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Special edition: Tuberculosis

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Tuberculosis (TB) continues to be a health threat to European citizens. This is due to the diverse epidemiological situation of tuberculosis burden in EU Member States with high rates of tuberculosis in vulnerable populations. Moreover, multi-drug resistance and now extensively drug-resistant (XDR TB) are a standing threat to tuberculosis control. Eurosurveillance reports on the resistance problem and analyses treatment outcomes in the European Union and European Economic area.

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Macrophage engulfing TB bacteria. Coloured scanning electron micrograph (SEM) of a macrophage white blood cell (red) engulfing a tuberculosis (Mycobacterium tuberculosis) bacterium (green). This process is called phagocytosis. Macrophages are cells of the body's immune system. They phagocytose and destroy pathogens, dead cells and cellular debris.

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High time to tackle childhood tuberculosis

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When Robert Koch published his groundbreaking paper on the aetiology of tuberculosis (TB) in 1882, he reported that about a third of the working population died of TB [1]. World TB Day today should remind us not only about the first identification of the tubercle bacillus but also that the main burden of the TB epidemic has shifted from Europe to other regions in the world. The 329,391 reported TB cases in the WHO European Region in 2009 contribute only 5.6% of all newly detected TB cases and relapses in the world, according to the latest report *Tuberculosis surveillance in Europe 2009*, jointly published by the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe [2]. Furthermore a sustained decline in TB can be noted with a mean annual reduction of 3.8% between 2005 and 2009, mainly attributable to the high- and intermediate-burden countries in the European Union (EU) and European Economic Area (EAA).

Efforts to build a comprehensive TB surveillance system in Europe date back 15 years, when recommendations for uniform reporting of TB were published in 1996 in the first issue of *Eurosurveillance* by an expert group including governmental and non-governmental representatives from 37 countries [3]. The system established has allowed developments to be monitored: despite the reassuring overall decline in TB incidence, several challenges lurk in these data, as the analysis by Hollo et al. in this issue reveals [4]. Their data show a marked geographic heterogeneity: some countries in the EU/EAA belong in the group with the highest proportions of multidrug-resistant TB in the world; also alarming proportions of patients lost to follow-up are observed and declining rates of culture confirmation of cases.

For the first time, the epidemiology of TB in children within the EU/EAA is put in the spotlight by Sandgren et al. [5]. Analysis of 10 years' data on this neglected aspect of TB shows that about half of the TB cases in children were less than five years of age. The incidence in this age group was higher than for children aged 5–14 years and the average annual percentage change in notification rates for 1–4 year-olds in low-incidence countries (defined as incidence less than 20 per 100,000 population) increased between 2000 and

2009 by 7.4%. Even though it remains unclear if this rise is due to an overall increase in the risk of infection in the population or is the result of recent transmission in outbreaks, it shows that TB prevention and control does not reach those in the most vulnerable age group in Europe. This is supported by the fact that the overall treatment success of 75% for culture-confirmed paediatric TB cases in low-incidence countries was well below the 85% WHO target and almost one third of children were lost to follow-up in 2008. The true burden of disease in children, however, remains unclear as only 16.9% of all cases in this analysis were confirmed by culture showing, as the authors conclude, that there is an urgent need to address TB diagnosis in children.

The occurrence of TB in children can serve as a marker for recent transmission, but at the same time, it also represents a failure of public health prevention [6]. For decades Bacillus Calmette-Guérin (BCG) vaccination has been a main element of prevention of primary TB in children; however, the efficacy of the vaccine varies substantially between different countries and regions worldwide [7]. Thus several low-incidence countries in Europe have revised their BCG policies in recent years, moving from universal to selective vaccination. Guthmann et al. report in this issue on two major changes in BCG vaccination in France, concerning vaccine administration technique and the introduction of a selective vaccination policy in 2007 [8]. The authors looked at vaccination coverage and TB incidence in two types of settings: a high-incidence area of the country with a policy of universal vaccination in comparison with other areas that have selective vaccination targeting high-risk children. While no difference in TB rates in children under three years of age was found, the authors demonstrated a notable decline in vaccination coverage, mainly due to the vaccination technique. Although detailed data on BCG vaccination coverage are regularly retrieved and published by WHO (for 2009, see [9]), data on the use of chemotherapy to prevent TB in children aged under five years in Europe are lacking. As Leung et al. point out, the efficacy of preventive isoniazid therapy for 6–12 months has been shown to reach 90%; however, acceptance and adherence are less than desired [10].

A study by Abubakar et al. in this issue describes a large outbreak investigation in the United Kingdom (UK) that demonstrates the contribution of interferon gamma release assays (IGRA) to active case finding and to our understanding of the risk of transmission [11]. The authors report on the use of IGRA for diagnosis of TB in a large outbreak among college students in the UK, involving 2,284 students between October 2008 and January 2009. In addition to being a close contact of the index case, travel to a high-prevalence area was independently associated with becoming a case. While no information about the type of travel and potential exposure could be collected retrospectively, this study demonstrates that the extent of recent infection in young adults born and living in a low-incidence country may be underestimated.

As this studies shows, important progress has been made in recent years in diagnostic techniques for TB infection. Unfortunately, however, the same cannot be said for the diagnosis in children. While a large number of studies have been published over the past few years on the use of IGRAs, including sensitivity, specificity and positive predictive values, corresponding data for children in the especially vulnerable age group, under five years, are still scarce. This holds also true for new methods of molecular detection of TB. Data on the rapid molecular detection of active TB and rifampicin drug resistance – a method endorsed by WHO as a 'major milestone for global TB diagnosis' [12] – have not been published for children, yet.

The studies in this special issue give insight into the epidemiological situation of TB in Europe and show that, despite the overall decreasing trend in incidence, transmission of TB is ongoing, even in low-incidence countries. Identification of *Mycobacterium tuberculosis* infection in children presents a key event allowing early recognition and at the same time intervention to prevent cases in children and adults. Even though the absolute number of active cases in children is much smaller than in adults, the risk of rapid progression to severe disease is much higher, adding a considerable burden to the health system. In addition, every undetected child infected today has the potential to progress to an infectious case of TB for decades in the future.

Thus, the elimination of tuberculosis requires a call for action [13], to put the focus on TB in children – it's about time.

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Marking 15 years of efforts towards a comprehensive European TB surveillance system: the epidemiological situation of TB in the EU/EEA in 2009

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Efforts have been ongoing since 1996 to strengthen tuberculosis (TB) surveillance in Europe, starting with the launch of the EuroTB initiative. We present TB surveillance data for the Member States of the European Union (EU) and of the European Economic Area (EEA) for the latest reporting year (2009), highlighting key areas of epidemiological and programmatic focus. Despite a sustained decline of TB notifications at EU/EEA level, several aspects of TB control can still be improved.

The role of surveillance in tuberculosis control in Europe

Surveillance is a basic component in the control and elimination of tuberculosis (TB) in Europe, and is one of the key areas of the Framework Action Plan to Fight TB in the European Union (EU) [1]. To attain a reliable surveillance system across Europe, a highly standardised data reporting system is needed. Persistent differences between national case definitions and reporting systems have, in the past, hampered the analysis of time trends, identification of population groups with high incidence and data comparability across the EU and the European Economic Area (EEA) and worldwide.

Efforts to standardise TB case reporting have been ongoing since at least 1996 in Europe [2]. The year 2011 marks the 15th anniversary of EuroTB, the European tuberculosis surveillance network. It was initiated as a project funded by the European Commission, housed and co-funded by Institut de Veille Sanitaire (the French Institute of Public Health Surveillance). Since 2008, EuroTB has been jointly coordinated by the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) Regional Office for Europe. The objective of this TB surveillance system has been to collect, validate, analyse and disseminate standardised high quality TB notification data covering the 53 countries of the WHO European Region and Liechtenstein. EuroTB had expanded the case-based surveillance towards participation of all countries from the WHO European Region, however after the transition of EuroTB to ECDC, the case-based surveillance

remained only for the 30 EU/EEA countries. Designated national disease surveillance institutions are responsible for reporting the data to the European level through a joint data collection entry point. For EU/EEA countries, data are transmitted, validated and processed using The European Surveillance System (TESSy) run by ECDC, while data from all other countries are handled by the Centralized Information System for Infectious Diseases (CISID) run by the WHO Regional Office for Europe.

Over the past three years, an increasingly complete and reliable picture of the TB situation in the EU/EEA and Europe has been achieved. In this article we present an overview of the most recent data reported in the latest Joint Annual TB surveillance Report for Europe [3] specifically for the 30 EU/EEA Member States, and highlight key areas of epidemiological and programmatic focus that represent pillars in TB control and thus benefit from a close and reliable monitoring at both national and regional level. At the start of the EuroTB, only 16 Member States of the EU/EEA were able to report case-based data to supranational level. After a constant increase in the number of countries reporting case-based data to European level, all 30 EU/EEA countries reported case-based TB surveillance data for 2007 and due to administrative constraints on the two last data collection rounds, Liechtenstein was not able to report to TESSy. The targets mentioned in the article are those endorsed by EU/EEA Member States in the follow-up to the Action Plan to Fight TB in the European Union [1].

Current situation of tuberculosis in the European Union / European Economic Area
Notifications

In 2009, 79,665 TB cases were reported by the 27 EU countries, Iceland and Norway, a decrease of 3,635 (4.5%) cases compared with 2008. The decrease between 2007 and 2008 has been 1.4%.

Over 75% of cases occurred in the seven countries (two high-incidence countries and five low-incidence countries) that reported 3,000 cases or more (France, Germany, Italy, Poland, Romania, Spain and United Kingdom). The overall notification rate in 2009 was 15.8 per 100,000 population, the lowest number since the start of EuroTB in 1995 (Table) [5]. The cut-off point for high incidence countries in EU settings of 20 per 100,000 has been adopted by the Wolfeheze group in the 2002 report [4]. Despite a decrease in notification rates of 4.5% since 2008, some countries still record high incidence with rates above 20 per 100,000 reported in Romania (108.2), Lithuania (62.1), Latvia (43.2), Estonia (30.7), Bulgaria (38.3), Portugal (27.0) and Poland (21.6). Seventy-nine percent of the cases were reported as new, while 13% were reported to have been previously treated. A new case (never treated) was defined as a case who had never previously received drug treatment for active TB, or who

had received anti-TB drugs for less than one month. Belgium, Denmark, Ireland and United Kingdom used "never diagnosed" as proxy. As many as 6,327 notified cases (7.9%) had no information on previous TB history, suggesting suboptimal surveillance in the reporting countries.

Drug resistance

In 2009, resistance to at least one first-line drug was reported for 3,870 (14.1%) of 27,487 (35.7% of all reported cases) tested cases in 28 EU/EEA countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom while unknown drug susceptibility testing results were indicated for 13,336 (34.8%) of 38,312 culture-positive cases in 25 of these 28 EU/

Table

Tuberculosis cases notification rates per 100,000 population, 1995 and 2009, EU/EEA (n=30 countries)

Country	Total cases 1995	Notification rate per 100,000 population 1995 (all cases)	Total cases 2009	Notification rate per 100,000 population 2009 (all cases)
Austria	1,383	17.4	707	8.5
Belgium	1,380	13.6	1,020	9.6
Bulgaria	3,245	37.0	2,911	38.3
Cyprus	36	5.6	55	6.9
Czech Republic	1,851	17.9	702	6.7
Denmark	448	8.6	329	6.0
Estonia	608	42.0	411	30.7
Finland	654	12.8	419	7.9
France	8,723	14.7	5,308	8.2
Germany	12,198	15.0	4,432	5.4
Greece	939	8.9	586	5.2
Hungary	4,339	42.0	1,448	14.4
Iceland	12	4.5	9	2.8
Ireland	458	12.7	472	10.6
Italy	5,225	9.2	3,877	6.5
Latvia	1,541	61.6	977	43.2
Liechtenstein	NA	NA	NA	NA
Lithuania	2,362	64.8	2,081	62.1
Luxembourg	32	7.9	27	5.5
Malta	10	2.7	44	10.6
Netherlands	1,619	10.5	1,160	7.0
Norway	236	5.4	363	7.6
Poland	15,959	41.4	8,236	21.6
Portugal	5,577	55.7	2,871	27.0
Romania	23,271	102.5	23,267	108.2
Slovakia	1,537	28.7	506	9.3
Slovenia	525	26.4	188	9.3
Spain	8,764	22.3	7,592	16.6
Sweden	564	6.4	627	6.8
United Kingdom	6,161	10.6	9,040	14.8
Total EU/EEA	**109,657**	**22.7**	**79,665**	**15.8**

EU/EEA: European Union/European Economic Area; NA: data not available.

EEA countries (no unknown drug susceptibility testing results reported by Iceland, and excluding Italy and Poland due to lack of data). The proportion of cases with multidrug-resistant tuberculosis (MDR TB) in the 28 countries mentioned above was 5.3%, a 0.7 percentage point decrease compared with 2008 and 2009, a 2.2 percentage point decrease compared with 2007 and 2008 [6], with the Baltic States and Romania reporting the highest proportions (17.4%–28.0% and 11.2%, respectively).

Childhood tuberculosis

The case notification rate of TB in children, especially infants, is a measure of the level of transmission in the community. In 2009, cases in children (under 15 years of age) accounted for 4.2% of all notified cases. Nearly all countries have experienced a decline or stabilisation at low levels in paediatric notification rates since 2005, suggesting low levels of transmission in the general population. In Bulgaria, Latvia, Lithuania and Romania, however, rates among children have remained high (12.9–29.6 per 100,000 child population) in 2009 and have increased in Bulgaria since 2000 (11.4–20.6 per 100,000). Although rates in children were low in Belgium, Finland, Germany, the Netherlands, Slovenia, Sweden (less than 10 per 100,000), some increase in paediatric notifications was recorded between 2008 and 2009 in these countries (Belgium: from 2.9 to 3.6; Finland: from 0.4 to 0.8; Germany: from 1.1 to 1.3; the Netherlands: from 1.7 to 2.0; Slovenia: from 1.1 to 2.1; Sweden: from 1.8 to 2.1).

