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Outbreak of tularaemia in central Norway, January to March 2011

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From January to March 2011, 39 cases of tularaemia were diagnosed in three counties in central Norway: 21 cases of oropharyngeal type, 10 cases of glandular/ulceroglandular type, two of respiratory and two of typhoid type. Three cases were asymptomatic and clinical information was unavailable for one case. The mean age was 40.3 years (range 2-89 years). Thirty-four reported use of drinking water from private wells. An increased rodent (lemming) population and snow melting may have led to contamination of the wells with infected rodents or rodent excreta.

Outbreak description

From 1 January to 25 March 2011, 39 confirmed cases (16 female and 23 male) of tularaemia were reported from the counties of Sør-Trøndelag (28 cases), Møre og Romsdal (5 cases) and Nord-Trøndelag (6 cases) in central Norway. A confirmed case was defined as a person who had clinical symptoms compatible with tularaemia or had used drinking water from the same source as a previous case, and in whom *Francisella tularensis* infection was confirmed by a laboratory test as described below. The cases were geographically scattered within each county, involving 13 different municipalities (Figure), and were not linked to one common source. In comparison, seven cases were reported in total from other parts of the country in the same period. In 2009 and 2010 four and eight cases respectively were reported from central Norway.

Tularaemia is a zoonotic disease caused by the bacterium *F. tularensis*. Four *F. tularensis* subspecies are recognised: *tularensis, holarctica, mediasiatica* and *novicida*. In Europe, the infection is due to subspecies holarctica which causes in general less severe disease than subspecies *tularensis*, which is common in North America. Several vectors may be involved in transmitting the disease to humans, commonly rodents and hares, but infection may also be transmitted via insect bites [1].

Several clinical forms are recognised, with oropharyngeal and ulceroglandular disease being the most common clinical presentations in Norway [2]. Oropharyngeal disease is commonly associated with contaminated food and water, while ulceroglandular forms are more often seen when there has been skin contact with infected animals or after insect bites [3].

Outbreaks of oropharyngeal tularaemia have previously been reported from several European countries [3,4]. Tularaemia is a notifiable disease in Norway and during the past 10 years, three outbreaks were reported in Norway [5-7] and all were associated with water sources in areas where dead lemmings (*Lemmus lemmus*) had been observed previously. From 2001 to 2010, between three and 66 cases of tularaemia were reported annually in the whole country, with an increase from 16 to 32 cases on average (data available from: www.msis.no). This increase may in part be explained by the outbreaks mentioned above.

Diagnosis and clinical presentation

In the outbreak described here, the most common clinical presentation was fever and pharyngitis (oropharyngeal type, 21 cases) and cervical lymphadenopathy (glandular/ulceroglandular type, 10 cases). Among the remaining eight tularaemia cases, two were classified as respiratory and two as typhoid type, while three were asymptomatic and clinical information was unavailable for one case.

The diagnosis was primarily established by serology (microagglutination and an in-house IgG/IgM Elisa) in 30 patients [8], by *F. tularensis* specific PCR analysis in seven patients [9] and by blood culture (BactAlert, BioMerieux) in two patients. The two bacterial isolates were verified as *F. tularensis* by PCR and sequencing of the 16S rDNA gene, and confirmed as non-subspecies *tularensis* by *pdpA* PCR [10].

Thirty-four of the 39 diagnosed cases had been drinking water from a private well or a stream. *F. tularensis* DNA was detected by PCR in filtered water from five different wells tested in Sør-Trøndelag. Seven cases in one municipality were linked to the same water source. Apart from that, only two cases have been confirmed to share a common well so far. Follow-up serology has been recommended for several of the persons exposed to some of the putative water sources.

Discussion

The current outbreak involves a large number of municipalities in three counties in central Norway. The clinical presentation with oropharyngeal tularaemia and cervical lymphadenopathy linked to the use of private wells in the winter season makes contaminated water the most likely source of infection in this outbreak. Detection of *F. tularensis* DNA by PCR analyses in some of the wells supports this assumption for some of the cases. Use of private wells is relatively common in rural areas of Norway although exact data on such use are not available.

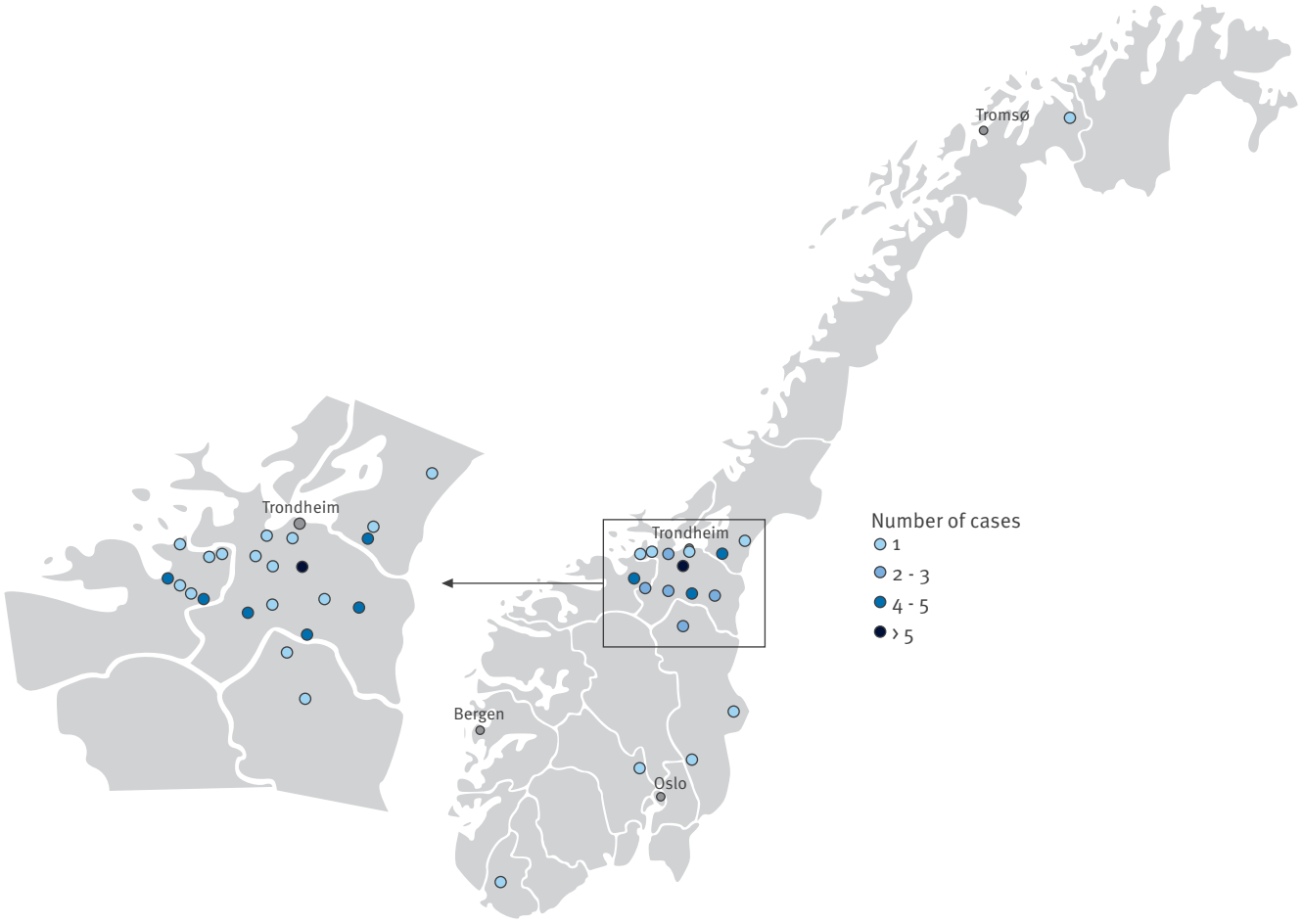
The precise mechanism of contamination of the wells with *F. tularensis* is as yet unknown. However, November and December 2010 were unusually cold months, while in January 2011 temperatures increased leading to melting of snow and possible contamination of private wells by surface water contaminated with bacteria from rodent cadavers or rodent excreta. Since the incubation period for tularaemia may be up to three weeks, and time from symptoms until seroconversion might be up to six weeks, more cases may follow.

