# Trends in multidrug-resistant tuberculosis in Scotland, 2000-7

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Overall numbers of multidrug-resistant (MDR) tuberculosis (TB) rose sharply in the United Kingdom and Scotland in 2007. Risk factors associated with MDR TB in the United Kingdom have been identified but there has been no previous report on risk factors associated with MDR TB in Scotland. Enhanced Surveillance of Mycobacterial Infections (ESMI) data were used to examine demographic and clinical characteristics and treatment outcome of MDR TB cases notified in Scotland between 2000-7. There was a total of 11 culture-positive cases of MDR TB, five of which were notified in 2007. The majority of patients were female, 15-44 years old and unemployed. All were born outside the United Kingdom and most had arrived within the past year from or frequently travelled to their home countries in China, the Indian subcontinent or Africa. Except for one individual, our patients did not self report a history of previous diagnosis of TB which was previously identified as a risk factor for MDR TB in the United Kingdom. Only three patients received directly observed treatment (DOT). Only two patients had completed treatment at 12 months, partially due to the inadequate length of follow-up under the current ESMI system. Our results suggest that most patients had primary resistance due to transmission of MDR TB in high incidence countries and thus point to the importance of international efforts to control MDR TB in these countries. In Scotland, national efforts should be made to increase the number of MDR TB patients receiving DOT and to extend follow-up to improve monitoring of treatment outcome. It is important to identify high risk groups for MDR TB infection in order to deliver effective community-based disease control measures.

## Introduction

There are an estimated nine million new cases of tuberculosis (TB) worldwide each year and 5.3% of these are multidrug-resistant (MDR) [1]. In 2007, the highest incidence rates for MDR TB ever recorded were detected in 14 countries which comprised China and countries that were members of the former Soviet Union [1]. In the United Kingdom the proportions of MDR TB currently remain low at 1.2% and have been stable since 2000 [2]. However, the number of MDR TB cases per year has increased from 28 in 2000 to 55 in 2007 [2]. This rise is important in terms of future public health planning and resource allocation. It is important to prevent the transmission and emergence of MDR TB because the second line antibiotics that are necessary for treatment are less effective, have toxic side effects and require extended treatment regimes for 18-24 months [3-5]. Treatment failure is therefore more common and subsequently leads to higher mortality rates and relapse [6-7]. It may also result in the emergence of extensively drug-resistant TB (XDR TB). Furthermore, due to increased drug, inpatient and directly observed therapy (DOT) costs, treatment of MDR TB is ten times more expensive than treatment of drug-sensitive TB. In the UK, the management of an MDR TB case has been estimated to cost the NHS £60,000 compared to £6,040 for a patient with drug-sensitive TB [8].

Effective community-based disease control measures, including contact tracing and optimal treatment outcome, rely on identification of patient groups at risk from MDR TB infection. For the United Kingdom specific risk factors associated with MDR TB include being male [9-10], although in 2008, more MDR TB patients were female [2], being 15-44 years old, or of younger age [2, 9-11], being born outside the United Kingdom [2, 10-12], having a history of previous diagnosis of TB [2, 9-13] and being of Black African, Indian-Pakistani-Bangladeshi or Chinese ethnicity [11]. Being HIV positive and living in London were associated with primary resistance [9-10, 12] whereas pulmonary disease and smear positivity were associated with secondary resistance [10, 12].

There has been no previous report on the risk factors associated with MDR TB in Scotland. The Enhanced Surveillance for Mycobacterial Infections (ESMI) scheme was introduced in 2000 by Health Protection Scotland as the routine surveillance system for the collection of demographic, clinical and laboratory data on patients notified with TB in Scotland. We have used data from the ESMI scheme to examine the demographic and clinical characteristics and treatment outcome of MDR TB cases notified in Scotland between 2000-7.

## Methods

The Scottish Mycobacteria Reference Laboratory (SMRL) provided data on mycobacterial strains and drug resistance profiles of isolates obtained through culture and antibiotic susceptibility testing. An MDR TB case was defined as a culture positive case of Mycobacterium tuberculosis complex resistant to at least isoniazid and rifampicin. ESMI data were used to calculate the proportions

of TB cases that were MDR TB, over time, with 95% confidence intervals (95% CI) using Wilson's method [14]. Descriptive epidemiology of MDR TB cases, notified between 2000-7 inclusive, was carried out using a case series to examine: sex, age group, country of birth, years since entry into the United Kingdom, travel outside the United Kingdom in the last two years for at least one month, occupation, previous diagnosis of TB (used as a proxy for secondary resistance), pulmonary disease defined as TB infection in the lungs and/or tracheo-bronchial tree, site of disease and whether patients had received DOT. Patients' ethnicity, health board of residence (health boards are the geographical administrative units for the National Health Service in Scotland), sputum positivity for acid fast bacilli (AFB) and additional risk factors such as being immunosuppressed, a refugee/asylum seeker, an excess alcohol user, a drug user, homeless/hostel dweller/rough sleeper or a health care worker were also captured. Treatment outcome and patient status (alive/dead) were recorded 12 months after treatment start date.

