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Improving tuberculosis surveillance in Europe is key to controlling the disease

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DNA of Tuberculosis (TB) bacteria were found in mammoth bones and in Egyptian mummies and TB has affected mankind since its appearance, despite many efforts to control and eliminate it [1].

It was already well known since the sanatoria period (Germany, 1857) when treatment against TB consisted of good food, rest, sun, and fresh air that about half of TB cases recovered almost spontaneously. Robert Koch's discovery of *Mycobacterium tuberculosis* in 1882, Carlo Forlanini introduced the artificial pneumothorax in 1907 [1] and streptomycin was introduced at the end of the Second World War. These discoveries revolutionised the understanding and treatment of TB.

In spite of these discoveries, the epidemic trend has tended more towards an increase in recent years. The interventions recommended by the directly observed treatment, short-course (DOTS) and the Stop TB Strategy introduced in 2006 [2], e.g. rapid diagnosis of 70% of existing sputum smear-positive cases and effective treatment of 85% of them, are very powerful in reversing the epidemic trend. This was demonstrated in several countries, e.g. in Peru and recently in Europe: Romania achieved 70/85% targets and, after an initial increase, was able to reduce both its case and case-fatality load [3].

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB mainly emerge as the result of mismanagement of TB, either by the prescribing physician (regimen, dose, duration) or the patient (compliance). Failure of the programme contributes as well: poor quality drugs, lack of public health action in ensuring patient support and correcting early signs of sub-optimal patient management represented by late sputum smear and culture conversion, presence of failures, defaulters and avoidable deaths.

As underlined by the joint ECDC and World Health Organization Regional Office for Europe TB report, launched on 18 March [11] the importance of good surveillance to stem this trend cannot be underestimated.

Where do we go with surveillance in Europe? Can we do more? How many MDR and XDR TB cases occur because of sub-optimal patient management?

This issue of Eurosurveillance casts light on these important questions with four interesting articles [4-7].

A paper by Manissero *et al*. from the ECDC reports on surveillance data in twenty-two countries of the European Union (EU) and European Economic Area (EEA) done by the ECDC Tuberculosis Programme [4]. Treatment outcome monitoring was performed on culture-confirmed pulmonary TB cases reported in 2007. While the overall treatment success rate was 73.8% (79.5% among new cases), only three countries achieved the 85% success rate target as a result of high defaulting and a relevant proportion of unknown outcomes.

A surveillance report by Devaux *et al*. [5] describes retrospectively the results of second-line drug susceptibility testing (DST) among MDR TB cases reported in 20 countries of the WHO European Region (15 being EU countries) aimed at identifying XDR TB. In 18 countries (only) DST was performed for two or more of the second-line drugs defining XDR TB, with relevant inter-country variation on the proportion of isolated tested. Overall, 10% of the MDR TB strains are found to be XDR.

A report by Ködmön *et al*. [6] describes the surveillance data collected by ECDC from EU and EEA countries. In 2008, the combined proportion of new and retreated MDR TB cases was 6.0% of the total case load for the 25 countries reporting data. Thirteen countries provided data on resistance to second-line drugs, allowing the identification of XDR TB cases. 68 XDR TB cases were reported in 2007 (6.1% of the MDR TB cases) and 90 in 2008 (7.3% of the MDR TB cases). Latvia and Romania notified the highest number of XDR TB cases in 2008.

Next is a surveillance report by Caley *et al*. on a retrospective cohort study performed in the UK to quantify the risk of developing TB infection or disease following school contact with an infectious student. The report results suggest that greater levels of classroom

contact with a sputum smear positive student significantly increases the risk of contracting both active TB disease and latent TB infection.

The results of the studies reported in this issue of Eurosurveillance allow us to point out some key topics:

- The completeness of reporting information (including treatment outcomes), the proportion of culture-confirmed TB cases reported as well as the proportion of strains on which DST for both first- and second-line drugs is performed and reported are still sub-optimal overall in Europe. The relevance of these pitfalls goes beyond the "simple" surveillance limitation, having the potential to affect other important TB control pillars, e.g. infection control and case-management.
- MDR and XDR TB still persist in Europe. The high proportion of MDR TB identified among new TB cases reported by certain countries indicates that sub-optimal infection control practices are likely to occur, while the high percentage of MDR TB notified among retreatment cases is probably the result of sub-optimal case management in the past decade.

ECDC is managing surveillance of TB at the EU level in collaboration with national correspondents, WHO Regional Office for Europe and partners. The joint ECDC and World Health Organization Regional Office for Europe TB report, launched on 18 March, shows that tuberculosis is still a matter of concern in Europe. *Tuberculosis Surveillance in Europe 2008* presents the latest data on TB cases and shows that the decline in cases has slowed down [11].

