

Isoniazid Resistant TB outbreak in London 2000 to 2006

Progress report and updated recommendations of the London Outbreak Control Committee

May 2006

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Summary

An outbreak of isoniazid mono-resistant tuberculosis (TB) in north London was first recognised in 2000. The earliest case, which was diagnosed retrospectively, was in 1995. Out of a total of 266 culture proven cases, 226 cases have been diagnosed in London, and 40 cases diagnosed outside London (table 1), 18 of which can be linked with the outbreak through contact with a case, previous residence in London, or imprisonment in London. The outbreak is continuing and statistical analysis of the data, taking into account reporting delay, indicates that the outbreak is showing no sign of slowing (figure 1 and appendix 1).

The majority (75%) of the culture proven cases are confirmed to have a unique genetic fingerprint on restriction fragment length polymorphism (RFLP) typing, and 25 percent are probable (included on the basis of RAPET or MIRU VNTR typing). The typing has been carried out at the Health Protection Agency Mycobacterium Reference Unit (HPA MRU) and this has allowed tracking of the strain.

The outbreak remains focused in north London, with over half of the cases resident in one of four Primary Care Trust /Local Authority areas (Enfield, Hackney, Haringey, and Islington) at the time of diagnosis (table 2). Seventy-two per cent of cases are male (compared to 54% cases in the London TB register (LTBR)), and over half were aged between 25 and 39 years at diagnosis (figure 2). Forty eight per cent of cases were born abroad compared to 75% overall in LTBR. The most frequently seen ethnic groups were White (32%) and Black-Caribbean (27%), compared to 12% and 3.55% respectively in LTBR (figure 3). Among those born abroad most were born in Jamaica or Ireland (figure 4). The outbreak continues to be centred in North London and the distribution of cases has changed little over time (figure 5)

Many of the cases are from high risk populations including the homeless, problem drug users, and prisoners. Seventeen per cent of cases are known to be homeless and approximately one-third are known to have a history of, or are currently in, prison. Class A drugs (cocaine, crack, or heroin) are used by at least 12% of cases (with some injecting). Cannabis use and alcohol misuse are also common among cases. Forty-two per cent of the outbreak cases use illegal drugs and/or misuse alcohol. These factors, in addition to drug resistance, present substantial challenges to management of cases and completion of treatment.

There have been nine cases of multi-drug resistant TB. Four of these cases are the result of poor adherence to treatment in cases initially resistant to just one drug. The three other cases, including a 15 year old schoolgirl, suggest likely transmission in the community. Of the 226 London cases, 57% are reported to have completed treatment compared to an average of 80% LTBR cases..

Twelve per cent are currently lost to follow-up, and 22% are still on treatment. In the remaining 9%, nine patients have died (TB caused or contributed in two cases), seven have refused treatment or had treatment stopped, three have transferred overseas, and two cases have unknown outcome. The problem of achieving treatment adherence in one third of the London outbreak cases has serious implications for continuing transmission of infection and further spread of multi drug resistant TB.

Recommendations made to date

The Outbreak Control Committee (OCC) current membership is found at Appendix 2. Recommendations made in late 2004 by the OCC can be found at Appendix 3.

More recently the OCC has made further recommendations including the following:

1 Early diagnosis and identification of those at high risk

- *To identify those at higher risk of drug resistant TB – those with a history of previous TB, homelessness, prison (work, remand or custody prior to diagnosis of TB), substance misuse, HIV – at initial consultation.*
- *To treat this 'higher risk' group as though they have drug resistant TB in line with BTS recommendations – to provide directly observed treatment (DOT), unless the clinician is confident patient is adhering and can document this based on individual patient assessment (40 – 50% of patients in this group adhere and complete treatment).*

2 Directly Observed Therapy (DOT)

- *To ensure that all outbreak cases receive directly observed therapy (DOT) unless adherence is confirmed.*

3 Treatment completion

- *To increase the treatment completion rate among all Isoniazid Resistant cases in incremental steps that reflect the position of treatment completion at individual TB centres to 90% for all TB patients and to set a target for the outbreak cases following review of reasons for failure to complete.*
- *To ensure that the needs of those with, or at risk of, TB is reflected in the commissioning of prison health care.*

4 Cases failing to complete treatment, lost to follow up cases and those not placed on DOT

It was agreed efforts should be made to track the reasons why treatment was stopped or refused, and how patients were lost to follow up. There may be opportunities to improve treatment completion with the second group, and potentially a risk assessment and tailored treatment plan could improve the treatment outcome for the first group.

- *To conduct an in-depth review led by the TB networks in North East and North Central London into outbreak cases lost to follow up, not placed on DOT or refused treatment, in order to determine what aspects of this can be avoided and what lessons can be learnt. This process will inform, and be followed by, a more formal case review.*

Londonwide relevance and work

The lessons from the outbreak are not unique to control of that problem but are applicable to TB control in general. They have been fed in to the new London TB quality standards and targets (Appendix 4), and to the performance management framework. The fact that the outbreak is not yet under control is a major concern and has been acknowledged by the London Cabinet of Strategic Health Authority (SHA) Chief Execs. The Cabinet has endorsed the proposed quality standards and targets for TB across London as the basis for the performance management of TB services. The proposal for a single London SHA has been agreed. The aim is to have the new SHA in place from 1 July 2006 and after that time it is hoped that the quality standards outlined at Appendix 4 will be adopted as an integral part of the new performance management framework.

Further Londonwide activity needed

Joint planning

Joint planning is necessary across London and each PCT and their Local Authority (LA) to ensure that a range of hostel accommodation and supported housing is available, together with local support systems to enable directly observed treatment as well as an increase in the availability of staff with the necessary skills to provide outreach and support to those who find it most difficult to complete treatment. These staff should be part of a multidisciplinary team approach but are not necessarily clinically qualified. In some sectors, at least, this more specialist service may be provided by one clinic on behalf of others.