Bacteriological confirmation of cases

The proportion of bacteriologically confirmed TB cases remains sub-optimal in the EU/EEA countries, with only seven countries achieving the target of 80% culture-confirmation among new pulmonary TB cases, as reflects the approach to use only new cases, adopted in the monitoring framework endorsed by the Member

States in the document A follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union [7]. This consensus was reached after several months of consultation including discussion with the experts in the European Reference Laboratory Network for TB. Again with this article we try to achieve consistency of messages with the Annual Surveillance Report and ongoing EU standard approaches for monitoring.

Confirmation by culture was reported for 57.8% of all cases, whereas the culture result was reported as unknown for as many as 28.1% of the cases. The levels in culture confirmation differed widely across countries (range: 44%-100%) and data were not complete for five countries.

High culture-coverage (75% or more of cases with known culture result for *Mycobacterium tuberculosis* complex among all TB cases) was reported by eight countries and an additional eight countries showed an improvement in culture confirmation between 2005 and 2009. There were however some discouraging trends, with a decline in the proportion of culture confirmed cases in five countries from 2008 to 2009.

Overall, 78% of the cases were reported as pulmonary TB with or without extrapulmonary involvement. Sputum smear-positive rates were lower than five cases per 100,000 population in 21 countries in the last three years. The rates were consistently higher than 10 per 100,000 in the Baltic States, Bulgaria, Portugal and Romania.

Treatment outcome

For the 2008 cohort of culture-confirmed pulmonary TB cases, the overall treatment success rate was 72.8%, with four countries reporting more than 85% treatment success (Malta, Portugal, Slovakia and Sweden). Compared with the situation in 2008, treatment success decreased slightly among culture-confirmed pulmonary TB cases of foreign origin (from 75.7% to 73.8%) and in cases of national origin (from 73.4% to 72.8%). A higher proportion of cases of national origin died compared with those of foreign origin.

Among previously untreated cases, 78.1% were cured, 6.7% died, 1.8% failed, 5.4% defaulted from treatment, 2.9% were still on treatment, and 5.2% were transferred or had an unknown outcome. Among countries with more than 20 previously untreated laboratory-confirmed pulmonary cases, success rates varied widely from 40.5% in Denmark to 87.4% in Sweden. In 1991, all WHO member states adopted a World Health Assembly (WHA) resolution setting two targets for global TB control to be reached by the year 2000: to detect at least 70% of all new infectious cases arising each year, and to cure at least 85% of those detected.

Six countries achieved treatment success in 85% or more of cases in this category: Bulgaria, 84.9%, the Netherlands, 85.0%, Slovakia, 87.0%, Portugal, 87.3%,

Treatment success rate among native and foreign confirmed tuberculosis cases, Europe, 2008 (n=24 countries)
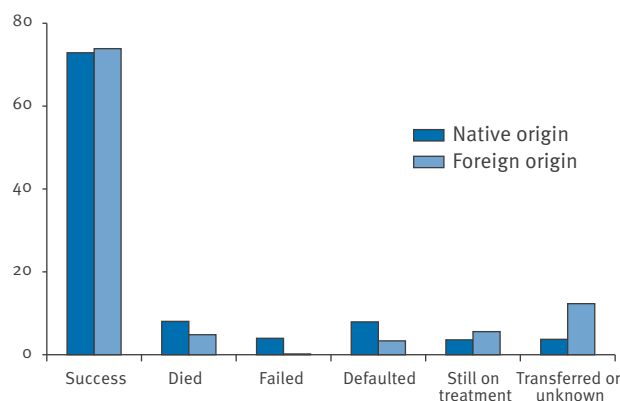
The geographical origin of tuberculosis cases is classified as native or foreign according to the place of birth (born in the country or foreign-born) or, if unavailable, according to citizenship (citizen/non-citizen).

Sweden, 87.4% and Malta, 92.3%. Treatment success rates below 75% were associated with a high loss to follow-up (defaulted, transferred or unknown: 4.5%–57.5%). The higher proportion of defaulters among the native population would warrant further analysis, however, data presently available in TESSy are not sufficient to allow such an analysis.

Conclusions

The latest data reported for TB in the EU/EEA countries provide a comprehensive picture of the overall epidemiological situation in the region, with some limitations in terms of data comparability due to differences among surveillance systems in the Member States. This comprehensive epidemiological picture is the result of 15 years of collaborative efforts that began with the launch of EuroTB in 1996.

Despite limitations related to underreporting for selected variables (i.e culture confirmation, HIV status, among others), it is evident that the current reporting system could potentially support a thorough assessment of TB control in the EU/EEA on the basis of the indicators proposed in the follow-up to the Framework Action Plan to Fight TB in the EU [7]. Such an analysis is planned for the upcoming 2012 report. A number of the epidemiological and operational indicators included in the monitoring framework can be directly measured and calculated using the data collected in the current surveillance system.

It is also worth mentioning that despite a sustained average decline of the TB epidemic recorded in the EU/EEA this is mainly attributable to the decline recorded in the high- and intermediate-burden countries. In addition several areas in need of strengthening like contact tracing, risk group management, laboratory data monitoring, treatment outcome reporting, were identified through the analysis of data.

Two crucial weaknesses in TB control in the EU/EEA are worth highlighting. The proportion of bacteriologically confirmed TB cases remains suboptimal, with only seven Member States achieving the target of 80% culture-confirmation among new pulmonary TB cases. This impedes the rapid detection of resistance and rapid provision of effective treatment to patients, thus preventing prompt interruption of transmission.

Although the number of countries achieving the target of 85% treatment success has doubled since 2008, from a Treatment Outcome Monitoring perspective, the overall treatment success rate in the EU/EEA has not improved, furthermore, the rates are marginally decreasing (79.5% to 78.1%) between the 2007 and 2008 cohorts [8].

The potential for improving TB control in the EU/EEA therefore remains and the current TB surveillance set-up, benefiting from 15 years of joint coordination, can provide direction and guidance in progressing towards TB elimination.

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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, myco-bacterial 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)
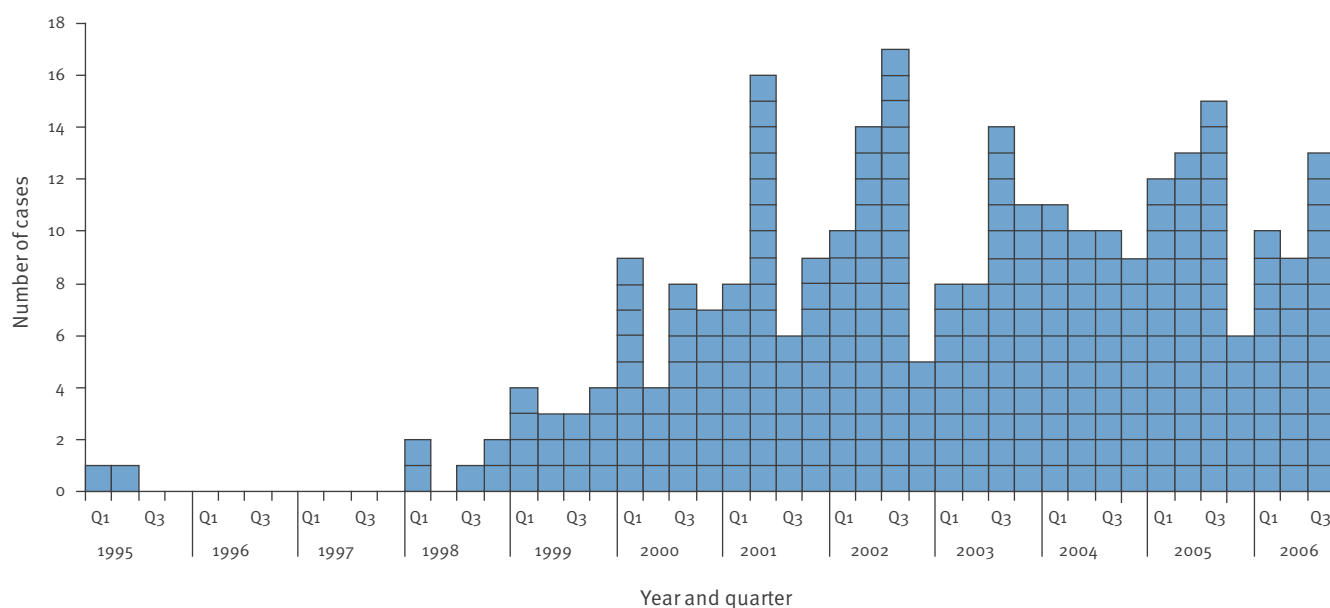
Q: quarter.

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

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**

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).

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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Childhood tuberculosis in the European Union/ European Economic Area, 2000 to 2009

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Childhood tuberculosis (TB) has been neglected for decades as a key component of TB control. However, ensuring proper monitoring of childhood TB has recently been given renewed emphasis. A descriptive analysis of surveillance data was performed to assess burden and trends of paediatric TB in the European Union/European Economic Area (EU/EEA) between 2000 and 2009. From 2000 to 2009, 39,695 notified paediatric (defined as 0–14 years of age) TB cases were reported by the 27 EU countries plus Norway, Iceland and Liechtenstein. These paediatric cases accounted for 4.3% of all notified cases. However, across the EU/EEA Member States, paediatric case notification rates ranged from 29.6 per 100,000 to 0.3 per 100,000 for the latest reporting year, 2009. Overall, though, these rates dropped from 5.5 per 100,000 in 2000 to 4.2 per 100,000 in 2009. The EU/EEA average annual percent changes (AAPC) in paediatric notification rates decreased between 2000 and 2004 by 1.3% and between 2005 and 2009 by 2.4%, with an overall decrease between 2000 and 2009 of 2.8%. Of all paediatric cases reported from 2000 to 2009, only 16.9% were culture-confirmed, amongst which the overall treatment success was 80.5% for all culture-confirmed pulmonary paediatric TB cases. Childhood TB in the EU/EEA remains a public health issue. Due attention should be paid to assessing paediatric trends as they could provide an insight in recent transmission. Whilst the primary aim of further reducing TB rates among children is paramount, better rates of appropriate diagnosis should also be achieved, along with a further improvement of therapeutic success rates.

Introduction

Childhood tuberculosis (TB) has long been an overlooked area within global TB control [1]. However, of the estimated 9 million cases of TB occurring annually in the world, approximately 1 million occur in children under the age of 15 years. Seventy-five per cent of the global childhood TB burden occurs in the 22 high-burden countries, where the proportion attributable to children ranges from 15% to 20% of all cases. In contrast, in low-burden countries, this proportion is reported to be approximately 5% [1].

It is, however, interesting to note that given the recent changes in the TB epidemic in low-incidence countries, with a resurgence of cases and a failure in further TB decline, we now see a renewed emphasis on ensuring correct monitoring of childhood TB [2-5]. In particular, the notion that childhood TB represents a sentinel event of ongoing transmission, and that children rapidly progress to active disease and represent a potential pool for disease in their adult life, further underlines the importance of analysing the epidemiology of childhood TB.

Despite previous attempts to provide an overview of the European situation [6], an in-depth analysis of childhood TB in the Member States of the European Union (EU) and European Economic Area (EEA) has not previously been undertaken. Epidemiological analysis of EU data over the past years [7-8] has highlighted the need to further describe the trends in paediatric TB in the EU/EEA Member States. The analysis presented here aims to provide a descriptive and analytic overview of the trends in childhood TB notifications, diagnosis and treatment outcome between 2000 and 2009.

Methods

Data source and collection

A descriptive analysis of surveillance data was performed to assess burden and trends of paediatric TB in EU/EEA countries between January 2000 and December 2009. Data for the years 2007 to 2009 were extracted from The European Surveillance System (TESSy), and for years 2000 to 2006 from the historical databases of the former EURO-TB network, the Individual Database of Tuberculosis (EITUD) and the aggregated database (TABORIG), held at the European Centre for Disease Prevention and Control (ECDC). Data from the 30 EU and EEA countries reporting to the ECDC were analysed. Not all countries have reported data for the whole period from 2000 to 2009, therefore we indicate, where appropriate, the number of countries the presented data are based on.

For the purposes of this study, country-specific data for cases under the age of 15 years were extracted for

the years of analysis, for both new and retreatment pulmonary and extra-pulmonary TB cases. Since the reporting year 2002, treatment outcome data have been collected for all individual cases. The cases eligible for analysis (cohorts) included all TB cases notified in the calendar year of interest, after exclusion of cases with final diagnosis other than TB. For comparison between paediatric and overall trends, we used the trends from the latest reported national five-year notification included in the TB surveillance report for 2009 [9].

Data inclusions and surveillance definitions

All TB cases, confirmed, probable or possible [7], notified at country level for the year of interest are included in the dataset uploaded to TESSy and were included in the study if they were under 15 years-old. Cases eligible for treatment but who never started treatment were also included, as well as cases diagnosed post mortem. Pulmonary TB was defined as TB affecting the lung parenchyma, the tracheobronchial tree or the larynx. Extrapulmonary TB was defined as TB with non-pulmonary presentations, and includes pleural and mediastinal/hilar forms. All definitions and categories of the data analysed are consistent with those published in the Tuberculosis surveillance in Europe 2008 report [7].

For the purpose of disaggregated data analysis, countries were grouped in high- and low-incidence TB countries, using the thresholds previously proposed by the Wolfeheze working group [10] and recently adopted in the EU monitoring framework [5]. Thus, low-incidence countries were defined as those with less than 20 cases per 100,000 population, of which there were 23 countries, and high-incidence countries as those with 20 or more cases per 100,000 population, which comprised seven countries: Bulgaria, Estonia, Latvia, Lithuania, Poland, Portugal and Romania.