With the enhanced and improved regular surveillance of anti-TB drugs and molecular surveillance of MDR TB cases, ECDC is offering an added value to the European surveillance [9,10]. Surveillance is an integral part of TB control, its contribution being essential to inform the programme on what is going on and what public health response is urgently needed. Investing in better "intelligence" is a pre-requisite to improve TB prevention and control in Europe, in order to reach the elimination goal for Europe committed to in the early 1990s [8].

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Multidrug- and extensively drug-resistant tuberculosis: a persistent problem in the European Union European Union and European Economic Area

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Since 2008, the European Centre for Disease Prevention and Control has been collecting data from the European Union (EU) and European Economic Area (EEA) on resistance to first- and second-line drugs against tuberculosis (TB). In 2008, the proportion of multidrug-resistant tuberculosis (MDR TB) was 6.0% of the total case load for 25 countries reporting data. Extensively drug-resistant (XDR TB) reporting has increased since 2007 and was observed in 7.3% of the MDR TB cases in 13 reporting countries. MDR TB remains a threat and XDR TB is now established within the EU/EEA borders.

Background

Tuberculosis (TB) is among the leading causes of death due to a single pathogen worldwide. The World Health Organization (WHO) estimates that 32% of the world population is infected with *Mycobacterium tuberculosis*, the causative agent of tuberculosis [1], with 9.2 million new TB cases and 1.7 million deaths from TB reported in 2007 [2]. Drug resistance to isoniazid and rifampicin (the definition for multidrug-resistant (MDR) TB), the two most potent first-line antimicrobial drugs for the treatment of TB, is a persisting global problem with surveillance data indicating increasing trends in several countries [3–7]. In 2007, the WHO reported the highest rates of MDR TB ever recorded, with up to 22% of new TB cases being resistant to both isoniazid and rifampicin in some areas of the former Soviet Union [2]. The increases in prevalence and incidence of MDR TB are caused by concurrent factors such as inadequate treatment regimens, poor case holding, suboptimal drug quality and transmission of resistant strains [8]. In recent years, public health awareness about MDR TB has been reinforced by the occurrence of extensively drug-resistant (XDR) TB outbreaks associated with human immunodeficiency virus (HIV) infections, particularly in South Africa [9,10]. XDR TB strains are defined as strains resistant to isoniazid and rifampicin (i.e. MDR) as well as to a fluoroquinolone and to one or more of the following injectable drugs: amikacin, capreomycin, or kanamycin).

In Europe, the prevalence of MDR TB is high, particularly in some areas [4], and past surveillance reports have highlighted that MDR TB and XDR TB are a threat to TB control and elimination, also within the borders of the Member States of the European Union (EU) and European Economic Area (EEA) [11,12]. We therefore aimed at analysing the most recent data for the EU and EEA to describe the current MDR/XDR TB situation in this region.

Methods

Surveillance of drug resistance, based on annual case-based reporting of drug susceptibility testing (DST) results, has been ongoing in Europe since 1998 through the EURO-TB network and has included annual reporting of MDR TB cases [13]. Since 2008, the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe have jointly been conducting TB surveillance for Europe. Data for the EU and EEA countries are reported to the ECDC through the European surveillance system, TESSy.

Since the reporting year 1998, DST results from initial *M. tuberculosis* isolates have been collected for isoniazid, rifampicin, ethambutol and streptomycin. Since 2009, DST data for MDR TB cases on fluoroquinolones (ciprofloxacin, ofloxacin) and second-line injectable anti-TB drugs (amikacin, kanamycin and capreomycin) have been collected and reports have included retrospective data from 2007 and 2008. In this study, data was extracted from TESSy for EU and EEA countries reporting resistance to first-line drugs for the reporting year 2008. For the reporting years 2007 and 2008, data was extracted for EU and EEA countries reporting resistance to second-line drugs for MDR TB cases.

