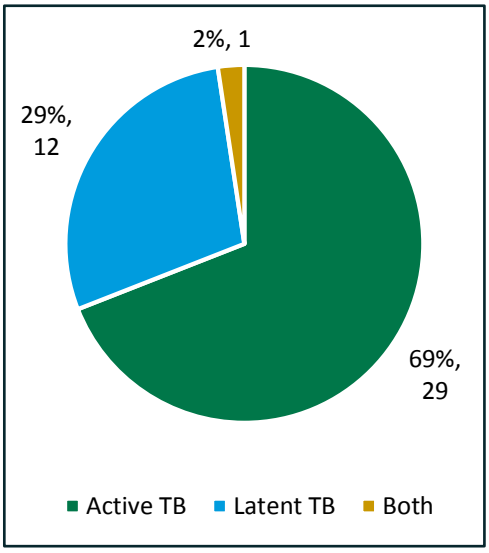


Figure 12: Previous TB treatment
Overall 30% (42/138) of patients in the XDR/MDR-TB cohort were known to have been treated for TB previously. Of these cases, 71% (29/42) involved prior active TB and 31% (13/42) latent TB (one patient had previously received treatment for both active and latent TB).

Contacts

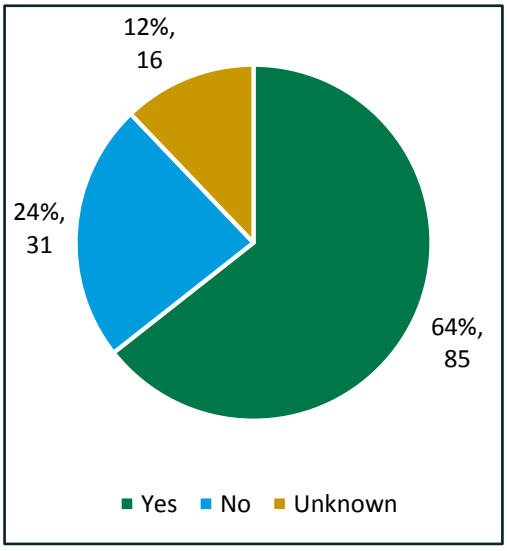


Figure 13: Contact tracing
64% (85/132) of patients were identified as having contacts who may need to be traced, while contact tracing requirements were unidentified in 12% (16/132) of cases.

Medication adherence

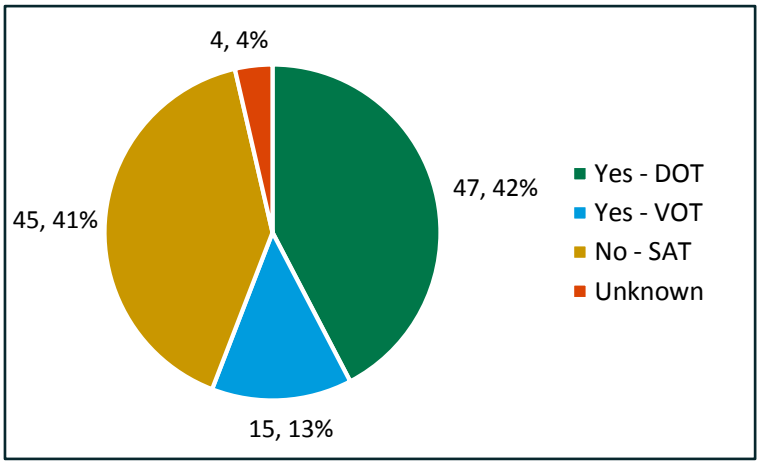


Figure 14:
Treatment observation
With regards to observed therapy; 42% (40/111) received directly observed therapy (DOT), 13% (15/111) received video-observed therapy (VOT), and 41% (45/111) of patients did not have therapy observed, instead self-administering therapy (SAT). For 4% (4/111) of cases treatment observation was not recorded.

Treatment outcomes are currently unavailable. However, from 2020 PHE data[1] we know that 60.9% of people in the drug-resistant cohort notified in 2017 completed treatment by 24 months, a lower proportion than for those notified in 2016 (65.2%).

2.3 DRUG RESISTANCE

Understanding drug resistance is essential in determining the appropriate approach to patient treatment, and is a significant factor in the complexity of treating tuberculosis.

Local molecular laboratory capacity was responsible for 57% of cases (79/86) of initial MTB identification by PCR, with rpoB mutation representing rifampicin resistance present in 48% of cases where known (66/73).

Susceptibility testing was conducted for all people with culture confirmed TB, with PHE providing Whole Genome Sequencing (WGS) reports providing resistance predictions for first and second line drugs.

The importance of accurate drug resistance data cannot be overstated. Resistance data presented in this report were entered by clinicians onto the BTS MDR-TB CAS site. Future data analysis could focus on the category of disease reported by the clinician (XDR or MDR-TB) compared to clinician-reported resistance and the final resistance pattern reported by the National Mycobacterial Reference Service.

