Extensively drug-resistant tuberculosis case in the Thames Valley, UK and public health interventions

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Received 15 April 2011; received in revised form 21 June 2011; accepted 25 June 2011

Summary This study describes the first case of extensively drug-resistant tuberculosis (XDR-TB) in the Thames Valley and South East Region and discuss the public health implications, highlighting the need to integrate current epidemiological knowledge with clinical expertise in order to diagnose drug-resistant tuberculosis (TB) early.

The management of the XDR-TB patients is challenging with few treatment options, expensive therapy, side effects of drugs and a longer course of the treatment.

Background

Tuberculosis (TB) causes 1.7 million deaths each year worldwide. Multi-drug resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) have become urgent and worrisome threats to global health. XDR-TB is resistant to both first and second line anti-tuberculosis therapy. As a result, it can be extremely difficult to treat and is associated with a higher mortality than non-resistant strains [1], especially in areas with a high prevalence of HIV.

In 2008, 963 XDR-TB cases were reported to the WHO worldwide [2]. Between 1995 and 2008 ten XDR-TB cases were reported in the UK, five of whom died [3]. Of the countries where it has been reported, XDR-TB is thought to represent, on average, 5.4% of all MDR-TB cases [2]. However, in Eastern European countries, such as Estonia and Lithuania, this proportion is much higher (12.5% and 14.5% respectively) [2].

This case report describes public health issues arising from a case of XDR-TB in the Thames Valley.
Table 1  Timeline of events in the clinical history and management of the case from presentation until XDR-TB diagnosis and subsequent discharge.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>4th May 08</td>
<td>Presented to A&amp;E</td>
</tr>
<tr>
<td>May, June, July 08</td>
<td>Saw GP several times over 3 month period with no improvement in symptoms</td>
</tr>
<tr>
<td>21st August 08</td>
<td>X-ray showed small area of consolidation</td>
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<tr>
<td>28th August 08</td>
<td>Acid fast bacilli on microscopy</td>
</tr>
<tr>
<td>29th August 08</td>
<td>TB treatment started with four drug regimen (rifampicin, isoniazid, ethambutol and pyrazinamide) – culture confirmed TB shortly after</td>
</tr>
<tr>
<td>29th September 08</td>
<td>Resistance to all first line drugs reported. Patient was admitted to Infectious Diseases Unit in a negative pressure room and TB treatment stopped.</td>
</tr>
<tr>
<td>20th October 08</td>
<td>Resistance to streptomycin, kanamycin, moxofloxacin, ofloxacin and p-aminosalicylic acid reported. Re-started treatment with clarithromycin, cycloserine, linezolid, protonamide, amikacin and clofazimine</td>
</tr>
<tr>
<td>3rd March 09</td>
<td>Discharge from hospital</td>
</tr>
<tr>
<td>April 10</td>
<td>Treatment stopped</td>
</tr>
<tr>
<td>February 11</td>
<td>Last reviewed (followed up every 6 months)</td>
</tr>
</tbody>
</table>

**Case investigation and management**

Thames Valley Health Protection Unit (TVHPU) was notified of a case of TB in August 2008. A 22-year-old student, HIV negative from Lithuania was initially treated for pneumonia but later found to have XDR-TB, the first case in Thames Valley and South East Region. The 24-locus Variable Number Tandem Repeat (VNTR) profile for a culture of *Mycobacterium tuberculosis* obtained from the patient matched with 14 other individuals in the UK, 5 of which were from Lithuania. No social or epidemiological ink was established with the other cases. After five months of hospitalization, the patient was discharged to continue treatment at home, completing 16 months of the planned two years of treatment due to intolerable side effects. The patient has had six monthly follow-up appointments and has had no progression of disease. The clinical details of the case were published as a case report in the British Medical Journal [4] and are outlined in the timeline (Table 1).

**Public health interventions (s)**

**Communication**

A TB incident control team was arranged shortly after the diagnosis of XDR-TB, to discuss contact tracing and screening. Guidance was sought from the National MDR-TB Clinical Advice Service [5], which helps clinicians implement the most effective treatment. The public health authorities provide a useful communications link by ensuring clinicians are aware of this service from the moment a case of MDR-TB is notified.

