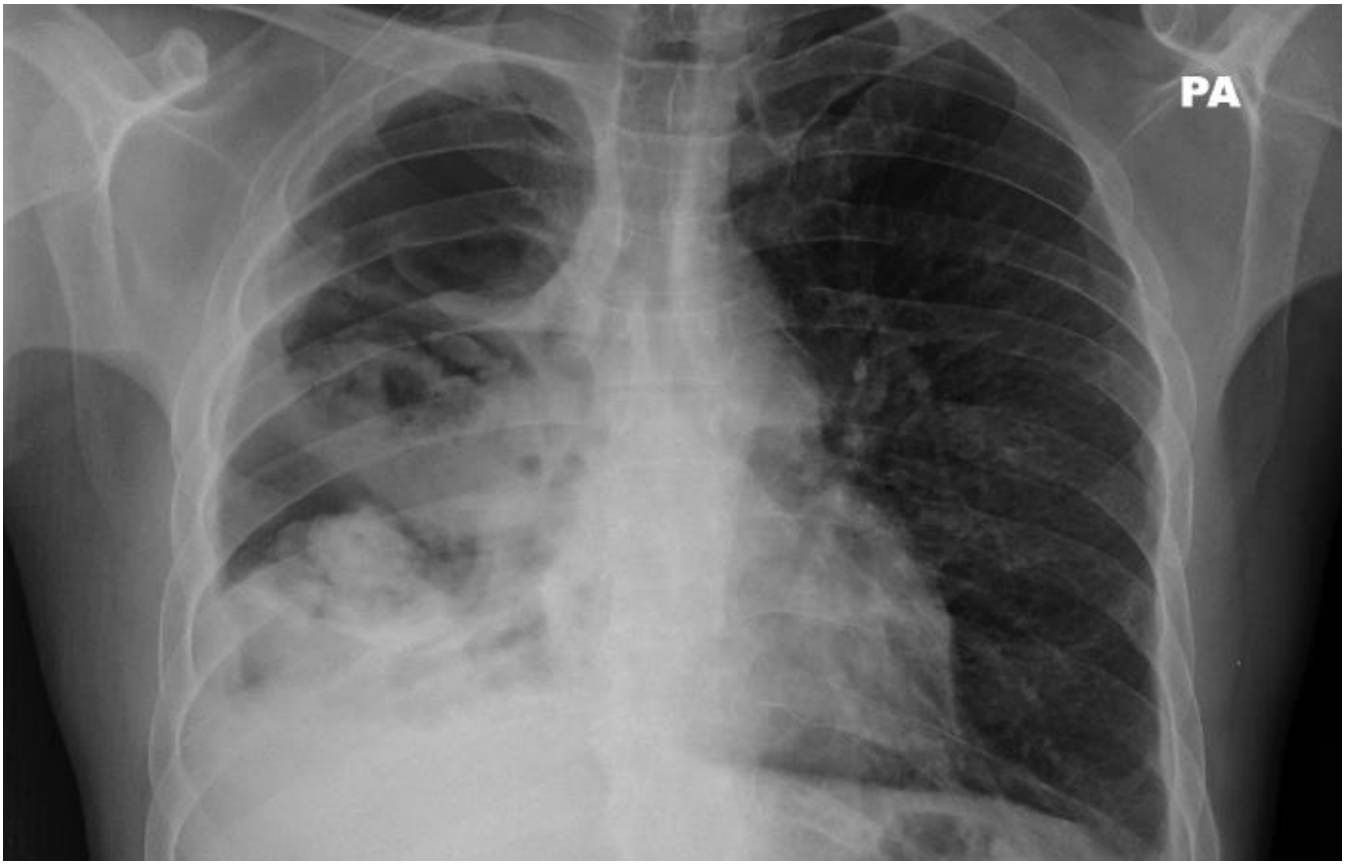
British Thoracic Society

BTS MDR-TB Clinical Advice Service Annual Report 2021



December 2021, ISSN 2040-2023
British Thoracic Society Reports
Vol 12, Issue 6, 2021

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 increasing and more 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 36 person-hours of clinician involvement in MDTs over 12 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. Over 12 months we recorded 36 person-hours of trainee involvement. 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 July 2020 to June 2021 our panel of expert Clinical Service Advisers (CSAs) had advised on 105 cases, of which 39% were reported as known or suspected MDR/XDR-TB. Many other cases involved sensitive TB that was functionally MDR due to toxicity.

Over 730 written advice messages were sent to clinicians in this period, 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

Clinicians using the Service provide details of the reasons for ceasing treatment with each drug. Reported toxicities are published in our supplemental report *MDR-TB Drug Toxicity in the UK* (available on the BTS website), forming a resource which may be referenced by clinicians.

Gatekeeping function – specialised commissioned and novel drugs

See Overview 2: 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. In the reporting period, 88% 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 crucial resource supporting the care of patients both directly and indirectly. Wider implications of the Service include facilitating ongoing training and development of the TB workforce. As the important work of this Service continues it is anticipated that further benefit will also be realised through research activities.

CONTENTS

FOREWORD

The Multidrug Resistant Tuberculosis Clinical Advice Service has been providing direct support to clinicians for four years, having a real and immediate impact on the treatment of patients with the most complex and challenging cases of tuberculosis across the UK. From January 2018 to June 2021 a total of 350 cases were discussed through the Service, covering XDR and MDR-TB, other complex TB and non-tuberculous mycobacterial infections (NTMs).