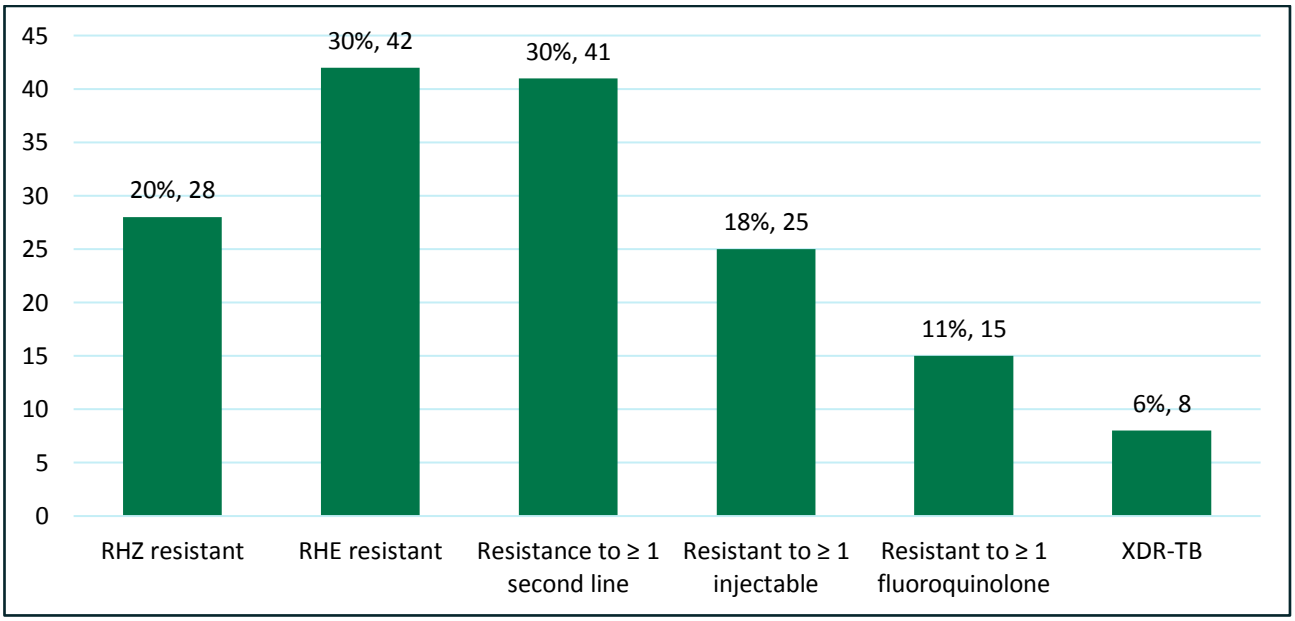


Figure 15: Reported resistance patterns at time of entry onto the Service
From January 2018 to June 2020, 138 patients were reported to have XDR-TB, MDR-TB or suspected MDR-TB. Of these, 20% (28/138) were reported to be resistant to each of rifampicin (R), isoniazid (H), and pyrazinamide (Z), and 30% (42/138) were reported to be resistant to each of R, H and ethambutol (E). Resistance to at least one injectable (18%, 25/138) or fluoroquinolone (11%, 15/138) was commonly reported.

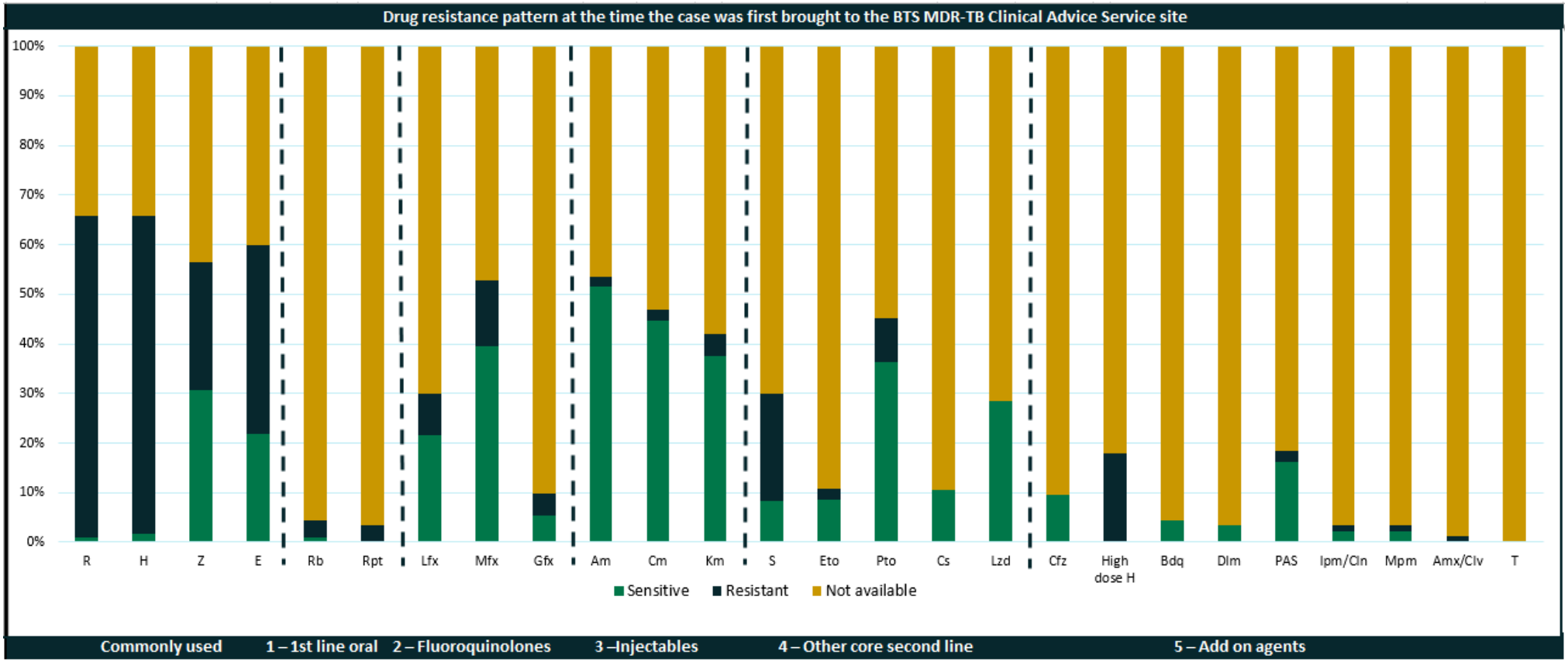


Figure 16: Reported drug resistance at time of entry onto the Clinical Advice Service

This figure shows the clinician-reported breakdown of drug resistance at the time of first entry onto the Clinical Advice Service. As with all data in Part 2 of this report, this figure refers only to patients reported by the clinician to have XDR-TB, MDR-TB or suspected MDR-TB.

2.4 DRUG TOXICITIES

Appendix 1 (page 37) shows a full breakdown of reasons reported for ceasing treatment with individual drugs (for cases of XDR-TB, MDR-TB and suspected MDR-TB only). The most commonly reported reason for a medication being changed was that a new drug sensitivity had become available.

The focus of this report will be on changes to the drug regimen due to drug toxicity. Overview 2 (page 26) provides a summary of reported adverse events and indicates which drugs were reported to have been linked to each adverse event.

First Line Drugs

Amongst the first line drugs rifampicin, isoniazid, pyrazinamide and ethambutol, toxicity was only reported for pyrazinamide, with hepatoxicity most commonly reported (12%, 3 of the 26 patients who ceased pyrazinamide treatment). Arthralgia, rash and gastrointestinal disturbance were reported in 8% (2/26) of patients, and hyperuricaemia in one patient.

Fluoroquinolones

The fluoroquinolones levofloxacin and moxifloxacin would be expected to have similar toxicity profiles. The numbers in our dataset are very small, with the comparatively high number of reports involving moxifloxacin reflecting its popularity compared to levofloxacin. Interestingly, two patients receiving levofloxacin (40%, 2 of the 5 patients who ceased levofloxacin treatment) developed rash compared to none receiving moxifloxacin.

All other adverse events associated with fluoroquinolones were seen with moxifloxacin, with cardiovascular reaction (presumably a prolonged cQT) reported in 26% of cases (6 of the 23 patients who ceased moxifloxacin treatment), musculoskeletal problems reported in 13% (3/23), and an immunological reaction reported in one.

Injectable agents

Aminoglycosides and cyclic peptides, known as the injectable agents, are no longer part of standard MDR tuberculosis treatment. They are associated with serious and often permanent toxicity, mainly in the form of hearing loss and renal toxicity. The data presented reflect cases treated mainly before the WHO treatment guideline changed in 2019[2] or cases where no alternative agents were suitable. Most reports of toxicity were for amikacin, followed by capreomycin and one report for kanamycin.

Audiological toxicity was reported in 47% (14/30) and 33% (4/12) of patients who ceased treatment with amikacin and capreomycin respectively. Renal toxicity was reported in 50% (6/12) and 10% (3/30) of all patients who ceased treatment with capreomycin and amikacin respectively. Neurological reaction was reported in 8% (1/12) of patients who ceased treatment with capreomycin, and a rash was reported in 3% (1/30) of patients who ceased treatment with amikacin. The number of reports is too small to comment on differential toxicity between amikacin and capreomycin. It is reassuring that these potentially toxic drugs will be used less frequently in future.