Table 1

Combined anti-tuberculosis drug resistance in EU/EEA countries, 2008

						Cases resistant to at least:											
	Total number of cases	Culture-positive cases		Cases with DST results to at least rifampicin and isoniazid[1]		Isoniazid		Rifampicin		Isoniazid and Rifampicin (multidrug-resistant)		Ethambutol		Streptomycin		Cases resistant to any anti-TB drug	
Country		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium	1,006	812	(80.7)	773	(95.2)	56	(7.2)	24	(3.1)	22	(2.8)	22	(2.8)	4	(0.5)	62	(8.0)
Bulgaria	3,151	1,361	(43.2)	938	(68.9)	121	(12.9)	43	(4.6)	32	(3.4)	84	(9.0)	55	(5.9)	179	(19.1)
Cyprus	50	36	(72.0)	36	(100.0)	4	(11.1)	1	(2.8)	1	(2.8)	0	(0.0)	3	(8.3)	6	(16.7)
Czech Republic	868	561	(64.6)	520	(92.7)	26	(5.0)	14	(2.7)	11	(2.1)	7	(1.3)	29	(5.6)	41	(7.9)
Denmark	367	283	(77.1)	281	(99.3)	11	(3.9)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	12	(4.3)
Estonia	444	347	(78.2)	347	(100.0)	103	(29.7)	74	(21.3)	74	(21.3)	78	(22.5)	122	(35.2)	130	(37.5)
Finland	350	248	(70.9)	247	(99.6)	12	(4.9)	2	(0.8)	1	(0.4)	0	(0.0)	6	(2.4)	15	(6.1)
France	5,812	2,296	(39.5)	1,556	(67.8)	103	(6.6)	32	(2.1)	27	(1.7)	18	(1.2)	112	(7.2)	171	(11.0)
Germany	4,543	3,112	(68.5)	2,854	(91.7)	197	(6.9)	55	(1.9)	45	(1.6)	45	(1.6)	194	(6.8)	287	(10.1)
Greece	669	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	1,606	766	(47.7)	611	(79.8)	48	(7.9)	18	(2.9)	16	(2.6)	19	(3.1)	37	(6.1)	71	(11.6)
Iceland	6	5	(83.3)	5	(100.0)	2	(40.0)	1	(20.0)	1	(20.0)	0	(0.0)	1	(20.0)	2	(40.0)
Ireland	470	209	(44.5)	146	(69.9)	9	(6.2)	4	(2.7)	3	(2.1)	2	(1.4)	5	(3.4)	13	(8.9)
Italy	4,418	2,026	(45.9)	1,932	(95.4)	244	(12.6)	89	(4.6)	71	(3.7)	71	(3.7)	238	(12.3)	381	(19.7)
Latvia	1,070	838	(78.3)	828	(98.8)	257	(31.0)	132	(15.9)	129	(15.6)	115	(13.9)	242	(29.2)	285	(34.4)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	2,250	1,616	(71.8)	1,616	(100.0)	469	(29.0)	287	(17.8)	276	(17.1)	167	(10.3)	412	(25.5)	513	(31.7)
Luxembourg	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Malta	53	25	(47.2)	25	(100.0)	2	(8.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(20.0)	5	(20.0)
Netherlands	997	728	(73.0)	728	(100.0)	55	(7.6)	14	(1.9)	13	(1.8)	3	(0.4)	0	(0.0)	56	(7.7)
Norway	324	227	(70.1)	227	(100.0)	36	(15.9)	6	(2.6)	4	(1.8)	6	(2.6)	29	(12.8)	48	(21.1)
Poland	8,081	5,094	(63.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Portugal	2,995	2,007	(67.0)	1,641	(81.8)	121	(7.4)	29	(1.8)	28	(1.7)	17	(1.0)	156	(9.5)	213	(13.0)
Romania	24,786	14,762	(59.6)	5,547	(37.6)	1,126	(20.3)	873	(15.7)	816	(14.7)	297	(5.4)	229	(4.1)	1,187	(21.4)
Slovakia	633	383	(60.5)	383	(100.0)	10	(2.6)	4	(1.0)	4	(1.0)	2	(0.5)	3	(0.8)	12	(3.1)
Slovenia	213	201	(94.4)	195	(97.0)	3	(1.5)	2	(1.0)	2	(1.0)	1	(0.5)	5	(2.6)	6	(3.1)
Spain	8,214	4,493	(54.7)	1,628	(36.2)	161	(9.9)	88	(5.4)	76	(4.7)	32	(2.0)	77	(4.7)	191	(11.7)
Sweden	552	436	(79.0)	423	(97.0)	49	(11.6)	13	(3.1)	12	(2.8)	15	(3.5)	9	(2.1)	52	(12.3)
United Kingdom	8,655	4,870	(56.3)	4,808	(98.7)	288	(6.0)	71	(1.5)	53	(1.1)	35	(0.7)	186	(3.9)	405	(8.4)
Total	**82 611**	**47,742[2]**	**(57.8)**	**28,295**	**(66.3)**	**3,513**	**(12.4)**	**1,876**	**(6.6)**	**1,717**	**(6.1)**	**1,037**	**(3.7)**	**2,159**	**(7.6)**	**4,343**	**(15.3)**

DST: drug sensitivity testing; EEA: European Economic Area; EU: European Union; TB: tuberculosis.

[1] Any resistance to isoniazid, rifampicin, ethambutol or streptomycin, expressed as a percentage of cases with available DST results at least to isoniasid and rifampicin. Testing for ethambutol and streptomycin not routine in all countries.