The involvement of a multi-disciplinary team (MDT) is essential to providing the best and most appropriate treatments for the patients in our care. Respiratory and infectious disease physicians, paediatricians, microbiologists, public health consultants, pharmacists and TB nurses all bring complementary knowledge and experience into the Service, and we are very fortunate that our colleagues volunteer their time so generously. This MDT working not only improves patient care but also continuously improves our own knowledge and understanding. This also provides a rich resource for the ongoing education of trainees across several specialties.

Through the Service we now routinely discuss around 100 new cases a year, giving advice on drug regimens, toxicity management, public health measures and non-medical interventions. The excellent engagement we have from our reference laboratory microbiology colleagues also means that whole genome sequencing data are at the core of our discussions. This additional detailed information and discussion allows for critical information that often provides 'game-changing' management choices as well as public health interventions.

This year we're expanded our work on drug toxicity into a separate report *Supplemental Report: MDR-TB Drug Toxicity in the UK*. Regimens used to treat patients with complex or drug-resistant TB involve multiple drugs, many of which are themselves toxic. When a patient experiences an adverse reaction to their TB treatment it can be challenging to determine which drug may be responsible; this supplemental report provides a rapid way to identify the likeliest causal agents. Managing adverse reactions is key to improving the quality of life and outcomes for patients.

The MDR-TB Clinical Advice Service is a core component of the new TB Action Plan for England and has secured continued NHSE funding for the year 2021-22 in recognition of its significant contribution to the most complex cases across the UK.

This report describes the cases supported by our panel of expert advisers from July 2020 to June 2021, highlighting the importance of this national resource in improving the care of MDR and complex TB patients in the UK.

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

The BTS MDR-TB Clinical Advice Service continues to provide exceptional support to clinicians across the UK. At a time when many services were necessarily paused, TB services were largely retained due to the significant associated individual patient and public health implications. Resources remain incredibly tight, so the work of the Clinical Advice Service has been all the more critical in ensuring appropriate early management for this complex, vulnerable patient cohort.

This detailed and engaging report is accompanied by a supplement; a practical tool supporting clinicians in minimising harmful drug reactions. The continued work to understand and communicate drug toxicity patterns in the UK is an excellent example of using real-world data to deliver immediate benefit to the patients in our care.

My sincere thanks to the Clinical Service Advisers across the UK, who generously volunteer their expertise. The last year has been incredibly challenging, and our advisers have continued to provide timely, high-quality advice over and above the commitments of their already demanding jobs. I'm confident my gratitude is echoed by the clinicians they support and by the patients they tirelessly serve.

Professor Jonathan Bennett
Chair, BTS Board of Trustees (2019-2021)

BTS MDR-TB Clinical Advice Service Steering Group Membership 2021:

Professor Onn Min Kon	Chair
Dr Toby Capstick	Consultant Pharmacist
Dr Suzi Coles	UK Health Security Agency representative
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)
Dr Esther Robinson	National Mycobacterial Reference Service (NMRS) representative
Professor Grace Smith	National Mycobacterial Reference Service (NMRS) representative
Dr Simon Tiberi	Infectious Diseases Consultant
Lynn Altass	NHSE (Corresponding member)
Miss Sally Welham	BTS 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 in 2021 is included on page 22.

Cover photograph: Radiograph of a patient with pulmonary tuberculosis.

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 complexity of cases is broad, and a substantial 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.

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

- **Facilitating the provision of advice to clinicians**
  After written patient consent is obtained clinicians may post their case to the Clinical Advice Service. The panel of expert Clinical Service Advisers (CSAs) reviews the anonymised case details, providing advice on treatment and monitoring through the website.

  Virtual multidisciplinary team meetings (MDTs) are held monthly, where CSAs 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 supported the use of these drugs.

- **Supporting research**
  All patients whose cases are discussed must give consent for their data to be processed for that purpose. 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. 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/

- **Increasing knowledge and understanding of drug toxicity patterns**
  In addition to providing clinicians with the tools needed to make the best clinical decisions for their patients, the intention is for the Service to support care across the UK by improving the understanding of drug toxicity patterns. To this end a supplemental report, *MDR-TB Drug Toxicity in the UK*, has been published alongside this annual report. The supplemental report includes a full breakdown of the clinician-reported reasons for ceasing treatment with each drug, and gives a guide to the possible culprits for each of the most common adverse effects experienced by patients.

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 2021, over 400 clinicians had registered to use the Service and cases had been entered from a total of 55 sites across the UK. Overall 346 cases had been discussed through the Service from January 2018 to June 2021.

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. 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) are encrypted at the point of entry and visible only to the hospital team in the centre responsible for treating the patient. 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*). 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. As well as directly supporting clinicians with advice, the Service has significant impacts on the TB workforce:

- **Supporting and developing trainees** by providing the opportunity to observe expert national multidisciplinary discussions, increasing and maintaining clinical expertise.
- **Supporting UK MDR-TB experts** by fostering closer ties among the expert community across the UK. The panel of expert advisers also includes a mix of new and more senior advisers, identifying and supporting the development of the new generation of MDR-TB and NTM experts.

The monthly virtual MDTs, which facilitate real-time discussion of individual cases, also have another important dimension: education. When treating clinicians dial in to discuss their own cases they often observe the other case discussions. Clinical Service Advisers have described the MDTs as a unique opportunity for them to discuss a range of complex MDR-TB and NTM cases, and to learn from colleagues across a range of specialist areas.