## Results

There were 2,199 culture confirmed cases of TB in Scotland between 2000-7 and 11 of these (0.5%; 95% CI 0.3-0.9) were MDR TB (Table 1). There were no differences in the numbers of MDR TB cases observed between 2000-6, with a range of 0-2 cases and proportions of 0-0.8%. However, in 2007 the number of cases increased to five which accounted for 1.7% of TB cases, although the increase was not significant due to the small numbers involved.

Demographic data are displayed in Table 2. Information was complete apart from single cases with missing values for number of years since entry into the UK, country travelled to and occupation. The majority of patients were female (8) and 15-44 years old (10). All were born outside the United Kingdom. Countries of birth included China (2), Pakistan (3), India (1), Zimbabwe (2), Somalia (1), Philippines (1) and Eastern Europe (1); ethnicities matched those of the native populations in the countries of origin. Most affected (8) had been resident in the United Kingdom for one year or less and all had been in the United Kingdom for less than five years. Seven had a history of travel abroad for at least one month in the past two years, as recorded by ESMI, and most had travelled to their home countries. The majority were unemployed (7); one of the only two employed patients was a health care worker. As additional risk factors immunosupression was identified for one patient. Between 2000-4 the majority of MDR TB patients (4) were resident in urban areas with large cities which were covered by larger health boards. Smaller health boards covering rural areas have also had MDR TB patients which has impacted on their TB services (data not shown to preserve patients' anonymity).

Clinical data are shown in Table 3. Overall they were complete, apart from pending information regarding treatment outcome in three cases and one case with this information missing. One patient had a history of previous diagnosis of TB and reported having received at least one month of treatment in his home country. Three patients had pulmonary disease and two were also smear-positive. Extra-pulmonary sites of disease included intrathoracic and extrathoracic lymph nodes, pleura and spine. Only three patients were commenced on DOT. After isoniazid and rifampicin, the majority of isolates were resistant to streptomycin (7), rifabutin (7), ethambutol (5), pyrazinamide (4) and clarithromycin (4). Resistance to prothionamide (1) and clofazimine (1) was also detected in two different isolates. Only two patients had completed treatment 12 months after treatment start date. For three patients having started treatment at the end of 2007 information on treatment outcomes were pending. Only one patient died whilst under treatment.

## Discussion

In 2007 there were five cases of MDR TB in Scotland and 55 in the UK representing the highest numbers ever recorded across the United Kingdom. The proportion of MDR TB in Scotland which was 1.7%, was higher than the UK national average [2]. However, it remained below the national guideline level of 2%, which was set to indicate adequate MDR TB control in the United Kingdom [15]. The increase in MDR TB cases in 2007 may indicate future trends and emphasizes the importance of maintaining or improving levels of control in high risk populations. The results of our study indicate that MDR TB cases in Scotland are imported into the country by young migrant populations recently arrived or returned from countries with high incidence rates of MDR TB. It is perhaps surprising that only one MDR TB patient was from Eastern Europe considering the recent influx of migrant workers from Eastern Europe into Scotland and the rest of the United Kingdom and the high incidence rates of MDR TB in this region [1]. It takes two to five years for the majority of new migrants, entering the UK with latent TB, to develop an active infection [2] and therefore it is possible that Scotland may experience a delay before detecting an increase in MDR TB patients from Eastern Europe. It is also possible that Eastern European patients from non-EU countries return home to seek health care and are thus not picked up by the United Kingdom notification systems.

MDR TB is often associated with a previous history of treatment [1-2, 16-17] and treatment failures or mismanagement leading to secondary resistance. However, in this case series, only one patient had a previous history of TB and treatment, suggesting that most patients had primary resistance, due to transmission of MDR-TB, in high incidence countries. However, previous history of TB diagnosis and treatment was self-reported, so these data may be biased.

The majority of MDR TB patients in our study had non-pulmonary infections with associated lower risks of transmission. Eight of the eleven patients were on self administered treatment, rather

**Table 1**

**Sputum-positive multidrug-resistant (MDR) tuberculosis (TB) in Scotland, 2000–2007 (n=11)**

| Year | MDR TB | | | Total TB sputum-positive cases (n) |
|---|---|---|---|---|
| | n | %* | (95% CI**) | |
| 2000 | 0 | 0 | (0.0-1.4) | 285 |
| 2001 | 2 | 0.8 | (0.1-2.8) | 248 |
| 2002 | 1 | 0.4 | (0.01-2.2) | 256 |
| 2003 | 1 | 0.4 | (0.01-2.1) | 265 |
| 2004 | 1 | 0.3 | (0.01-1.8) | 302 |
| 2005 | 0 | 0 | (0.0-1.3) | 270 |
| 2006 | 1 | 0.4 | (0.01-1.9) | 282 |
| 2007 | 5 | 1.7 | (0.6-3.9) | 291 |
| Total | 11 | 0.5 | (0.3-0.9) | 2,199 |

* proportion of total number of TB cases
** 95% confidence intervals (CI)

than on DOT which can aid treatment completion, especially with extended treatment regimes. Partially due to inadequate length of follow-up (12 months) under the current ESMI system, only two patients were recorded as completing treatment 12 months after treatment start date. As MDR TB usually requires treatment for at least 18 months, the recorded treatment completion at 12 months is likely to be an artifact. Both outcome forms for these patients were received with a delay of six months, which suggests that they also took 18 months to complete treatment. In Scotland, it has recently been agreed to introduce further follow-up of TB patients at 24 months, for those individuals who had not completed treatment at 12 months. In order to improve monitoring of MDR TB patients, the Health Protection Agency in England has similarly revised its system to monitor specific patients at 24 months [2].