Core second line agents

Core second line agents – ethionamide, prothionamide, cycloserine, linezolid and clofazimine – have a wide range of toxicities and can be poorly tolerated. The number of reactions reported is small but in line with known adverse effects. The most frequent reaction for each agent was: prothionamide, gastrointestinal; linezolid, neurological; and clofazimine and cycloserine, dermatological.

Linezolid is now a first choice agent for XDR/MDR-TB. Where a reason for ceasing treatment with linezolid was known, toxicities seen were neurological (presumably peripheral neuropathy or optic neuritis, in 40% of cases, 10/25) and haematological (32%, 8/25). Clofazimine, also now a first choice agent, was associated with three cases of rash (38%) and one case of gastrointestinal reaction (usually abdominal pain).

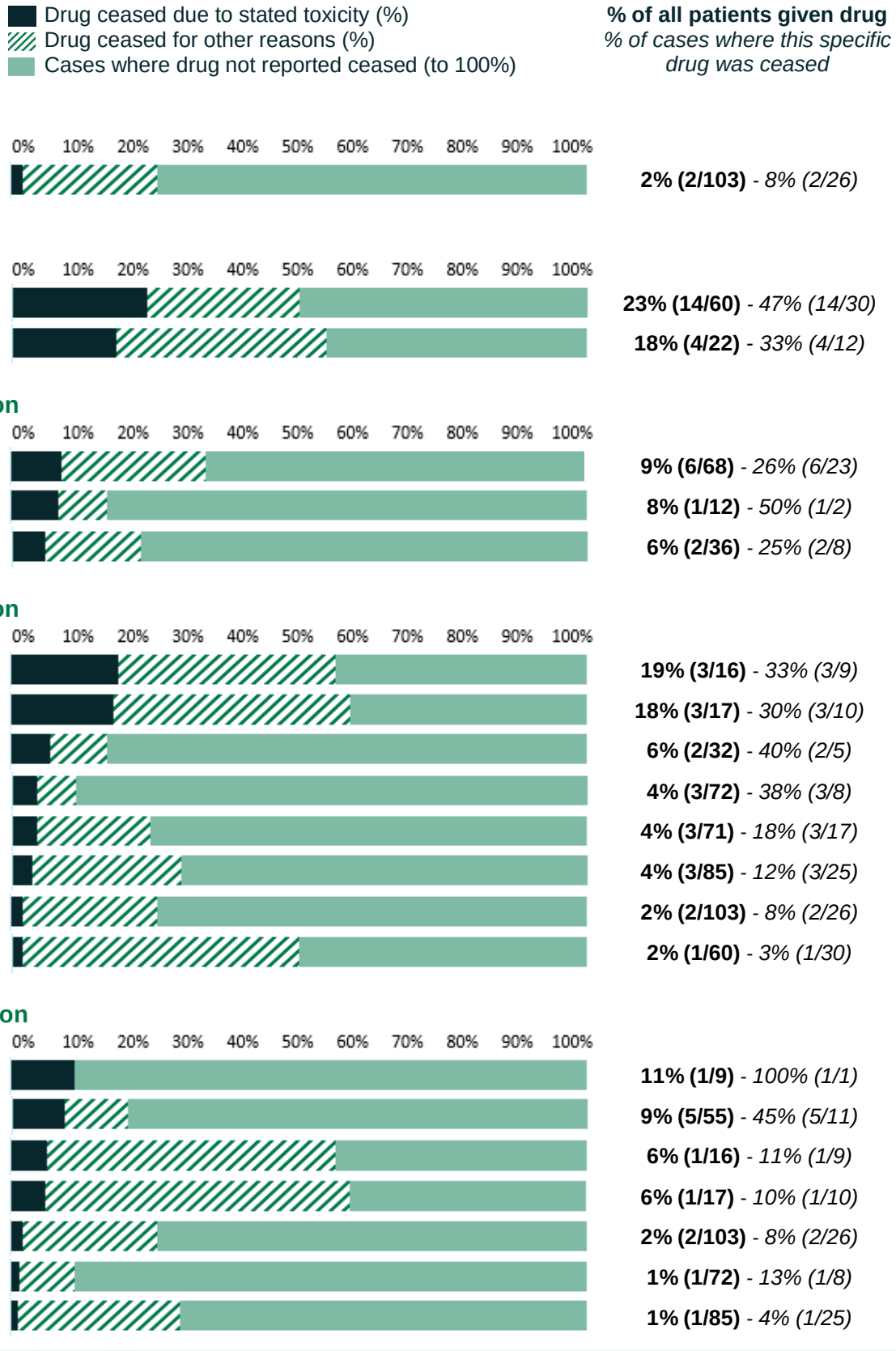
Add-on agents

The final group of agents were previously classified as add-on agents. Adverse events were seen with a number of these drugs. Patients who ceased treatment with bedaquiline and delamanid tended to report cardiac toxicity with prolonged cQT recorded for each drug (25%, 2/8 and 50%, 1/2 of patients who ceased treatment with bedaquiline and delamanid respectively). In one case PAS was ceased due to a gastrointestinal reaction. Meropenem and the co-amoxiclav combination were most commonly ceased due to rash (33%, 3/9 and 30%, 3/10 of patients who ceased treatment with each respectively) and gastrointestinal reaction (one patient in each case). Meropenem was also ceased due to haematological reaction in one patient.

British Thoracic Society

Overview 2: Drug Toxicity

This figure gives an overview of reported drug toxicity for cases of XDR, MDR and suspected MDR-TB from January 2018 to June 2020. Bars represent total cases where each drug was given (100%) with proportions shown for cases ceased due to the stated toxicity (navy) or other reasons (striped).



% of all patients given drug
% of cases where this specific drug was ceased

Arthralgia

Pyrazinamide (Z)	**2% (2/103)** - *8% (2/26)*

Audiological reaction

Amikacin (Am)	**23% (14/60)** - *47% (14/30)*
Capreomycin (Cm)	**18% (4/22)** - *33% (4/12)*

Cardiovascular reaction

Moxifloxacin (Mfx)	**9% (6/68)** - *26% (6/23)*
Delamanid (Dlm)	**8% (1/12)** - *50% (1/2)*
Bedaquiline (Bdq)	**6% (2/36)** - *25% (2/8)*

Dermatological reaction

Meropenem (Mpm)	**19% (3/16)** - *33% (3/9)*
Co-amoxiclav (Amx/Clv)	**18% (3/17)** - *30% (3/10)*
Levofloxacin (Lfx)	**6% (2/32)** - *40% (2/5)*
Clofazimine (Cfz)	**4% (3/72)** - *38% (3/8)*
Cycloserine (Cs)	**4% (3/71)** - *18% (3/17)*
Linezolid (Lzd)	**4% (3/85)** - *12% (3/25)*
Pyrazinamide (Z)	**2% (2/103)** - *8% (2/26)*
Amikacin (Am)	**2% (1/60)** - *3% (1/30)*