[2] Total number of culture-positive cases excluding Poland, which did not report DST data: 42,648.

The total number of cases, the total number of culture-positive cases and the total number of cases with DST results (sensitive or resistant to at least isoniazid and rifampicin) were extracted to assess the interpretability of DST data.

The proportions of drug-resistant cases were calculated using the total number of cases with available DST results for at least isoniazid and rifampicin as a denominator; if these cases also included results for ethambutol and streptomycin, DST results for these antibiotics were also analysed. Cases of MDR TB were defined as cases resistant to at least isoniazid and rifampicin. In order to analyse findings on MDR TB among new and retreatment cases, MDR TB data among reported cases were stratified by history of previous treatment. New cases were defined as cases who had never previously received drug treatment for active TB, or who had received anti-TB drugs for less than one month. Retreatment cases were defined as cases who had received treatment with anti-TB drugs (excluding preventive therapy) for at least one month.

Among MDR TB cases reported for 2007 and 2008, those with positive DST results for any of the reportable fluoroquinolones as well as to at least one of the reportable injectables were classified as XDR TB cases. The standard international definition for XDR TB was

Table 2

Multidrug-resistant cases by previous history of tuberculosis treatment in the EU/EEA, 2008

Country	New		Retreatment		Treatment history unknown	
	Cases with DST results	Multidrug-resistant	Cases with DST results	Multidrug-resistant	Cases with DST results	Multidrug-resistant
		N (%)		N (%)		N (%)
Austria	-	- -	-	- -	-	- -
Belgium[1]	621	14 (2.3)	57	7 (12.3)	95	1 (1.1)
Bulgaria	833	14 (1.7)	105	18 (17.1)	0	0 -
Cyprus	11	0 (0.0)	3	1 (33.3)	22	0 (0.0)
Czech Republic	483	10 (2.1)	37	1 (2.7)	0	0 -
Denmark[1]	253	0 (0.0)	28	0 (0.0)	0	0 -
Estonia	272	42 (15.4)	75	32 (42.7)	0	0 -
Finland	238	1 (0.4)	9	0 (0.0)	0	0 -
France	1,313	16 (1.2)	104	10 (9.6)	139	1 (0.7)
Germany	2,450	16 (0.7)	153	21 (13.7)	343	8 (2.3)
Greece	-	- -	-	- -	-	- -
Hungary	509	8 (1.6)	97	6 (6.2)	5	2 (40.0)
Iceland	4	1 (25.0)	0	0 (0.0)	1	0 (0.0)
Ireland[1]	113	2 (1.8)	9	0 (0.0)	24	1 (4.2)
Italy	1,018	27 (2.7)	165	24 (14.5)	749	20 (2.7)
Latvia	684	83 (12.1)	144	46 (31.9)	0	0 -
Liechtenstein	-	- -	-	- -	-	- -
Lithuania	1,259	113 (9.0)	356	162 (45.5)	1	1 (100.0)
Luxembourg	-	- -	-	- -	-	- -
Malta	22	0 (0.0)	3	0 (0.0)	0	0 -
Netherlands	696	11 (1.6)	23	2 (8.7)	9	0 (0.0)
Norway[1]	174	1 (0.6)	20	2 (10.0)	33	1 (3.0)
Poland	-	- -	-	- -	-	- -
Portugal	1,496	19 (1.3)	145	9 (6.2)	0	0 -
Romania	3,025	130 (4.3)	2,522	686 (27.2)	0	0 -
Slovakia	300	1 (0.3)	61	2 (3.3)	22	1 (4.5)
Slovenia	183	1 (0.5)	12	1 (8.3)	0	0 -
Spain	1,080	31 (2.9)	174	23 (13.2)	374	22 (5.9)
Sweden	341	7 (2.1)	38	4 (10.5)	44	1 (2.3)
United Kingdom[1]	3,707	38 (1.0)	228	7 (3.1)	873	8 (0.9)
Total EU/EEA	**21,085**	**586 (2.8)**	**4,568**	**1,064 (23.3)**	**2,734**	**67 (2.5)**

DST: drug sensitivity testing; EEA: European Economic Area; EU: European Union; TB: tuberculosis.

- : not reported

1 Any resistance to isoniazid, rifampicin, ethambutol or streptomycin, expressed as a percentage of cases with available DST results at least to isoniasid and rifampicin. Testing for ethambutol and streptomycin not routine in all countries.

therefore applied [14]. Changes in the prevalence of XDR TB among MDR TB cases between 2007 and 2008 were analysed.

Findings

In 2008, 47,742 culture-positive TB cases were reported by 27 EU and EEA Member States. This represents 57.8% of the total TB case load (82,611), with the percentage ranging from 36.2% to 100% among the reporting countries (Table 1). Data on resistance to first-line drugs in 2008 were available for 25 countries, representing a total of 28,295 cases (66.3% of the total culture-positive cases, excluding culture-confirmed cases from Poland as DST data was not reported) (Table 1).