Data quality

The data uploaded to TESSy went through automated checks for completeness and accuracy. Until 2007, only 27 out of the 30 EU/EEA current Member States were able to report case-based data. Aggregated data for paediatric cases allowed only analysis of the origin of cases and site of the disease.

Analysis

STATA 11 (StataCorp LP, College Station, Texas, USA) and Microsoft Excel 2007 were used for data analyses. The collected data from 2000 to 2009 were collated and tabulated in an aggregated fashion. Population size was obtained from the EUROSTAT database for the period 2000 to 2009.

Childhood TB rates were calculated as age-specific notification rates for the population aged 0 to 14 years. The trends in notification rates were expressed as the average annual percentage change (AAPC) [7,8]. The AAPC was calculated for the whole period from 2000 to

2009, and in some cases from 2000 to 2004 and from 2005 to 2009, to allow comparisons with previously published trends in the EU [7,8]. The relation between national AAPC of paediatric cases versus that of all TB cases was analysed using the Pearson correlation (R^2). Countries with less than 10 cases per year for each year between 2005 and 2009 were excluded from the analyses, to avoid introducing bias from countries with low absolute numbers of cases, where the AAPC would be strongly affected by small absolute changes. Separate analyses were done for low-incidence countries and high-incidence countries, to investigate possible differences in trends between these two distinct epidemiological settings.

Linear regression models were applied to investigate statistically significant differences in time trends of notification rates between 0–4 year-olds and 5–14 year-olds, and between high- and low- incidence countries for the age groups of under one year-olds, 1–4 year-olds, as well as all paediatric cases. The Fisher's z-transformation was used to compare correlation coefficients. Fisher's exact test or chi-square tests were used to compare proportions and notification rates between groups. A $p < 0.05$ was considered as statistically significant.

Results
Paediatric tuberculosis notification and trends

During the period 2000 to 2009, 39,695 notified paediatric TB cases were reported by 27 EU countries plus Norway, Iceland and Liechtenstein: these accounted for 4.3% of the total TB burden in the EU/EEA. The notification rates of paediatric cases ranged from 29.6 per 100,000 to 0.3 per 100,000 across the EU/EEA Member States for the latest reporting year 2009. During the ten years, the EU/EEA overall paediatric notification rates dropped from 5.5 per 100,000 in 2000 to 4.2 per 100,000 in 2009. The EU/EEA AAPC in paediatric notification rates decreased between 2000 and 2004 by 1.3% and between 2005 and 2009 by 2.4%, with an overall decrease between 2000 and 2009 of 2.8% (five-year interval trends will allow a better comparison with previously published data on trends in EU/EEA [8]). However, 13 countries had an increase in notification rates between 2000 and 2004, 15 countries had an increase between 2005 and 2009, and seven had a stable increase for both of these periods.

When excluding the five countries that did not report data for all years, 11 countries, including four high-incidence countries, had a decrease in AAPC in paediatric notification rates for the period from 2000 to 2009. Conversely, 14 countries had an increase in AAPC in notification rates, three of them high-incidence countries (Figure 1).

Correlation analysis between AAPC (2005-2009) for paediatric and all cases (data from [7,8]), excluding countries with less than 10 cases per year during that period, showed a poor overall correlation ($R^2=0.32$,

FIGURE 1

Average annual percentage change of childhood tuberculosis notification rates for EU/EEA countries, 2000–2009 (n=25)
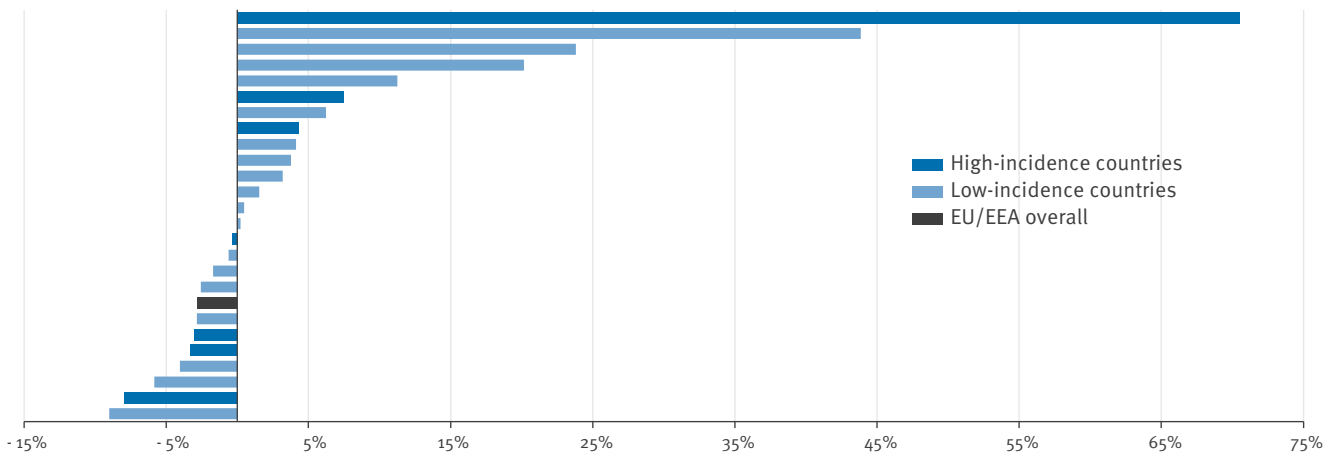
EU/EEA: European Union/European Economic Area.

FIGURE 2

Correlation between average annual percentage change of all cases and of paediatric cases in (A) low-incidence countries (n=14) and (B) high-incidence countries (n=6), EU/EEA, 2005–2009
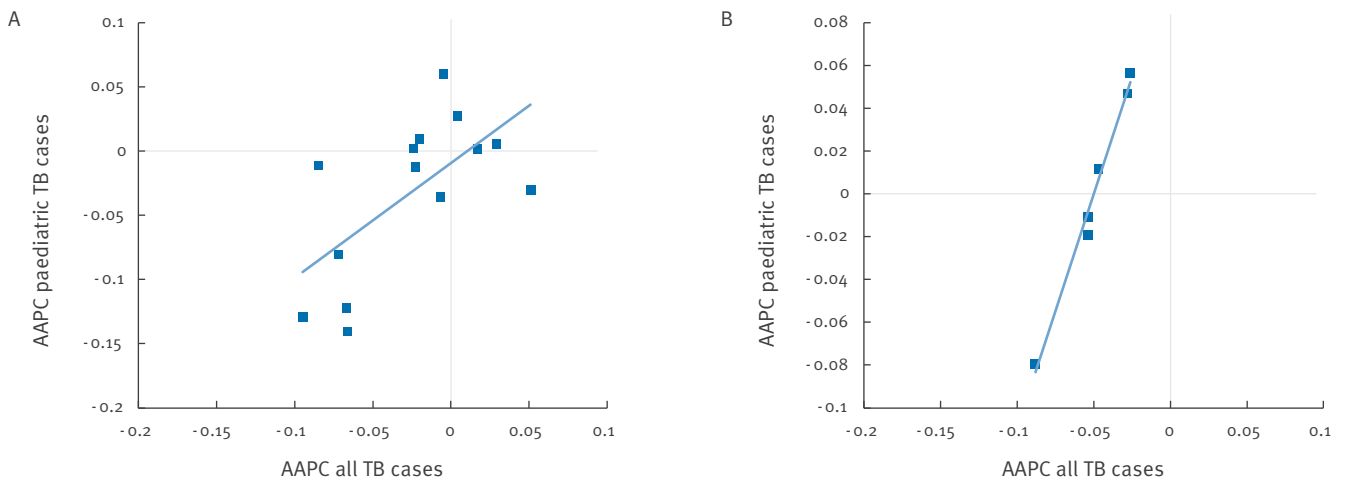
AAPC: average annual percentage change; EU/EEA: European Union/European Economic Area; TB: tuberculosis.

FIGURE 3
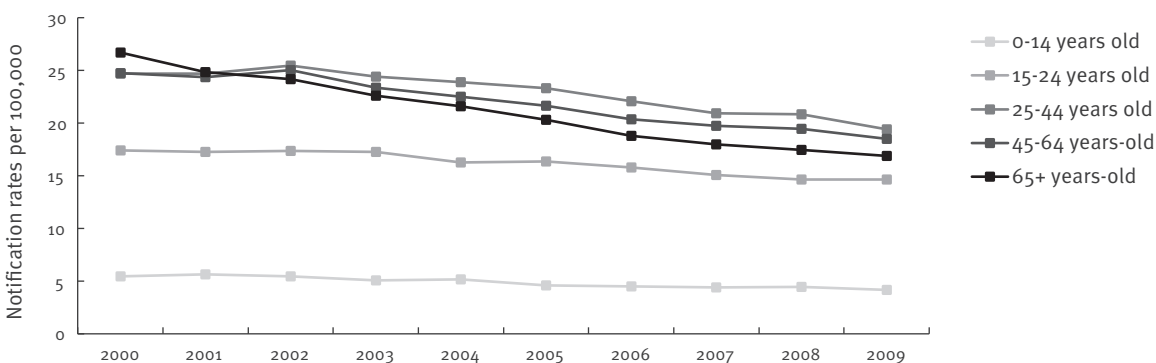
Trends of tuberculosis notification rate in all age groups, EU/EEA, 2000–2009

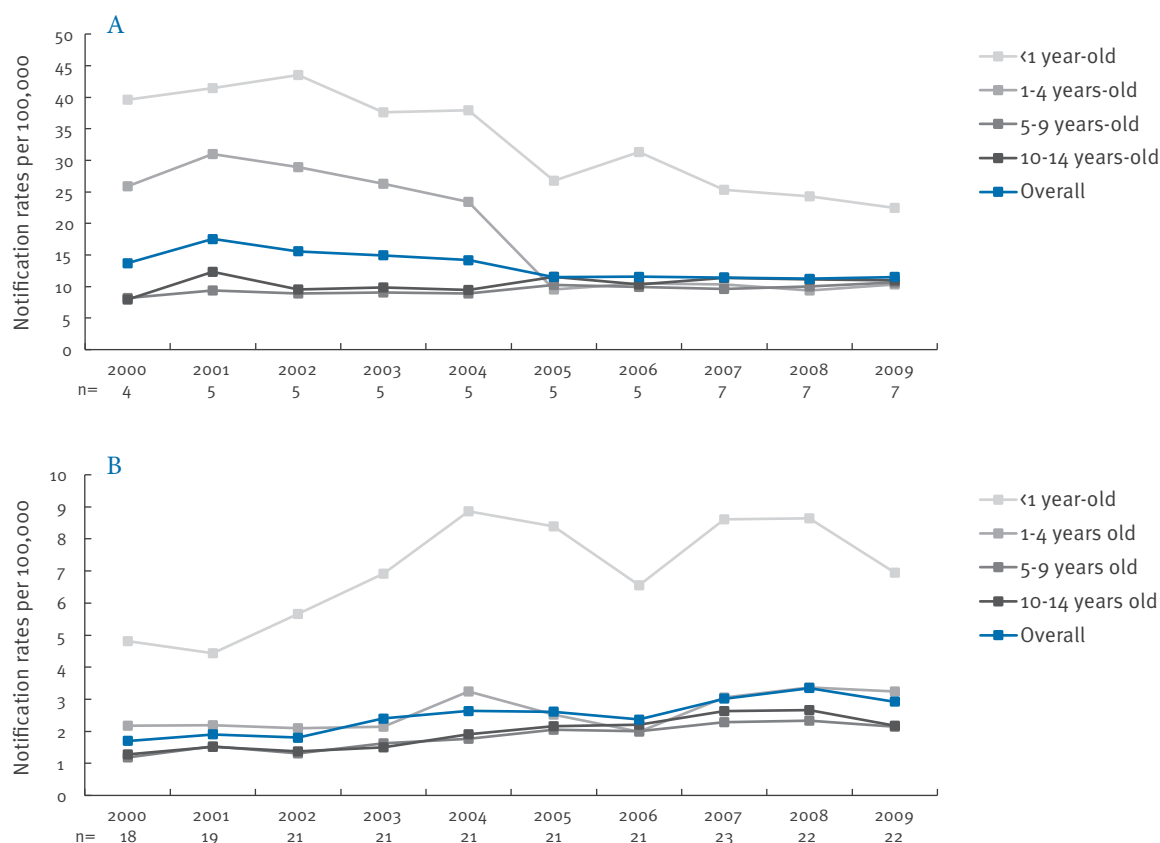EU/EEA: European Union/European Economic Area.

n=20). Closer investigation however, revealed that this correlation was significantly weaker for low-incidence countries (R^2=0.42, n=14) (Figure 2A) than for high-incidence countries (R^2=0.99, n=6) (Fisher Z=-3.17, p=0.0015) (Figure 2B).

Although the notification rates for children were lower than those for other age groups (Figure 3), very young children (‹5 years-old), who represented 48% of all paediatric cases, stood out as having significantly higher notification rates than the 5-14 year-olds (ranges: 5.42–9.21 per 100,000 in ‹5 year-olds and 3.03–3.91 per 100,000 in 5-14 year-olds; p‹0.001).

Although high-incidence countries contribute most paediatric cases, we observed decreases in the AAPC

Paediatric age-specific tuberculosis trends in (A) high-incidence and (B) low-incidence countries, EU/EEA, 2000-2009

EU/EEA: European Union/European Economic Area.
n: number of countries reporting data for the particular year.