Monitoring and evaluation

Each TB Network should take a sector-wide lead in monitoring and evaluation; in identifying priorities for service improvement; and in ensuring clinical and cost effectiveness together with improving patient experience.

Each PCT needs to review quarterly monitoring TB data; ensure that future LDPs recognise the need to improve services for people with, or at risk of, TB especially those at high risk of non-adherence to treatment; and work through Local Service Partnerships to secure L A commitment. There should be performance management through the local TB Network.

Table 1

Number of Isoniazid Resistant Outbreak Cases by Place of Diagnosis and Classification

Place of Diagnosis	Classification		Grand Total
	Confirmed (RFLP)	Probable (RAPET and/or MIRU)	
Outside M25	32	8	40
Inside M25	165	61	226
Grand Total	197	69	266

Figure 1

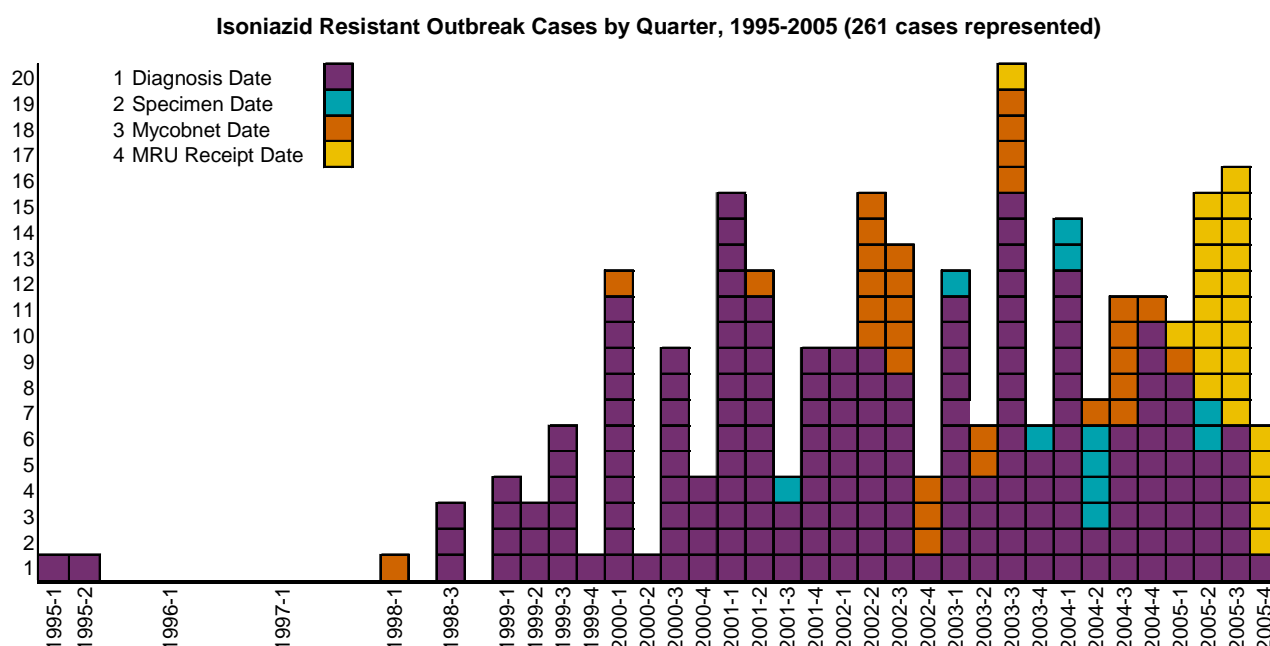
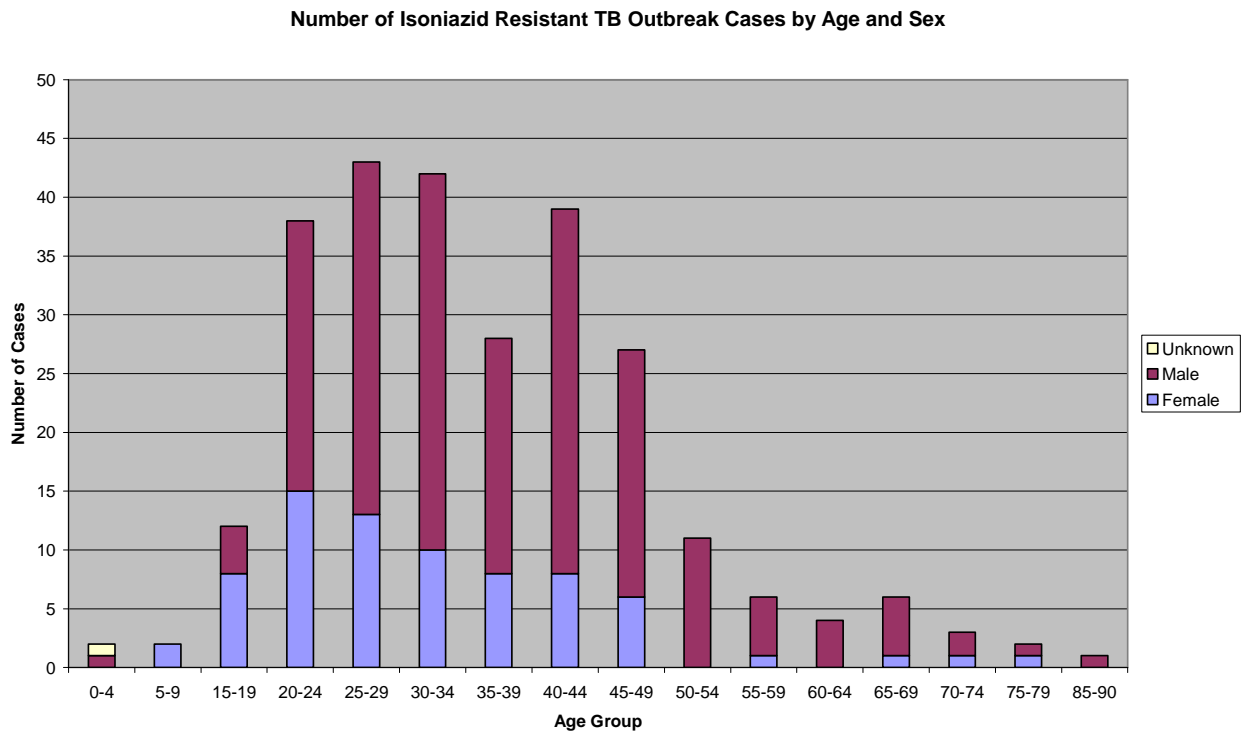