Tularaemia has traditionally been called both 'lemming fever' and 'hare plague' and this clearly indicates rodents and hares as transmitters of disease. Years with a great increase in the rodent population are seen with intervals of about three to four years [11] and in the summer and autumn of 2010, a high density of lemmings could be observed in the southern and central parts of Norway. Simultaneously, the Norwegian Veterinary Institute observed a wide geographical distribution of fatal cases of tularaemia in the mountain hare (*Lepus timidus*) in these regions [12]. The mountain hare is very susceptible to this infection and normally dies from septicaemia within a few days after exposure.

The use of small streams and private wells as a source of drinking water and for other purposes in rural areas of Norway is a matter of concern. In existing guidelines issued by the National Institute of Public Health the population is advised to boil drinking water and

Figure

Geographical distribution of confirmed cases of tularaemia in Norway, January to March 2011 (n=39)



inspect the wells for dead rodents in case of suspected or confirmed cases of waterborne tularaemia. Every well owner should make the necessary effort to prevent small rodents from entering the well water by carefully covering every opening and plugging every small holes where the rodents can enter. It is also important to secure the well from contamination by surface water after snow melting. In case of proven or suspected contaminated wells, the water should be disinfected before further use. However, this may not be feasible for persons who use drinking water from a stream. The Norwegian Food Safety Authority has recently released information to the media and to the general public with similar advice and information in relation to the current outbreak. The local health authority in each municipality is responsible for instituting infection control measures including advice to the public and investigations of the putative drinking water sources.

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Zoonoses in the European Union: origin, distribution and dynamics - the EFSA-ECDC summary report 2009

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We present a summary of the main findings of the latest report of the European Food Safety Authority and European Centre for Disease Prevention and Control on zoonoses, zoonotic agents and food-borne outbreaks in the European Union (EU), based on data from 2009. Zoonoses are prevalent and widely distributed across several countries in the EU. The most important highlight of this report was the continuous decrease of human salmonellosis since 2005, probably due to effective control programmes in livestock.

Background

The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2009, produced by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) on 22 March 2011, describes the five-year trends (2005–2009) and occurrence of zoonotic infections and agents in humans, animals and foodstuffs in the 27 European Union (EU) Member States. Reported cases from countries of the European Economic Area (EEA)/ European Free Trade Association (EFTA), namely Iceland, Liechtenstein, Norway and Switzerland [1] are also included in the preliminary description but not in further analysis or trends.

Zoonoses are diseases that are transmissible between animals and humans. Humans can acquire these infections directly from contact with sick or carrier animals, or through the ingestion of contaminated foodstuffs or from other environmental sources. The severity of these diseases in humans can vary from mild symptoms to chronic sequelae or life-threatening conditions.

In order to prevent zoonoses from occurring in humans and to control such diseases, it is important to identify which animals and foodstuffs are the main sources of the infections. Thorough analysis and description of the distribution of zoonotic diseases among EU countries allows targeting of control measures and monitoring of the progress of food-safety policies in the EU. The annual EU summary report compiles information from human surveillance systems and from monitoring programmes for food and animals, with the aim of protecting human and animal health according to the Zoonoses Directive 2003/99/EC [2].

Assisted by the Zoonoses Collaboration Centre-Technical University of Denmark (ZCC-DTU), EFSA and ECDC jointly analysed the data and a summary of the main findings are presented in this article.

Trends in the main zoonoses and zoonotic agents

Campylobacteriosis

In 2009, as in the previous four years, campylobacteriosis was the most commonly reported zoonotic disease in humans (198,252 confirmed cases). There was a 4% increase in the number of reported cases compared with 2008. The notification rate was 45.6 cases per 100,000 population, with children aged under five years having the highest notification rate (128 cases per 100,000 population). The number of reports of human campylobacteriosis was stable over the five-year period, but the incidence was always higher during the summer months. This could be due to a seasonal effect that has not been addressed through traditional *Campylobacter* control programmes for food and animals.

In foodstuffs, as in previous years, *Campylobacter* was most commonly isolated from fresh broiler meat at different stages of production: 31% of samples (n=7,312) were positive. According to the recent scientific opinion of EFSA biological hazards panel, about 20–30% of human campylobacteriosis cases can be attributed to the consumption and handling of chicken meat [3]. In pig meat samples, *Campylobacter* was detected much less frequently (0.6%, n=1,006) than in broiler meat. However, there was high variability in the number of reporting countries and sample size, depending on animal species and type of meat.

C. jejuni was the most frequently reported species in humans as well as in poultry and cattle, while *C. coli*

was less prevalent in humans and was isolated mainly from pigs.

Salmonellosis

Salmonellosis was the second most commonly reported zoonotic infection in humans in 2009, with 108,614 confirmed cases reported and a notification rate of 23.7 cases per 100,000 population, which is 17% less than in 2008. There has been a statistically significant decreasing trend in the notification rate during 2005 to 2009, with a mean reduction of 12% per year. The decrease has been particularly sharp for the most commonly reported serovar in humans, *Salmonella* Enteritidis: notifications fell by 24% from 2008 to 2009. The second most common serovar, *S.* Typhimurium, was also reported less frequently in 2009 compared with 2008, presenting a decrease of 10%.

In food, *Salmonella* was the most commonly identified pathogen in fresh poultry and fresh pork meat, where 8.7% (n=30,544) and 0.7% (n=83,797) of samples were found positive, respectively. The bacterium was rarely detected in vegetables, fruit or dairy products.

Harmonized *Salmonella* EU control programmes in poultry have been implemented progressively since 1994, starting with primary production. In 2009, Member States had to meet the EU reduction target of having ≤1% of breeding flocks of *Gallus gallus* (chickens) infected with the five target serovars (*S.* Enteritidis, *S.* Typhimurium, *S.* Hadar, *S.* Infantis and *S.* Virchow) [4,5]. Control efforts at poultry-farm level in Member States are considered to have contributed remarkably to a positive public-health effect in reducing the number of reported human salmonellosis cases.

It is reassuring that the declining trend of human salmonellosis continued in 2009. This is likely to be the result of intensified control programmes of *Salmonella* in animal reservoirs, particularly in poultry, and better hygiene practices throughout the food production chain. The introduction of molecular surveillance at the EU level in the future will provide more clues about the importance of different animal and food sources of infection and the impact of *Salmonella* control programmes in livestock.

Yersiniosis

The number of reported human cases of yersiniosis in 2009 was 7,595, with a notification rate of 1.65 cases per 100,000 population. Although the notification rate decreased significantly ($p < 0.01$) since 2005 (2.6 cases per 100,000 population), the disease continues to be the third most frequently reported zoonosis in the EU.

In animals, *Yersinia* spp. were reported mainly in pigs and pork products. *Yersinia enterocolitica* was isolated from 4.8% of pork samples (n=2,134).