Proportion of tuberculosis cases by age group and origin of total paediatric cases in low-incidence countries, EU/EEA, 2000–2009
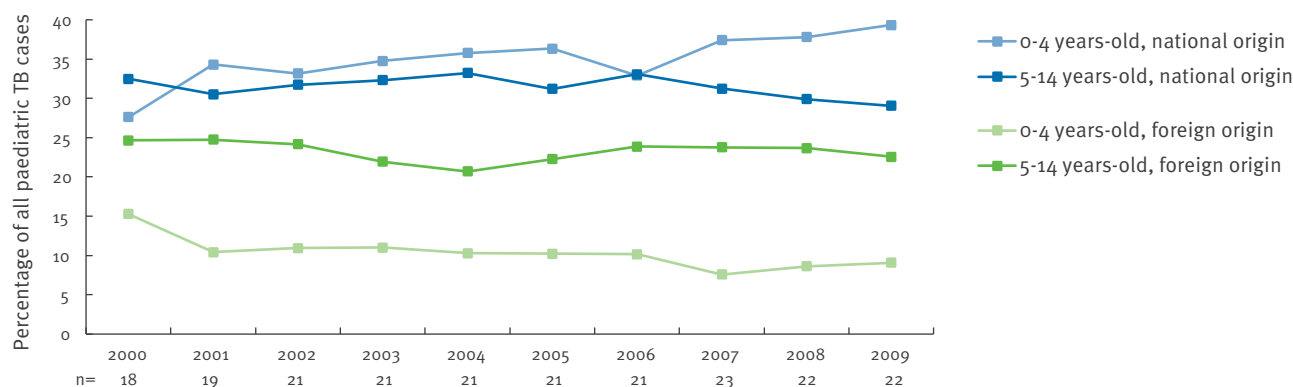
EU/EEA: European Union/European Economic Area.
n: number of countries reporting data for the particular year.

FIGURE 6

Culture-positive paediatric tuberculosis cases and their proportion with respect to the total paediatric cases, EU/EEA, 2000-2009
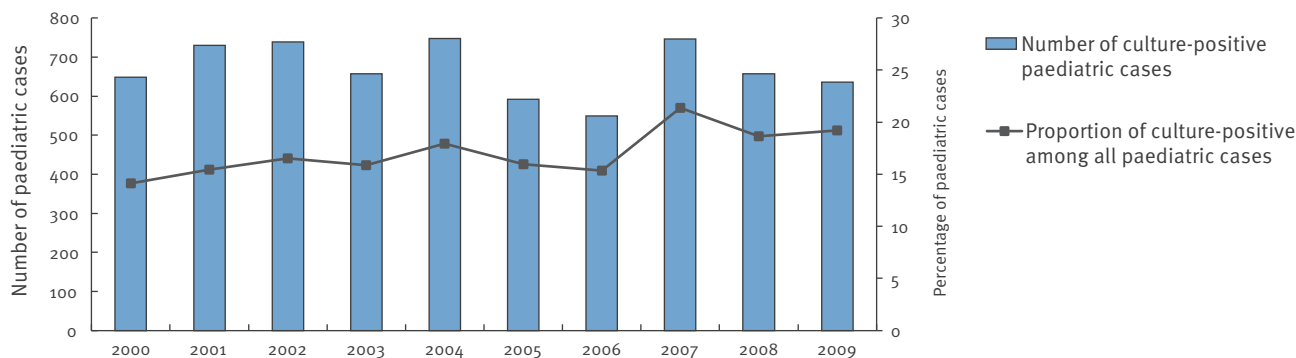
EU/EEA: European Union/European Economic Area; FO: foreign origin; NP: national origin; TB: tuberculosis.

FIGURE 7

Anti-tuberculosis drug resistance among paediatric cases, EU/EAA, 2000–2009
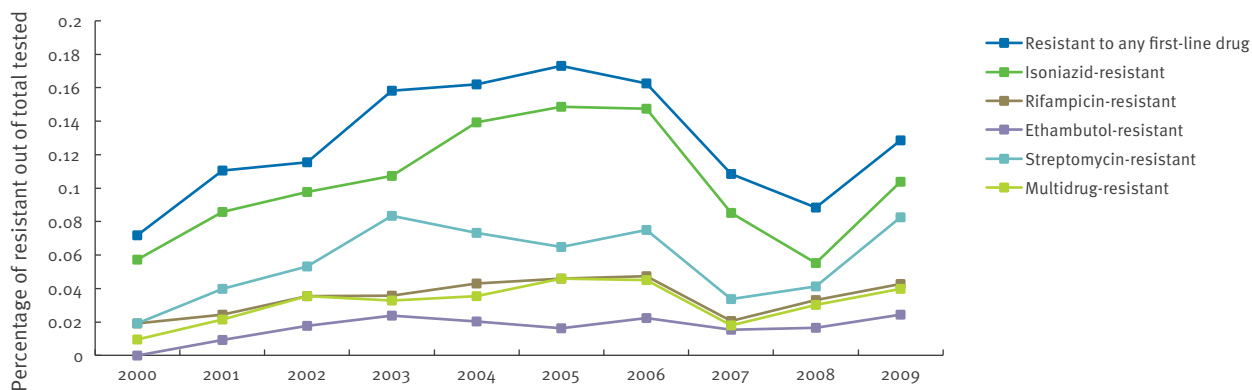
EU/EEA: European Union/European Economic Area.

FIGURE 8

Treatment outcome for new pulmonary culture-confirmed paediatric tuberculosis cases in high- and low-incidence EU/EEA countries, 2002–2008
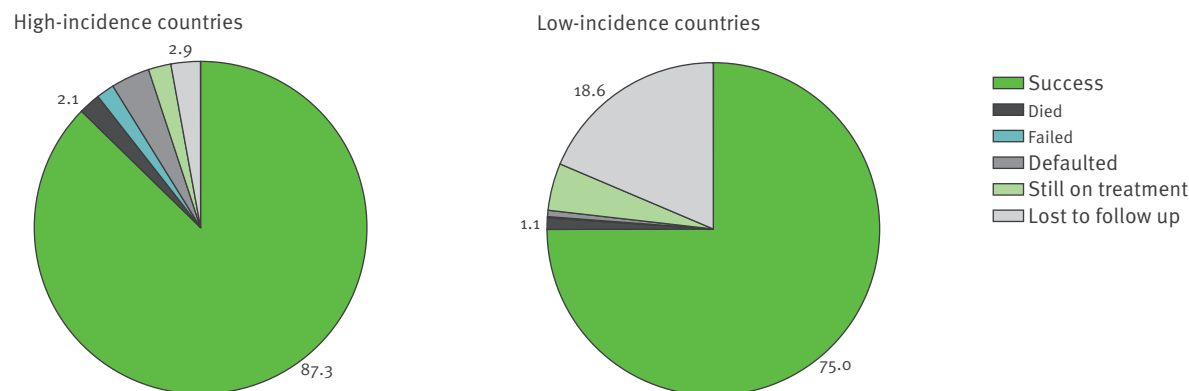
EU/EEA: European Union/European Economic Area.

of paediatric notification rates between 2000 and 2009: by 5.1% for the under 1 year-olds and 6.2% for the 1-4 year-olds. In contrast, in low-incidence countries, there were increases in the AAPC in paediatric notification rates between 2000 and 2009, by 6.1% for the under 1 year-olds and 7.4% for the 1–4 year-olds (Figure 4). The trends in notified cases for the under 1 year-olds, the 1-4 year-olds and all paediatric cases differed significantly between high- and low-incidence in the period from 2000 to 2009 (p<0.001 for all three comparisons).

Origin of cases

From 2000 to 2009, 15.3% of the 39,695 paediatric cases were registered as of foreign origin overall in Europe. Most of these foreign cases were in low-incidence countries, where 29.2% of the paediatric cases were of foreign origin, as opposed to 0.6% in high-incidence countries. The proportion of unknown origin decreased during the study period, but 5.2% were still of unknown origin in low-incidence countries in 2009. When these cases of unknown origin were excluded, the relative proportions of foreign-born and national-born cases appeared stable in low-incidence countries for all paediatric age-groups during the period (Figure 5).

Classification and bacterial confirmation of cases

From 2000 to 2009, 76.7% of the reported cases had been previously untreated; this proportion was higher (89.9%) in the last three years, 2007 to 2009. For countries that reported on previous treatment, the proportion of previously treated remained stable during the study period (range: 1.1%-2.1%). In contrast, the proportion of unknown status regarding previous treatment decreased.

Pulmonary TB accounted for 53.4% of all paediatric TB cases, but only 14.1% of these were sputum smear-positive. Extra-pulmonary TB accounted for 27.8% of all paediatric cases, of which 64.4% had intra-thoracic or pleural TB. Unknown site of disease was frequent among children overall: 18.4%, with higher proportions for those of foreign compared with national origin. Nevertheless, the proportion with unknown site of disease significantly dropped during the study period (from 33.7% in 2000 to 1.1% in 2009, p<0.001).

Of the paediatric cases reported between 2000 and 2009 (n=39,695), only 42.3% of all paediatric cases were tested by culture; of these 39.9% were culture-positive. During that period, the AAPC in proportion of culture-tested cases increased by 5.9%. Thus, case confirmation after culture was 16.9% among all paediatric cases, although its range varied widely across countries. However, the AAPC in the proportion of culture-confirmed cases increased by 4.5% during the study period. Nevertheless the proportion of culture-confirmed cases in 2009 was still only 19.2%, compared to 14.1% in 2000 (Figure 6).

Drug-resistant TB

The proportion of notified cases for whom drug susceptibility testing (DST) was performed increased from 4.6% of 4,589 cases in 2000 to 9.9% of 3,308 cases in 2009 (p<0.001), but levelled off after 2006. The same trend was seen for the proportion of culture-positive cases with a DST, which increased from 32.3% of 648 in 2000 to 51.4% of 636 in 2009 (p<0.001). Until 2006, there was a steady increase in resistance rates to first-line drugs and isoniazid (Figure 7). However, after 2006, this trend was interrupted, only to re-emerge in 2009 with an increase of 4.0 percentage points to 12.8% for any first-line drug resistance and an increase of 4.9 percentage points to 10.4% isoniazid resistance. Thus, the AAPC for rate of resistance to isoniazid increased by 13.3% from 2000 to 2009 (p<0.001, total: 365 cases). The rates and trends in rifampicin resistance and multidrug resistance increased similarly to those for isoniazid.

Treatment outcome and mortality

Treatment outcome was reported by 23 countries. The overall treatment success for the year cohorts 2002 to 2008 for which outcome data were available during the study period, was 80.5% for all culture-confirmed pulmonary paediatric TB cases (n=2,958). For the seven high-incidence countries (n=1,324), the overall treatment success was 87.3% with an increase from 81.5% in 2002 to 89.4% in 2008 and an AAPC of 1.6%. For the 16 low-incidence countries (n=1,634), the overall treatment success rate was 75.0%. It should be noted, however, that the proportion of cases that were lost to follow-up was high in 2002 to 2008, with as many as 27.6% in 2008 (Figure 8).

During 2000-2009, 1.6% of all culture-confirmed pulmonary paediatric TB cases died: a total of 160 children. High-incidence countries accounted for 76.9% of these deaths.

Discussion

Overall, in the EU/EEA, childhood TB is declining, as is TB in other age groups (see Figure 3). No significant differences in the childhood TB trends compared to the other age groups were observed.
However, the picture changes when looking separately at high-incidence and low-incidence countries (see Figure 4).

In high-incidence countries, over a 10 year period, there has been a decline and/or stabilisation of notifications in all paediatric age groups, with a particularly marked decrease in infants, suggesting a decline in recent transmission. In contrast, these rates have increased in low-incidence countries, but with a large variation over time, in particular for infants.

Separate correlation analyses for high-incidence and low-incidence countries to their five-year AAPC clearly demonstrated that childhood TB trends correlate better to the overall trends in high-incidence countries, compared with low-incidence countries. This could

reflect two different epidemiological scenarios. The poor correlation between childhood and overall rates in low-incidence countries could be attributable to a number of factors. Childhood TB might be particularly sensitive to TB outbreaks in contrast to the overall epidemic trends. Since outbreaks, i.e. isolated events in a non-endemic setting, will not necessarily nor entirely reflect overall disease trends within a country, it is possible that paediatric TB increases due to outbreaks among children might occur against a background of low incidence and stable trends.

In high-incidence countries, where the epidemiological situation of TB is more uniform among the population, paediatric trends will reflect more directly overall TB transmission. In contrast, in low-incidence countries, the impact of foreign-born cases could affect this relationship, particularly if many of the cases are infected before entering the country and are thus unrelated to the local epidemiological situation.

The overall percentage of foreign-born childhood TB cases in the EU/EEA remains low (15.9%). However, in low-incidence countries, it is similar (29%) to that in the United States, where 31% of cases between 1994 and 2007 were attributable to foreign-born children [4]. Nevertheless, this percentage of TB cases among foreign-born children in low-incidence countries has remained stable, whilst the only marked increase in the paediatric population was recorded among national-born children under the age of five years (AAPC 4.4%). A similar observation has been reported previously by a number of EU Member States [7,11], and could be a reflection of children being classified as national-born although born to foreign-born parents, and/or living in a foreign-born household, and thus exposed to a higher transmission risk.

Analysis of bacteriological confirmation of childhood TB cases emphasised that appropriate diagnosis remains a major challenge of childhood TB, even within the EU/EEA. Although microbiologically confirmed cases in this area were frequent when placed in an international context [12,13], the actual percentage of 16.9% signals an urgent need for improvement in microbiological diagnosis of TB in children. This becomes particularly important in view of the threat posed by multi- and extensively drug-resistant TB, and the need to rapidly initiate an appropriate treatment regimen.

Treatment outcome analysis for new pulmonary culture-confirmed childhood TB cases was in line with that reported for the general population [7,14]. However, a better outcome performance in high-incidence countries was also evident. Whether this is attributable to better case management or better reporting, cannot be deduced from the available data.