Table 2 Number and Percentage of Total Cases by Region and Local Authority of Residence at Diagnosis

Region of Diagnosis	Number	Percentage	Local Authority of Diagnosis	Number	Percentage
London - North Central	121	45.5%	Barnet	10	3.8%
			Camden	9	3.4%
			Enfield	33	12.4%
			Haringey	44	16.5%
			Islington	25	9.4%
London - North East	74	27.8%	Barking and Dagenham	1	0.4%
			Hackney	45	16.9%
			Newham	8	3.0%
			Redbridge	5	1.9%

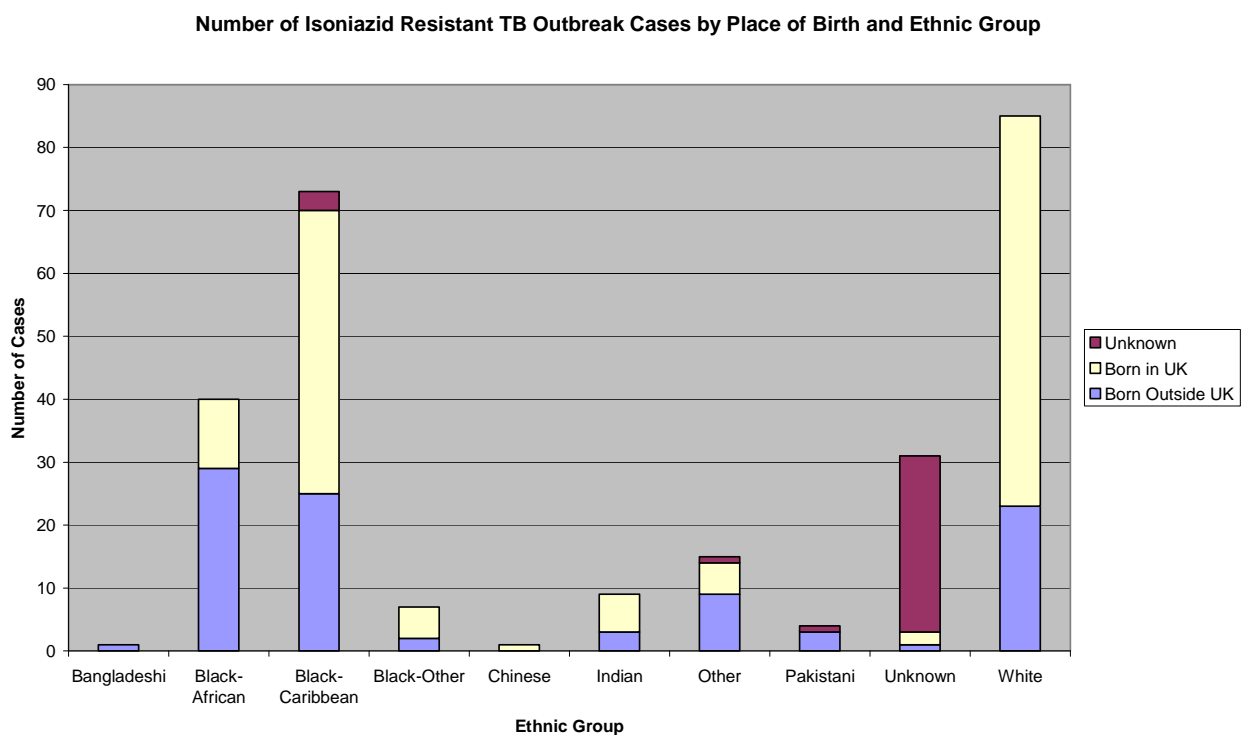
			Tower Hamlets	8	3.0%
			Waltham Forest	7	2.6%
London - North West	14	5.3%	Brent	3	1.1%
			Harrow	2	0.8%
			Havering	2	0.8%
			Hillingdon	4	1.5%
			Westminster	3	1.1%
London - South East	14	5.3%	Bexley	1	0.4%
			Bromley	1	0.4%
			Greenwich	1	0.4%
			Lambeth	5	1.9%
			Lewisham	4	1.5%
			Southwark	2	0.8%
London - South West	1	0.4%	Croydon	1	0.4%
East of England	18	6.8%	Basildon	2	0.8%
			Breckland	1	0.4%
			Broxbourne	1	0.4%
			East Hertfordshire	5	1.9%
			Epping Forest	1	0.4%
			Great Yarmouth	1	0.4%
			Ipswich	1	0.4%
			Luton	3	1.1%
			South Norfolk	1	0.4%
			Stevenage	1	0.4%
			Waveney	1	0.4%
South East	7	2.6%	Canterbury	1	0.4%
			Isle of Wight	1	0.4%
			Milton Keynes	1	0.4%
			Reigate and Banstead	1	0.4%
			Southampton	1	0.4%
			Surrey Heath	1	0.4%
			Woking	1	0.4%
East Midlands	4	1.5%	Leicester	1	0.4%
			Northampton	3	1.1%
South West	2	0.8%	South Gloucestershire	1	0.4%
			Taunton Deane	1	0.4%
North East	1	0.4%	Newcastle upon Tyne	1	0.4%
Yorkshire & The Humber	2	0.8%	Scarborough	1	0.4%
			Sheffield	1	0.4%
Wales	1	0.4%	The Vale of Glamorgan	1	0.4%
Dublin	5	1.9%	Dublin	5	1.9%
Jersey	2	0.8%	Jersey	2	0.8%
Grand Total				266	100.0%