Listeriosis

In 2009, the notification rate of human listeriosis was 0.36 cases per 100,000 population. The number of confirmed cases increased by 19% in 2009 (n=1,645) compared with 2008 (n=1,381). Listeriosis is an important food-borne disease due to its severity: it can lead to a high risk of abortion in pregnant women and high levels of mortality in elderly people (a case fatality rate of 19% was reported in people aged 65 years and over). The highest notification rate was also reported in this age group (1.1 cases per 100,000 population), representing 59% of all reported cases. Only 4.2% of the reported cases were detected among children aged under five years.

Foodstuffs that are considered the main source of *Listeria* in the EU include ready-to-eat (RTE) products (fish and meat) and soft cheeses. According to the EU microbiological criteria, foodstuffs that contain less than 100 colony-forming units (cfu)/g of *L. monocytogenes* at the retail level are considered acceptable for human consumption [6]. In 2009, the highest proportions of non-compliant food products at retail level were found in RTE fish products, cheese (especially soft and semi-soft) and RTE products of meat origin, although the level was lower than in the previous two years.

The high proportion of deaths among elderly people as a result of *Listeria* infection is of particular concern. An EFSA-ECDC collaboration on typing of *Listeria* in RTE products and clinical cases of human listeriosis started in 2010 and continues to 2012. The results provided by this study will contribute to a better understanding of listeriosis epidemiology in the EU and should help to target effective control and preventive measures within both food safety and public health.

Verotoxigenic *Escherichia coli* (VTEC) infection

A total of 3,573 confirmed human cases of verotoxigenic *E. coli* (VTEC) infection (0.75 cases per 100,000 population) were reported in 2009, a 13% increase compared with 2008 (n=3,159). The notification rate has increased since 2007 (0.6 cases per 100,000 population). VTEC O157 was again the serotype most commonly reported, although VTEC isolates were not characterised at the serotype level in 28% of the cases in 2009. As in previous years, the notification rate was highest in children aged 0–4 years. A considerable increase (of 66%) in the number of reported cases who developed haemolytic uremic syndrome was detected in 2009 (n=242) compared with 2008 (n=146), occurring mainly among 0–4 year-olds. Several outbreaks of VTEC infection were detected in United Kingdom and the Netherlands in 2009 and have contributed to the increasing trend in Europe and increased the number of haemolytic uremic syndrome cases [7-9]

In animals, VTEC was mainly isolated from cattle and, to a lesser extent, from small ruminants such as sheep and goats. In food, VTEC was detected mainly in meat

from ruminants: 3.2% (n=248) of sheep meat samples, followed by 2.3% (n=9,285) of bovine meat samples. It was also isolated from raw cow's milk. The reported occurrence of VTEC bacteria in food was generally low, and the levels have been relatively constant between 2005 and 2009.

Q fever

A total of 1,987 confirmed human cases of Q fever were reported in 2009, representing a 25% increase compared with 2008 (n=1,594). However, the majority of cases (91%) was detected in two countries: the Netherlands (n=1,623) and Germany (n=190). Adults aged 45–64 years had the highest notification rate (1.2 cases per 100,000 population).

The continued increase in Q fever in 2009 was the result of several outbreaks in which people were exposed to infected sheep and goats, mainly in the Netherlands.

Trends in zoonotic parasitic diseases and zoonotic parasites

Trichinellosis

Reported cases of human trichinellosis increased by 12% in 2009 (n=748) compared with 2008 (n= 670). The distribution of reported cases was not homogeneous across EU Member States, as the majority of cases (94%) was reported by four eastern European countries (Bulgaria, Romania, Poland and Lithuania). The reason for this large proportion of human cases in these countries may be linked to particular regional habits, such as raising pigs in backyards for private consumption, for which official meat inspection for the presence of *Trichinella* spp. is not carried out.

The increased number of cases of trichinellosis in these countries is of major concern because the disease is easily preventable when appropriate veterinary meat inspection is carried out and preventive measures are taken.

Echinococcosis

There were 790 reported human cases of echinococcosis in 2009, which is 11% fewer than in 2008 (n=891). Among reported cases with a known species, the predominant species was still *E. granulosus* (77%) while *E. multilocularis* was reported three times less frequently.

In animal populations, 18 Member States submitted data on *Echinococcus* spp. found in domestic livestock (cattle, pigs, sheep, goats and solipeds) as part of routine screening at slaughter. In addition, 10 Member States reported data on foxes positive for *E. multilocularis* (15.6% of tested foxes carried this species). Control measures implemented for dogs, such as deworming treatment, can restrict the spread of echinococcosis. However, foxes remain a potential source of exposure and vehicle for spread in some EU countries.

Toxoplasmosis

In 2009, a total of 1,259 confirmed human cases of toxoplasmosis were reported . The highest proportion was recorded in women aged 24–44 years, probably due to routine screening for antibodies against *Toxoplasma* during pregnancy.

Sheep and goats were the animal species with the highest proportion of *Toxoplasma*-positive samples reported (24.4%, n=4,217).

Trends in other zoonoses: brucellosis, tuberculosis due to *Mycobacterium bovis* and rabies

In 2009, human cases of brucellosis (n=401) decreased by 35.2% compared with 2008 (n=619). The number of cases has been decreasing significantly ($p < 0.01$) in the EU since 2005.

Cases of human tuberculosis due to *Mycobacterium bovis* in 2009 were not reported to the European Surveillance System (TESSy) at the time of the report production. Therefore the trends and epidemiological analysis were based on 2008 data. The number of confirmed human cases of tuberculosis due to *M. bovis* increased in the EU by 7.5% in 2008 (n=115) compared with 2007 (n=108). However, this could be a normal variation in the disease occurrence. Overall, the numbers of human cases decreased during the previous four years, mainly due to effective disease eradication programmes implemented by Member States in cattle herds.

In 2009, one indigenous case of rabies – in a woman bitten by a rabid fox – was reported in Romania. This is the second autochthonous case of rabies that occurred in Romania in the previous two years.

Conclusion

In 2009, campylobacteriosis, salmonellosis and yersiniosis were the most commonly reported zoonotic infections in humans of those monitored for this report in the EU, as in previous years. Parasitic zoonoses – trichinellosis, echinococcosis and toxoplasmosis – are still present in the EU. While some diseases, such as salmonellosis, have continued to decline, probably due to effective EU control measures in animal reservoirs, others have increased considerably, such as trichinellosis, even though the disease can be easily prevented.

The results of this report highlight the importance of close collaboration between veterinarians and public health specialists and the need for robust surveillance systems, in the animal/food sector and in humans, in order to monitor the impact of EU-wide control measures, detect emerging trends and sources and unexpected changes in the disease dynamics of zoonoses in Europe.

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Malaria among patients and aid workers consulting a primary healthcare centre in Leogane, Haiti, November 2010 to February 2011 – a prospective observational study

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Plasmodium falciparum malaria is endemic in Haiti, but epidemiological data are scarce. A total of 61 cases of malaria were diagnosed between November 2010 and February 2011 among 130 Haitian patients with undifferentiated fever. Three additional cases were diagnosed in expatriates not taking the recommended chemoprophylaxis. No cases were diagnosed among aid workers using chemoprophylaxis. In conclusion, malaria is a significant health problem in Leogane, Haiti. Aid workers and visitors should use chemoprophylaxis according to existing guidelines.

Introduction

Plasmodium falciparum malaria is endemic in Haiti [1-5]. Epidemiological data from Haiti are scarce, but before 2010 the prevalence of malaria in most areas of Haiti was estimated to be low [2-5]. The effects of the 2010 earthquake and the severe flooding that followed the 2010 hurricane on the incidence of malaria are unknown. We report the incidence of malaria among febrile patients in two primary-care clinics in the West (Ouest) Province of Haiti. In addition we report all cases of malaria in expatriate aid workers seen in our clinic.