This study is the first to describe the patterns and characteristics of MDR TB in Scotland. The results point to the importance of international efforts to improve treatment and control of MDR TB transmission in high incidence countries, as addressed by the World Health Organization (WHO) Plan to stop TB in 18 High-Priority countries in the WHO European region [3]. This is essential not only to alleviate the associated morbidity and mortality in these countries, but also to prevent the spread of resistant TB strains to low incidence countries, which could impede all future hopes of global control of tuberculosis. National efforts should be made to encourage all new entrants to Scotland to register with general medical practices as soon as possible and research is being carried out to identify incentives which may help to increase NHS registration in these populations [18]. Clinicians should suspect MDR in TB patients from all regions of the world with a high incidence of MDR TB and should ensure timely susceptibility testing is carried out on isolates, that appropriate drug regimes are prescribed and contact tracing is carried out as required following appropriate guidance, including guidance on long haul air travel.

**Table 2**

**Demographic characteristics of multidrug-resistant (MDR) tuberculosis (TB) cases in Scotland, 2000-2007 (n=11)**

| Patient | Year | Sex | Age group | UK born | Country of origin | Years since entry into the UK | Significant travel outside the UK | Occupation |
|---|---|---|---|---|---|---|---|---|
| 1 | 2001 | M | 15-44 | No | China | <1 | Home country | Unemployed |
| 2 | 2001 | M | 15-44 | No | Pakistan | 4 | Unknown | Unemployed |
| 3 | 2002 | F | 15-44 | No | Pakistan | 1 | Home country | Unemployed |
| 4 | 2003 | F | 45-65 | No | Zimbabwe | <1 | Home country | Health care worker |
| 5 | 2004 | F | 15-44 | No | Philippines | <1 | Western Europe | Unemployed |
| 6 | 2006 | F | 15-44 | No | Zimbabwe | 1 | Home country | Unknown |
| 7 | 2007 | F | 15-44 | No | India | 2 | No | Employed |
| 8 | 2007 | F | 15-44 | No | Somalia | 1 | No | Unemployed |
| 9 | 2007 | F | 15-44 | No | Eastern Europe | <1 | Unknown country | Unemployed |
| 10 | 2007 | M | 15-44 | No | Pakistan | Unknown | Home country | Unemployed |
| 11 | 2007 | F | 15-44 | No | China | <1 | No | Further Education |

M=Male, F=Female

**Table 3**

**Clinical characteristics and treatment outcomes of multidrug-resistant (MDR) tuberculosis (TB) cases in Scotland, 2000-2007 (n=11)**

| Patient | Previous diagnosis | Pulmonary TB | Site of disease | Follow up at 12 months | DOT | Alive | Resistance |
|---|---|---|---|---|---|---|---|
| 1 | Yes | Yes | Lung | Still on treatment | Yes | Yes | INH,RMP,STM,RFB,CLR |
| 2 | No | No | Cervical LN | Treatment completed | Yes | Yes | INH,RMP,EMB,RFB,CLR |
| 3 | No | Yes | Lung | Missing | Yes | Yes | INH,RMP,EMB,PZA,STM |
| 4 | No | No | Axillary LN | Still on treatment | No | Yes | INH,RMP,EMB,RFB |
| 5 | No | No | Cervical LN | Still on treatment | No | Yes | INH,RMP,RFB,PTH |
| 6 | No | No | ITH and cervical LN's | Treatment completed | No | Yes | INH,RMP,EMB,PZA,STM |
| 7 | No | No | ITH, abdominal LN's, spine | Still on treatment | No | No | INH,RMP,EMB,RFB,CLR |
| 8 | No | No | Supraclavicular LN | Still on treatment | No | Yes | INH,RMP,PZA,STM,RFB,CFZ |
| 9 | No | No | Pleural | Pending | No | Pending | INH,RMP,PZA,STM,RFB |
| 10 | No | No | Spine | Pending | No | Pending | INH,RMP,STM |
| 11 | No | Yes | Lung | Pending | No | Pending | INH,RMP,STM, RFB,CLR |

Key: INH=Isoniazid, RMP=Rifampicin, EMB=Ethambutol, PZA=Pyrazinamide, STM=Streptomycin, RFB=Rifabutin, CLR=Clarithromycin, CFZ=Clofazimine, PTH=Prothionamide, ITH=Intrathoracic and LN=lymph node.

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