Figure 2



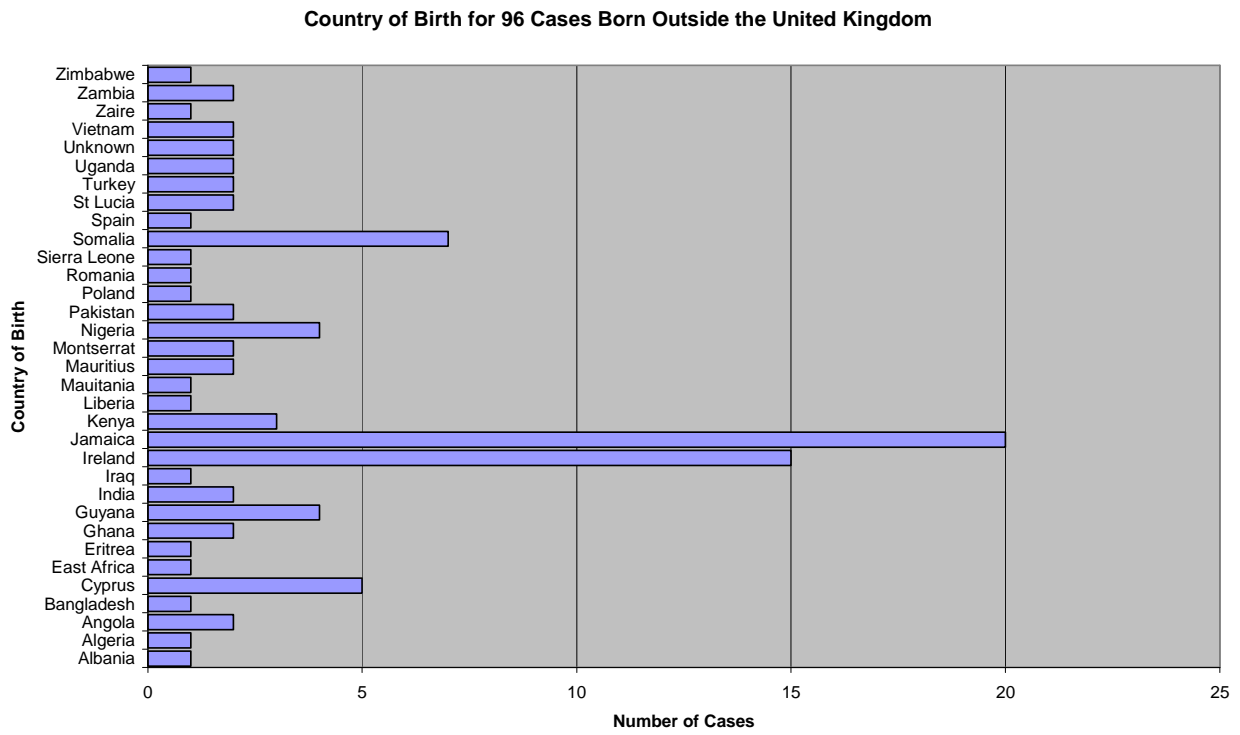
Note: Median Age for outbreak cases is 34 years, range 1-88 years. Male cases make up 72% overall.

Figure 3



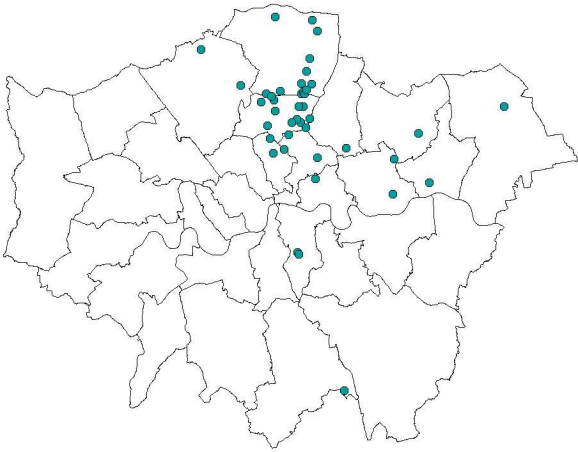
Note: UK Born make up 52% of outbreak cases. Cases born outside the UK make up 36%, and place of birth is unknown for 12% of cases. The predominant ethnic groups in this outbreak continue to be White and Black-Caribbean at 32% and 27% respectively.

Figure4

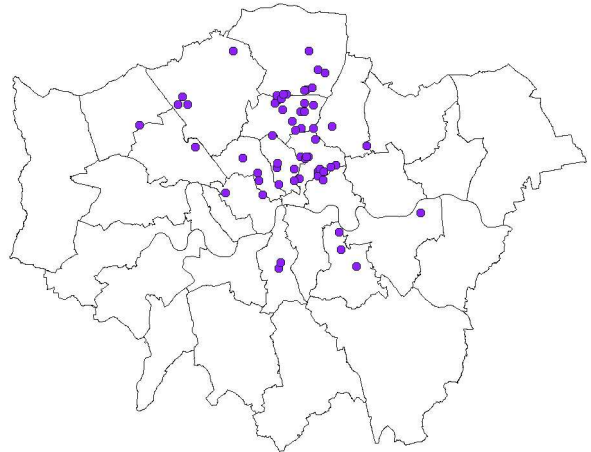


Note: There are an additional 33 cases where place of birth is unknown.