In 2008, the proportion of culture-positive TB cases resistant to any first-line anti-TB drug was 15.3% (N=4,343). The proportion of resistance to either isoniazid or rifampicin among culture-positive cases was 12.4% (N=3,513) and 6.6% (N=1,876), respectively (Table 1). The proportion of combined (new and retreatment) MDR TB cases in the 25 countries was 6.0%, as shown in Table 1. The Baltic States (Latvia, Lithuania and Estonia) and Romania showed the highest proportions (15.6%, 17.1% 21.3% and 14.7%, respectively) of MDR TB cases (Table 1). The overall proportion of MDR TB among new cases was 2.8%, ranging from 0% to 25%, and was again highest in the Baltic States (9.0%–15.4%) and Iceland (25.0%, one case). Among retreatment cases, the overall proportion of MDR cases was 23.2%, with the highest proportions in the Baltic States (31.9%-45.5%), Cyprus (33.3%, one case) and Romania (27.2%) (Table 2).

Thirteen countries provided data on resistance to second-line drugs, allowing the identification of XDR TB cases for the reporting years 2007 and 2008. Among the total of 1,122 MDR TB cases (new and retreatment cases) reported by these 13 countries in 2007, 68 were XDR TB cases, representing 6.1% of the total MDR TB burden. In 2008, 90 XDR TB cases were notified, with the proportion of XDR TB cases among MDR TB cases increasing to 7.3%. Latvia and Romania had the highest number of XDR TB cases in 2008 (19 and 54 cases, respectively). In Estonia, a decline in the total number and proportion of XDR TB cases from 12 to nine cases (15.0% to 12.2%) was observed compared to 2007, while in Latvia had an increase in the number of reported XDR TB cases in 2008 relative to 2007 from six to 19 cases (6.1% to 14.7%) (Table 3).

Conclusions

The data highlight two important findings concerning the MDR/XDR TB situation in the EU/EEA Member States. First, it is evident that reporting completeness remains suboptimal in this region. In particular, the percentage of the total TB case load for which the drug resistance profile for at least isoniazid and rifampicin is known, remains low. The DST results were available for only 34.4% of the total notified cases (28,295 of 82,611 cases in 2008), reflecting a low culture positivity rate (57.5%) and a low DST coverage (66.4% of culture-positive cases). This represents not only a surveillance limitation, but it could also hamper the implementation of proper TB control practices such as infection control and case management.

Secondly, the data highlights the fact that MDR TB persists as a threat to the EU/EEA. This is underlined by four of the five WHO High Priority Countries within the EU/EEA (Estonia, Latvia, Lithuania and Romania) reporting proportions of combined MDR TB of well over 10% of the total case load [15]. The analysis of MDR

Table 3

Extensively drug-resistant tuberculosis cases in the EU/EEA, 2007-2008

	Total MDR-TB	Total XDR-TB	XDR/MDR %	Total MDR-TB	Total XDR-TB	XDR/MDR %
Belgium	14	1	(7.1)	22	2	(9.1)
Bulgaria	76	0	(0.0)	32	0	(0.0)
Cyprus	3	0	(0.0)	1	0	(0.0)
Czech Republic	8	0	(0.0)	11	1	(9.1)
Estonia	80	12	(15.0)	74	9	(12.2)
Iceland	1	0	(0.0)	1	0	(0.0)
Latvia	99	6	(6.1)	129	19	(14.7)
Norway	3	1	(33.3)	4	0	(0.0)
Romania	701	47	(6.7)	816	54	(6.6)
Slovakia	7	0	(0.0)	4	0	(0.0)
Spain	59	0	-	76	3	(3.9)
Sweden	15	1	(6.7)	12	1	(8.3)
United Kingdom	56	0	(0.0)	53	1	(1.9)
Total EU/EEA	**1,122**	**68**	**(6.1)**	**1,235**	**90**	**(7.3)**

MDR: multidrug-resistant; EEA: European Economic Area; EU: European Union; TB: tuberculosis; XDR: extensively drug-resistant.

TB reporting can be used to indicate weaknesses in TB control programmes. The high proportion of MDR TB among new TB cases reported by certain countries could suggest suboptimal infection control, whilst the high percentage of MDR TB among retreatment cases (23.3%) could suggest poor case holding and follow-up or suboptimal use of TB regimens during the past decade.