Methods

The study was conducted in two newly established primary healthcare clinics in the West Province of Haiti. The main clinic is situated in the town of Leogane, 30 km west of Port-au-Prince. Leogane has an estimated population of 200,000. The other clinic is situated in Magandou, a rural village in the same region. Since November 2010 the Leogane clinic has been operating daily, and the Magandou clinic is open once a week. Both clinics are staffed by nurses and doctors from Haiti, Israel, and Canada. Medical services are provided free of charge. All cases of undifferentiated fever were tested for malaria. Diagnoses of malaria were reached with the help of a rapid diagnostic test for detection of histidine-rich protein II (Paracheck Rapid Test, Orchid Biomedical Systems). The tests were performed in both clinics by the same experienced doctors using the same diagnostic kits. The clinical and epidemiological features of all cases of malaria were collected prospectively.

Results

Over a period of 14 weeks, between November 2010 and February 2011, a total of 61 cases of falciparum malaria were diagnosed among Haitian patients in the Leogane clinic. This period roughly correlates with the peak malaria transmission season in Haiti [3]. These 61 cases accounted for 46.9% of the 130 patients with undifferentiated fever, and 1.9% of all 3,166 patient visits. The average age of the patients with malaria was 22.5 years (range 3 to 67 years) with 25 of 61 cases occurring in patients younger than 16 years. Thirty-two cases occurred in females. All malaria cases were acquired in Leogane, as none of the patients had travelled outside the Leogane area during the three weeks preceding the onset of symptoms.

All patients with malaria reported a febrile disease; although upon presentation only 43 of 61 had a fever higher than 37.5°C. Two patients had severe malaria and were transferred to a referral hospital. Nearly all patients (60 of 63) were treated with chloroquine. Three patients were treated with artemether/lumefantrine; two because of difficulty in accurately dividing the chloroquine pills for young children, and one because of an allergic reaction to chloroquine.

No cases of malaria were found among a total of 258 patients examined in the village of Magandou. Eleven of these patients had presented with an undifferentiated fever.

Three expatriates diagnosed with malaria were aid workers living in Leogane. None of the three were using anti-malaria chemoprophylaxis. Since the total number of aid workers residing in the area of Leogane is unknown, the risk of acquiring malaria in this population can not be calculated. In our organisation two out of the ten aid workers who stayed in Haiti for a total of 57 person-weeks and did not use chemoprophylaxis contracted malaria. No cases of malaria occurred in 52 additional aid workers who stayed in Haiti for a total of 346 person-weeks and used chemoprophylaxis with chloroquine.

Discussion

Studies before the earthquake reported a low risk of acquiring malaria in most areas of the country [2-5]; data from Leogane itself were not available. According to our data, collected after the earthquake and hurricane of 2010, the incidence of malaria among patients with undifferentiated fever in Leogane, Haiti was around 47%. Although the sensitivity of the Paracheck Rapid Test has been reported to be sub-optimal [6], its specificity is very high. Therefore we think that the number of malaria cases has not been overestimated. A recent report from a post-earthquake national surveillance system indicated that suspected malaria and fever of unknown cause accounted for 10.3% and 10%, respectively, of total visits to 51 pre-specified clinics [1]. Although laboratory diagnoses of malaria were not performed, these results seem to indicate that the incidence of malaria in certain parts of post-earthquake Haiti may be appreciable.

In a study published in 1995 only 4% of peripheral blood smears taken from febrile patients in several different provinces of Haiti were positive for *P. falciparum* [4]. It is not known whether the incidence of malaria among febrile patients was underreported in the past, or whether the natural disasters that recently affected the country have caused an increase in malaria incidence. It is also unclear whether the incidence of malaria in other areas of the country is similar to the one in Leogane. Leogane is situated near the epicenter of the 2010 earthquake. Approximately 80% of Leogane was destroyed, and tens of thousands of its inhabitants were made homeless. Since *Anopheles albimanus*, the mosquito vector of malaria in Haiti, usually bites outdoors, people living in temporary shelters are probably at an increased risk of contracting malaria in post-earthquake Haiti. In addition hurricane Tomas caused severe floods in Leogane in November 2010, and may therefore have expanded the breeding sites for the vector.

In contrast, no cases were found in Magandou, located in the hilly areas 25 km south-west of Leogane. The elevation of Magandou (941 meters above sea level) does not fully explain this finding. The reasons for such a significant regional variation in the incidence of malaria within a relatively small area are unclear. Possible explanations include a more mountainous terrain, and less damage caused by both the 2010 earthquake and hurricane Tomas.

Not surprisingly cases of malaria also occurred among aid workers residing in the Leogane area. Cases of malaria among emergency responders after the 2010 earthquake were reported in other areas in Haiti, too, but since data regarding incidence are unavailable, a comparison of the risk of infection in different areas is impossible [7]. It is important to note that no cases of malaria were detected among aid workers receiving chloroquine chemoprophylaxis. Apparently, the risk of acquiring malaria in expatriates using chemoprophylaxis is appropriately low.

In conclusion, malaria is a significant health problem in Leogane, Haiti. It is unknown whether this holds true for other areas of Haiti. It is also unclear whether the high malaria incidence among febrile patients was underreported in the past, or whether it is related to the deteriorated infrastructure of the area following the earthquake and the hurricane that occurred in 2010. Aid workers and visitors should use chemoprophylaxis according to existing guidelines. We have not detected any cases of chloroquine chemoprophylaxis failure, thus supporting the current malaria prevention guidelines [8]. Further entomologic surveys and vector control efforts are warranted if malaria incidence is to be reduced in Leogane, Haiti.

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Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case–control study and recommendations

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We conducted a case–control study to examine risk factors for isoniazid-monoresistant *Mycobacterium tuberculosis* in an ongoing outbreak in London. Cases were defined as individuals with an isoniazid-monoresistant strain diagnosed from 1995 to the third quarter of 2006 with an indistinguishable restriction fragment length polymorphism (RFLP) or mycobacterial interspersed repetitive unit (MIRU)-variable number tandem repeats (VNTR) pattern who were resident in or had epidemiological links with London. Controls were all other individuals reported with tuberculosis to the Health Protection Agency London regional epidemiology unit or the HPA London TB Register during 2000 to 2005. Of 293 cases, 153 (52%) were sputum smear-positive compared with 3,266 (18%) of controls. Cases were more likely to be young adults (aged between 15 and 34 years), born in the United Kingdom (OR: 2.4; 95% CI: 1.7–3.4) and of white (OR: 2.9; 95% CI: 1.8–4.8) or black Caribbean (OR: 12.5; 95% CI: 7.7–20.4) ethnicity, a prisoner at the time of diagnosis (OR: 20.2; 95% CI: 6.7–60.6), unemployed (OR: 4.1; 95% CI: 3.0–5.6), or a drug dealer or sex worker (OR: 187.1; 95% CI: 28.4–1,232.3). A total of 113 (39%) of cases used drugs and 54 (18%) were homeless. Completion of treatment gradually improved in cases from 55% among those diagnosed up to the end of 2002 compared with 65% by the end of 2006. Treatment completion increased from 79% to 83% in controls from 2000 to 2005. There are complex social challenges facing many cases in this outbreak that need to be addressed if medical interventions are to be successful.