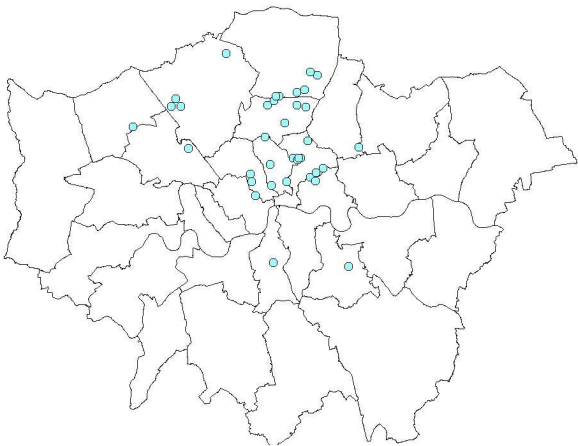
Figure 5



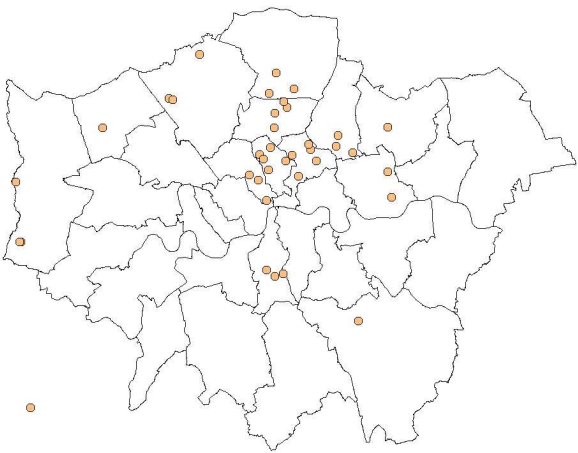
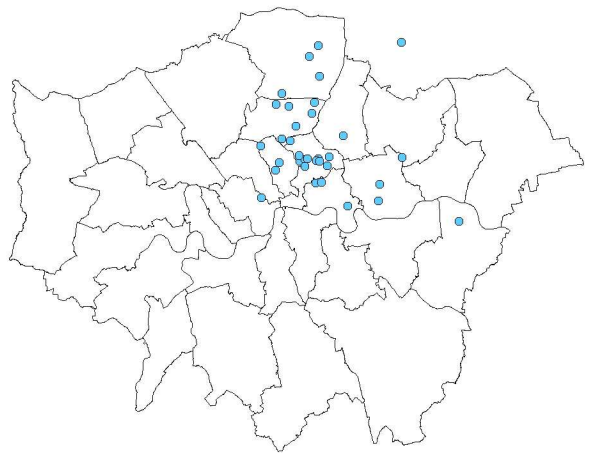
IRTB cases before 2000



IRTB cases in 2001 and 2002



IRTB cases in 2003



IRTB cases in 2005

Appendix 1 Isoniazid Resistant TB Outbreak in North London

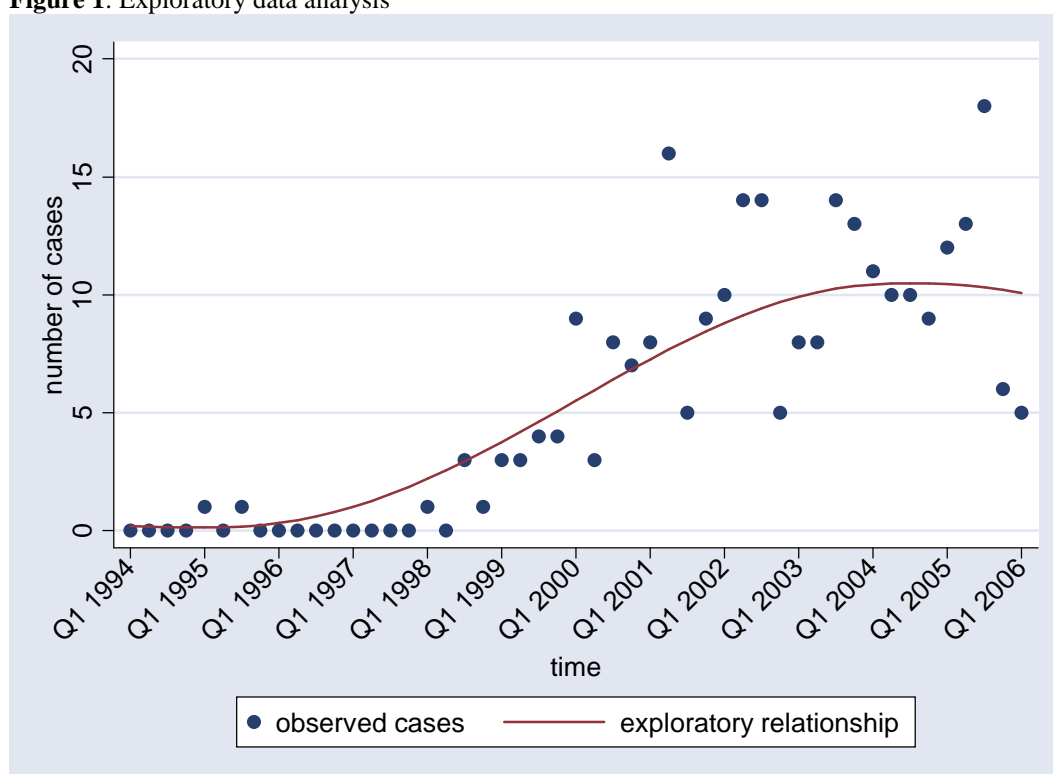
Introduction

In the most recent IRTB database received in April 2006 there are currently 266 cases of isoniazid resistant TB associated with this outbreak, which is eight more than when the previous statistical analysis was performed in December 2005. As with the previous analysis the date of *sample received at MRU*, or when missing the date entered on MycobNet has been used. For seven cases neither of these dates were available and the MRU reference number was used to estimate the date, by interpolation. All cases within this outbreak have been used regardless of whether the case occurred in North London or elsewhere.