> The MDR-TB Clinical Advice Service brings together multiple experts, across the whole spectrum of TB specialities, to provide expert guidance. My patients and TB team have benefited immensely from this outstanding service.
>
> **Dr Moerida Belton, Consultant Respiratory Physician Lewisham and Greenwich NHS Trust (London)**

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).

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.

Figure 1: **Location of submitted cases**
Map showing the location of centres which have brought at least one case to the BTS MDR-TB CAS since the Service launch in January 2018.

The History of the BTS MDR-TB CAS

The BTS MDR-TB Clinical Advice Service launched in January 2018, building on the longstanding work of the previous MDR-TB Forum.

The original MDR Advisory Service Forum was launched in 2008, with Professor Peter Davies as the lead physician. This service was a huge step forward in the management of MDR-TB in the UK, providing a means of centralising case discussion. From 2011 this forum was managed by BTS, with Drs John Watson and Martin Dedicoat acting as lead clinicians. This forum included fully anonymised patient data only.

The forum was very well received and provided an essential resource for clinicians. As a direct result of the success of this forum a new service was planned, expanding on the work of the existing forum. This new BTS MDR-TB Clinical Advice Service was launched in January 2018, formally collecting a range of patient information crucial for the provision of advice and essential for understanding patterns of drug toxicity in the UK.

Since the launch of the first Clinical Advisory Service forum the number of cases covered in the UK each year has significantly increased. This is due to the hard work and dedication of all those involved at each stage, from the launch of the first forum in 2008 to all those who generously give their time to the Service today.

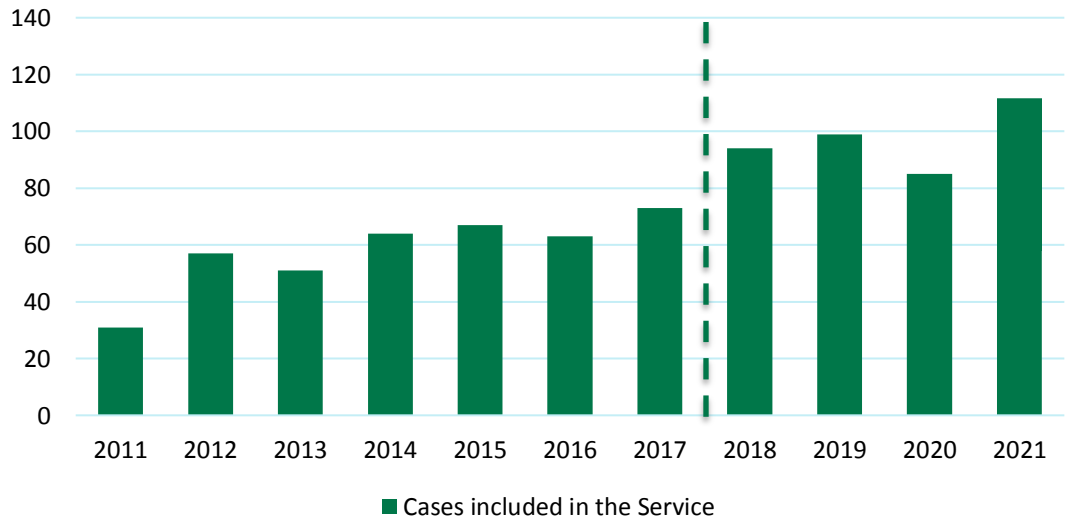

Figure 2: Cases in the MDR Clinical Advisory Service Forum and CAS over time
This chart shows the increase in numbers of cases discussed through the MDR Clinical Advisory Service Forum and the BTS MDR-TB Clinical Advice Service over time, for all categories of disease (including NTM and complex sensitive TB). Cases are counted in the year they were first discussed. The vertical line indicates the closure/archiving of the previous MDR Clinical Advisory Service and the launch of the BTS MDR-TB Clinical Advice Service.

This increase does not correlate with any increase in cases nationally, therefore the Service is providing advice to support an increased proportion of UK cases over time.

The next stage of development will be to carry out a detailed service evaluation, investigating the real-world impact of the Clinical Advice Service for clinicians and patients across the UK.

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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 for the reporting period of July 2020 to June 2021.

405 clinicians are registered on the Clinical Advice Service from a total of **130** hospitals across all four nations of the UK, and the Isle of Man

40

Expert Clinical Service Advisers

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

105

Cases discussed by our panel of expert advisers

- **6** XDR-TB
- **22** MDR-TB
- **13** Suspected MDR-TB
- **13** Resistant non-MDR-TB

- NTM **22**
- Other/Unknown **6**
- Other complex TB **4**
- Complex sensitive TB **19**

731

Individual messages from expert Clinical Service Advisers to clinicians who have posted cases. These messages are separate to the MDT discussions, and 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 2021

British Thoracic Society

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 new cases with discussion pending at the end of June 2021.

12

Virtual MDTs were held, with a mean of 13 cases discussed per meeting. Cases may be discussed at MDT as often as needed.

24

Hours of **MDT** discussion, with one two-hour MDT every month

36

Person-hours of **clinician MDT involvement.** This assumes 20 minutes per case, whereas many clinicians stay on the call for much longer (as a learning opportunity)

260

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

36

Person-hours of **trainee MDT involvement**

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 2019.

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)

This section of the report deals with cases reviewed from July 2020 to the end of June 2021, initially categorised by the clinician as being either XDR-TB, MDR-TB or suspected MDR-TB.

From July 2020 to June 2021, 23 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:

41 patient demographic records

41 complete clinical/diagnosis records

18 follow-up records representing 11 unique patients.