Our data and analysis have a number of limitations which need to be taken into consideration when interpretating of our results. Despite its comprehensiveness,

TB surveillance in the EU/EEA relies on the quality of the surveillance systems in the Member States. The completeness and quality of external data cannot be measured directly at EU level (TESSy). In particular, the childhood TB data could be biased by over-diagnosis that is not uncommon in certain settings. At present we do not have appropriate data to evaluate quality of diagnostic practices and or sensitivities (commonly known as case detection), and if this differs between high- and low-incidence countries or where it has been constant over time. The variation in quality and case detection of TB surveillance data is assumed on the basis of published peer-reviewed articles on capture–recapture analysis reporting under-notification [15,16]. This could in turn affect an interpretation of the real disease burden. With respect to the analysis of foreign-born versus national-born childhood TB burden, it would have been appropriate to carry out the analysis on disaggregated data, however the lack of reliable population denominators for the foreign-born populations in the EU/EEA made this impossible.

Conclusions
This work represents the first comprehensive attempt at an in-depth analysis of childhood TB epidemiology for the EU/EEA Member States. The data were deliberately presented in an aggregated fashion: it would have been impractical to comment on trends in single Member States because a number of these report very low case loads, affecting the significance of results.

Our findings agree with the international literature on the percentages of paediatric cases and notification rates (with rates peaking during infancy) [4,17]. The overall declining trend also mirrors what is observed in other similar settings [17]. However, if we focus on the low-incidence EU/EEA Member States, the trends are not consistently declining and contradict what is seen in other similar settings, such as the United States, where a constant decline has been recorded since 1994 in both foreign-born and native populations. [4]

The findings make it plausible to assume that within a context of overall epidemiological assessment, childhood TB trends can be used as a monitoring component. The recently launched EU TB monitoring framework proposes the trend in the ratio of TB in children versus adults as an EU/EEA epidemiological indicator [5]. The incidence of TB in children, especially the younger cohorts (under one year of age), is an indirect measure of the level of transmission in the community. Because young children have a much higher rate of primary disease progression, a lower transmission rate should be reflected in a decrease in the ratio of notification rates in children over adults. These features make childhood TB epidemiology worth exploring for the purpose of epidemiological monitoring.

The concept that childhood TB cases represent the results of recent transmission and infection is important from an advocacy point of view. Some authors

have highlighted that complete TB elimination in the low-incidence European setting in not feasible because in our globalised times, importation of both active and latent cases might hamper local elimination. Even if this were true, elimination of transmission, particularly to children, within the borders of the EU should remain an achievable commitment.

Last but not least, it should be emphasised that surveillance data point towards suboptimal diagnostic practices in childhood TB in the EU/EEA. The low proportion of bacteriological confirmation of cases seriously limits childhood TB control and appropriate clinical management of cases. This, along with the need of interrupting transmission of TB from adults to children, needs to be addressed in order to progress towards elimination and to ensure the highest standards of TB care and control in a highly vulnerable population.

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Assessing BCG vaccination coverage and incidence of paediatric tuberculosis following two major changes in BCG vaccination policy in France

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We report data on BCG vaccination coverage and paediatric tuberculosis (TB) incidence collected after the disappearance of the multipuncture device for BCG vaccination in January 2006 and the shift from universal to targeted vaccination in July 2007 in France. Vaccination coverage estimates in children for whom BCG is recommended allow assessing whether the recommendations are followed by doctors and/or accepted by the target population. In January and February 2006, BCG sales to the private sector in Île-de-France region were 74.2% and 41.3% of the ones for the same months the previous year. Total sales in 2006 amounted to 57.3% of those in 2005. Coverage decreased immediately after withdrawal of the multipuncture device, and remained generally insufficient in high risk children in the following years. However, the impact on paediatric TB incidence in 2008 seems very limited, although the duration of follow-up is still short. Training of doctors in intra-dermal vaccination and communication on the new vaccination policy should be strengthened.

Background

In France, until July 2007, primary BCG immunisation was mandatory for children before entering daycare centres or being taken care of by child minders and at the latest at the age of six, when school becomes compulsory. BCG was also recommended in the first month of life, for high risk children [1]. Until the end of 2005, the vaccine was applied by using a multipuncture device (Monovax, Sanofi Pasteur MSD, France), whereby several needles simultaneously introduced the vaccine intradermally. In January 2006, this multipuncture device was removed from the French market and replaced by an intradermal Bacille Calmette-Guérin (BCG) device (Statens Serum Institut - SSI, Denmark), the technique recommended by the World Health Organization (WHO) [2]. The main reason for the withdrawal was that the production process of Monovax did no longer fulfill the standards required by the European regulation bodies [3]. Taking into account the important efforts needed to respond to these requirements and considering that France was one of the last

countries in Europe to use the multipuncture technique [4], the manufacturer decided to cease the production. However, the difficulty of untrained medical staff to use the intradermal technique in young infants as well as its less favourable safety profile compared with the multipuncture technique, led to an estimated 54% decrease in BCG coverage, despite the still mandatory vaccination [5].

In July 2007, the mandatory BCG vaccination for all children was replaced by a strong recommendation to vaccinate only children considered at high risk of tuberculosis (TB) [6]. The decision to shift from universal to targeted vaccination was taken by the French government after a consultation of bodies involved in TB control and a multidisciplinary assessment of the impact of a vaccination policy change on the incidence of TB and the social acceptability of a BCG vaccination strategy targeting high risk children [7]. The main rationale for the change was the decreasing incidence of TB in France from more than 30,000 cases notified in 1972 to about 6,000 in 2005 and the heterogeneity of risk of disease [7]. On the one hand, the incidence of the disease had significantly decreased and was very close to the threshold values proposed by the International Union Against Tuberculosis and Lung Diseases for possible discontinuation of BCG vaccination [7,8], on the other, the incidence of TB was much higher in some groups of the population. For example, the incidence of TB in people born abroad (foreign-born) was eightfold higher compared with those born in France (41.5 per 100,000 population versus 5.0) in 2005 [9]. Therefore, target groups for BCG vaccination are mainly children who were born, or whose parents were born, in TB-endemic countries or with a family history of TB. The high risk group also includes children, irrespective of the country of birth, living in the two French regions with the highest incidence of TB: French Guiana, a French overseas department (22.6 per 100,000 in 2008) and Île-de-France, a French mainland region (17.9 per 100,000 in 2008) [10]. The 2007 BCG vaccination policy recommends vaccination of the target groups as soon as possible after birth, with a

catch-up vaccination for non-vaccinated at risk children aged 15 years or less [6].

Following these changes, an estimation of BCG vaccination coverage in the group of children targeted by the new recommendations was needed, in order to assess whether they had been put into practice. Until 2007, BCG vaccination coverage was routinely estimated by analysing the information in health certificates of all children and filled-in by doctors in early childhood [11]. However, this method was no longer appropriate after the new recommendations because coverage was to be evaluated only for a fraction of children. We therefore used alternative approaches to perform an evaluation which aimed to assess the impact of the changes that occurred in 2006-2007 on BCG coverage in target groups. In this paper, we report both these results and the trends of paediatric TB incidence after the 2006-2007 changes and discuss possible implications for TB control.

Methods
Estimation of tuberculosis vaccination coverage from BCG sales, 2005-2009
Vaccine sales to the private and public sector are used by the French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS) as an indirect indicator of vaccination coverage in France. The Groupement pour l'Elaboration et la Réalisation de Statistiques (GERS, Partnership to Collect and Prepare Statistics) compiles data from the pharmaceutical industry every month and provides data of BCG sales to private pharmacies, which cover more than 90% of vaccine sales outside Île-de-France and about 60-70% of sales in Île-de-France. Sales to the public sector, mainly to maternal and child health clinics (MCHC), are provided by Sanofi Pasteur MSD which markets SSI BCG in France.

For Île-de-France, where BCG vaccination is recommended for every child, vaccination sales grossly reflect vaccination coverage. We estimated vaccination coverage based on the number of vaccines sold and assuming that one vial of SSI BCG is used to vaccinate one child in the private sector and an average of 1.5 children in the public sector (D. Lévy-Bruhl, personal communication, Oct 2006). We report BCG sales after 2005 by month, compared with the respective month of 2005, which was taken as reference, since up to the end of 2005, virtually all children were vaccinated before reaching six years of age. It was not possible to compare data for earlier years because they included revaccination which was discontinued in 2004.

Outside Île-de-France, BCG sales cannot be used to estimate vaccination coverage trends because the number of children in the target population is unknown and the decrease in vaccine sales mainly reflects the decrease in the number of children for whom vaccination has been recommended since July 2007.

Survey in the private sector, February 2008
We performed a retrospective cross-sectional survey among general practitioners and paediatricians. This survey was performed seven months after the change in vaccination policy, with the objective of providing a timely follow-up of the new recommendations for the Ministry of Health. The targeted general practitioners and paediatricians belonged to a well organised network of physicians who are particularly aware of recent changes in the field of vaccination (convenience sample). Thus they form a special group which is not representative for physicians in general. They were asked to fill in a structured online questionnaire where demographic information, information on previous BCG vaccination and reasons for non-vaccination were

FIGURE

Percentage of Bacille Calmette-Guérin (BCG) sales to private pharmacies in Île-de-France between January 2006 and December 2009 compared with the same month of 2005
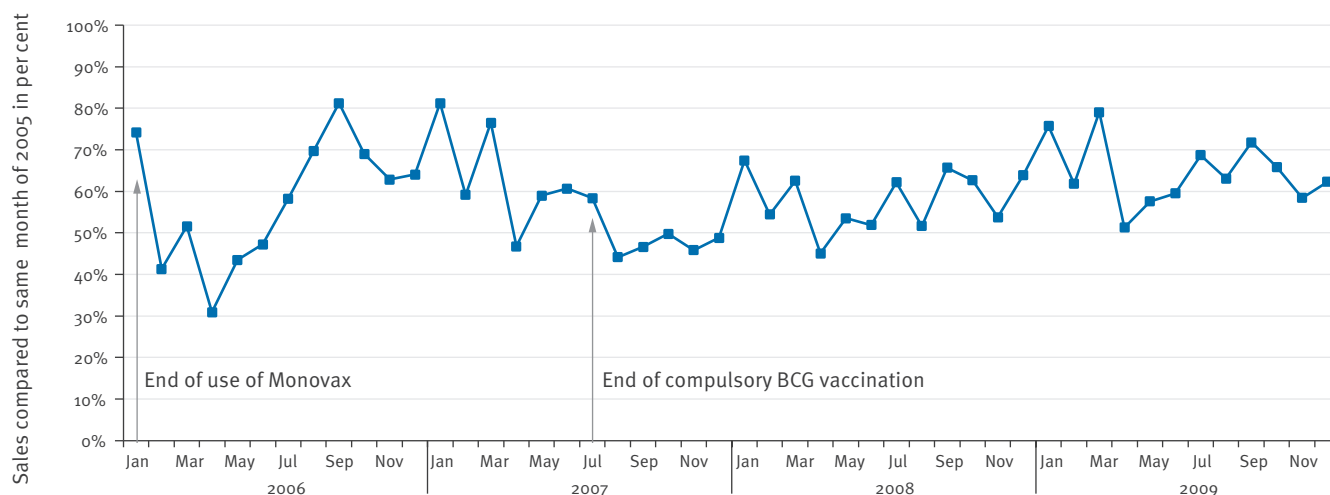
Note: BCG sales to private pharmacies cover more than 90% of vaccine sales outside Île-de-France and about 60-70% of sales in Île-de-France.
Source: Groupement pour l'Elaboration et la Réalisation de Statistiques (GERS)

collected. Each doctor was asked to recruit, during his or her medical consultation, at least six consecutive at risk children aged two to seven months (born after BCG policy change) and eight to 23 months (born after withdrawal of Monovax and before BCG policy change). This stratification was made in order to estimate vaccination coverage separately in the two age groups. We allowed a two months delay to give a child the chance to be vaccinated and set a lower age limit of two months because this is the usual starting age for vaccinations in France. The full methodology, results and limitations of this survey are reported elsewhere [12].

Survey in the public sector, May 2009

We performed a retrospective cross-sectional survey in a random sample of at-risk children born after the change of vaccination policy i.e. after July 2007, and recruited at MCHC by physicians during medical consultation. This survey was conducted under the assumption that children taken care of by the public sector were likely to have a different coverage i.e. higher coverage than children vaccinated in the private sector. It would therefore complete the picture of vaccination coverage in the at-risk population in France. The full methodology and results of this survey are reported elsewhere [13]. Children were selected through a two-stage random sampling in Île-de-France (first stage: MCHC; second stage: patients) and a three-stage random sampling outside Île-de-France, where we first selected a district and then MCHC within districts. We stratified children in two age groups to see whether younger children, aged two to 12 months at the time

TABLE 1

Number of children vaccinated with Bacille Calmette-Guérin (BCG) in the private and public sector, Île-de-France, 2005-2009

	Number of children vaccinated					Variation 2009-2005
	2005	2006	2007	2008	2009	
Private sector						
Monovax	158,108	0	0	0	0	
BCG SSI	11,796	97,623	94,611	97,772	108,905	
Total	169,904	97,623	94,611	97,772	108,905	-36%
Public sector						
Monovax	47,733	0	0	0	0	
BCG SSI[a]	16,959	63,705	53,548	53,739	57,989	
Total	64,692	63,705	53,548	53,739	57,989	-10%
Total	**234,596**	**161,328**	**148,159**	**151,511**	**166,894**	**-29%**

BCG: Bacille Calmette-Guérin; SSI: Statens Serum Institut.
[a] Number of children based on assumption of 1.5 children vaccinated per vial of BCG SSI in the public sector.
Source: Groupement pour l'Elaboration et la Réalisation de Statistiques (GERS), Sanofi Pasteur MSD.