Results

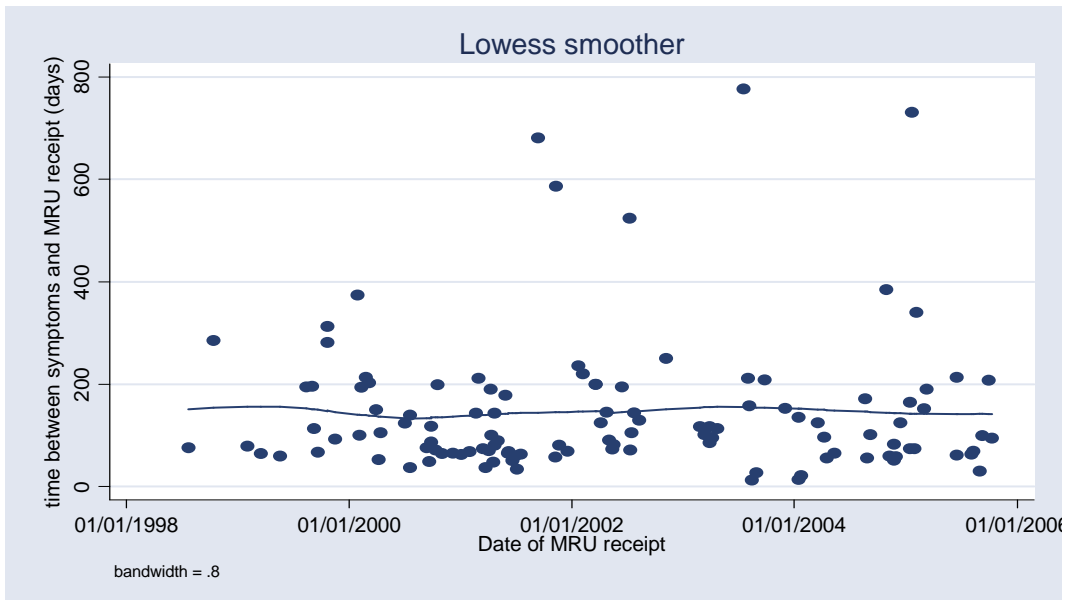
Initial exploratory data analysis using a locally weighted scatter smoothing technique is shown in Figure 1 below.

Figure 1: Exploratory data analysis



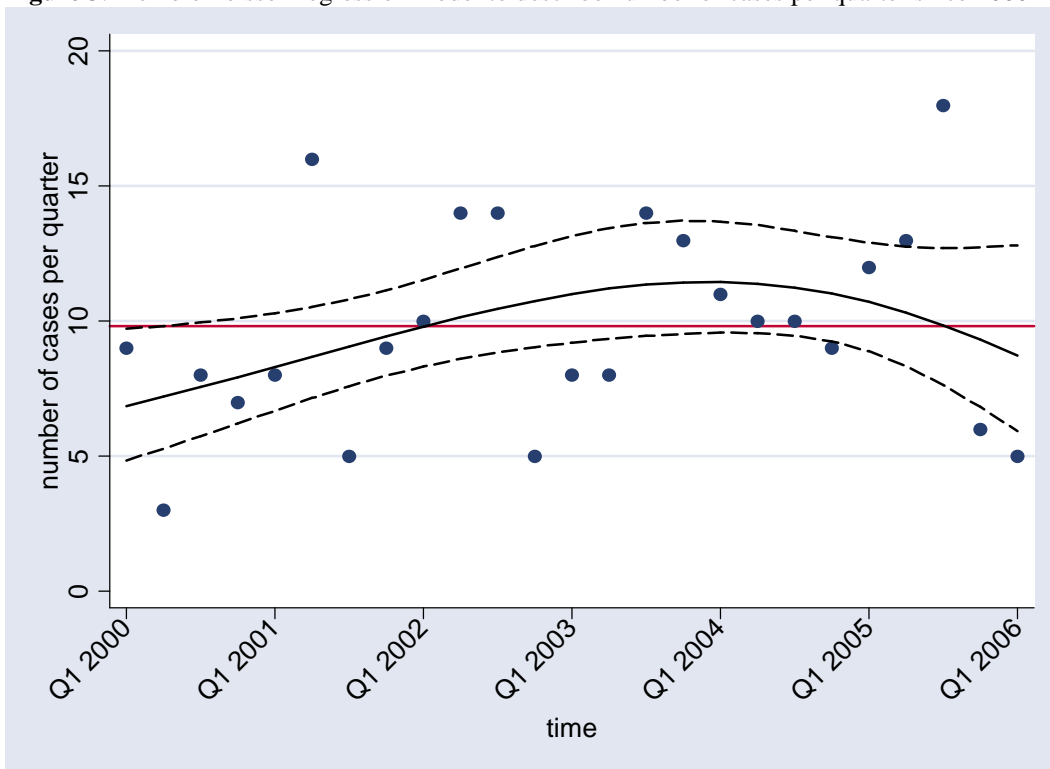
Even though the two most recent quarters have only six and five cases identified at the MRU, this exploratory analysis shows little evidence of a downturn. It is possible that the low numbers of cases identified in the two most recent quarters are due to a changing pattern in the delay between symptoms and identification of the outbreak strain of IRTB at the MRU. However, as can be seen in Figure 2 there is little evidence to suggest the “reporting delay” is changing over time.

Figure 2: Observed difference between symptoms and receipt at MRU in those subjects where both dates are present



If just the 245 (92.1%) cases with the date of receipt at the MRU since January 2000 are used, that is, ignoring the “take off” phase of the outbreak then there is little evidence of any change in the quarterly count over time, the average count per quarter being 9.8. Figure 3 gives results of a “flexible” Poisson regression model using a “fractional polynomial” approach which fits a range of transformed predictor variables.

Figure 3: Flexible Poisson regression model to describe number of cases per quarter since 2000



The horizontal line in Figure 3 represents the “average” number of cases identified at the MRU per quarter, and this line falls within the 95% confidence intervals which indicates that the “flexible model” doesn’t represent a substantially better “fit” to the data than the “null” model of a simple mean of 9.8 cases per quarter.