2.1 THE MDR/XDR-TB PATIENT COHORT

Over half (59%, 24/41) the patients were male, and the majority were of either White (33%), Black African (28%) or South Asian (25%) ethnicity

The mean age of patients at the time their case was first discussed on the CAS was 36.0 (± *11.5*), with ages ranging from 6 to 55. Half of patients (49%%, 20/41) were aged 20 – 39.

Over a third of patients (41%, 11/27) had no listed clinical risk factors. Where present the most common were smoking, chronic liver disease and hepatitis B. Immunosuppression was also reported in 13% of cases, although biological therapy (anti TNFα) was not the cause for any of these.

The majority (76%, 29/38) of patients had no listed social risk factors. Of those who did the most common were prison history (56%) or alcohol addiction (44%). Where drug use was a known risk factor (1 patient - 11% of cases) that patient was still actively using drugs.

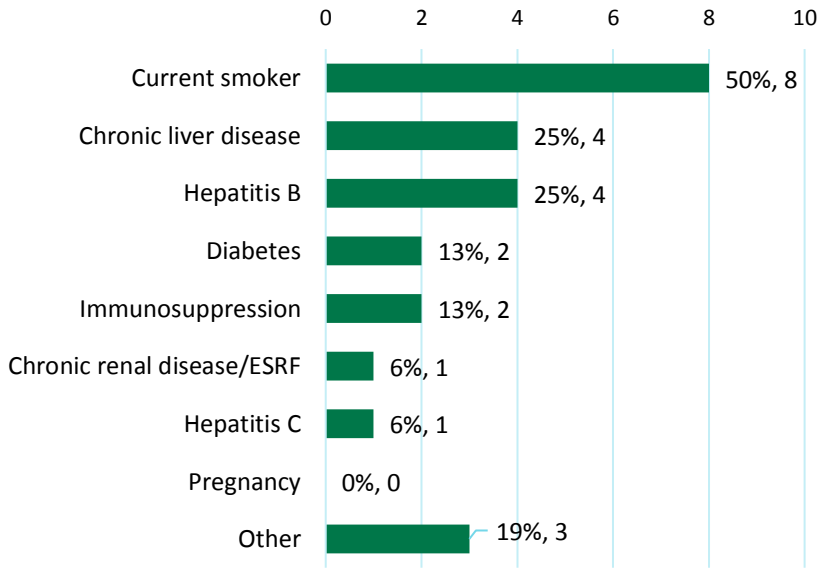


Figure 3: Clinical risk factors at first discussion
Clinical risk factors recorded for all patients with known or suspected MDR/XDR-TB from July 2020 to the end of June 2021.

Overall 29% (10/35) of the cases discussed between July 2020 and June 2021 involved a patient who was known not to be in work. Occupation categories where the risk of exposure to TB may be elevated include education (9% of all cases) and healthcare (3%).

2.2 CLINICAL/DIAGNOSTIC DATA

Cough (54%), weight loss (54%), fevers (38%) and night sweats (32%) were the most commonly reported symptoms. Overall 8% (3/37) of patients were reported to be asymptomatic. The majority of patients (76%) experienced symptoms for between one and six months before their case was entered onto the Service. No patients reported experiencing symptoms for over a year.

Excluding sputa, where smear samples were obtained the most commonly reported techniques were lymph node aspirate (3% of cases) and bronchoalveolar lavage (BAL) /endobronchial washing (2% of cases).

Overall 73% (29/40) of cases had pulmonary involvement, with extra-thoracic and intra-thoracic lymph node involvement (23% and 13%) and pleural disease (13%) also frequently reported.

Overall 20% (8/41) of patients were known to have a previous diagnosis of TB. Of these, 87.5% (7/8) involved active and 12.5% (1/8) latent TB (one patient was previously diagnosed with both).

Key Figures

- **8%** of patients asymptomatic
- **20%** previously diagnosed with TB *(88% active, 13% latent)*
- **76%** required contact tracing
- **14%** did not identify if any contact tracing was required
- **64%** had therapy observed in some way (e.g. DOT/VOT)

Contact tracing was required in 76% (28/37) of cases, while contact tracing requirements were unidentified in 14% (5/37) of cases. Therapy was directly observed (DOT) in 39% (14/26) and video-observed (VOT) in 25% (9/36) of cases. Therapy was self-administered (SAT) in 36% (13/36) of cases.

2.3 DRUG RESISTANCE

Local molecular laboratory capacity was responsible for 97% of cases (29/30) of initial MTB identification by PCR, with rpoB mutation representing rifampicin resistance present in 93% of cases where known (28/30).

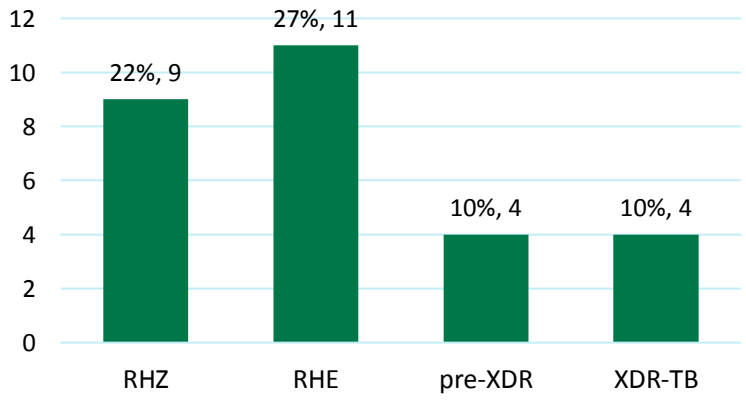


Figure 4: Clinician-reported resistance pattern
Resistance patterns as reported by clinicians. These figures do not draw from whole genome sequencing (WGS) data.