TABLE 2

Bacille Calmette-Guérin (BCG) vaccination coverage in Île-de-France (n=286) and outside Île-de-France (n=122) in children at risk for whom BCG is recommended, data from general practitioners and paediatricians, France, February 2008

Age (months)	Children at risk living in Île-de-France (n=286)		Children at risk living outside Île-de-France (n=122)		Children at risk living in France (n=408)	
	N	Coverage*	N	Coverage*	N	Coverage*
2-7	144	51.4%	64	39.9%	208	44.8%
8-23	142	79.8%	58	82.8%	200	81.1%
Total	**286**	**67,4%**	**122**	**56.8%**	**408**	**62.1%**

* Proportion adjusted for age, speciality and region of residency of the doctor.
Source: InVS (Institut de Veille Sanitaire, Saint Maurice, France) ACTIV.

TABLE 3

Bacille Calmette-Guérin (BCG) vaccination coverage in Île-de-France (n=481) and outside Île-de-France (n=375) in children at risk for whom BCG is recommended, data from maternal and child health clinics, France, May 2009

Age group	Children at risk living in Île-de-France (n=481)		Children at risk living outside Île-de-France (n=375)		Children at risk living in France (n=856)	
	Coverage	95%CI	Coverage	95%CI	Coverage	95%CI
2-12 months	86.7%	75.0 - 93.4	53.1%	44.6 - 61.5	66.2%	59.1 – 72.7
13-23 months	95.0%	86.3 - 98.3	75.5%	62.5 - 85.1	83.0%	74.2 – 89.2
Total	**89.8%**	**81.4 - 94.7**	**61.7%**	**53.8 - 69.0**	**72.6%**	**66.3 - 78.0**

CI: Confidence interval.
Source: InVS (Institut de Veille Sanitaire, Saint Maurice, France).

of the survey, were better vaccinated than older children, aged from 13 to 23 months, and hence to evaluate whether compliance with new recommendations was improving over time. The information collected was similar to that of the survey in the private sector.

For both the private and the public surveys, as well as for TB incidence, we present figures separately for Île-de-France, as this is the only region of mainland France where BCG remains recommended for all children.

Childhood tuberculosis incidence in 2008

TB is mandatorily notifiable in France and case-based data are collected and analysed at the Institut de veille sanitaire (InVS). Patients are notified if they have clinical and/or radiological signs of TB and are treated, irrespective if TB was confirmed by culture or not. We restricted our analysis to TB cases aged less than three years-old in 2008, since they were born after the withdrawal of Monovax and thus the impact of the changes is likely to be observed in this group. We estimated both the proportion of cases and severe cases, i.e.meningitis and miliary TB, that belong to the at-risk population and their vaccination status. Information about miliary TB and at-risk status for children aged less than 15 years are collected only since 2007 when the mandatory notification form was modified.

Results
Estimation of children vaccinated from BCG sales

Withdrawal of Monovax in January 2006 led to an immediate and sharp decrease in BCG sales. In January and February 2006, BCG sales to the private sector in Île-de-France were 8,435 and 5,196 vaccines respectively (2005: 11,374 and 12,583 vaccines), 74.2% and 41.3% of those for the same months the previous year (Figure). Overall, total sales in 2006 amounted to 57.3% of those in 2005. This sharp decrease preceded the policy change in July 2007. In 2009, the estimated number of children vaccinated with BCG was 29% lower than in 2005, but showed a slight increase when compared with 2006, 2007 and 2008 when the decrease was 31%, 37% and 35%, respectively (Table 1). The decrease from 2005-2009 was significantly higher in the private (-36%) than in the public (- 10%) sector (p<0.001).

Survey in the private sector, February 2008

Among children in whom BCG was recommended and who were born after the change in vaccination policy (two to seven months-old), 51.4% had been vaccinated in Île-de-France and 39.9% outside Île-de-France seven months after this change. Vaccination coverage was higher in children eight to 23 months-old and born between the withdrawal of Monovax and the change in vaccination policy (79.8 and 82.8 % respectively in and outside Île-de-France) (Table 2).

Survey in the public sector, May 2009

Vaccination coverage in children at risk was overall 72.6% (95% confidence interval (CI): 66.3 – 78.0). It was 89.8% (95% CI: 81.4 – 94.7) in Île-de-France and 61.7% (95% CI: 53.8 – 69.0) outside Île-de-France (Table 3). Children, aged 13-23 months, had higher vaccination coverage compared with children aged two to 12 months, however this difference was only statistically significant outside Île-de-France (p<0.01).

Tuberculosis incidence in 2008

In 2008, 105 newly diagnosed cases of TB were reported in France in children aged less than three years (Table 4). In Île-de-France, 43 new cases were reported, a figure comparable with the average annual number of cases for the years 2000-2005 (45 cases) (InVS, unpublished data). No case was reported in children aged less than three years in French Guiana in 2008. The 62 cases reported outside Île-de-France in 2008, represent an increase compared with the average annual number of cases for the years 2000-2005 (46 cases). Of the 105 newly diagnosed cases in children aged less than three years reported in 2008, 75% (79 cases) belonged to the at-risk group: 100% (43 cases) in Île-de-France and 58% (36 of 62 cases) outside Île-de-France. Twenty of 43 and five of 36 cases were vaccinated respectively. In Île-de-France, five of 43 cases were not vaccinated and for 18 vaccination status was unknown; outside Île-de-France 23 of 36 cases were not vaccinated and information was not available for eight. In 2008, three miliary TB and no TB meningitis cases were detected in under three year-olds. Of these three cases, two were at risk (family history of TB for one child and father born in a TB endemic country for both) and were unvaccinated. The vaccination status of the third child was unknown. These figures are very close to those reported in the three previous years. In

TABLE 4

Number of tuberculosis cases reported in children aged less than three years old by region, France (French Guiana not included), 2000-2008

Region	Year									
	2000	2001	2002	2003	2004	2005	2006	2007	2008	Average 2000-2005
Île -de-France	60	41	42	44	43	39	31	35	43	45
Outside Île-de-France	36	26	51	59	44	60	49	62	62	46
Total	**96**	**67**	**94**	**103**	**87**	**101**	**82**	**98**	**105**	**91**

Source: InVS (Institut de Veille Sanitaire, Saint Maurice, France).

2005, three TB meningitis cases, one vaccinated, one non-vaccinated, one with unknown vaccination status were notified; in 2006 there were four TB meningitis cases, two vaccinated, two unvaccinated and in 2007 there were two vaccinated milliary TB cases and one non-vaccinated meningitis/milliary TB case.

Discussion

Estimates of BCG vaccination coverage in France, after the withdrawal of the multipuncture device for BCG (Monovax) in 2006 and the shift from universal vaccination to immunisation of children at risk in 2007, are essential to evaluate the new BCG vaccination policy. Vaccination coverage estimates in children in whom BCG is recommended allow assessing whether recommendations are followed by doctors and/or accepted by the target population. The number of newly diagnosed TB cases in small children informs on the possible impact of BCG coverage on the disease incidence. Our coverage figures, provided by three different sources of information, each with their own strengths and limitations [12-14], indicate insufficient vaccination coverage in children at risk of TB. This is especially true outside Île-de-France where incidence is very low and for children followed in the private sector where the majority of childhood vaccinations are performed. Our figures show the greatest decrease in vaccination coverage after the shift from the multipuncture device to intradermal BCG application. The emphasis given in 2007 to vaccination of high risk children did not allow catch up for this decrease. The insufficient coverage indicates that further efforts are needed to improve implementation of vaccination against TB. Information from our previous surveys [12,13] shows that target groups are not well identified and indications of vaccination are not always understood by doctors, and also that doctors may have difficulties in using the intradermal technique. This was especially the case in low incidence areas i.e. outside Île-de-France, where practitioners are rarely confronted with at-risk children and therefore may lack practice of intradermal vaccination. To tackle this, their respective knowledge and practice should be strengthened through information about the new French BCG vaccination policy and on-going training in intradermal BCG vaccination.

An important question is whether the insufficient vaccination coverage will affect the incidence of TB and whether France is likely to experience a similar situation to countries such as Sweden, where universal BCG vaccination was discontinued in 1975 and replaced by a targeted vaccination [15,16]. After this change, BCG vaccination coverage in target groups remained low in Sweden (under 5%), leading to a fifteenfold increase in TB incidence in children born to parents of foreign origin: from 2.6 per 100,000 in 1975 to 39.5 in 1980. An increase in vaccination coverage in 1985 close to 80%, led to a decrease in incidence in this group, although it was still higher than when BCG was given to all children.

Our data suggest a limited impact of the changes in BCG vaccination on the incidence of paediatric TB in France. Compared with 2005, when BCG coverage was close to 100%, the number of cases in under three year-olds is almost unchanged (105 cases in 2008 vs. 101 cases in 2005). The slight increase of 2.3% in TB cases in 2008 when compared with 2007, could be due to a real increase in the number of newly diagnosed TB cases, but could also reflect an improvement of the TB control programme which was reinforced in 2007, with a better identification and reporting of cases. Moreover, the slight increase in cases observed in 2008 affected only the Île-de-France region where the BCG coverage is better than elsewhere in France. This does not support a direct relationship between vaccination coverage and incidence of TB. Also, the number of meningitis/miliary TB cases remained very low in this age group.

The decision to change the vaccination strategy and the choice for universal or targeted vaccination or total interruption needs to be made after a risk-benefit analysis where the expected increase in the number of TB cases is weighted against the number of adverse vaccine events prevented by the reduction in vaccinations [17]. In France, the shift to a targeted strategy was made after an evaluation showing that if immunisation was restricted to children at risk with stable vaccination coverage in this population, this would result, 15 years after the change, in about 80 additional TB cases per year in the no longer vaccinated low risk population. This increase had to be balanced against the prevention of an estimated 10 disseminated BCG infections and 260 cases of BCG associated lymphadenitis [7,18]. These numbers would increase to around 200 additional TB cases, also affecting children at risk, and prevention of 12 disseminated BCG infections and 280 cases of lymphadenitis if coverage decreased to 50%. The slight increase in the number of cases outside Île-de-France in our data, of which the majority are not vaccinated, could reflect the anticipated impact of the discontinuation of BCG vaccination in low risk children. It is however too early to assess the full consequences of the low BCG coverage.

Conclusion

Measuring vaccination coverage is a key issue in public health surveillance, and following this indicator after a change in vaccination policy informs on whether the new policy is satisfactorily implemented. As other countries in Europe [19], France has reviewed its national BCG policy in 2007 and after having changed to intradermal BCG vaccination in 2006 already. Our assessment shows that BCG coverage is insufficient after these changes, although it is too early to assess the full consequences of this situation. The rather stable incidence of TB cases in children under three years of age in Île-de-France and the very low number of severe cases reported in 2008 is reassuring, but the duration of follow-up is very limited. We need to remain vigilant and keep in mind that TB in high risk groups is still a challenge in France, given the European context where TB remains an important public health issue [20].

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Assessing the effect of foreign travel and protection by BCG vaccination on the spread of tuberculosis in a low incidence country, United Kingdom, October 2008 to December 2009

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The contribution of travel to high incidence countries and the impact of the discontinuation of universal Bacillus Calmette–Guérin (BCG) vaccination to the recent rise in tuberculosis (TB) in the United Kingdom remain unclear. An outbreak in a college presented an opportunity to assess these. A cohort of students answered a questionnaire assessing risk factors for TB. Participants were screened with an interferon gamma release assay (IGRA). Unadjusted and adjusted odds ratios (OR) were calculated using logistic regression. Among 2,284 students, 400 (17.5%) were diagnosed with TB infection. A higher risk was noted for travel to a high incidence area in the past two years (OR: 1.39; 95% confidence interval (CI): 1.04–1.89) and among those with the greatest exposure to the index case (OR: 3.94; 95% CI: 2.60–5.97). There was no association between BCG and risk of infection (OR: 1.05; 95% CI: 0.80–1.39). The lack of a protective effect by BCG on TB infection supports the discontinuation of universal vaccination. The association with foreign travel suggests the need to assess the cost-effectiveness of serial IGRA testing and treatment of positive persons among returning travellers.

Introduction

Countries with a low tuberculosis (TB) incidence, especially those heading towards elimination of the disease, have a policy of identifying individuals with presumed latent TB infection and offering prophylactic treatment [1,2]. In general, the policy prioritises the screening of recently exposed persons due to a higher risk of progression to active TB, often using a 'stone in the pond' approach [3]. This, together with the prompt diagnosis and adequate treatment of active cases, forms the cor-nerstone of TB control policy in countries with a low TB incidence.

The major burden of TB in many low-incidence high-income countries is in immigrants, their descendants and in particular high-risk groups such as the homeless, drug users and prisoners [4-6]. By contrast, for the rest of the population in these countries, the risk of TB remains low outside of outbreaks. The higher risk among the foreign-born is thought to be a function of infection prior to immigration and, to a lesser extent, travel to high TB incidence countries and transmission within immigrant communities. It is not clear however, to what extent each of these factors increases the risk of TB.

The Bacillus Calmette–Guérin (BCG) vaccine is the only preventive immunisation currently available against TB. Evidence suggests that it is effective in preventing meningitis and miliary TB in young children [7,8]. In the United Kingdom (UK), there is also evidence that BCG protects against pulmonary TB among school-aged children [9,10]. Most countries, including those with low TB incidence, have a BCG vaccination policy that may be universal or targeted. For low-incidence countries, a policy switch from universal to targeted BCG vaccination was supported by criteria put forward by the International Union Against Tuberculosis and Lung Disease in the 1990s [11]. Several countries with a low TB incidence, including the UK [12], have now changed their BCG vaccination policy to target high-risk groups. To date, the effect of this policy change has not been evaluated in the UK. In the United States (US), the poor efficacy of BCG following initial trials and its confounding effect on tuberculin skin testing led to the

exclusion of BCG from the immunisation schedule [13]. The US guidelines allow the use of BCG in specific circumstances such as in children who cannot be removed from the source case. Arguably, if BCG is found to be efficacious against latent infection [14], and a person is travelling to a country with a high TB incidence and significant levels of anti-TB drug resistance, it may be justifiable to use the same rationale to offer BCG.