For the first time since the surveillance of anti-TB drugs has been performed at EU level, notification data on XDR TB is available through the joint surveillance system. Although the quality and completeness of second-line resistance data remains questionable, the numbers confirm that XDR TB is now established in the EU. The increase of 32.4% in reported XDR TB cases is difficult to interpret as this could well represent an improvement in DST coverage for second-line drugs, as opposed to representing a true increase in the prevalence of XDR TB.

The link and interdependence between TB surveillance, TB case management and control of drug-resistant TB is well reflected by these data. Improvement in the quality and completeness of MDR/XDR TB surveillance data is needed. This will be achieved by the countries' serious commitment to optimise TB control practices as well as improve TB case management, which in turn should reverse the of MDR/XDR TB trends observed in recent years.

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A possible foodborne outbreak of hepatitis A in the Netherlands, January-February 2010

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As of 1 March 2010, a total of 11 primary cases with onset of symptoms between 31 December 2009 and 10 February 2010, have been identified with identical hepatitis A genotype IB strains in the Netherlands. A relation with Australian and French foodborne outbreaks occurring in 2009 and 2010 is suspected. Ten of the 11 primary cases indicated that they had consumed one or more products containing semi-dried tomatoes during their incubation period.

On 12 February 2010, the virology reference laboratory for hepatitis A sequencing in the Netherlands detected a new hepatitis A virus (HAV) strain in five patients with acute hepatitis. The patients did not reveal common exposures and they were geographically dispersed. Their onset of disease ranged between 11 and 22 January 2010. Although the number of reported cases was normal for the time of the year, finding five identical HAV genotype IB strains was unusual and led to an outbreak investigation that is still ongoing in the Netherlands. Here we describe the preliminary results of this ongoing investigation.

Epidemiological investigation

The cases included in the cluster were defined as all reported hepatitis A infections in the Netherlands with date of onset of disease from 15 December 2009 until present, with viruses with an identical sequence in a fragment of the VP1-2A region [1,2].

The cases included for a case control study were defined as all reported hepatitis A infections in the Netherlands with date of onset of disease from 15 December 2009 until present. Exclusion criteria were:

- most probable source of infection outside the Netherlands or outside any western European country,
- most probable route of transmission sexual contact between men,
- detection of a non-related HAV strain,
- secondary cases.

The absolute number of reported cases in the period under investigation, January and February 2010, was 39 and the proportion of cases that contracted their infection in the Netherlands was 82%. This number is not elevated compared with previous years. Between 2005 and 2009, the number of HAV reports in the Netherlands in January and February had ranged between 23 and 44, with a median of 33. The proportion of cases that contracted their infection in the Netherlands in these months ranged between 66% and 80%, with a median of 68%, and mostly reflects onward transmissions following the wave of travel-associated primary cases that is usually seen in autumn [3,4].

Of the 39 cases notified in January and February 2010 (Figure 1), 24 had no history of recent travel abroad, denied sexual contact between men and had no known relation to another patient or cluster.

Serum samples from 31 of the 39 notified persons were available for PCR. Of these, 21 yielded a PCR product that could be used for sequencing. The genotypes identified were IA (three patients), IIIA (two patients) and IB (16 patients). Of the 16 IB sequences, 13 were identical with closest genetic relatedness to viruses identified in travellers returning from Turkey, and three were distinct and clustered with strains commonly identified in travellers from Morocco. The 13 patients with identical strains were contacted for further investigation.

As of 1 March 2010, a total of 11 primary cases, six male and five female aged between 20 and 63 years, with onset of symptoms between 31 December 2009 and 10 February 2010, have been identified with identical HAV

genotype 1B strains. Ten of the 11 primary cases indicated that they had consumed one or more products containing semi-dried tomatoes during their incubation period. The 11th case could not be reached. Two additional cases infected with the same strain are considered to be secondary cases (Figure 1). Both were closely related to a primary case and their onset of symptoms was approximately two weeks after the onset date of the suspected index case.

Two male patients in their late 30s and 50s developed liver failure, for which they needed a liver transplantation. They did not have underlying liver disease. We are unable to explain the severe outcome of these two patients. Usually, the rate of fulminant liver disease is less than 1,5% of hospitalised hepatitis A patients [5].

Related outbreaks

The HAV strain was found to be identical to an HAV IB strain involved in food-related hepatitis A outbreaks in Australia during 2009, based on a 300 nt overlapping sequence of the VP1-2A part of the genome (kindly provided by MJ Lyon, Public Health Virology Laboratory, Queensland, Australia) [6,7]. Furthermore, an outbreak of hepatitis A had occurred in France between November 2009 and January 2010 (personal communication). The strain identified in the French outbreak (kindly provided by AM Roque-Afonso, Laboratoire de Virologie, Hôpital Paul Brousse, Villejuif, France) also belonged to the IB genotype, but differed in 2 nt from the Australian strain (based on a 300 nt fragment), and in 3 nt from the Dutch strain (based on a 430 nt fragment).