Of the 41 patients known or suspected XDR/MDR-TB (as described by the treating clinician), 20% (9/41) were specifically reported as resistant to each of rifampicin (R), isoniazid (H), and pyrazinamide (Z), and 27% (11/41) to R, H and Ethambutol (E).

Using the 2020 World Health Organisation (WHO) definitions[1], 10% (4/41) of cases would be considered to meet the definition of pre-XDR TB, and those same 4 cases also met the definition for XDR-TB.

PART 3 – Complex Sensitive TB and Drug Resistant Non-MDR TB

This section of the report deals with cases reviewed from July 2020 to the end of June 2021, initially categorised by the clinician as being either complex sensitive TB, drug resistant non-MDR TB or other complex TB. The cases included in this section were contributed by 22 different centres.

36 patient demographic records

36 complete clinical/diagnosis records

19 follow-up records representing 11 unique patients.

3.1 THE COMPLEX SENSITIVE/RESISTANT NON-MDR TB PATIENT COHORT

Over half (56%, 20/36) the patients were male, and the majority were of either White (36%), South Asian (31%) or Black African (17%) ethnicity

The mean age of patients at the time their case was first discussed on the CAS was 39.0 (± *14.2*), with ages ranging from 15 to 76. Over half of patients (53%, 19/36) were aged 20 – 39.

One fifth of patients (20%, 6/30) had no listed clinical risk factors. Where present the most common were immune-suppression, smoking and chronic liver disease. Where immunosuppression was a factor, biological therapy (anti TNFα) was the cause in 25% (2/8) of cases.

The majority (80%, 24/30) of patients had no listed social risk factors. Of those who did the most common were alcohol addiction (50%), drug use (33%) and prison history (33%). Where drug use was a factor all patients reported use taking place within the previous 5 years but not current use.

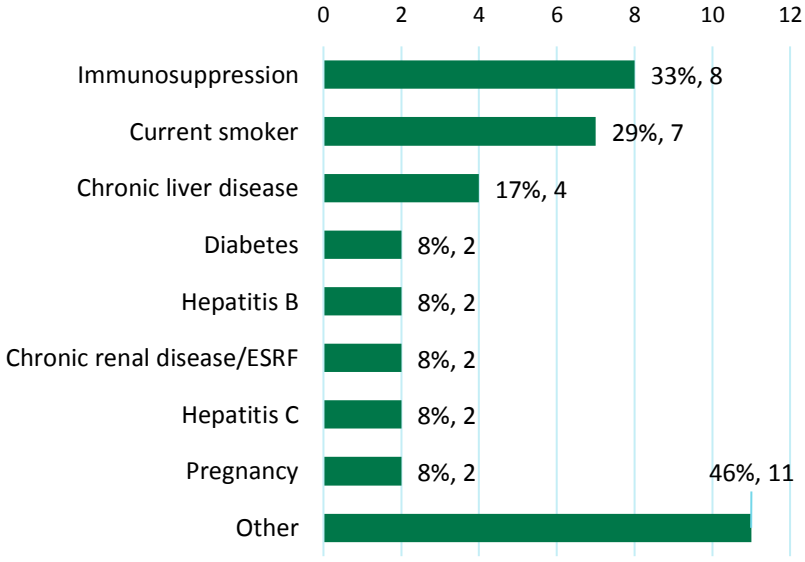


Figure 5: Clinical risk factors at first discussion
Clinical risk factors recorded for all patients with complex sensitive TB or resistant non-MDR TB from July 2020 to the end of June 2021.

Overall 35% (12/34) of the cases discussed between July 2020 and June 2021 involved a patient who was known not to be in work. Occupation categories where the risk of exposure to TB may be elevated include healthcare (12% of all cases), social services/prison sector workers (6%) and education (3%).

3.2 CLINICAL/DIAGNOSTIC DATA

Cough (67%), weight loss (58%), fevers (50%), fatigue (50%) and night sweats (50%) were the most commonly reported symptoms. Overall 8% (1/12) of patients were reported to be asymptomatic. The majority of patients (83%) experienced symptoms for between one and six months before their case was entered onto the Service, with 8% of patients experiencing symptoms for over a year.

Excluding sputa, where smear samples were obtained the most common techniques reported were bronchoalveolar lavage (BAL) /endobronchial washing (2% all cases) and lymph node aspirate (2%).

Overall 62% (8/13) of cases had pulmonary involvement, with intra-thoracic and extra-thoracic lymph node involvement also frequently reported (31% and 23%).

Overall 11% (4/36) of patients were known to have a previous diagnosis of TB. Of these, 100% (4/4) involved active TB and none involved latent TB.

Key Figures

- **8%** of patients asymptomatic
- **11%** previously diagnosed with TB *(all of which were active TB)*
- **77%** required contact tracing
- **55%** had therapy observed in some way (e.g. DOT/VOT)

Contact tracing was required in 77% (10/13) of cases. Therapy was directly observed (DOT) in 46% (5/11) and video-observed (VOT) in 9% (1/11) of cases. Therapy was self-administered (SAT) in 46% (5/11) of cases.

PART 4 – 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[2], 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 drugs.