Chi square tests of association were performed on the broad categories of ethnic group, region of residence, and whether the case is a prisoner or works in a Prison.

Ethnic group

Table 1: Broad ethnic group of cases by time

Ethnic group	Year							Total
	Pre 2000	2000	2001	2002	2003	2004	2005 or later	
White	8 (38%)	8 (30%)	12 (32%)	14 (33%)	13 (30%)	11 (28%)	19 (35%)	85 (32%)
Black Caribbean	4 (19%)	7 (26%)	10 (26%)	14 (33%)	14 (33%)	13 (33%)	11 (20%)	73 (27%)
Black – Other	4 (19%)	6 (22%)	5 (13%)	9 (21%)	6 (14%)	11 (28%)	6 (11%)	47 (18%)
Asian and Other	3 (14%)	4 (15%)	6 (16%)	5 (12%)	5 (12%)	1 (3%)	6 (11%)	30 (11%)
Unknown	2 (10%)	2 (7%)	5 (13%)	1 (2%)	5 (12%)	4 (10%)	12 (22%)	31 (12%)
Total	21	27	38	43	43	40	54	266

There is no evidence to suggest that the distribution of ethnic group of the cases changes over time ($\chi^2 = 21.3$, 24 d.f., $p=0.6$).

Prison mentioned

Prison was mentioned in 95 (36.0%) of cases, 93 of these as prisoners and 2 as prison workers.

Table 2: Prison mentioned by time

Prison mentioned	Year							Total
	Pre 2000	2000	2001	2002	2003	2004	2005 or later	
No	17 (81%)	16 (59%)	22 (58%)	29 (67%)	25 (58%)	23 (58%)	39 (72%)	171 (64%)
Yes	4 (19%)	11 (41%)	16 (42%)	14 (33%)	18 (41%)	17 (43%)	15 (28%)	95 (36%)
Total	21	27	38	43	43	40	54	266

There is no evidence to suggest that the proportion of cases that are prisoners or who worked in prison changes over time ($\chi^2 = 6.69$, 6 d.f., $p=0.35$).

Region of residence of case when diagnosed

Overall 121 (46%) of the cases were residence in North Central London, 74 (28%) in North East London, and 71 (27%) outside these two areas when diagnosed. The proportion in each of these three broad regions over time is given in Table 3.

Table 3: Region of residence at diagnosis by time

Prison mentioned	Year							Total
	Pre 2000	2000	2001	2002	2003	2004	2005 or later	
London _North Central	16 (76%)	17 (63%)	17 (45%)	21 (49%)	14 (33%)	16 (40%)	20 (37%)	121 (45%)
London – North East	2 (10%)	5 (19%)	8 (21%)	11 (26%)	19 (44%)	14 (35%)	15 (28%)	74 (28%)
Other	3 (14%)	5 (19%)	12 (34%)	11 (26%)	10 (23%)	10 (25%)	19 (35%)	71 (27%)
Total	21	27	38	43	43	40	54	266

There is some evidence to suggest that the distribution of region of residence of the cases changes over time ($\chi^2 = 22.3$, 12 d.f., $p=0.03$). In the early years the outbreak was predominantly confined to the North Central sector of

London, however, the proportion of cases in North East London and occurring outside these two regions have increased over time with similar number of cases occurring in each of the three regions in 2005/06.

Conclusions

While the most recent two quarters have lower observed cases than seen previously there is no strong evidence to suggest that the number of reported cases in this outbreak is reducing.

The ethnic group distribution and the proportion of prisoners remain stable over time.

The one factor that does seem to be changing is the region of residence. In 2005, nineteen cases occurred in people living outside North Central and North East London. These were mainly in the rest of London and the South East: Basildon, Bromley, Harrow, Havering, Hillingdon, Lambeth, Luton, Stevenage, Surrey Heath, and Woking. Four were outside the South East, with three in Dublin and the other in Newcastle upon Tyne.

André Charlett

11th April 2006

Appendix 2: Current core members of ICC

Name	Role/comments
MEMBERS PROVIDING EXPERT ADVICE & SUPPORT (INVESTIGATION, COMMUNICATION, CO-ORDINATION)	
Prof S Gillespie	HPA Regional Microbiologist -expert input TB control
Dr Ibrahim Abubakar	Consultant Epidemiologist, HPA Centre for Infections Colindale. Responsible for liaison national group
Dr Helen Maguire	Regional Epidemiologist, HPA London. Responsible for TB. Chair ICC during 2001 to 2005– knowledge and experience this incident and links other London-wide/national TB initiatives
Dr Mary Piper	Consultant Prison Health Policy Unit, DH
Sarah Forrester	Epidemiological support for ICC – based at HPA Regional Epidemiology Unit
Isabelle Giraudon	Fellow of the European Programme for Intervention Epidemiology Training
Mr Alistair Story	Nurse Scientist and Epidemiologist, HPA Cfl Colindale and Department of Health
Mr Malcolm Yates	Representing Dulwich MRU [Porf F Drobniewski],-expert input related cases
Mr Andre Charlett	Statistician HPA Cfl Colindale
<i>To receive papers</i>	<i>Prof Francis Drobniewski</i>
MEMBERS WITH DIRECT RESPONSIBILITY FOR INCIDENT CONTROL WITHIN SECTORS (CLINICAL MANAGEMENT, HEALTH PROTECTION, COMMUNICATION/LIAISON)	
<i>North Central</i>	
Ms Lynn Altass	TB Network ManagerCo-ordinator, North Central London Sector
Dr Marc Lipman	Consultant Chest Physician, Royal Free NHS Trust and TB Clinical lead North Central
Dr Stefan Lozewicz	Consultant Chest Physician, North Middlesex University Hospital NHS Trust
Ms Sue Yates	TB Nurse Pentonville Prison, Camden and Islington TB team
<i>North East Sector</i>	
Dr Graham Bothamley	Chest Physician, Homerton. TB clinical lead, NE London sector.
Mr William Roberts	TB Network Manager, NE London sector
<i>HPA PCT and SHA leads</i>	
Dr Sudy Anaraki	CCDC, HPA North Central and North East London HPU
Dr Ann Marie Connolly	DPH Haringey PCT . Member of TB network and TB Strategic Group, NC London sector.
Dr Sheila Adam	DPH, NE London SHA and chair of ICC.