Introduction

The incidence of active tuberculosis (TB) increased in London from 20 per 100,000 population in 1987 to 44 per 100,000 in 2006 [1]. TB in London is concentrated in certain geographical areas and in specific subgroups of the population. During 2000 to 2006, TB rates were consistently higher in north London, among people born outside the United Kingdom (UK) and in those aged 20–29 years [2,3]. The Health Protection Agency (HPA) Mycobacterium Reference Unit in London provides a service for the National Health Service (NHS) in London and the rest of south-east England, confirming the identity of TB isolates and determining drug sensitivities. The proportion of *Mycobacterium tuberculosis* strains in London that were isoniazid resistant was relatively stable at 8–9% during 2000 to 2006 [2]. There are over 30 TB clinics in London, which are widely distributed across the city, with reasonable access to them by public or other transport. The 2001 census showed that there were 7.2 million residents in London, living in 31 different boroughs across five areas or sectors (three in the north and two in the south) [4]. Within each sector, levels of deprivation and overcrowding vary and inner London areas are usually more deprived. Overall 30% of the population were of non-white ethnicity in 2001 [4].

An outbreak of isoniazid-monoresistant TB was first identified in north London in 2000 when microbiologists at a local hospital noted an increase in isoniazid-monoresistant *M. tuberculosis* infections in young men [5]. When strain typing was carried out retrospectively of isoniazid-monoresistant strains from 1995 from that hospital and three neighbouring hospitals – carried out at the HPA Mycobacterium Reference Unit using restriction fragment length polymorphism (RFLP) – 11 individuals with strains with indistinguishable

RFLP patterns were identified. As a result of this, a London-wide Incident Control Committee was established. It was agreed that the HPA Mycobacterium Reference Unit would type isoniazid-monoresistant *M. tuberculosis* strains from across London prospectively and retrospectively to 1999 (the most recent strains that were then available). Control measures recommended by the Committee, which were outlined in a comprehensive report in 2004 [6], together with progress achieved at the time of this review, are described in Table 1.

There were some service improvements across the city by the end of 2006, including a reported increase in the number of TB nurses and outreach (community-based) initiatives. In addition, since 2002 all TB clinics have been using the HPA London TB Register, a web-based electronic case management and surveillance system. It was developed and has been maintained by the HPA, in collaboration with clinical staff in the city.

The Incident Control Committee also recommended directly observed treatment (DOT) for all cases, following either one of two regimens at the discretion of the clinician (Box).

In this paper we provide results of a case–control study that aimed to determine the risk factors associated with becoming infected with the outbreak isoniazid-monoresistant *M. tuberculosis* strain. We also report on treatment outcome of the cases and describe the particular challenges encountered in implementing the recommended control measures.

Methods

Microbiological methods

Microbiological methods included typing of isoniazid-monoresistant *M. tuberculosis* isolates at the HPA Mycobacterium Reference Unit. Other *Mycobacterium* reference units in England were asked to send isoni-

Table 1

Incident Control Committee recommendations, outcomes and actions, isoniazid-monoresistant tuberculosis outbreak, north London, 1995–2006

Issue	Recommendations made in 2002–2004[a]	Outcomes and actions by the end of 2006
Interagency working	Awareness of TB should be raised in at-risk groups and professionals who work with them to encourage early presentation and diagnosis of TB.	Information about the outbreak advising them to have a low threshold of suspicion of TB was provided to a range of healthcare and social care professionals, including those working in drug and alcohol services.
Identification of cases	All TB cases in London should be confirmed by microbiological culture so that drug-sensitivity testing can be done and molecular typing carried out for those isoniazid monoresistant.	Rate of identification and typing of strains improved.
Patients lost to follow-up	There should be a case-management approach, including directly observed therapy (DOT), social support and outreach (community-based health services including home visits). Incentives should be used, e.g. providing travel vouchers or paying travel costs.	Many cases have been non-adherent despite support and follow-up. Patients have multiple social problems and health is not always a high priority for them. Patients often need cash to pay for travel to the clinic. Incentives have been used successfully in some instances.
Availability of treatment	All TB therapy should be available free of charge. Outreach services should be developed.	Good progress made with free treatment but outreach (home visit) services could be better.
Contact tracing	Enhanced contact tracing (to include social and work contacts) should be undertaken for all cases particularly for any susceptible contacts (e.g. children, immunosuppressed patients, injecting drug users). Contacts of outbreak cases should be screened again after six months, and only discharged after two clear screens.	Many patients were reluctant to give names of contacts or do not know the names of their contacts. Contacts of drug users often did not attend for screening.
Cases with history of imprisonment	Better liaison between prison services and health services is necessary.	Remand prisoners were still being released without contacting health services. A specialist nurse was appointed at a London prison where several cases had been inmates. A mobile digital TB X-ray unit has been used to detect cases in London prisons since 2005.
Lack of isolation facilities in north London hospitals	More isolation facilities should be accessible in London. Awareness of TB should be raised in hospital accident and emergency departments to ensure suspected pulmonary TB cases are isolated on admission.	Awareness raising in accident and emergency departments and National Health Service trusts was carried out.

TB: tuberculosis.

[a] Described in [6].

azid-monoresistant strains to London for typing if the patient had an epidemiological link with London.

Strains from 1999 available at the HPA Mycobacterium Reference Unit in London were retrospectively typed. The typing techniques used were restriction length fragment polymorphism (RFLP) or, since 2006, mycobacterial interspersed repetitive sequence (MIRU)-variable number tandem repeat (VNTR) [7].

Epidemiological methods

Case definition

A case was defined as an individual with an isoniazid-monoresistant *M. tuberculosis* strain diagnosed from 1995 to the third quarter of 2006 with an indistinguishable RFLP or MIRU-VNTR pattern who was resident in or had an epidemiological link with London [5].

Control group

Cases in the outbreak (n=293) were compared in a case–control study with a control group of all other individuals with TB reported during 2000 to 2001 to the HPA London regional epidemiology unit as part of routine surveillance on a paper-based questionnaire and those reported during 2002 to 2005 electronically by clinicians to the HPA London TB Register. Thus controls were chosen for the time frame for which complete data were readily available (2000–2005) (n=17,747). Although cases had been diagnosed in 1995, there had been few between 1995 and 1999. National surveillance of TB was introduced in 1999, but the data available that year were incomplete and there had been no routine surveillance before then. The controls included those clinically diagnosed by a physician and started on TB treatment as well as others who had culture-confirmed TB. We did not match the cases and controls or restrict the comparison to culture-confirmed controls as we did not wish them to be selected on the basis of similarity in respect of certain characteristics of interest, such as pulmonary disease or sputum smear status, for example.

Data collection and analysis

A paper-based questionnaire specific for the outbreak was completed retrospectively by TB clinic nurses, once the patient was known to have the outbreak strain, providing details of factors potentially relating to transmission of *M. tuberculosis*, e.g. drug and alcohol use or dependence, imprisonment and any common venues cases may have frequented. The nurses also enquired whether the patient had received DOT, which had been recommended for cases. Interpretation of the meaning and implementation of DOT in practice varied across London. It included the use of dosette boxes, pill counts, urine testing for the presence of anti-tuberculosis drugs or family members acting as supervisors without necessarily directly observing the taking