Following the diagnosis of sputum smear-positive cavitatory pulmonary TB in a college student, the local Health Protection Unit, working closely with the Respiratory Medicine Service and Primary Care Trust, screened 2,284 students and 299 staff members with an interferon gamma release assay (IGRA) and, where appropriate, chest X-ray examination. The students at the college were evenly divided in two groups: the age group vaccinated as part of the universal school-age BCG vaccination policy in the UK, and the group who reached the relevant age after the policy was changed. The investigation identified 19 cases of active TB. This outbreak presented an opportunity to assess the relative contribution of foreign birth, recent travel to a high incidence setting, community transmission (based on contact with a TB case and non-white ethnicity) and the protective effect of BCG vaccination.

We formed the hypotheses that, in addition to place of birth and exposure to the index case, travel to a high incidence country and BCG vaccination may predict latent infection as measured by a positive IGRA. The BCG policy change and a well-defined cohort exposed to a known infectious case allowed us to test these hypotheses.

Methods
Participants
The study population consisted of all students attending the college during daytime. All participants were aged over 16 years. Staff who directly taught these students were also screened. Between October 2008 and December 2009, students, friends of the index case and staff at the college were interviewed. It took a long time to complete the examination of all contacts because we used the 'stone in the pond' approach, where a small proportion of contacts were screened and further circles for testing were identified if the level of infection found was higher than expected, until eventually all exposed students were screened.

Ascertainment of risk factors
Interviews were used to collect information from all 2,284 students about:

- place of birth, and if born abroad, year of entry in the UK,
- previous contact with TB in the household,
- age,
- sex,
- ethnic group, broadly classified as Asian, White, Black, mixed or other,

- history of travel to a country outside western Europe, North America and Australasia in the preceding two years,
- history of BCG vaccination ascertained through the inspection of a scar or reliable recollection of vaccination,
- symptoms suggestive of TB.

The incidence of TB in the local area in 2007 was 4 per 100,000 with most cases occurring in non-White ethnic groups (T. Matthews, personal communication, Jan 2009). Based on this, we used non-White ethnicity as a marker of community risk of TB. At the same time a blood sample was drawn from each participant for IGRA testing. IGRA tests have been shown to have at least an equivalent level of diagnostic accuracy for latent TB infection compared with the tuberculin skin test (TST) [15]. Emerging evidence suggests that the predictive value of IGRAs for the development of active TB is also higher than [16] or equivalent to TST [17,18].

Clinical and laboratory investigation
Contacts were investigated in concentric circles of decreasing exposure in three groups based on exposure times over the 17 days that the index case was at the college while infectious. Group 1 was screened between November 2008 and January 2009 and included students who shared classrooms with the index case with cumulative exposures of more than two hours, or friends of the index case. Group 2 was screened in February 2009 and included students who attended the same general study class as the index case, with cumulative exposure time between one and two hours in a large hall setting. Group 3 was screened between July and August 2009 and included the rest of the college. Following the first two circles of screening, 270 students whose initial IGRA test had been negative or indeterminate were tested again.

Two IGRA tests were used, Quantiferon-TB Gold in tube test (QGIT, Cellestis) and T-Spot TB (Oxford Immunotec). For the majority of participants, the QGIT test was used. A small proportion of individuals were tested with T-Spot TB, and those with a negative result were retested using QGIT during the third circle of screening. Both IGRA tests use the region of difference-1 antigens early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP 10), and in addition QGIT includes TB7.7, to stimulate T-effector cells specific for *Mycobacterium tuberculosis* to produce gamma-interferon. Those with a positive IGRA result from any screening round were recalled for a chest X-ray examination and clinical review at a respiratory medicine clinic. Preventive therapy was offered to individuals younger than 35 years with a positive IGRA result but no evidence of active TB, according to national guidelines [1]. No formal ethical review was required as this was done as part of a service response.

Table 1

Characteristic[a] — Characteristics of the student population, tuberculosis college outbreak, United Kingdom, October 2008–December 2009 (n=2,284)

Characteristic[a]	Category	n (%)
Demographic		
Age, median (IQR)		17.8 (17.3–18.5)
Sex	Male	1,055 (46.2)
	Female	1,229 (53.8)
Exposure	Group 1[b]	131 (5.7)
	Group 2	244 (10.7)
	Group 3	1,909 (83.6)
Household history	Yes	82 (3.6)
	No	2,162 (96.4)
Place of birth	UK	2,089 (91.6)
	Not UK	192 (8.4)
Travel in the last two years[c]	Yes	422 (19)
	No	1,799 (81)
Ethnicity	White	2,061 (90.2)
	Asian	170 (7.4)
	Black	10 (0.4)
	Mixed	29 (1.27)
	Other	14 (0.6)
Clinical		
BCG-vaccinated	Yes	1,067 (49.6)
	No	1,082 (50.4)
IGRA	Positive	400 (17.5)
	Negative	1,884 (82.5)
Chemoprophylaxis	Yes	349 (15.7)
	No	1,912 (84.3)

BCG: Bacillus Calmette–Guérin; IGRA: interferon gamma release assay; IQR: inter-quartile range; UK: United Kingdom.

[a] For participants for whom information on the respective variable was available.

[b] This number is different from the Figure 2 as it only includes students (not friends).

[c] Countries travelled to include Bangladesh, China, India, Russia and several countries in Sub-Saharan Africa.

Figure 1

Active tuberculosis cases, college outbreak, United Kingdom, October 2008–December 2009 (n=20)
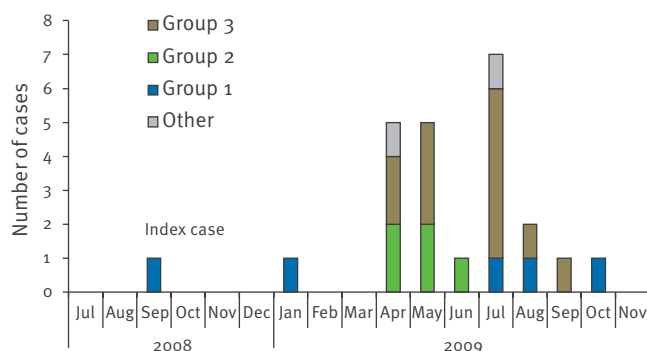
Group 1: cumulative exposure ≥ 2h in classroom groups to the index case and friends of the index case. Numbers here differ from those in the Tables, where only students are taken into account .

Group 2: students exposed 1–2h in a large hall setting.

Group 3: rest of the college. Other: screened in Groups 2 and 3 but diagnosed subsequently by their family doctor or local hospital.

Definitions

Participants were considered to have TB infection if they had a positive IGRA test or had active disease.

Statistical methods

Data were entered into a specifically designed database in Microsoft Access. Proportions were calculated for categorical variables and medians with inter-quartile ranges for continuous variables. We used univariable and multivariable logistic regression to investigate factors associated with a positive IGRA result as a proxy for latent infection. All variables considered a priori to be risk factors for TB were included in the model. We investigated the interaction between risk factors for TB using the likelihood ratio test. Data were analysed using the statistical software Stata 11.

Results

The median age of students was 17.8 years (interquartile range (IQR): 17.3–18.5 years) and 1,055 (46.2%) were male (Table 1). Characteristics of the students are summarised in Table 1. Among the students, 49.6% were BCG-vaccinated, 90.2% were of white ethnicity, and 18.8% had travelled within the last two years to a high incidence country, including Bangladesh, China, India, Russia, and several countries in Sub-Saharan Africa.

Figure 2

Proportion of students with latent tuberculosis infection and active tuberculosis by screening circles, college outbreak, United Kingdom, October 2008–December 2009 (n=2,284)
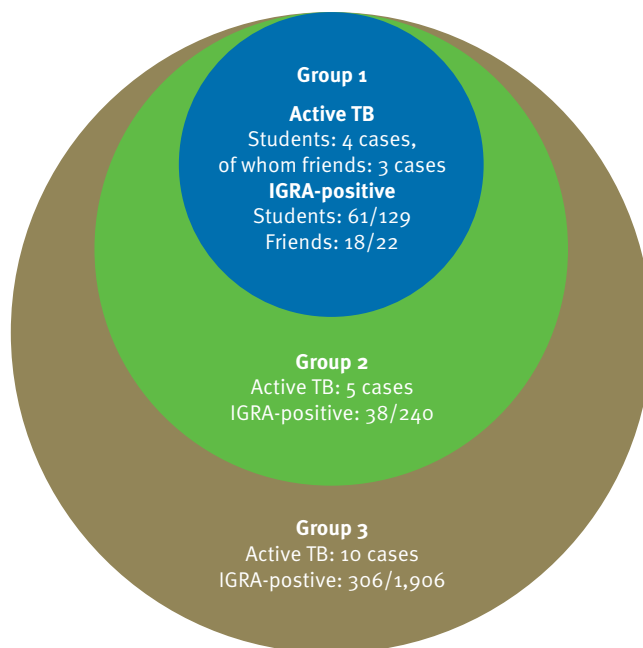
IGRA: interferon gamma release assay; TB: tuberculosis.

Group 1: cumulative exposure ≥ 2h in classroom groups to the index case and friends of the index case. Nine of the 22 friends were also students. Numbers here differ from those in the tables, where only students are taken into account.

Group 2: students exposed 1–2h in a large hall setting.

Group 3: rest of the college.

The characteristics of the 19 active TB cases are described in detail elsewhere [19]. In brief, Figure 1 shows the distribution of cases over time with seven of the eight cases confirmed by bacterial culture sharing an identical 24 loci myeobacterial interspersed repetitive unit variable number tandem repeat pattern (42234 2742511334 422423255) with the index case.

The median age of all the staff was 46.8 years (IQR: 38.5 to 55.3 years), and 114 (38.1%) were male. Of 299 staff members, 48 (16.1%) had a positive IGRA test. No active TB cases were diagnosed among staff members.

Characteristics of and factors associated with TB infection among students

Of the 2,284 students screened, 400 (17.5%) had evidence of TB infection. A further five friends had a positive IGRA test (shown in Figure 2) but were not included in this analysis as they were not students at the college. Figure 2 shows the number of individuals with a positive IGRA result including those with active TB in each circle of screening. The proportion of participants positive in the first, second and third circle of screening were 49.6%, 15.8% and 16.0% respectively. In addition, 11 of 270 students converted from an initial negative to a positive IGRA result in the third round of screening. The index case had 22 friends who were identified as close contacts, 16 of whom also attended the same college. Thirteen of those 16 were positive. Five of the six non-college friends had a positive IGRA result. All 400 students were offered preventive treatment according to national guidelines.

In the univariable analysis, being male and/or having a history of travel to a high-incidence country in the last two years were both positively associated with an increased risk of a positive IGRA result (Table 2). A sub-analysis conducted with only UK-born individuals did not change the outcome (data not shown). Being of white ethnicity and/or being in exposure Groups 2 or 3 were both associated with a lower risk of a positive IGRA result. In the fully adjusted model, being male (odds ratio (OR): 1.28; 95% confidence interval (CI): 1.02–1.62; p=0.035), being more exposed (exposure Group 1 compared to Group 3) (OR: 3.94; 95% CI: 2.60–5.97), and having a history of travel to a high incidence country in the last two years (OR: 1.39; 95% CI: 1.04–1.89; p=0.028) remained associated with an increased risk of being infected at statistically significant level (Table 2). There was no evidence of a protective effect of BCG vaccination on TB infection (OR: 1.05; 95% CI: 0.80–1.39) and no statistically significant evidence of interaction between any of the risk factors.

Discussion

This study found a significant association between travel to high-incidence countries and the risk of latent TB infection among students. As expected, students in close contact with the index case were more likely to have evidence of latent infection. BCG vaccination did not have an effect on TB infection among the student population.

The level of latent infection found is higher than would be expected in a low incidence area. Although the incidence of TB has increased in the UK over the last two

Risk factors for tuberculosis infection[a] among students, college outbreak, United Kingdom, October 2008–December 2009 (n=2,284)

Characteristic		n (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)	p value[b]
Age, median (IQR)		17 (17-18)	1.01 (0.88-1.17)	1.04 (0.87-1.24)	0.694
Sex	Female	192 (15.8)	1	1	
	Male	209 (19.9)	1.32 (1.06-1.64)	1.28 (1.02-1.62)	0.035
Exposure	Group 1	58 (47.1)	4.84 (3.35-6.98)	3.94 (2.60-5.97)	
	Group 2	38 (15.8)	0 (0.13-0.36)	0.84 (0.55-1.29)	
	Group 3	306 (16.5)	1	1	0.001
Household history	No	379 (17.6)	1	1	
	Yes	16 (19.5)	1.13 (0.65-1.98)	1.41 (0.79-2.53)	0.247
Place of birth	Not UK	41 (21.3)	1	1	
	UK	357 (17.2)	0.77 (0.53-1.10)	1.05 (0.61-1.81)	0.852
Travel in last 2 years	No	299 (16.7)	1	1	
	Yes	91 (21.6)	1.38 (1.06-1.79)	1.39 (1.04-1.89)	0.028
Ethnicity	Non-White	51 (22.9)	1	1	
	White	349 (17.1)	0.69 (0.50-0.97)	0.84 (0.51-1.37)	0.491
BCG-vaccinated	No	185 (17.2)	1	1	
	Yes	186 (17.5)	1.02 (0.81-1.28)	1.05 (0.80-1.39)	0.723

BCG: Bacillus Calmette-Guérin; CI: confidence Interval; IQR: interquartile range; OR: odds ratio; UK: United Kingdom.