Although this is a small difference, it should be considered significant, as typically a single unique strain is observed in outbreaks of HAV. Having said that, both strains cluster with viruses known to circulate in the same geographic region that includes Turkey. This is concluded on the basis of sequence data obtained from HAV-infected returning travellers. It does not provide robust evidence for a source of infection, because the level of sampling in populations in the wider region is insufficient.

Source tracing

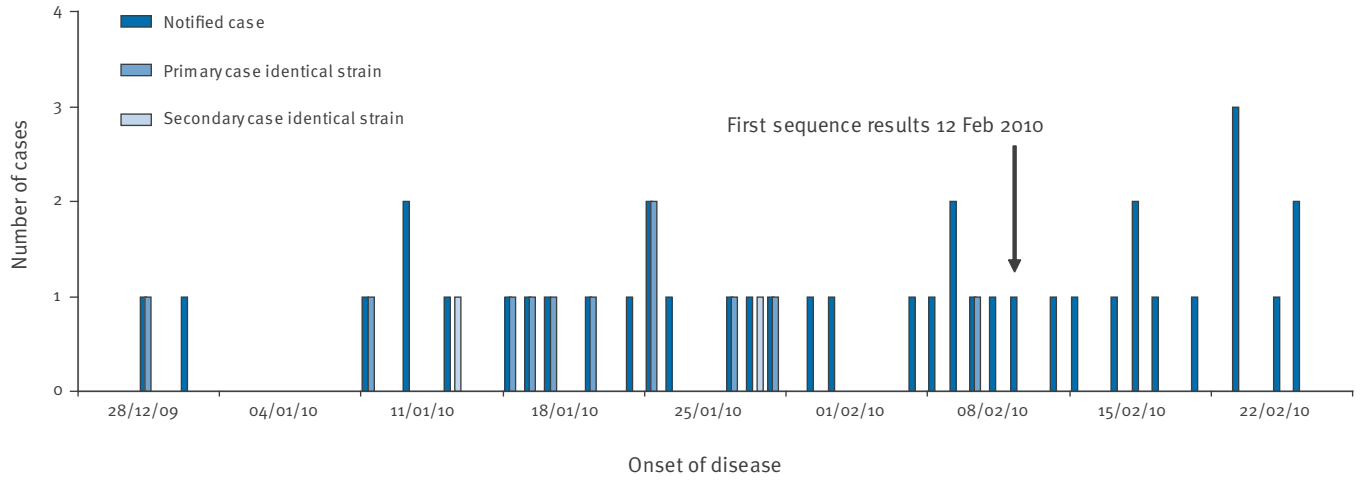
Since no other epidemiological connection between the cases could be made, a common food source was considered most likely. A case control study was initiated to assist in identifying the food product involved, and results are not yet available.

In case control studies in Australia and France, the recent occurrence of HAV infection was associated with consumption of semi-dried tomatoes. Therefore, the Dutch Food and Consumer Product Safety Authority started an investigation focusing on products containing this ingredient eaten by the primary cases in the current outbreak. These differed in the way they were presented for purchase and were purchased in different supermarkets, markets or delicacy stores. Full trace back to the area of production is ongoing. So far, ten different product types of semi-dried tomatoes have been identified as consumed by the Dutch cases, imported from three different countries. No original samples are available for investigation, but as yet, 52 food samples of similar products have been tested, in which HAV RNA could not be detected. No common producer or distributor could be identified so far that would explain all the Dutch cases.

The same applies for a link between the outbreaks in the Netherlands, Australia and France. France was able to trace the batch of semi-dried tomatoes implicated in the French outbreak, but no leftovers of this specific batch were found. Because the French and Dutch/Australian HAV strains were not identical, the exact

Figure

Cases of hepatitis A notified in the Netherlands in January and February 2010 (n=39)



Notified cases include all notifications in this period. Primary and secondary cases include those cases with an identical strain related to the possible food-borne cluster, identified as of 1 March 2010.

sources and modes of transmission of the outbreak in the Netherlands remain to be established.

Conclusions

We have identified a cluster of patients infected with an identical HAV IB strain. As the partial strain sequence showed a 100% match with viruses found as the cause of foodborne outbreaks in Australia, and high similarity with the HAV strain causing a recent foodborne outbreak in France, a possible common source to these outbreaks is currently being investigated. Trace back investigations so far showed a highly complex market for one of the products considered as a possible source (semi-dried tomatoes), and failed to identify a common link between all cases. This is similar to observations in Australia where after an initial small outbreak, a second wave was observed that involved a large increase in locally-acquired cases compared to previous years [6,7 and personal communication]. Therefore, although we have not received reports of confirmed primary cases since 17 Feb 2010 (onset of disease 10 Feb 2010), this calls for vigilance in the weeks to come.