Appendix 3

Summary of key recommendations made by the Outbreak Control Committee in late 2004

Early identification of incident cases

The risk of TB transmission is reduced by early diagnosis of cases. Priorities are to:

- Increase early presentation and diagnosis by raising awareness in at-risk groups and the professionals working with them, both in prisons and in the community.
- Increase the proportion of TB diagnoses with microbiological confirmation.

Treatment

The approach to TB treatment should be to 'step down' with proven good adherence, rather than to 'step up' when problems develop. Ensuring treatment adherence remains a challenge in this incident. Incident control depends on appropriate treatment for isoniazid-resistant TB and treatment completion. Poor treatment adherence increases the risk of TB transmission and of the development of MDR-TB. Priorities are:

- Use a case management approach.
- Use Directly observed therapy (DOT) at outset for patients who:
 - Are at risk of non-adherence (BTS criteria);
 - Are identified as part of INH-R TB incident *unless* the clinician is confident that patient is adhering to treatment and has demonstrated this.
- Provide support, outreach and incentives as appropriate. The literature shows that these measures improve adherence.
- Monitor DOT. Where DOT is failing adjust support measures and incentives as appropriate. Use sanctions when needed. Supervision of treatment can be 'stepped down' with good adherence.
- Ensure that resources are in place to provide support and incentives as necessary. These measures are less expensive than detention, hospital care and the treatment of MDR-TB.
- Provide TB treatment without charge to all patients.

Contact tracing and treatment

Contact tracing and treatment are important for early diagnosis and to reduce TB transmission.

- No change to current recommendations for contact tracing. However the results of the contact studies were reviewed and was discussed at the OCC meeting in **June 2004**.
- Close social and work contacts should continue to be included in contact tracing for this incident.

Incident monitoring and communication

The OCC will continue to meet twice a year and maintain responsibility for overall monitoring and co-ordination of incident management. The following are recommended to enhance existing measures:

- Review existing incident database to provide robust and timely information on outcomes and adverse events.
- Undertake qualitative evaluation of reasons for adverse events. Could use care pathway approach to highlight areas of risk and as evaluation tool.

Appendix 4

STOPPING TB IN LONDON QUALITY STANDARDS FOR THE FIVE TB NETWORKS – work in progress

Introduction

The overall aim of TB services is to reduce the incidence of TB.

The London TB programme agreed a series of targets in the late 1990s, targets which have been largely achieved.

A small number of high level quality standards have now been developed by the TB network managers to focus service improvement over the next phase of work, and to enable networks and SHAs to monitor progress. These have been agreed by the London NHS Cabinet.

Quality standards

Eight quality standards or targets are proposed.

Target 1: TB prevention in babies and young children

Rationale: the effective use of BCG within universal neonatal BCG programmes in high incidence areas to prevent TB in babies and young children.

Achieve as minimum 70% coverage by 4 months, and 75% by 12 months, in boroughs with universal BCG, aspiring to 80% and 90% respectively.

Measured by an extended child health system **[needs further work]**

Target 2: access

Rationale: early access to specialist TB services for those suspected as having pulmonary TB to ensure early treatment and prevent further infection.

Each patient who is suspected by a health professional to have pulmonary TB is seen in a specialist TB service within 2 weeks of first contact with the NHS.

Measured by integrating existing information systems (EPR, nursing front sheet, LTBR).

Targets 3/4: early diagnosis

Rationale: rapid microbiological diagnosis to ensure early treatment and prevent further infection.

All samples should be processed using liquid culture technology.

All results on sputum smears should be available within 1 working day of the sample reaching the laboratory.

Measured using Microbiology System.

Target 5: identification of those with complex needs

Rationale: those patients with the most complex needs are known to be at greatest risk of not completing their treatment, and unless treatment is completed there is a risk of disease recurrence, continuing transmission and the development of drug resistance. Clinical outcomes, patient experience and value for money are all compromised.

A standardised risk assessment is carried out on each patient to identify those at risk of not completing their treatment.

Measured using an extended London TB Register [needs two additional fields for risk score and clinical pathway]

Target 6: effective treatment

Rationale: unless treatment is completed there is a risk of disease recurrence, continuing transmission and the development of drug resistance. Clinical outcomes, patient experience and value for money are all compromised.

Achieve, as a minimum, 85% treatment completion (national target) building towards 90% (if the epidemic is to be controlled).

Measured using London TB Register

Target 7: prevention of further infection

Rationale: effective contact tracing is essential for infection control.

All defined contacts of TB should be identified using a standardised risk assessment (based on that developed for isoniazid resistance) and screened [as recommended in NICE guidelines].

Measured using local clinical systems (either clinic book or sheet in notes)

Target 8: effective NHS occupational health services

Rationale: NHS occupational health services should ensure effective pre-employment assessment, and an awareness of the risk of TB within the NHS workforce.

There should be a year-on-year reduction in the incidence of TB among NHS staff.

Measured using SUI reports (any case of TB in a member of staff should be reported as an SUI) or alternative system if better

Target 9: raising awareness of TB

Rationale: TB awareness is essential to ensure early presentation, diagnosis and treatment.

- Analyse the current pathway, and specifically the length of time from first symptom to presentation – a target will then be set on the basis of this analysis to reduce the longest waits.
Measured using London TB Register
- Map current activity to raise TB awareness – national, London-wide, sector, local – including opportunities to extend this eg new GCSE curriculum.
Eva Hrobonova to undertake this over next 3 months
- Identify any opportunity to include a question to test TB awareness in a broader survey.

Target 9 to be finalized

12 April 2006