[a] Tuberculosis infection includes all students with a positive IGRA and all students with active tuberculosis. The numbers therefore differ from the Table 1 which includes only IGRA positives.

[b] p values derived using likelihood ratio tests.

decades [20], the rate of active TB identified in this college is several times higher than the rate for England in the equivalent age group. Indeed, in the preceding six years in the local Health Protection Unit area, only 10 people aged 16 to 20 years were diagnosed with TB. The proportion of students with latent infection in this college was similar to that observed in previously reported school outbreaks in the UK [21,22]. These other outbreaks occurred in schools with a high ethnic minority population where the high proportion with latent infection could, at least in part, be explained by a high background rate. This is unlikely in the setting described here as the proportion of ethnic minorities in the local population was very low. The low proportion of non-White ethnicity may also explain the lack of association with TB in the regression model. It is possible that in addition to the index case, other pulmonary TB cases within the school, possibly the smear-negative culture-positive cases, contributed to the transmission [23]. Figure 1 suggests this explanation is possible but does not prove it. An alternative explanation is that the index case was particularly infectious. Eighteen of 22 friends of the index case were infected, suggesting high infectiousness.

The significant association observed with travel to countries with a high incidence of TB, independent of exposure to the index case, provides an alternative explanation for the higher than expected rate of latent infection observed in the school. Previous studies have linked travel to high incidence countries with a higher risk of infection [24,25]. Based on these studies, Cobelens et al. [25] recommend that people travelling from low incidence countries to areas highly endemic for TB should be offered serial testing or BCG vaccination. To detect an effect, Cobelens et al. followed a cohort travelling to countries with very high TB endemicity with an annual risk of infection above 1% and found an increased risk associated with travel to high TB endemic countries. A previous descriptive UK study suggested a higher risk of active TB among individuals from the Indian sub-continent following return visits [26], although subsequent comparison with a control group found no association [27]. The study presented here provides the first evidence in the UK that travel to countries with high levels of TB infection may be an independent risk factor for acquiring latent TB infection. This effect was not mitigated by BCG vaccination. Unlike previous studies, we utilised IGRA tests not confounded by the majority of non-tuberculous mycobacteria or BCG vaccination. The observed increased risk is therefore likely to be a result of true latent TB infection acquired either during or prior to the current incident.

Acquisition of TB during foreign travel is particularly important because the incidence of multi- and extensively drug-resistant TB is higher in many parts of the world compared to the UK [28,29]. These strains may be acquired while travelling, with the potential for subsequent spread upon return to a low incidence

country. An approach to reduce the incidence of travel-acquired TB is to use serial TST before and after travel and treat those converting to a positive test for latent infection [25]. Unfortunately the acquisition of resistant strains would make this approach less effective, with limited options for the treatment of latent infection due to multi- and extensively drug-resistant TB [30]. Furthermore, some individuals will convert from a negative to a positive TST due to previous exposure to non-tuberculous mycobacteria.

That we did not observe protection by BCG against latent infection may reflect a true lack of effect against latent infection. It is widely accepted that BCG only protects against severe forms of TB in infants [31], however, emerging evidence suggests that it may also protect against latent infection [32,14]. As a result, alternative explanations for the absence of a protective BCG effect against latent infection among students have to be considered. As BCG immunisation policy in the UK includes the selective vaccination of infants at high risk, it is possible that vaccinated individuals were more likely to have been exposed to TB, leading to a failure to detect a protective effect. Analysis of our data, however, suggests that this is unlikely, as the observation was independent of the age at BCG vaccination. In addition, controlling for ethnic origin, the main criterion for selecting who to vaccinate, did not change the findings. Significant variation in the efficacy of BCG has been observed in different countries [8]. The reasons for variation, including exposure to non-tuberculous mycobacteria, latitude, use of different strains of the vaccine and genetic differences of the vaccinees have been discussed extensively [33] but do not provide an obvious explanation for the observed lack of effect in this study.

The retrospective collection of data on risk factors in our investigation limits the ability to infer a causal link with exposures such as travel history and BCG vaccination status due to the possibility of recall bias. For the majority of participants, we obtained TB exposure history and risk factor data at the time of initial screening, before the IGRA test results were known, and thereby minimised recall bias. Any bias would therefore have been non-differential reducing the probability of detecting a true effect. We did not collect baseline IGRA data, therefore some of the IGRA-positive persons may have acquired their latent infection remotely. Nevertheless, the high proportion of students with latent infection in a low-incidence area, the proportion of students who converted and the high proportion of cases of active TB with the same genotype suggest that we were observing the effects of recent transmission. As we identified, interviewed and tested the vast majority of the target population, our findings are not affected by non-response bias. Travel history, on the other hand, may have been biased because the exposure recorded over the preceding two years may merely reflect longer-term travel. However, this is unlikely to invalidate the observed association with travel. A

further source of bias relates to the lack of vaccination cards to confirm the history of BCG vaccination. This is particularly important for children born abroad or from ethnic minority groups where scars may be less reliable due to vaccination at birth. Finally, although we used multivariable regression to adjust for the effect of several factors, residual confounding cannot be excluded.

The long time it took to screen the entire school possibly contributed to the emergence of secondary cases. While this may in part question the 'stone in the pond' approach, we contend that this incident is unusual. It is likely that controlling for exposure group accounted for the effect of secondary transmission in the analysis with infection as the outcome measure.

This study has found a significant association between travel to countries with a high TB incidence and the risk of latent TB infection among college students. The lack of a protective effect by BCG shows that an increased risk for TB infection during outbreaks may not be mitigated by a universal vaccination approach. This provides support for the discontinuation of universal BCG vaccination of children at school age. Travel appears to be an independent risk factor for the acquisition of TB infection. In the UK, BCG vaccination is currently recommended to people travelling to high-incidence countries for longer than three months. A cost-effectiveness analysis of the screening of travellers suggested that a single post-travel tuberculin skin test is the best approach [34]. However, this study did not assess the use of IGRAs. As IGRAs are not confounded by non-tuberculous mycobacterial infection, future studies should evaluate the effectiveness and cost-effectiveness of a policy requiring serial IGRA testing of travellers and treatment of IGRA-positive persons upon their return from high-incidence countries.

Acknowledgements

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Launch of free online database of international TB vaccination policies: the BCG World Atlas

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A team of researchers from McGill University and the Research Institute of the McGill University Health Centre in Canada created an interactive website that provides free detailed information on current and past tuberculosis (TB) vaccination policies and practices for more than 180 countries: the BCG World Atlas [1].

The Atlas is intended to be a useful resource for clinicians, policymakers, and researchers and provides information that may be helpful for better interpretation of TB diagnostics as well as design of new TB vaccines [2]. The Bacille Calmette-Guérin (BCG) vaccine was introduced in 1921 and continues to be the only vaccine used to prevent TB. Clinicians need to be aware of the various BCG policies in different parts of the world, as well as of the changes made to those policies over time.

This project began in 2007 with the compilation of detailed information on past and present BCG vaccination policies on as many countries as possible. Data were assembled through questionnaires, published papers, reports, government policy documents and information available from the World Health Organization Vaccine Preventable Diseases Monitoring System [3]. Based on the data generated by all methods, countries were grouped into three main categories: (i) the country currently recommends universal BCG vaccination at a certain age; (ii) the country used to recommend universal BCG vaccination but currently does not; (iii) BCG vaccination is recommended only for selected high-risk groups or was never recommended.

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Notes

National Bulletins

Austria

Mitteilungen der Sanitätsverwaltung
Bundesministerium für Gesundheit Familie und Jugend, Vienna.
Monthly, print only. In German.
http://www.bmgfj.gv.at/cms/site/thema.html?channel=CH0951

Belgium

Vlaams Infectieziektebulletin
Department of Infectious Diseases Control, Flanders.
Quarterly, print and online. In Dutch, summaries in English.
http://www.infectieziektebulletin.be

Bulletin d'information de la section d'Epidémiologie
Institut Scientifique de la Santé Publique, Brussels
Monthly, online. In French.
http://www.iph.fgov.be/epidemio/epifr/episcoop/episcoop.htm

Bulgaria

Bulletin of the National Centre of Infectious and Parasitic Diseases, Sofia.
Print version. In Bulgarian.
http://www.ncipd.org/

Cyprus

Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus
Medical and Public Health Services, Ministry of Health, Nicosia
Biannual, print and online. In Greek.
http://www.moh.gov.cy

Czech Republic

Zpravy CEM (Bulletin of the Centre of Epidemiology and Microbiology)
Centrum Epidemiologie a Mikrobiologie Státního Zdravotního Ústavu, Prague.
Monthly, print and online. In Czech, titles in English.
http://www.szu.cz/cema/adefaultt.htm

EPIDAT (Notifications of infectious diseases in the Czech Republic)
http://www.szu.cz/cema/epidat/epidat.htm

Denmark

EPI-NEWS
Department of Epidemiology, Statens Serum Institut, Copenhagen.
Weekly, print and online. In Danish and English.
http://www.ssi.dk

Finland

Kansanterveyslaitos
Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki.
Monthly, print and online. In Finnish.
http://www.ktl.fi/portal/suomi/osastot/infe/tutkimus/tartuntatautien_seuranta/tartuntatautilaakarin_kommentit/

France

Bulletin épidémiologique hebdomadaire
Institut de veille sanitaire, Saint-Maurice Cedex.
Weekly, print and online. In French.
http://www.invs.sante.fr/beh/default.htm

Germany

Epidemiologisches Bulletin
Robert Koch-Institut, Berlin
Weekly, print and online. In German.
http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html

Hungary

Epinfo (az Országos Epidemiológiai Központ epidemiológiai információs hetilapja)
National Center For Epidemiology, Budapest.
Weekly, online. In Hungarian.
http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun

Iceland

EPI-ICE
Landlæknisembættið
Directorate Of Health, Seltjarnarnes
Monthly, online. In Icelandic and English.
http://www.landlaeknir.is

Ireland

EPI-INSIGHT
Health Protection Surveillance Centre, Dublin.
Monthly, print and online. In English.
http://www.hpsc.ie/hpsc/EPI-Insight

Italy

Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.iss.it/publ/noti/index.php?lang=1&tipo=4

Bolletino Epidemiologico Nazionale (BEN)
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.epicentro.iss.it/ben

Latvia

Epidemiologijas Bileteni
Sabiedribas veselibas agentura
Public Health Agency, Riga.
Online. In Latvian.
http://www.sva.lv/epidemiologija/bileteni

Lithuania

Epidemiologijos žinios
Užkreciamuju ligu profilaktikos ir kontroles centras
Center for Communicable Disease Prevention and Control, Vilnius.
Online. In Lithuanian.
http://www.ulac.lt/index.php?pl=26

Netherlands

Infectieziekten Bulletin
Rijksinstituut voor Volksgezondheid en Milieu
National Institute of Public Health and the Environment, Bilthoven
Monthly, print and online. In Dutch.
http://www.rivm.nl/infectieziektenbulletin

Norway

MSIS-rapport
Folkehelseinstituttet, Oslo.
Weekly, print and online. In Norwegian.
http://www.folkehelsa.no/nyhetsbrev/msis

Poland

Meldunki o zachorowaniach na choroby zakazne i zatruciach w Polsce
Panstwowy Zaklad Higieny,
National Institute of Hygiene, Warsaw.
Fortnightly, online. In Polish and English.
http://www.pzh.gov.pl/epimeld/index_p.html#01

Portugal

Saúde em Números
Ministério da Saúde,
Direcção-Geral da Saúde, Lisbon.
Sporadic, print only. In Portuguese.
http://www.dgs.pt

Slovenia

CNB Novice
Inštitut za varovanje zdravja, Center za nalezljive bolezni, Institute of Public Health, Center for Infectious Diseases, Ljubljana.
Monthly, online. In Slovene.
http://www.ivz.si

Romania

Info Epidemiologia
Centrul pentru Prevenirea si Controlul Bolilor Transmisibile, National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest.
Sporadic, print only. In Romanian.
Sporadic, print only. In Romanian.http://www.insp.gov.ro/cnscbt/index.php?option=com_docman&Itemid=12

Spain

Boletín Epidemiológico Semanal
Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid.
Fortnightly, print and online. In Spanish.
http://www.isciii.es/ htdocs/centros/epidemiologia/epi_boletines.jsp

Sweden

EPI-aktuellt
Smittskyddsinstitutet, Stockholm.
Weekly, online. In Swedish.
htpp://www.smittskyddsinstitutet.se/publikationer/smis-nyhetsbrev/epi-aktuellt

United Kingdom

England and Wales
Health Protection Report
Health Protection Agency, London.
Weekly, online only. In English.
http://www.hpa.org.uk/hpr

Northern Ireland
Communicable Diseases Monthly Report
Communicable Disease Surveillance Centre, Northern Ireland, Belfast.
Monthly, print and online. In English.
http://www.cdscni.org.uk/publications

Scotland
Health Protection Scotland Weekly Report
Health Protection Scotland, Glasgow.
Weekly, print and online. In English.
http://www.hps.scot.nhs.uk/ewr/index.aspx

Other journals

EpiNorth journal
Norwegian Institute of Public Health, Folkehelseinstituttet, Oslo, Norway
Published four times a year in English and Russian.
http://www.epinorth.org

European Union
"Europa" is the official portal of the European Union. It provides up-to-date coverage of main events and information on activities and institutions of the European Union.
http://europa.eu

European Commission - Public Health
The website of European Commission Directorate General for Health and Consumer Protection (DG SANCO).
http://ec.europa.eu/health/index_en.htm

Health-EU Portal
The Health-EU Portal (the official public health portal of the European Union) includes a wide range of information and data on health-related issues and activities at both European and international level.
http://ec.europa.eu/health-eu/index_en.htm

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