Gastrointestinal reaction

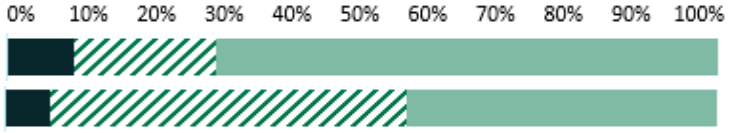
PAS	**11% (1/9)** - *100% (1/1)*
Prothionamide (Pto)	**9% (5/55)** - *45% (5/11)*
Meropenem (Mpm)	**6% (1/16)** - *11% (1/9)*
Co-amoxiclav (Amx/Clv)	**6% (1/17)** - *10% (1/10)*
Pyrazinamide (Z)	**2% (2/103)** - *8% (2/26)*
Clofazimine (Cfz)	**1% (1/72)** - *13% (1/8)*
Linezolid (Lzd)	**1% (1/85)** - *4% (1/25)*

British Thoracic Society

Drug ceased due to stated toxicity (%)
Drug ceased for other reasons (%)
Cases where drug not reported ceased (to 100%)

% of all patients given drug
% of cases where this specific drug was ceased

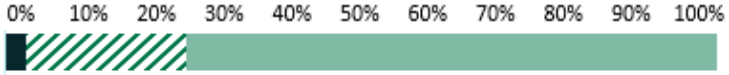
Haematological reaction



Linezolid (Lzd) — **9% (8/85)** - *32% (8/25)*

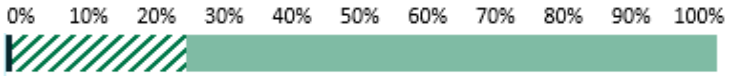
Meropenem (Mpm) — **6% (1/16)** - *11% (1/9)*

Hepatic reaction



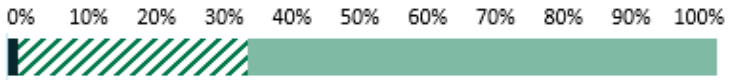
Pyrazinamide (Z) — **3% (3/103)** - *12% (3/26)*

Hyperuricaemia



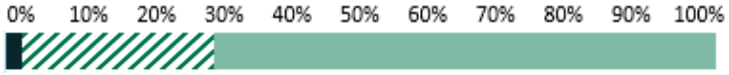
Pyrazinamide (Z) — **1% (1/103)** - *4% (1/26)*

Immunological reaction



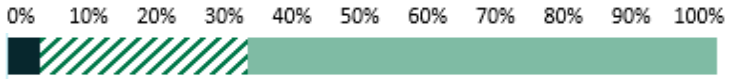
Moxifloxacin (Mfx) — **1% (1/68)** - *4% (1/23)*

Metabolic reaction



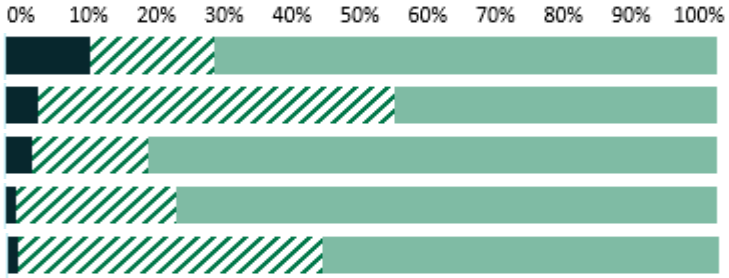
Linezolid (Lzd) — **2% (2/85)** - *8% (2/25)*

Musculoskeletal reaction



Moxifloxacin (Mfx) — **4% (3/68)** - *13% (3/23)*

Neurological reaction



Linezolid (Lzd) — **12% (10/85)** - *40% (10/25)*

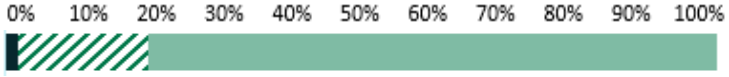
Capreomycin (Cm) — **5% (1/22)** - *8% (1/12)*

Prothionamide (Pto) — **4% (2/55)** - *18% (2/11)*

Cycloserine (Cs) — **1% (1/71)** - *6% (1/17)*

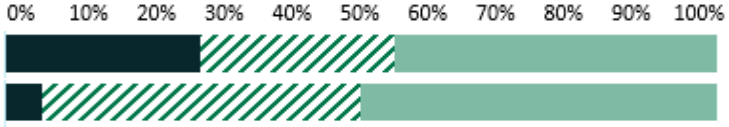
Isoniazid (H) — **1% (1/68)** - *3% (1/30)*

Psychiatric reaction



Prothionamide (Pto) — **2% (1/55)** - *9% (1/11)*

Renal reaction



Capreomycin (Cm) — **27% (6/22)** - *50% (6/12)*

Amikacin (Am) — **5% (3/60)** - *10% (3/30)*

PART 3 – Specialised Commissioned and Novel Drugs

NHS England have commissioned the use of bedaquiline (Bdq) and delamanid (Dlm) for the treatment of MDR-TB and XDR-TB in patients who meet the following criteria:

- Treatment agreed following discussion with the MDT of the MDR-TB treatment centre or the regional MDT in conjunction with a MDR-TB treatment centre; treatment of children must also be agreed after discussion with a Paediatric Infectious Diseases Centre.
- The patient must be managed under directly observed therapy.
- The treatment regimen must be designed according to current WHO recommendations, based on known resistance patterns and tolerance to individual drugs.

The BTS MDR-TB Clinical Advice Service can be considered as providing the function of a regional/national MDT to consider support of Blueteq applications for the use of these two antituberculosis drugs.

The information on bedaquiline and delamanid treatment relates to individual patient treatment history at first entry onto the site only, and data on clinicians requesting consideration for prescribing (or continuing use of) bedaquiline or delamanid and the panel supporting for use of these drugs is based on the outcome of virtual MDT case discussion meetings and, on a small number of occasions, support through consensus reached outside MDT discussion.

Where data are presented regarding clinician requests for support and the panel consensus decision, a subjective assessment was sometimes made when categorising cases (as this information was gleaned from written discussions and MDT notes). For example, cases where the clinician mentioned but did not specifically request support to use bedaquiline or delamanid have not been included as clinician 'requests'. Additionally, cases where advisers indicated their support conditional to additional criteria being met in the future (e.g. should a drug in the current regime need to be ceased) have also not been counted as formal support.

These figures should be interpreted with caution, as WHO guidance upgrading bedaquiline to a Group A agent in 2018 (then in 2020 replacing injectables in the short course treatment) means the proportion of cases where bedaquiline is used has increased over the duration of the period covered by the report.