The information presented here relates to individual patient treatment history at first entry. Data on the panel supporting the prescription (or continuing use of) bedaquiline or delamanid 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.

These figures cover the period of July 2020 to the end of June 2021 (unless otherwise stated). WHO guidance upgrading bedaquiline to a Group A agent was released in 2018, then in 2020 bedaquiline was listed as replacing injectables in the short course treatment.

Of the 105 cases registered with the BTS MDR-TB CAS, 41% (43/105) involved a clinician requesting support to use bedaquiline (91%, 39/43) or either of bedaquiline or delamanid (9%, 4/43).

Overall the panel recommended at least one of bedaquiline and delamanid in 51% (52/105) of all cases. Of these 71% (37/52) were made in response to requests from the clinician (representing 86%, 37/43, of clinician requests), and 29% (15/52) were made in the absence of any clinician request.

Key Figures

- **41%** of all cases involved a clinician seeking to use bedaquiline, or bedaquiline and delamanid
- The panel supported using Bdq and/or Dlm in **51%** of all cases, and in **88%** of cases of known or suspected XDR/MDR-TB
- The panel supported concomitant use of Bdq and Dlm in **33%** of all XDR-TB cases
- Support for the use of Bdq has increased over time, as expected from the WHO Guidelines promoting Bdq to Group A agent

The use of bedaquiline without delamanid was more likely to be supported (89%, 46/52) than delamanid (2%, 1/52) or combined bedaquiline and delamanid therapy (10%, 5/52), 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. Concomitant use of bedaquiline and delamanid was supported in 33% (2/6) of all XDR-TB cases discussed.

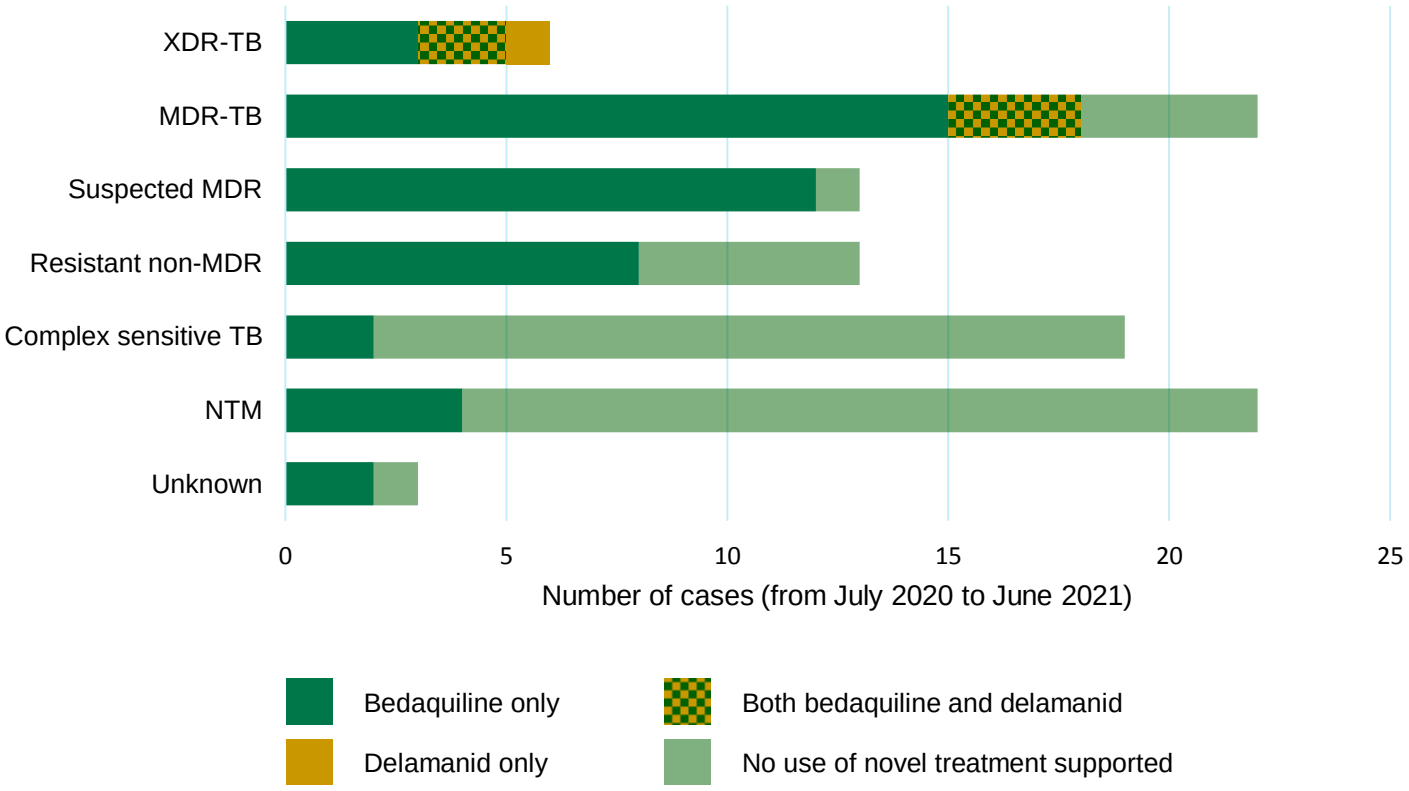
A full breakdown of support for the use of bedaquiline and/or delamanid is included in Overview 2 (page 18).

British Thoracic Society

Overview 2: 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.

