

Extensively drug resistant tuberculosis in the United Kingdom: 1995 to 2007

Ibrahim Abubakar^{1,7*}, Jonathan Moore¹, Francis Drobniewski¹, Michelle Kruijshaar¹, Tim Brown¹, Malcolm Yates¹, Charlotte Anderson¹, E Grace Smith², John Magee³, Marc Lipman⁴, Jim McMenamin⁵, Michael Ruddy⁶ and John M Watson¹

1. Respiratory and Systemic Infections Department, Centre for Infections, Health Protection Agency, London, NW9 5EQ

2. Health Protection Agency Regional Centre for Mycobacteriology, Heart of England NHS Foundation Trust, Bordesley Green East, Birmingham B9 5SS

3. Health Protection Agency Regional Centre for Mycobacteriology, General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE

4. Royal Free Hospital NHS Trust, Pond Street London NW3 2QG

5. Health Protection Scotland, Glasgow G3 7LN

6. Wales Centre for Mycobacteriology, Llandough Hospital, Penlan Road, Penarth CF64 2XX

7. School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ

* Author for correspondence

Tuberculosis Section, Respiratory and Systemic Infections Department, Centre for Infections, Health Protection Agency, London, NW9 5EQ

Email: Ibrahim.abubakar@hpa.org.uk

Tel: 0208 200 6868

Fax: 0208 200 7868

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Abstract

Background: The emergence of multi-drug resistant tuberculosis (MDRTB) and extensively drug resistant tuberculosis (XDRTB) is a threat to global tuberculosis control. Limited information is, however, available on the outcome of XDRTB cases. This study describes the susceptibility to second and third line anti-tuberculosis drugs among MDRTB cases and treatment outcome of identified XDRTB cases.

Method: Results of second line anti-tuberculosis drug susceptibility tests in the UK between January 1995 and December 2007 were retrospectively reviewed and clinicians contacted for treatment outcome of XDRTB cases. Participants included all 678 patients with culture confirmed MDRTB in the UK. The main outcome measures were the proportion of isolates resistant to second line anti-tuberculosis drugs and treatment outcome for XDRTB cases.

Results: Among MDRTB isolates, levels of resistance to amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide and PAS were 5.5%, 3.4%, 5.6%, 5.1%, 14.0% and 16.7% respectively. Six XDRTB cases (0.9% of MDR cases) were identified during this period. Two further cases of XDRTB were reported in 2008. Five individuals with XDRTB died of tuberculosis within 3 years of diagnosis and three are still on treatment

Conclusion: Levels of MDRTB remain low, and XDR very low, in this high income country. Case fatality ratio among XDRTB cases was high despite low levels of HIV co-infection.

Background

The emergence of multi-drug resistant tuberculosis (MDRTB) and extensively drug resistant tuberculosis (XDRTB) is a threat to global tuberculosis control. These forms of tuberculosis are difficult and expensive to treat and often associated with a poor clinical outcome.^{1;2} In the case of MDRTB, this relates to the loss of the highly potent anti-tuberculosis drugs isoniazid, the drug with the strongest early bactericidal action against *Mycobacterium tuberculosis* complex, and rifampicin, which acts against bacilli that are no longer in the active phase of replication. Therapeutic options are fairly limited and associated with a variety of side effects.³ Although survival is improved by the administration of drugs to which the bacteria are susceptible,^{1;4} the development of resistance to second and third line drugs (especially fluoroquinolones and injectable agents) among cases with MDRTB further worsens the prognosis of these patients.²

The World Health Organisation describes increasing levels of MDRTB globally.⁵ In the UK the incidence of MDRTB has risen, although the magnitude of increase is small.⁶ Here we describe the susceptibility to second and third line anti-tuberculosis drugs among MDRTB cases in the UK between January 1995 and December 2007 and report the number, characteristics and treatment outcome of identified XDRTB cases.