Treatment of multidrug resistant cases at first registration

Receiving bedaquiline	22% *(31/138)*
XDR-TB	*4*
MDR-TB	*23*
Suspected MDR-TB	*4*
Receiving delamanid	9% *(12/138)*
XDR-TB	*1*
MDR-TB	*8*
Suspected MDR-TB	*3*

These data, which reflect case registration over the entire timescale of the MDR-TB CAS, should be interpreted carefully. The greater use of bedaquiline reflects differences in the published evidence base and WHO recommendations for treating drug-resistant TB.

CSA support for the use of bedaquiline or delamanid for all categories of disease

Total eligible cases	242
Total clinician requests	39% *(94/242)*
Recommendations following requests	75
Bedaquiline only (of which 3 were in response to requests for support to use *either* Bdq or Dlm (2) and Dlm only (1))	*66*
Delamanid only (of which 1 was in response to requests for support to use *either* Bdq or Dlm)	*3*
Both Bdq and Dlm (of which 3 were in response to requests for support to use Bdq)	*6*
Recommendations where no request	17
Bedaquiline only	*13*
Delamanid only	*3*
Both Bdq and Dlm	*1*

Of the 242 cases registered with the BTS MDR-TB CAS, 39% (94/230) of all cases involved a clinician requesting support to use bedaquiline (88%, 83/94), delamanid (4%, 4/94), or either of bedaquiline or delamanid (7%, 7/94).

Overall the panel recommended at least one of bedaquiline and delamanid in 38% (92/242) of all cases (including all categories of disease). Of these 82% (75/92) were made in response to requests from the clinician (representing 80%, 75/94, of clinician requests), and 18% (17/92) were made in the absence of any request from the treating clinician.

NB/ These numbers do not accurately reflect actual use of bedaquiline and delamanid in the UK, as case registration with the MDR-TB CAS is not mandatory. Furthermore, recommendations for using bedaquiline and delamanid may not always be acted on by the treating clinician.

Support for the use of bedaquiline and delamanid by disease category

The use of bedaquiline without delamanid was more likely to be supported (86% of cases) than delamanid (7%) or combined bedaquiline and delamanid therapy (8%), across all categories of disease. Support for combined therapy generally occurred in cases with extensive drug resistance or intolerance patterns, with very limited effective drug options were available.

	XDR-TB	MDR-TB	Suspected MDR	Resistant non-MDR	Complex sensitive TB	NTM	Unknown	Total
Supported Bdq only	7 *8%*	33 *36%*	22 *24%*	9 *10%*	1 1%	6 *7%*	1 1%	79 86%
Supported Dlm only		4 *4%*	1 *1%*	1 *1%*				6 7%
Supported use of both	3 *3%*	3 *3%*		1 *1%*				7 8%
Total	**10 *11%***	**40 *43%***	**23 *25%***	**11 *12%***	**1 1%**	**6 *7%***	**1 1%**	**92 100%**

Table 1: Panel support for the use of bedaquiline and/or delamanid by disease category
This table shows the cases where the panel of expert Clinical Service Advisers has supported the use of bedaquiline and/or delamanid, broken down by category of disease.

Support for the use of bedaquiline over time

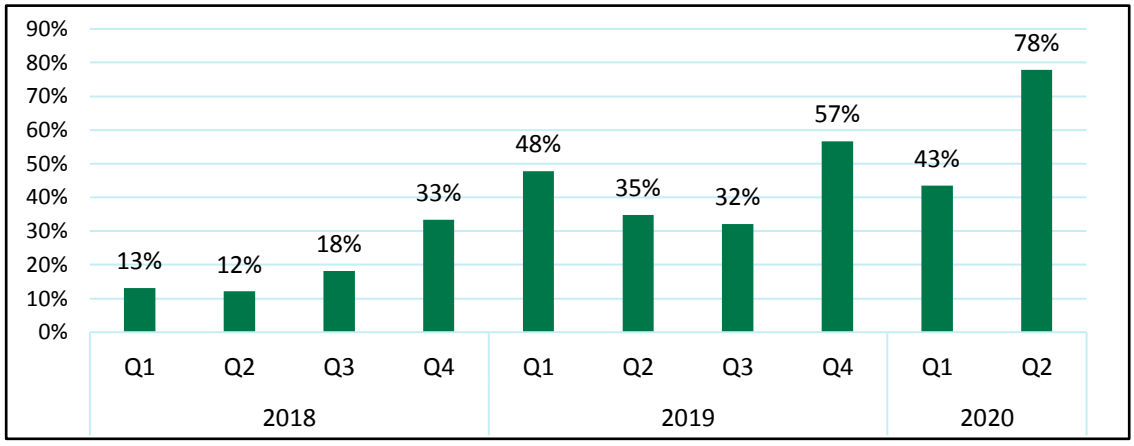


Figure 17: Panel support for the use of bedaquiline over time

This chart shows the percentage of cases (from all categories of disease) where the panel supported use of bedaquiline (with or without delamanid). These are grouped by the date each case was first posted to the Service, and while this typically coincides with the time the use of bedaquiline was supported this was not always the case. From January 2018 to June 2020 there appears to have been an increase in the proportion of cases where bedaquiline use was supported, which may be due to the publication of WHO guidelines promoting bedaquiline to a Group A agent (to be used in all long-course regimens for drug-resistant TB)[3]. No comparable analysis could be undertaken for delamanid, the use of which was only supported in 13 cases.

Reasons for ceasing treatment

These data take into account the first treatment session with each drug only, for each category of disease.

Bedaquiline

There were 8 cases where the reason for ceasing treatment was known:

Potential/actual drug interaction	1 *(13%)*
Cardiovascular reaction	2 *(25%)*
Rash	1 *(13%)*
Completed planned course	4 *(50%)*

Delamanid

There were 2 cases where the reason for ceasing treatment was known:

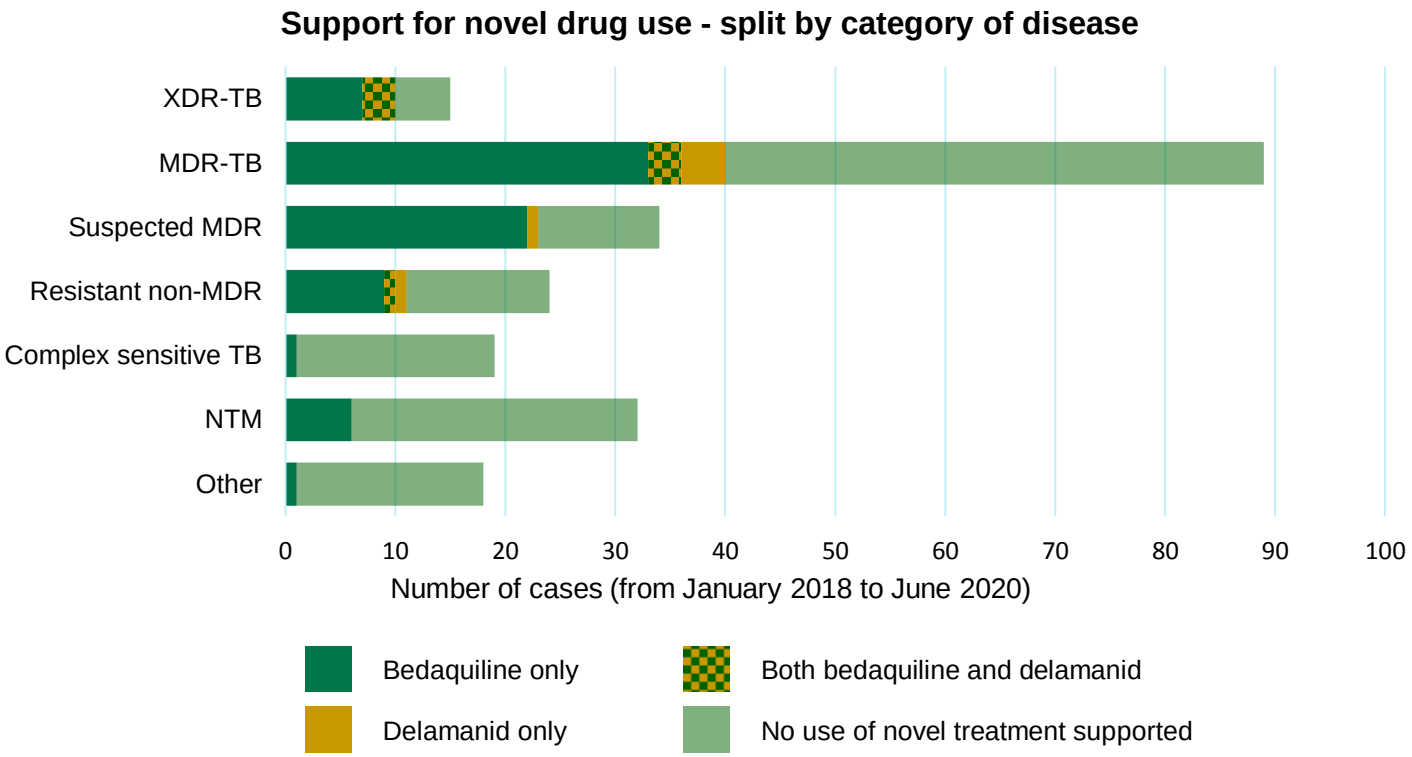
Potential/actual drug interaction	1 *(50%)*
Cardiovascular reaction	1 *(50%)*

These data should be interpreted carefully, as they likely represent under-reporting of cessation of treatment. This is particularly so for those who completed a planned course of therapy, as bedaquiline and delamanid are licensed for an initial 24 week duration of treatment and so are usually stopped much earlier than other antituberculosis drugs in the treatment regimen (*NB/ treatment may be extended only on a case by case basis and under close safety surveillance*).

For details on the reasons for ceasing treatment with other drugs please see Section 2.4 (page 24). (*NB/ Some of the reasons given here for ceasing treatment with bedaquiline were gleaned from descriptive 'free text' posts and are not referenced in Section 2.4).*

Overview 3: Specialised Commissioned and Novel Drugs

The BTS MDR-TB Clinical Advice Service provides an important gatekeeping function for the use of specialised commissioned and novel drug therapies, conducting independent reviews and providing consensus on whether to support use (or continued use beyond 24 weeks) of bedaquiline and delamanid.



This figure shows the absolute numbers of cases discussed within the Clinical Advice Service from each category of disease as reported at entry to the Service (excluding 'Other complex TB', as support to use novel drug therapy was neither requested nor given for any of these cases). Further data analysis is required to determine whether cases reported as suspected MDR-TB at presentation are later confirmed to be so.

Percentage breakdowns are included in the table below. The proportion of cases where the panel of expert CSAs advised the clinician to use one or more novel drug treatments is high (over half – 53% - of cases reported to have XDR, MDR or suspected MDR-TB). Considering the gatekeeping function carried out by the Service, these data highlight the essential role of expert discussion in case management.

These figures may be artificially low, as cases where advisers indicated conditional support (e.g. dependent on pending sensitivity results, or on the loss of another drug) have not been counted. Given the change in WHO recommendation, 100% of all new MDR and XDR-TB patients should be prescribed bedaquiline.

	Bedaquiline only	Both bedaquiline and delamanid	Delamanid only	No use of novel treatment supported
XDR-TB	47% (7/15)	20% (3/15)		33% (5/15)
MDR-TB	37% (33/89)	3% (3/89)	4% (4/89)	55% (49/89)
Suspected MDR-TB	65% (22/34)		3% (1/34)	32% (11/34)
Resistant non-MDR	38% (9/24)	4% (1/24)	4% (1/24)	54% (13/24)
Complex sensitive TB	5% (1/19)			95% (18/19)
NTM	19% (6/32)			81% (26/32)
Other	6% (1/18)			94% (17/18)

PART 4 – Non-Tuberculous Mycobacteria (NTM)

From January 2018 to June 2020, of 215 cases discussed at the virtual MDT, 26 (12%) were due to NTM. A further six cases were submitted but were not discussed (likely because the discussion point had been resolved through the online forum prior to the next MDT meeting). Overall, although this equates to <1 case per month, it still represents the largest group of cases discussed that are neither known nor suspected MDR/XDR-TB. There has been no apparent change in the number of cases submitted over the last year.

Age

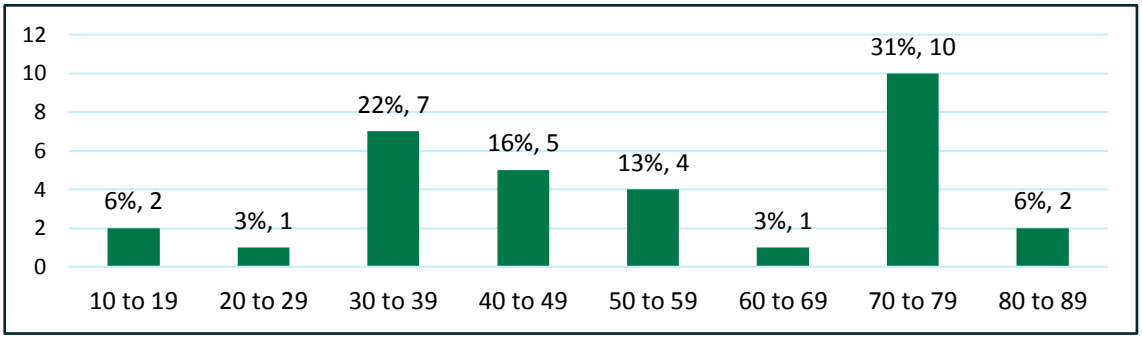
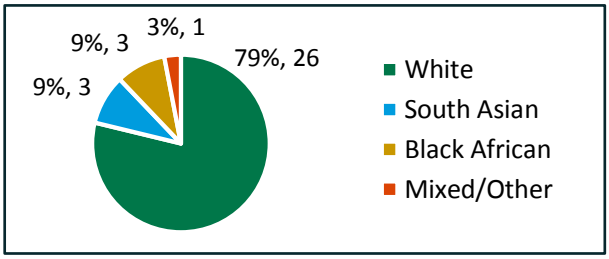


Figure 18: **Age of patients with NTM when first discussed in the Clinical Advice Service**
Information on the 32 NTM patients shows that their age had a bimodal distribution, with peaks at age bands 30-39 and 70-79. This particular two-peaked age demographic has been reported in recent national data for some species, e.g. *M. abscessus* – though not other NTM species – and is thought to reflect its association with cystic fibrosis in younger patients with NTM[4]. Here, the age distribution may arise as generally more complex NTM cases identified as needing treatment are presented to the CAS; and they often have e.g. either disseminated NTM (as seen in HIV) or significant structural lung disease.