Box

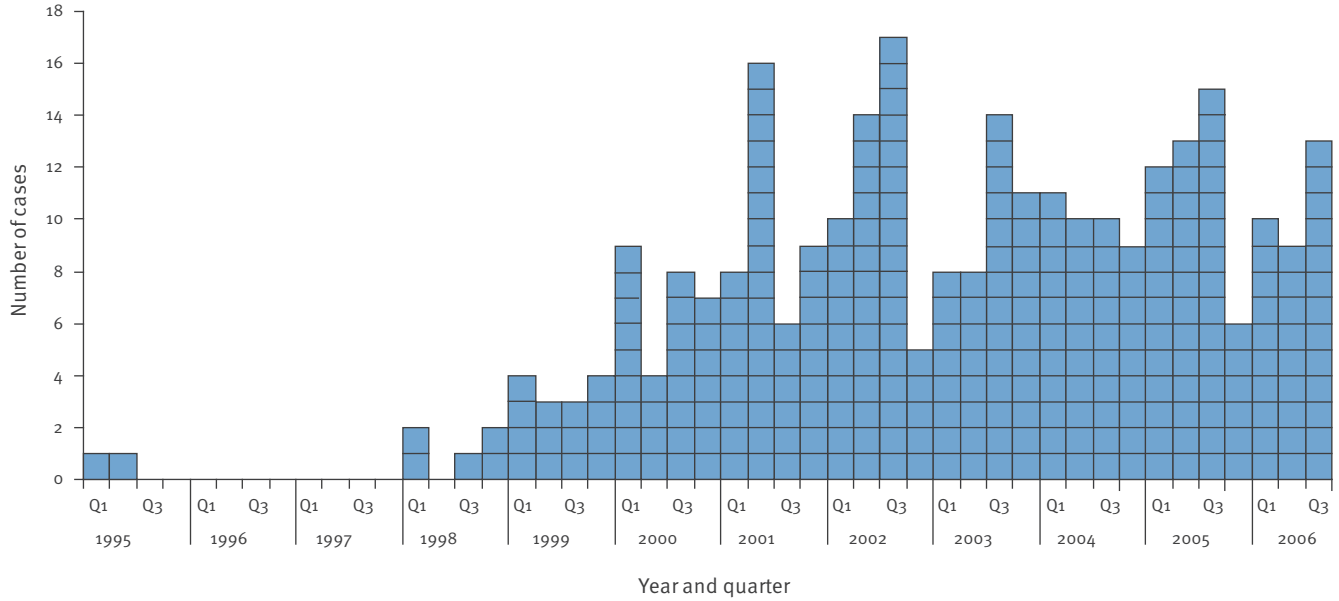
Recommended treatment options for isoniazid-monoresistant tuberculosis, north London outbreak, 1995–2006

Option 1
Pyrazinamide for the first two months
Moxifloxacin for the first four months
Rifampicin for nine months
Ethambutol for nine months

Option 2
Pyrazinamide for the first two months
Rifampicin for 12 months
Ethambutol for 12 months

Figure

Cases of isoniazid-monoresistant tuberculosis by quarter of diagnosis or report, north London outbreak, 1995 to third quarter 2006 (n=293)



Q: quarter.

Table 2

Univariable analysis of association between risk factors and being a case, isoniazid-monoresistant tuberculosis outbreak, north London, 1995 to third quarter 2006

Variable	Cases 2000 to third quarter 2006 n=293		Controls 2000–2005 n=17,747[a]		Odds ratio	95% CI	P value
	n	%	n	%			
Place of residence							
North-east London	89	30.4	4,421	24.9	Reference	–	–
South-east London	15	5.1	2,670	15.0	0.28	0.15–0.49	<0.0001
South-west London	1	0.3	1,786	10.1	0.03	<0.01–0.2	<0.0001
North-west London	11	3.8	5,362	30.2	0.10	0.05–0.19	<0.0001
North-central London	136	46.4	3,501	19.7	1.93	1.46–2.56	<0.0001
Outside London	41	14.0	0	0	NE	NE	NE
Unknown	0	0	7	0.04	NE	NE	NE
Sex							
Male	206	70.3	9,753	54.9	1.96	1.51–2.55	<0.0001
Female	86	29.3	7,959	44.9	Reference	–	–
Unknown	1	0.3	28	0.15	NE	NE	NE
Age (years)							
0–14	5	1.7	1,035	5.8	0.28	0.08–0.70	<0.0001
15–24	53	18.1	3,109	17.5	Reference	–	–
25–34	91	31.1	5,363	30.2	1.00	0.70–1.4	0.97
35–44	83	28.3	3,184	17.9	1.53	1.07–2.21	0.02
45–64	47	16.0	3,116	17.6	0.88	0.58–1.34	0.54
≥65	14	4.8	1,902	10.7	0.43	0.22–0.79	0.004
Unknown	0	0	31	0.17	NE	NE	NE
Ethnicity							
Black African	43	14.7	5,617	31.7	Reference	–	–
Black Caribbean	85	29.0	605	3.4	18.35	12.4–27.3	<0.0001
Black other	8	2.7	264	1.5	3.96	1.6–8.6	0.0001
White	99	33.8	2,434	13.8	5.31	3.7–7.8	<0.0001
Indian subcontinent	15	5.1	5,691	32.1	0.34	0.18–0.63	0.0002
Chinese	1	0.3	251	1.4	0.52	0.13–3.09	0.51
Other	18	6.1	2,282	12.9	1.03	0.56–1.83	0.91
Unknown	24	8.2	596	3.3	NE	NE	NE
Country of birth							
Abroad	112	38.2	12,953	73.1	Reference	–	–
United Kingdom	153	52.2	2,930	16.5	6.03	4.68–7.80	<0.0001
Unknown	28	9.6	1857	10.5	NE	NE	NE
Employment status							
Prisoner	13	4.4	26	0.1	52.62	24.12–109.1	<0.0001
Healthcare	9	3.1	523	2.9	1.81	0.8–3.59	0.08
Unemployed	120	41.0	2,095	11.8	6.03	4.65–7.89	<0.0001
Asylum seeker/refugee	2	0.7	52	0.3	4.05	0.47–15.7	0.037
Drug dealer/sex worker	7	2.4	3	0.02	245.55	54.89–1480.8	<0.0001
Educational setting	18	6.1	2,269	12.8	0.84	0.48-1.38	0.48
Retired	10	3.4	759	4.3	1.39	0.64–2.66	0.32
Other	114	38.9	11,997	67.6	Reference	–	–
Unknown	0	0	16	0.1	NE	NE	NE
Pulmonary disease							
No	40	13.7	8,531	48.1	Reference	–	–
Yes	253	86.3	9,193	51.8	5.87	4.20–8.40	<0.0001
Unknown	0	0	16	0.1	NE	NE	NE
Sputum smear status							
Negative	79	27.0	4,138	23.3	Reference	–	–
Positive	153	52.2	3,266	18.4	2.45	1.85–3.27	<0.0001
Unknown	51	17.4	4,365	24.6	NE	NE	NE
Not tested	10	3.4	5,971	33.7	NE	NE	NE

NE: not estimated.

[a] For all variables except place of residence, only controls with a known place of residence were included (n=17,740).

of medication. Nurses obtained the relevant information in interviews with cases and supplementary data were obtained from medical records. Investigations were also carried out by a nurse at a London prison where many early cases were linked. This was part of an ongoing outbreak investigation and ethical approval was not sought. Patients, as per normal clinical practice, were able to refuse to answer questions if they wished.

Once outbreak questionnaires were returned, the information was entered into a database and aligned with data from routine surveillance and the HPA London TB Register, to ensure consistency and completeness. Since 2002, questionnaire data were supplemented by, aligned with and cross-checked against data retrieved directly from the Register. For those cases who did not receive DOT, we telephoned the case manager at the clinic to enquire about the reasons for this. We asked whether the case was homeless, for example, or had been initially thought likely to have poor adherence to treatment or had had a history of poor adherence in any previous episode of TB.

Odds ratios (ORs) were estimated for cases (n=293) and controls (n=17,747) for place of residence. For the following variables, only controls with a known place of residence were included (n=17,740): sex, age, site of disease, sputum smear status, type of employment, ethnicity and country of birth. Logistic regression was used to obtain unadjusted odds ratios for each variable. Those variables found to be statistically significant were included in a multivariable analysis using logistic regression to control for confounders. Statistical analysis was carried out using Stata version 10.