Methods

Study population

The results of drug susceptibility testing of all *M. tuberculosis* complex isolates undertaken between 1995 and 2007 have been collated through the UK Mycobacterial Surveillance Network (MycobNet) collaboration. Drug susceptibility results to the six main classes of drugs used to treat MDRTB (fluoroquinolones, serine analogues, aminoglycosides, capreomycin, para-aminosalicylic acid and the thionamides) and other agents (clarithromycin, azithromycin, rifabutin, streptomycin and clofazimine) were analysed. Duplicate results from isolates were manually removed by using patient names, date of birth and address where available. It is, however, possible that a small number of duplicate records remain due to the limited amount of demographic information in the MycobNet database.

Definitions

MDRTB was defined as resistance to at least isoniazid and rifampicin and XDRTB as resistance to at least isoniazid, rifampicin, a fluoroquinolone, and one of three injectable second line drugs (amikacin, kanamycin, capreomycin). First line drugs in the UK include rifampicin, isoniazid, pyrazinamide and ethambutol.

Data collection

In addition to data on drug susceptibility collected through the MycobNet collaboration, we retrospectively contacted the reporting clinician to determine the outcome of treatment as well as additional clinical and demographic information on patients with XDRTB. With the exception of one recent XDRTB case, the information was collected more than 3 years after initial diagnosis. Strain typing information based on 15 loci Mycobacterial Interspersed Repetitive Units Variable Number Tandem Repeats (MIRU-VNTR), performed as described previously,⁷ was

collated for all XDRTB cases to investigate the possibility of person to person transmission. MIRU-VNTR typing became available in 1999 and isolates from cases diagnosed prior to this date were typed retrospectively where available.

Statistical analysis

Analysis of second line drug susceptibility results among MDRTB cases was carried out to examine long term trends and determine the extent of XDRTB. Proportions were calculated and where appropriate an extension of the Wilcoxon rank-sum test for trend across ordered groups was used to assess the statistical significance of trends.

Results

Between 1995 and 2007, a total of 678 MDRTB cases were reported to the MycobNet collaboration, an average of 52 cases per year. The median age of the group was 32 years (inter-quartile range 26 to 43 years) and 59% (377/639 cases where gender was known) were male. Table 1 shows the proportion of MDRTB cases resistant to second line anti-tuberculosis drugs. Among MDRTB isolates, levels of resistance to amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide and PAS were 5.5%, 3.4%, 5.6%, 5.1%, 14.0% and 16.7% respectively. Where tested, resistance to rifabutin and streptomycin was very high. Resistance to the first line drugs, pyrazinamide and ethambutol was 28.0% and 36.1% respectively.

Table 1. Second line anti-tuberculosis drug resistance among Multi Drug Resistant isolates of *M. tuberculosis* complex, UK, 1995-2007

| Class | Drug | Resistant/Tested* (%) |
|------------------|---------------------|-----------------------|
| Fluoroquinolones | Ciprofloxacin | 34/610 (5.6) |
| | Moxifloxacin | 1/24 (4.2) |
| | Ofloxacin | 1/26 (3.9) |
| | Any fluoroquinolone | 36/647 (5.6) |
| Serine Analogues | Cycloserine | 28/551 (5.1) |
| Aminoglycosides | Amikacin | 32/583 (5.5) |
| | Kanamycin | 1/24 (4.2) |
| Polypeptides | Capreomycin | 20/592 (3.4) |
| Thionamides | Ethionamide | 84/601 (14.0) |
| | Prothionamide | 2/5 (40.0) |
| | Any thionamide | 86/606 (14.2) |
| PAS | PAS | 77/462 (16.7) |
| Others | Clarithromycin | 70/587 (11.9) |
| | Azithromycin | 8/92 (8.7) |
| | Streptomycin | 327/636 (51.4) |
| | Rifabutin | 138/160 (86.3) |
| | Clofazimine | 33/94 (35.1) |