Ethnicity

Figure 19: **Ethnicity of patients with NTM**
Four-fifths of patients with NTM were born in the UK, with a similar proportion (79%) being of white ethnicity. Other frequently reported ethnicities were South Asian (9%) and Black-African (9%).



Site of disease

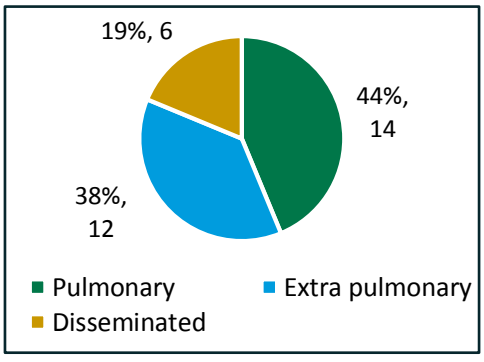


Figure 20: **Site of disease**
The most common site of NTM infection was pulmonary – with 44% (14/32) patients reported to have pulmonary disease – followed by 'extra-pulmonary' (38%) and 'disseminated' (19%).

Where extra pulmonary infection was present the most common site was the heart (25%, 3/12 extra-pulmonary cases). Other sites included skin, surgery wounds (excluding heart surgery) and blood (each reported in 17%, 2/12). The high proportion of cardiac-associated disease likely represents cases of infection due to *M. chimera* resulting from infected cardiac bypass heater-cooler units.

Clinical risk factors

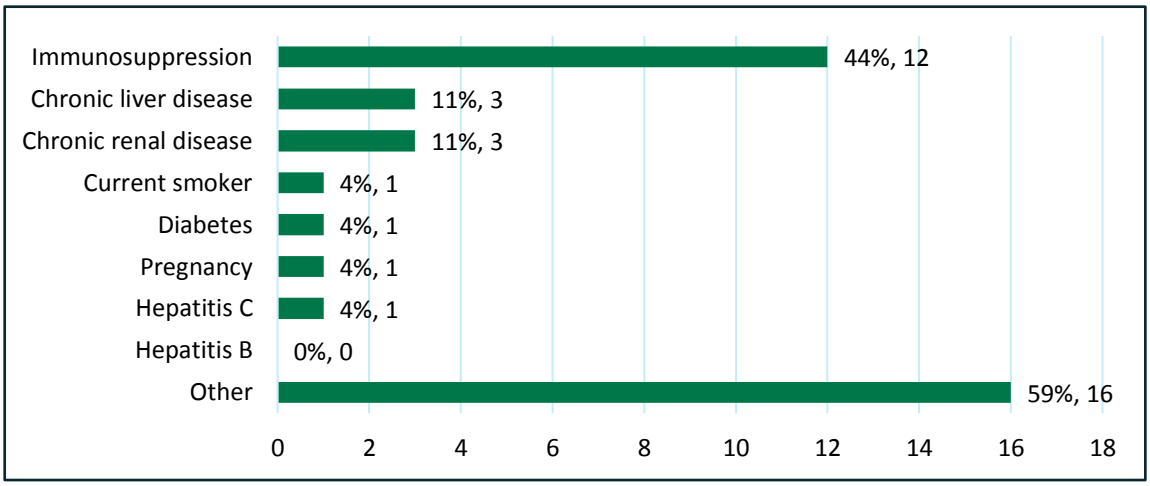


Figure 21: **Reported clinical risk factors of patients with NTM**
Social risk factors for were rare, though clinical risk factors were common (reported in 84% - 27/32 – of cases). The most frequent clinical risk factor was immunosuppression (44%, 12/27), which was predominantly the result of HIV (38%), transplantation (15%) or anti-TNFα treatment (15%). Chronic liver disease and chronic renal disease were also commonly reported

Species of NTM

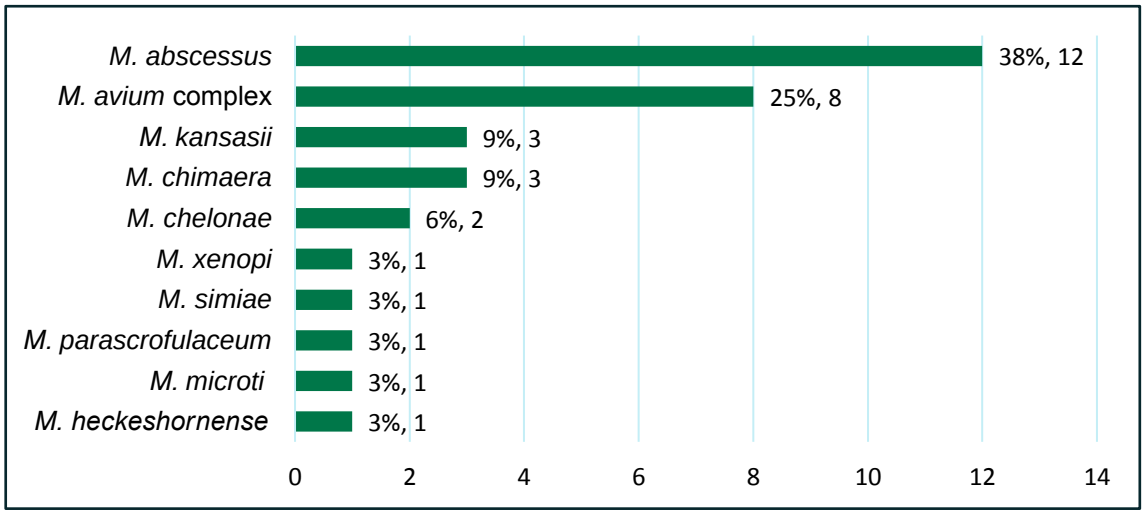


Figure 22: **Species of NTM reported to be involved in infections**
The most frequently reported organisms were *M. abscessus* (38%) and *M. avium* complex (25% - of which a further 3, 9%, were *M. chimaera*). There was also 1 case each of *M. heckeshornense*, *M. microti* (one of the *M. tuberculosis* complex group), *M. parascrofulaceum*, *M. simiae* and *M. xenopi*. The total number of isolates is >32 (100% of cases) as there were 2 cases of multiple infection (*M. avium* and *M. kansasii*; one of *M. abscessus* and *M. avium*).

Although national data indicate the *M. avium* complex group are most frequently isolated[4], there is more treatment guidance available for them, and in pulmonary patients they generally occur associated with less complex comorbidities. This may explain the pattern of referral to the CAS where *M. abscessus* was so frequent.