Support for novel drug use - split by category of disease



This figure shows the absolute numbers of cases discussed, as reported at entry to the Service. Further analysis is required to determine the eventual categorisation of cases of suspected MDR-TB.

The proportion of cases where the panel supported the use of one or more novel drug treatments is high (88% - of cases reported to have known or suspected XDR/MDR-TB). Considering the gatekeeping function of 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.

	Bedaquiline only	Both bedaquiline and delamanid	Delamanid only	No use of novel treatment supported
XDR-TB	50% (3/6)	33% (2/6)	17% (1/6)	
MDR-TB	68% (15/22)	14% (3/22)		18% (4/22)
Suspected MDR-TB	92% (12/13)			8% (1/13)
Resistant non-MDR	62% (8/13)			39% (5/13)
Complex sensitive TB	11% (2/19)			90% (17/19)
NTM	18% (4/22)			82% (18/22)
Unknown	67% (2/3)			33% (1/3)

From January 2018 to June 2021 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)[2]. No comparable analysis could be undertaken for delamanid, the use of which was only supported in 22 cases over the lifetime of the Service.

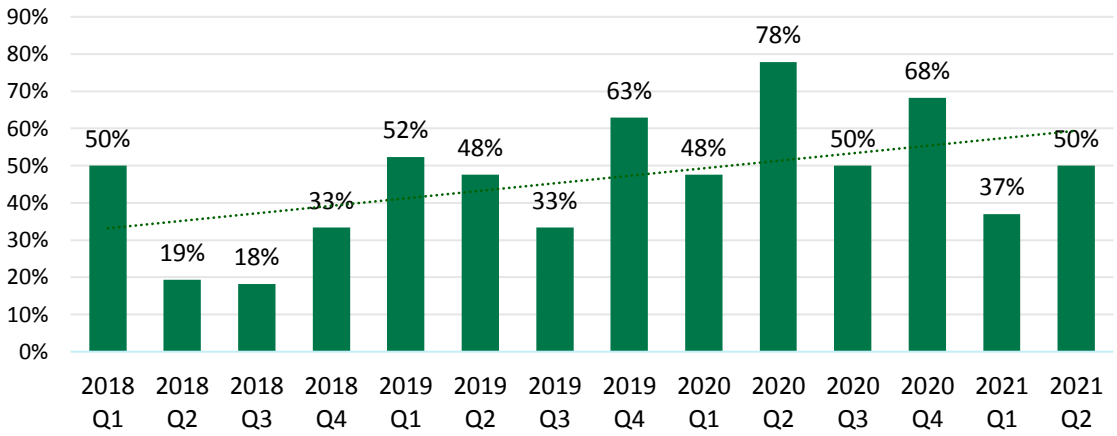


Figure 6: Panel support for the use of bedaquiline over time

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.

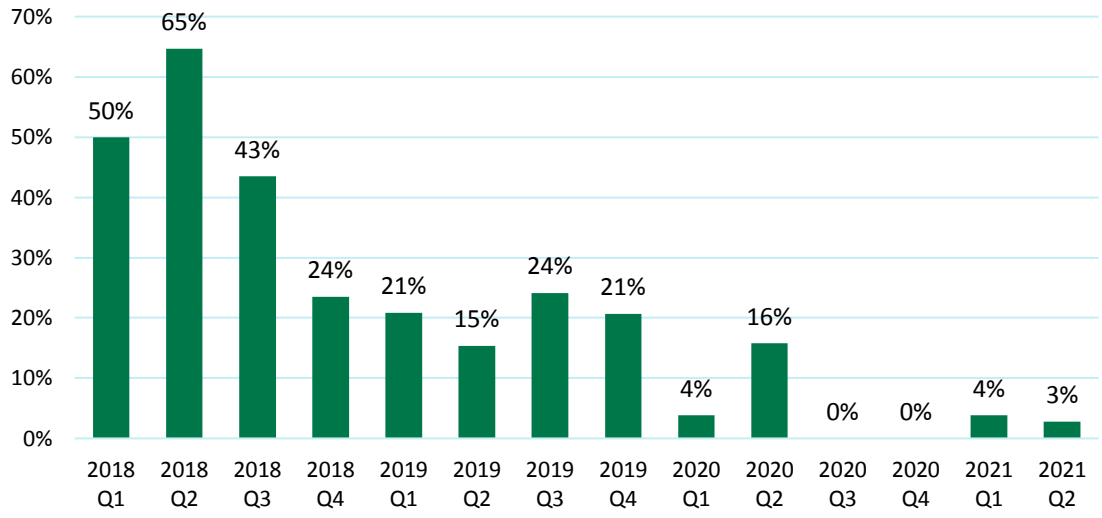


Figure 7: Reported use of injectables at entry onto the Service over time

This chart shows the percentage of cases (from all categories of disease) where the patient had received at least one injectable drug at the time of presentation. As expected, this chart shows a decrease in the use of injectables as the use of bedaquiline increased.

It is anticipated that future reports will also include details for support to use the drug pretomanid, which is not currently available for use in the UK (as of June 2021).

The BTS MDR-TB CAS Annual Report 2020 also included information regarding reasons for ceasing drug treatment. This year that information is included in the Supplemental Report *MDR-TB Drug Toxicity in the UK.*

PART 5 – Non-Tuberculous Mycobacteria (NTM)

From July 2020 to the end of June 2021, 22 of the 105 cases discussed (21%) were due to NTM. This represents the largest group of cases discussed that are not known or suspected MDR/XDR-TB.