Outcome after 12 months of treatment was also examined for cases resident in London (as this information was not available for those resident elsewhere). Reasons for non-completion of the prescribed treatment, recorded in the HPA London TB Register, included death of the patient, moving out of London or overseas, treatment stopped, lost to follow-up or treatment continuing.

Results

By the end of 2006, 293 people with the same strain of isoniazid-monoresistant TB (cases) were identified, of whom 252 (86%) were diagnosed in London. By the third quarter of 2006, the incidence of new cases appeared to have levelled at about 10 per quarter, with no evidence of a decline (Figure).

The outbreak remained focused in north London: 136 (46%) of the cases were resident in north-central London and 89 (30%) in north-east London. A total of 13 cases (4.4%) were prisoners at the time of their diagnosis and two of these were known to have close social links with at least 14 others cases diagnosed before 2003. Another prisoner had close social links with a further four cases who in turn were known contacts of a further eight cases [5]. Social links such as these were frequently observed among cases in north London, but no specific venues, such as hostels or churches, were commonly reported.

Sex, age and sociodemography

Univariable analysis of the clinical and demographic details of cases and controls are shown in Table 2.

Cases were more likely to reside in north-central or north-east London than any other sector. They were likely to be male (70% vs 55%; OR 1.96; 95% CI: 1.51–2.55) and be younger than controls (28% vs 18% aged 35–44 years: OR: 1.53; 95% CI: 1.07–2.21 and 5% vs 11% aged 65 years or older, OR: 0.43; 95% CI: 0.22–0.79).

A total of 99 (34%) cases were white and 85 (29%) black Caribbean: cases were significantly more likely to belong to these ethnic groups. Cases were more likely to be born in the UK than abroad: 153 (52%) of the cases were born in the UK compared with 2,930 (17%) of controls. The predominant countries of birth among cases born abroad were Jamaica (n=23, 21%), Ireland (n=15, 13%), Somalia (n=8, 7%) and Nigeria (n=6, 5%). A different pattern was observed among controls born abroad, with the majority born in India (17%), Somalia (16%) and Pakistan (7%).

Employment status

A total of 120 (41%) of the cases were unemployed at the time of diagnosis compared with 2,095 (12%) of controls (OR: 6.03; 95% CI: 4.6–7.9). Cases were more likely to be a prisoner at the time of diagnosis (4.4% vs 0.1%; OR: 52.6; 95% CI: 24–109) and to be a drug dealer or sex worker (n=7) (2.4% vs 0.02%; OR: 245; 95% CI: 55–1,480), although the numbers were small.

Other risk factors

A total of 101 (34%) cases had a known history of prison detention at some point in the past. There were 113 (39%) with a history of recreational drug use: injecting drug use was reported by 15 (5%) cases, 24 (8%) stated that they used crack cocaine and the remainder reported the use of drugs such as cannabis. Of the cases, 54 (18%) were known to be homeless at the time of diagnosis, while 20 (7%) had a history of alcohol dependence. Data on these risk factors – prior prison detention, as distinct from being a prisoner at the time of diagnosis, homelessness and recreational drug use – were not routinely collected in the HPA London TB Register and therefore could not be compared among cases and controls. However, we describe their frequency among cases here and compare them with expected frequencies in the London population on the basis of published reports.

Site of disease and sputum smear status

There were 253 (86%) cases with pulmonary TB compared with 9,193 (52%) of controls (OR: 5.9; 95% CI: 4.2–8.4). Cases were more likely to be sputum smear-

positive at the first clinic visit compared with controls (52% vs 18%; OR: 2.4; 95% CI: 1.9–3.3).

Multivariable analysis

In a multivariable analysis, cases were significantly more likely to live in north-central London, be young (aged 15–34 years), UK born (OR: 2.4; 95% CI: 1.7–3.4) and of white (OR: 2.9; 95% CI: 1.8–4.8) or black Caribbean (OR: 12.5; 95% CI: 7.7–20.4) ethnicity, a current prisoner (OR: 20.2; 95% CI: 6.7–60.6), unemployed (OR: 4.1; 95% CI: 3.0–5.6) or a drug dealer or sex worker (OR: 187.1; 95% CI: 28.4–1,232.3) compared with controls (Table 3).

Multidrug-resistant tuberculosis and previous treatment

Eight (3%) of the 293 cases had multidrug-resistant (MDR) TB, by definition resistant to rifampicin and

Table 3

Multivariable analysis of association between risk factors and being a case, isoniazid-monoresistant tuberculosis outbreak, north London, 1995 to third quarter 2006 (n=293)

Variable	Odds ratio	95% CI	P value[a]
Place of residence			
North-east London	Reference	–	–
South-east London	0.23	0.13–0.40	0.002
South-west London	0.04	0.13–0.40	<0.001
North-west London	0.17	0.09–0.32	<0.001
North-central London	1.67	1.22–2.29	0.001
Sex			
Male	1.34	0.98–1.83	0.07
Female	Reference	–	–
Age (years)			
0–14	0.30	0.09–1.01	0.05
15–24	Reference	–	–
25–34	0.79	0.52-1.20	0.27
35–44	0.64	0.41–1.00	0.05
45–64	0.45	0.27–0.74	0.002
≥65	0.23	0.10–0.51	<0.001
Ethnicity			
Black African	Reference	–	–
Black Caribbean	12.52	7.69–20.37	<0.001
Black other	3.29	1.35–8.02	0.009
White	2.94	1.79–4.83	<0.001
Indian subcontinent	0.57	0.30–1.10	0.092
Chinese	0.68	0.09–5.05	0.703
Other	1.210	0.67–2.19	0.528
Country of birth			
Abroad	Reference	–	–
United Kingdom	2.40	1.68–3.43	<0.001
Employment status			
Prisoner	20.21	6.75–60.56	<0.001
Healthcare	1.53	0.67–3.51	0.316
Unemployed	4.09	2.97–5.63	<0.001
Asylum seeker/refugee	8.09	1.02–64.41	0.048
Drug dealer/sex worker	187.07	28.40–1,232.35	<0.001
Educational setting	1.22	0.67–2.23	0.524
Retired	1.69	0.71–4.06	0.239
Other	Reference	–	–
Pulmonary disease			
No	Reference	–	–
Yes	1.52	0.98–2.36	0.61
Sputum smear status			
Negative	Reference	–	–
Positive	1.37	0.98–1.93	0.067

[a] A p value of <0.05 was considered statistically significant.

isoniazid [8]; three of these were initially resistant to isoniazid alone. Five, including a 15-year-old girl, appear to have become infected in the community with an MDR strain [9].

In addition to the three cases with MDR TB mentioned above, there were 10 cases who had previously been treated for TB. Seven of the 10 had successfully completed treatment for the previous TB episode and had been diagnosed 1, 5, 6, 14, 29 and 32 years previously (the date of the previous TB episode was unknown in one of the seven cases). One further case had been diagnosed seven years previously and had transferred out of London to complete treatment at that time and was then subsequently diagnosed in London with the outbreak strain. One further case diagnosed in 2005 had been treated one year previously and at that time, had not been identified as part of the outbreak. This case had been lost to follow-up. A case who died had apparently been treated for TB previously, but we were unable to confirm the date of treatment.

Directly observed treatment

By the end of 2006, all but 11 cases had received DOT. Of these 11, four had no documented risk factors at the time of diagnosis (according to the National Institute for Health and Clinical Excellence (NICE) criteria [10]) i.e. homelessness, thought by clinic staff to be likely to have poor adherence to treatment or had a history of poor adherence. Of the remaining seven, six were homeless.