Discussion of NTM cases

Overall 81% (26/32) of NTM cases were discussed at MDT. Of these 85% (22/26) were discussed once, with 15% discussed at MDT either two or three times to date. The remaining six NTM cases were discussed without being brought to MDT. A number of common themes arose when discussing these cases.

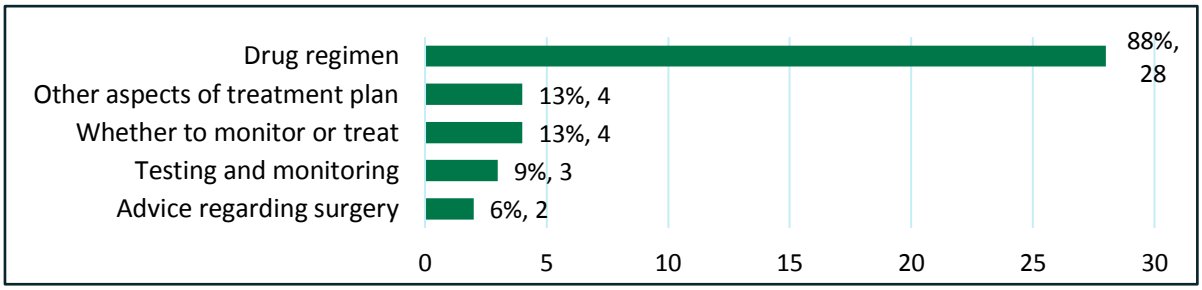


Figure 23: **Common themes of queries raised by treating clinicians**

Reasons for referral were largely related to selection of a treatment drug regimen (88%, 28/32) of which the most common were duration of treatment (21%, 6/28), specific complications relating to drug toxicity (18%, 5/28) and how best to accommodate a preference for an all-oral regimen (7%, 2/28). As would be expected, there were often multiple queries for each individual case.

Some major themes of CSA advice could be identified. CSAs most commonly advised on the content and duration of a proposed regimen (78%, 25/32). Advice also covered specific requests for additional tests/investigations (16%, 5/32), as well as advising clinicians to proceed with surgery, monitoring with/ without treatment (the latter typically if the patient were frail), and a preference for treating another existing condition before commencing NTM treatment (13%, 4/32, for each of these).

Use of bedaquiline

Nine cases included a request for the panel of expert Clinical Service Advisers to support the use of bedaquiline, comprising 11% of all 83 requests specifically for the drug. Of these six were approved. This proportion (67%) is, as would be expected, much less than for either MDR or XDR-TB. No requests for support to use delamanid were made.

Overall 19% (6/32) of all NTM cases discussed through the forum had support for the use of bedaquiline. As of November 2020, NHS England had not commissioned bedaquiline for use in the treatment of patients with NTM. Therefore, clinicians in England must submit an individual funding request (IFR) before bedaquiline may be prescribed.

Outcomes

Outcome data are fairly limited at present, though it is anticipated more data will be available in the future. In 5 cases, the CAS received specific feedback that the treatment plan was working well and the patient was improving (in 4 cases this was following drug therapy, and in one case surgery).

The data presented in this report highlight diversity in both the clinical presentation of NTM infections and the organisms involved. Cases discussed have not involved patients with cystic fibrosis, as they are generally seen in centres with a great deal of experience in managing complex NTM. Therefore, it seems the cases supported through the Service represent complex cases that are being seen in a variety of specialist and less-specialist settings.

NTM Network UK is a recently established clinical and research organisation which aims to improve the management of NTM cases in the UK by generating evidence to improve care. To learn more about NTM Network UK please visit their website at https://www.ntmnetworkuk.com/.

CLINICAL SERVICE ADVISERS

We would like to extend our sincere thanks to all the current and former expert Clinical Service Advisers who have generously volunteered their time since the BTS MDR-TB Clinical Advice Service launched in January 2018.

Dr Eliza Alexander
Dr Sarah Anderson
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Dr Delane Shingadia
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Ms Helen Thuraisingam
Dr Simon Tiberi
Ms Adele Torkington
Dr Naomi Walker
Dr John Watson
Dr Steven Welch
Dr Natasha Weston
Dr Elizabeth Whittaker
Dr Stephen Wilson

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Appendix 1: Reported reasons for ceasing drug treatment

This table shows the reported reasons for patients ceasing the first treatment session with each drug at any time (i.e. including data from the start of their TB treatment to their most recent follow-up data). This table refers only to patients reported by the clinician to have XDR-TB, MDR-TB or suspected MDR-TB. Percentages given describe the proportion of patients for each drug where both treatment had ceased and a reason was provided for stopping treatment.

Aside from the drug toxicities listed this table also includes a column for 'New sensitivity' – this refers to cases where new drug sensitivity information led to a change in treatment regimen. This is likely due to a report of genotypic or phenotypic resistance to the drug in question.

Drug	Cases where reason given	New sensitivity	Potential/ actual drug interaction	Arthralgia	Audiological reaction	Cardiovascular reaction	Chest pain	Dermatological reaction	Endocrine reaction	Gastrointestinal reaction	Haematological reaction	Hepatic reaction	Hyperuricaemia	Immunological reaction	Infective reaction	Metabolic reaction	Musculoskeletal reaction	Neurological reaction	Opthalmic reaction	Psychiatric reaction	Renal reaction	Respiratory reaction	Further information/ Other
Commonly used																							
Rifampicin (R)	**31**	74%																					29%
Isoniazid (H)	**30**	63%																3%					37%
Pyrazinamide (Z)	**26**	38%		8%				8%		8%		12%	4%										42%
Ethambutol (E)	**26**	58%																					46%
1 – First line oral																							
Rifabutin (Rb)																							
Rifapentine (Rpt)																							
2 – Fluoroquinolones																							
Levofloxacin (Lfx)	**5**							40%															60%
Moxifloxacin (Mfx)	**23**	9%	13%			26%								4%			13%						52%
Gatifloxacin (Gfx)																							
3 –Injectables																							
Amikacin (Am)	**30**				47%			3%												10%			57%
Capreomycin (Cm)	**12**		8%		33%													8%		50%			50%
Kanamycin (Km)	**1**																						100%
Streptomycin (S)																							
4 – Other core second line																							
Ethionamide (Eto)	**1**	100%																					
Prothionamide (Pto)	**11**	18%								45%								18%		9%			27%
Cycloserine (Cs)	**17**		6%					18%										6%					59%
Linezolid (Lzd)	**25**		8%					12%		4%	32%					8%		40%					52%
Clofazimine (Cfz)	**8**		13%					38%		13%													75%
5 – Add on agents																							
High-dose isoniazid (High dose H)																							
Bedaquiline (Bdq)	**8**		13%			25%																	63%
Delamanid (Dlm)	**2**		50%			50%																	
p-aminosalicylic acid (PAS)	**1**									100%													
Imipenem/Cilastatin (Ipm/Cln)																							
Meropenem (Mpm)	**9**	11%						33%		11%	11%												78%
Amoxicilin/Clavulanate (Amx/Clv)	**10**	10%						30%		10%													90%
Thioacetazone (T)																							