Half (50%, 11/22) of patients were aged 60 or above, and 18% (4/22) 70 and above, highlighting the importance of considering frailty when determining the appropriate course of treatment.

86% of patients with NTM were born in the UK, with the same proportion being of White ethnicity. The next most common ethnicities were South Asian (5%) and Black-African (5%).

The most frequent site of infection was pulmonary (55%, 12/22) followed by 'extra-pulmonary' (32%) and 'disseminated' (10%).

Extra-pulmonary infection often followed wounds from surgery or body piercings.

Key Figures

- Almost one fifth of patients ≥70
- Population roughly 86% White and 86% UK-born
- Over half of patients have pulmonary infection, and 10% have disseminated NTM
- *M. abscessus* and *M. avium* complex were the most frequently reported organisms
- 31% of patients were immunosuppressed
- No cases reported associated cystic fibrosis

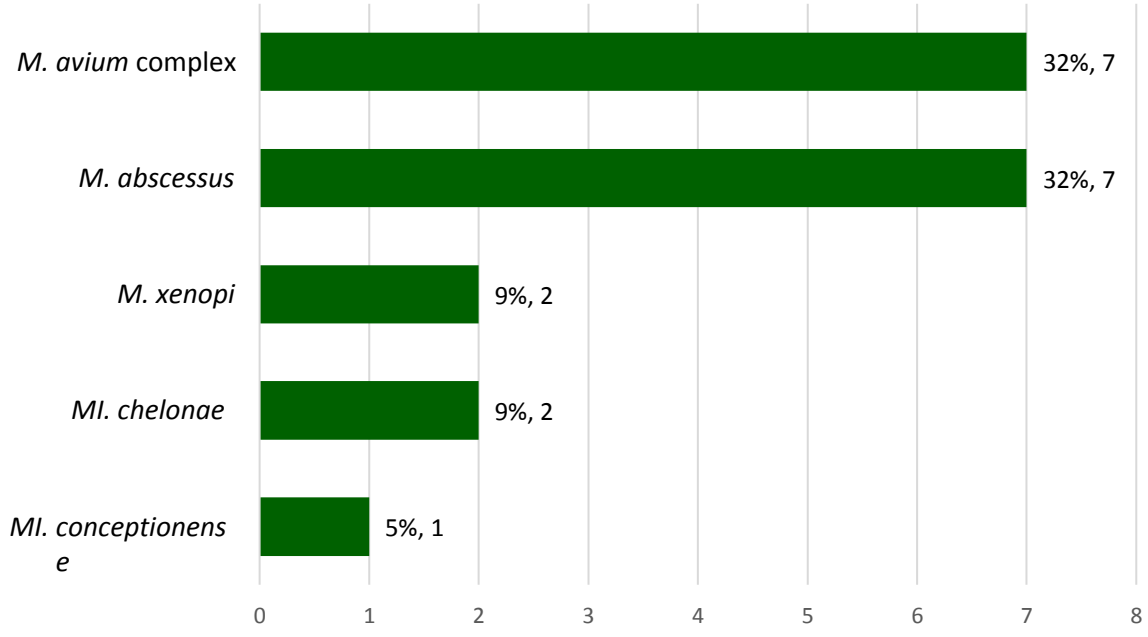


Figure 8: Species of NTM involved in infections
The most frequently reported organisms were *M. avium* complex (32%) and *M. abscessus* (32%). There were a small number of cases of multiple infection, often involving *M. chimaera*.

In this chart *M. avium* complex includes *M. avium* (5) and *M. chimaera* (3), where one case involved coinfection.

Social risk factors for were rare (6% of cases), though clinical risk factors were common (89% - 16/18). The most frequent clinical risk factor was immunosuppression (31%, 5/16), and aside from HIV this immunosuppression was predominantly the result of transplantation (20%). Chronic kidney disease, smoking and diabetes were also commonly reported

Overall 82% (18/22) of NTM cases were discussed at MDT. Of these 89% (16/18) were discussed once, with 11% discussed twice.

Six cases included a request for the panel of expert Clinical Service Advisers to support the use of bedaquiline, comprising 14% of all 43 requests specifically for the drug. Of these three were approved. This proportion (50%) is, as would be expected, much less than for either MDR or XDR-TB. In one case the panel supported the use of bedaquiline where the clinician had not originally requested support to use the drug. No requests for support to use delamanid were made

Thus, over the reporting period 18% (4/22) of all NTM cases discussed through the forum had support for the use of bedaquiline. As of November 2021, 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.

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/.

NTM Patient Care UK is the first UK patient association, and provides information and support for NTM patients and carers. It also works with healthcare professionals to improve understanding of patient needs. To learn more please visit their website at https://www.ntmpatientcare.uk/.

CLINICAL SERVICE ADVISERS

We would like to extend our sincere thanks to all the expert Clinical Service Advisers who have generously volunteered their time in 2021:

Dr Sarah Anderson
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Mr Mark Gilchrist
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Dr Merav Kliner
Professor Onn Min Kon
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Dr Naomi Walker
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Dr Steven Welch
Dr Natasha Weston
Dr Elizabeth Whittaker
Dr Stephen Wilson
Dr David Wyllie

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1. World Health Organisation. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis (2020)
   [Available from: https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis accessed 04/11/2021]

2. World Health Organisation. WHO consolidated guidelines on drug-resistant tuberculosis treatment (2019)
   [Available from: https://apps.who.int/iris/rest/bitstreams/1211676/retrieve accessed 04/112021]