PAS – para-aminosalicylic acid

*Where information on testing was available among a total of 678 isolates

Extensively drug resistant cases

Six XDRTB cases (0.9% of MDR cases) were identified during this period. Two further cases of XDRTB were reported in 2008. Of the eight cases, six were male and all were adults (Table 2). Three cases were of white ethnic group and six were known to be born outside the UK. Five cases had pulmonary disease with or without extra-pulmonary involvement and six cases were not known or suspected to be HIV positive. All cases had isolates resistant to a variety of second line drugs with a minimum resistance to five drugs. Five individuals died of tuberculosis within 3 years of diagnosis and three are still on treatment (including the two diagnosed in 2008). Strain typing data were available for five out of the eight XDR isolates; all five were distinguishable using 15 loci MIRU-VNTR. A search of the national strain typing database identified a limited number of MDRTB cases which shared indistinguishable MIRU VNTR type with two of these cases. The 15 digit MIRU VNTR code for these two isolates was 424352332517333 and 224331432615324 also associated with a further 11 and 3 MDRTB cases respectively. These MDRTB cases were reported from a geographically widespread area. Stored isolates from 3 cases could not be recovered. Lack of strain typing data prior to 2003 limits the interpretation of transmission in this context.

A further 12 MDRTB cases had resistance to at least three of the six second line anti-tuberculosis drugs, fulfilling the initial, but not the subsequently revised, definition for XDRTB.⁸

Table 2. Characteristics of extensively drug resistant tuberculosis cases in the UK, 1995 to January 2008

| Year | Sex | Age | Ethnicity and place of birth | Previous TB? | Drug resistance additional to UK first line agents* | Site of disease | Outcome |
|------|--------|-------|------------------------------|--------------|---|---------------------|--------------------|
| 2008 | Female | 20-29 | White, Non-UK | No | Kan, Mox, OfI, PAS, Strep | Pulmonary | Still on treatment |
| 2008 | Male | 20-29 | Black African, Non UK | Yes | AK, Cap, Eth, Kan, OfI, Pro, Strep | Pulmonary | Still on treatment |
| 2003 | Male | 30-39 | White, UK | No | Cap, Cip, Eth | Pulmonary | Still on treatment |
| 2002 | Male | 30-39 | White, Non-UK | No | Cap, Cip, Cla, Clo, Cyc, RB | Cervical Lymph Node | Died of TB |
| 1999 | Male | 20-29 | Indian sub-continent, Non UK | Yes | AK, Cap, Cip, Cla, Clo, Eth, RB | Pulmonary | Died of TB |
| 1997 | Male | 40-49 | Indian sub-continent Non UK | Yes | AK, Cap, Cip, Cla, Clo, Cyc, PAS, Strep | Pulmonary | Died of TB |
| 1997 | Male | 80-89 | Unknown | Unknown | Cap, Cip, Cyc, Strep | Abdominal | Died of TB |
| 1995 | Female | 50-60 | Indian sub-continent Non UK | Unknown | AK, Cip, Cla, RB, Strep | Pulmonary | Died of TB |

AK – amikacin, Cap – capreomycin, Cip – ciprofloxacin, Cla – clarithromycin, Clo – clofazimine, Cyc – cycloserine, Eth – ethionamide, Kan – kanamycin, OfI – ofloxacin, Pro – prothionamide, RB – rifabutin, and Strep – streptomycin,

* - First line drugs in the UK include rifampicin, isoniazid, pyrazinamide and ethambutol.

Discussion

The level of XDRTB in the UK remains low despite the occurrence of about 50 new MDRTB cases each year and an increase in the incidence of tuberculosis over the last two decades. Eight patients between January 1995 and October 2008 had drug susceptibility results consistent with the current definition of XDRTB. Five of the eight cases died of their disease.

The low levels of XDRTB in the UK compared to other European countries² may reflect minimal incidence of second and third-line drug resistance in the country of origin of the majority of non-UK born tuberculosis patients. Alternatively, this may be due to high levels of appropriate clinical management of patients with MDRTB.⁴ Our finding of poor clinical outcome in these XDRTB patients is consistent with previous studies where a large proportion of cases died of tuberculosis^{2,9} especially among HIV co-infected individuals. In contrast to the South African experience, our patient population had, as far as known, low levels of HIV infection.