Other Health Protection Units nearby were contacted to identify potential links with other cases.

**Contact tracing and screening**

The TB nurse arranged contact tracing following initial TB diagnosis. Five close contacts were screened using Mantoux testing, Interferon gamma assay and a chest radiograph. Only one positive contact was identified who was asymptomatic. UK National guidelines on tuberculosis [6] were followed to manage this contact; no chemoprophylaxis was given, yearly follow up was arranged and advice was given to contact TB services immediately if any symptoms suggestive of TB develop. This contact has remained asymptomatic and is in contact with the TB nurse. Public health advice was also given to the patient’s place of work and study in order to identify other potential contacts.

A relative who had stayed with the patient in the UK while the patient had been symptomatic and had since returned to Lithuania was later identified as an additional contact. Direct contact with the relative was not possible, but the patient was asked to advise the relative to be screened locally. The relative was a medical student and the public health authorities in Lithuania were informed. This contact had no respiratory symptoms and there were no abnormal changes on the chest X-ray.

**Discussion**

XDR-TB exists in Europe and 149 cases of XDR-TB were reported during 2003–2007, the majority of
which were from East European countries (58 were Estonia; 53 from Latvia and 25 from Lithuania) [7]. In the UK 10 cases of XDR-TB were reported in the period of 1995—2008 [3]. Increasing migration within the European Union and worldwide will certainly see these numbers rise in low risk countries such as UK.

The Eastern European background of this patient reflects epidemiological trends in drug-resistant TB and could have alerted clinicians earlier to the possibility of XDR-TB. Current NICE guidelines [6], however, do not specifically highlight the risk of drug-resistant TB in patients from countries, such as Lithuania, where there is a relatively low incidence of TB overall, but a high proportion of MDR/XDR-TB cases. Future UK cases of XDR-TB may have similar demographic profiles and guidelines in management could be reviewed to include this epidemiological knowledge.

This case illustrates some of the difficulties encountered when tracing contacts living outside the UK, raising the question of how far to go when investigating the source of infection. There is a need for agreements between other national authorities to overcome these problems.

Successful management of XDR-TB relies upon prompt diagnosis, notification and treatment of cases, a problem with TB generally. This patient remained symptomatic for three months before effective treatment was started, allowing prolonged exposure to contacts and increasing the risk of a potential outbreak. Concerns were raised regarding the delay in diagnosis of this case and the speed of the laboratory diagnostic tests. The sputum culture on this case did not grow very well which delayed the drug susceptibility testing (DST) for the first and second line drugs. DST is done as a twostage process initially for first-line drugs and then for secondline drugs. Testing a wider panel early when drug resistance is suspected would increase the speed of reporting. The Infectious Diseases Unit involved in this case now fast-tracks all smear positive sputum samples to the reference laboratory for rapid drug sensitivity testing.

After diagnosis, strict monitoring of treatment is essential to ensure successful outcomes. The patient started directly observed therapy (DOT) in hospital, but was trained to self-administer medication prior to discharge, making it difficult to ensure 100% adherence. National guidelines recommend DOT for treating MDR and XDR-TB cases but its enforcement can be difficult.

At present, cases of XDR-TB are expected to be sporadic, however, a single outbreak could lead to XDR-TB being established within the UK population or sub-population. The resources needed to manage this case were substantial, including costs of clinical care, expensive anti-TB medications, work load of contact tracing and follow up.

Conclusion

XDR-TB has a high mortality rate and is a significant public health threat. Highlighting patients from countries with a high proportion of MDR-TB and expediting drug susceptibility testing in these patients would aid more rapid diagnosis. Efficient contact tracing, resource management and strict adherence to medication, will all be essential in the successful prevention of future cases.

Conflict of interest statement

Funding: No funding sources. Competing interests: None declared. Ethical approval: Not required.

Acknowledgments

Prof. Francis Drobniewski and his team at the National Mycobacterium Reference Unit, London.
John Warin Ward staff at The Churchill Hospital, Oxford.

References