Treatment outcome

By the end of 2006, of the cases living in London (n=252), 164 (65%) had reportedly completed treatment (either a nine- or 12-month regimen), 35 (14%) were described as continuing treatment and 24 (10%) were lost to follow-up, 11 had died and six had stopped treatment (Table 4).

Completion of treatment among cases gradually improved over time from 55% among those diagnosed up to the end of 2002 to 65% in 2006, compared with 79% in 2000 to 83% in 2005 observed among controls. All the cases subsequently lost to follow-up (n=24) were either recreational drug users or were homeless. In an effort to ensure their adherence to treatment, two of the cases were admitted to hospital under a public health section (force of law).

Table 4

Treatment outcome after 12 months among London cases, isoniazid-monoresistant tuberculosis outbreak, north London, 1995–2006 (n=252)

Outcome	Number of cases	Percentage
Treatment completed	164	65.1
Treatment continuing	35	13.9
Lost to follow-up	24	9.5
Died	11	4.4
Stopped treatment	6	2.4
Transferred to another TB service	5	2.0
Refused treatment	3	1.2
Relapsed	2	0.8
Unknown	2	0.8
Total	**252**	**100**

Discussion

This outbreak of isoniazid-monoresistant TB, first identified in 2000, is ongoing. We have analysed here the early part of the outbreak. In 2000, there were 28 cases (with 21 in the five years before that) and by the third quarter of 2006, there were 293 in total, with no evidence of a decline. By the end of 2010, the total was just over 400 cases, with some evidence of a decline in the rate of emergence of new cases, to about five per quarter (unpublished data). Information about the outbreak has been presented locally [11,12]: in this paper, we describe the case–control study, to share the lessons learnt. This has been a large and complex outbreak with many demands placed on health services and clinical staff in London as well as the HPA regional epidemiology unit, which has been providing support for data collection, collation and reporting on the outbreak.

Cases were more likely to be born in the UK than controls and were also more likely to be white or Black Caribbean. The proportion born in Jamaica rose considerably since December 2001, when there was just one Jamaican case (of 77 cases, 1.3%) [5], but by the end of 2006, there were 61 such cases (20.8%). The Irish-born proportion rose modestly from 11% to 13%. We do not have accurate immigration data for north central London to explore the reasons for this.

Recreational drug use was reported by nearly one in four cases, with 5% injecting and 8% using crack cocaine. Although a direct comparison with controls was not possible for these behaviours, previous research into TB in London suggests we might expect 6% of people to report any ‘problem’ drug use (recreational drug use, crack cocaine use and injecting drug use). While we observed that 18% of cases were homeless, we might expect the figure to be 4–12% [13,14]. One third of outbreak cases had a known history of prison detention while up to 18% of TB cases in London might be expected to ever have been detained in prison [13,14]. Such social factors are recognised to play an important role in TB acquisition as well as management in London [15,16].

A high proportion of cases were sputum smear-positive. Adherence to treatment has been poor and thus the degree and duration of infectiousness was likely to have been greater than among other TB cases. As per NICE guidance [10], each TB patient had a named case manager. Some TB clinics have reported successfully using incentives including cash, food, clothes and travel cards to ensure treatment adherence. Research carried out in the United States (US) comparing cash incentives with an alternative to the same value

showed that more follow-up time was required in the non-cash group. These American studies showed independent predictors of completion were stable housing at the outset of treatment and being male [17].

Outbreak cases often have been reluctant to provide contact details and those identified by drug users were especially unlikely to attend for screening [18]. In the US, a small outbreak of 89 drug-sensitive TB cases among drug users in California [19] was controlled using an outreach community-based approach to deliver preventive treatment to contacts with latent TB. We also used home visits to try and ensure treatment adherence. A digital X-ray screening van was initially introduced in 2005 in London and has been used since then across London among susceptible populations, e.g. prisoners and drug users, to try to engage marginalised people who are unable or do not want to use conventional health services.

There are a number of limitations to our study. We used data collected from London TB surveillance systems and questionnaires completed by TB nurses. Because of the particular interest in the outbreak cases, some information, such as being a prisoner, drug dealer or sex worker at the time of diagnosis, may have been obtained more systematically for cases than for controls and therefore the findings should be interpreted cautiously. There were also very wide confidence intervals for the measure of association for being a drug dealer or sex worker, reflecting the small numbers involved. In addition, the typing strategy has been to type isolates that display isoniazid monoresistance. Universal molecular typing was not being done in London during the study period. We have compared the relative odds of risk factors in cases and controls. The control group included individuals with clinically diagnosed TB as well as culture-confirmed TB, excluding those with the outbreak strain. Some cases may have been misclassified as controls because some individuals diagnosed clinically may have been infected with the outbreak strain but were not culture confirmed. This could lead to bias in estimates of association [20]. A more appropriate control group may be one that reflects the base exposures in the population from which the cases were drawn [21]. Since early 2010, universal strain typing has been introduced across London and it is anticipated that this will allow the full extent of the current outbreak to be better elucidated in the future. Nonetheless, the epidemiology of the outbreak has allowed the Incident Control Committee to develop an understanding of the factors associated and to target their control efforts.

Many lessons in this outbreak are applicable to TB control in general, including the need for DOT for vulnerable patients (as per NICE recommendations) as well as multidisciplinary case conferences to plan treatment and housing and social support for cases who are difficult to treat. With nearly one in 10 outbreak cases lost to follow-up, clearly there is a need to do better. Education of healthcare professionals and those working in drug and alcohol services about TB in general and this outbreak in particular has been stepped up and a centralised team has been created to find and treat cases that are lost to follow-up. There is also a need for more prompt identification of pulmonary TB cases in London including, for example, in settings such as hospital accident and emergency departments.

We noted that the rapid movement of prisoners between prisons made it very difficult to keep track of prisoners and several recommendations were made for improved TB control in this setting, including reducing the movement of infected prisoners where possible, raising general awareness of TB in prisons and introducing TB screening on entry to prison. Additionally, the use of DOT for all prisoners with TB was recommended, as well as better communication with community teams on the release of any prisoners with TB. The advent of the use of a mobile digital X-ray screening facility in London has resulted in its regular use in prisons and this has been found to be helpful (an evaluation is underway). Support for ex-prisoners with TB is essential and health and social services, including the voluntary sector and criminal justice system, need to work together to ensure that the release of prisoners is properly planned.

We have identified a number of large outbreaks of drug-resistant TB in Europe, including one community outbreak in Sweden, reported in 2011, involving 115 isoniazid-resistant cases over a nine-year period that were characterised by RFLP and spoligotyping [22]. RFLP was also used to identify cases in an outbreak of MDR TB among HIV-infected injecting drug users attending a large HIV unit in central Lisbon, Portugal, in 1995 to 1996 [23]. There were 95 cases of MDR TB and 80% of the strains were available for typing. These clustered into one of two large clusters. Transmission occurred among HIV-infected injecting drug users exposed to infectious TB cases on open wards in the HIV unit. Although we were not systematically collecting HIV status data on the TB cases in our London outbreak, clinicians reported that among those tested, 12% were HIV positive (M. Lipman, personal communication, Jun 2005).

We believe that our outbreak is the largest documented outbreak of drug-resistant TB in Europe so far. It has highlighted the need for greatly improved TB services in London and enhanced integration of health and social services. DOT should form part of a wider holistic care package addressing housing and other social needs. The voluntary sector and local authorities, working together with drug and alcohol services, have a key role to play in ensuring that secure housing and supportive care accompany appropriate medical treatment.

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