There was neither evidence of transmission, of XDRTB nor, from an MDRTB strain with the same MIRU VNTR pattern, based on typing results. This can not, however, be excluded as six cases were non-UK born and could have acquired the infection from an MDR or XDR TB case outside the UK. Due to the lack of strain typing data prior to 2003, we can not exclude the possibility that some of the isolates identified prior to widespread typing were responsible for transmission. We were also unable to obtain detailed clinical information on other factors contributing to the death of these patients due to the retrospective nature of this study.

The poor outcome in these XDRTB cases, however, suggests that UK clinicians should ensure that a package of care which includes directly observed therapy is available for all MDRTB patients to prevent the development of XDRTB. The experience of most clinicians is likely to be limited, even in parts of the UK with a higher incidence of tuberculosis, given the small number of cases. As the management of these patients is complex, the use of second line anti-tuberculosis drugs, especially fluoroquinolones, kanamycin, amikacin and capreomycin, in patients infected with MDRTB strains should always be undertaken by those with appropriate experience and expertise.¹⁰

The management of MDRTB cases involves the choice of a combination of second-line anti-tuberculosis drugs, and occasionally first line agents, which should be based on drug susceptibility tests.¹¹ It is sometimes necessary to start second line therapy while awaiting these results. Our data suggest that certain drugs, such as rifabutin and clofazimine, are unlikely to be useful for empirical therapy in the UK in this situation. In addition, over 60% of MDRTB isolates and three XDRTB cases were susceptible to ethambutol, a drug which has synergistic effects with others due to its action on the cell membrane of mycobacteria¹², allowing the use of this agent in such patients. Newer fluoroquinolones such as moxifloxacin should still be considered in the management of these patients as there is evidence that the efficacy of later-generation fluoroquinolones may be preserved, despite resistance to ciprofloxacin.¹³ The Peruvian study suggests that clinicians may also want to reinforce regimens with pyrazinamide and ethambutol with clarithromycin, clofazimine and rifabutin.¹³

Where drug susceptibility information on these agents is available, our data suggests that these agents may have a role in the management of XDRTB.

This study is limited by the small number of XDRTB cases reported. A further limitation relates to the lack of information on the long term treatment outcome for all MDRTB cases to allow a comparison with the XDRTB patients. National surveillance is being developed to collect information on clinical outcome at 24 months to inform future analysis. As in other developed countries, not all cases of tuberculosis in the UK are culture confirmed. These data therefore represent the susceptibility results from those with a proven bacterial culture only. Nevertheless, this sample included all culture confirmed cases and is unlikely to be affected by survival bias which many XDRTB studies may be prone to.¹³

Despite the low incidence of MDRTB and XDRTB in the UK, this study found high case fatality among XDRTB patients. A recent postal survey by the British Thoracic Society (BTS) suggested that clinicians with no experience of managing MDRTB remain willing to treat these patients.¹⁴ Evidence from countries with high rates of drug resistance that have successfully tackled this problem, suggests that an alternative approach is likely to be more successful.¹⁵ The BTS has recently been commissioned by the Department of Health to set up multidisciplinary TB teams (MDT) working in every area of England and Wales, together with an expert clinical advisory service to underpin and advise the MDTs as needed. In tandem with this a group of UK clinicians have recently started a national MDRTB service, providing advice on a voluntary basis to colleagues.¹⁶ The aim is that these developments will help reduce the likelihood that cases of MDRTB will emerge, that they are detected promptly when they do occur, that they are managed effectively (including choice of anti tuberculosis therapy) and, as a result their outcomes are improved with minimal occurrence of further second line anti-tuberculosis drug resistance.

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Ibrahim Abubakar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors satisfy the minimum requirement for authorship, have approved the final version of the paper and do not have a conflict of interest to declare.

Ethics approval

The Health Protection Agency has Patient Information Advisory Group approval to hold and analyse national surveillance data for public health purposes under Section 60 of the Health and Social Care Act 2001.

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