We are interested in all cases that may be linked to this outbreak. Strains can be compared using the HAV database of the Food-borne Viruses in Europe (FBVE) network at the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM). For details, please contact fbve@rivm.nl.

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Cases of Salmonella Urbana in Finland, the Czech Republic and Latvia, January-February 2010

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A cluster of 14 cases of *Salmonella* Urbana cases in Finland, the Czech Republic and Latvia were identified in January-February, 2010. The majority of cases (11) were male and children under 16 years of age. The investigation is currently ongoing and comparison of pulsed-field gel electrophoresis (PFGE) profiles of the isolates suggests that the cases may have a common source of infection.

On 5 February, the Finnish National Salmonella Centre (NSC) in the Bacteriology Unit of the Finnish National Institute for Health and Welfare (THL) reported four laboratory confirmed cases of *S.* Urbana (30:b:enx) to the THL Unit of Epidemiologic Surveillance and Response. Isolates originated from different parts of the country. The samples were taken between 13 and 30 January. According to the patients' physicians, none of them had been travelling abroad prior to the onset of illness with symptoms of diarrhoea and fever. Three of the cases were children under four years. A link between the cases was suspected because of temporal association of isolates of a very unusual *Salmonella* serotype. During the last 30 years, only three human cases of domestically acquired *S.* Urbana were reported in Finland. According to the Finnish Food Safety Authority, *S.* Urbana was found once in peanuts (in 2003) and in dog treats (in 2008). [H. Kuronen; personal communication].

In order to build a hypothesis of the source of the infection, cases or their guardians were interviewed using an extensive questionnaire focussing especially on food items generally consumed by children and to animal contacts, or contacts to animal feed. To map the occurrence of *S.* Urbana infection in other European countries, an inquiry to detect potentially linked cases in other countries was conducted through the Programme on Food- and Waterborne Diseases and Zoonoses network [5].

Table

Clinical characteristics of *S.* Urbana cases, Finland, Latvia and the Czech Republic, 2010

Country	Age	Gender	Clinical picture	Sample	Hospital care
Finland	11 months	F	bloody diarrhoea	faecal	yes
Finland	1 year	F	bloody diarrhoea	faecal	yes
Finland	13 years	F	bacteraemia, no gastrointestinal symptoms	blood	yes
Finland	3,5 years	M	diarrhoea	faecal	no
Finland	2 years	M	bacterial arthritis, no gastrointestinal symptoms	faecal+synovial fluid	yes
Finland	13 years	M	diarrhoea	faecal	no
Finland	35 year	M	diarrhoea	faecal	yes
Latvia	2 years	M	diarrhoea	faecal	
Czech Republic	7 years	M	watery diarrhoea	faecal	yes
Czech Republic	4 years	M	diarrhoea	faecal	no
Czech Republic	6 years	M	vomiting*	faecal	yes
Czech Republic	1,3 years	M	diarrhoea	faecal	yes
Czech Republic	20 years	M	bacteraemia, no gastrointestinal symptoms	blood	yes
Czech Republic	2,5 years	M	diarrhoea	faecal	yes

* Vomiting since November 2009, no diarrhoea/abdominal pain, hospitalised 18.1.2010

Investigations to date

A case was defined as a person with *S.* Urbana (30:b:enx, PFGE profile SURBXB.0002 and SURBXB.0003) infection in the European Union (EU) with the date of sampling between 1 January and 14 February 2010. In total 14 cases met the case definition (Table 1).

Twelve of the cases were children under 16 years. The median age was five years (age range 11 months old to 35 years old). Eleven were males. Three cases had a bacterial invasive disease, *Salmonella* isolated from blood or synovial fluid. Ten cases were hospitalised. Seven cases were from different parts of Finland, six from different parts of the Czech Republic and one from Latvia. In Finland, the descriptive epidemiological study suggested that all cases could have been exposed to dogs and all children had eaten raisins. In the Czech Republic, the epidemiological investigation revealed contact with dogs only in two cases and consumption of raisins in one case. No potential common source was detected in the Czech cases. The Latvian case had had no contact with dogs and had not consumed raisins, but the family had a cat whose feed was sampled and tested with negative results. The dog faeces, dog treats and raisins collected from the homes of the Finnish cases tested negative for salmonella.

PFGE profiles from the three countries, Finland, the Czech Republic and Latvia, were indistinguishable when compared to each other (Figure 1) indicating that the infections might have had a common source.

One Finnish PFGE profile (SURBXB.0003) had an extra band. This minor difference might be caused by a plasmid which salmonellae can spontaneously lose or acquire. It is also possible that a recent point mutation, deletion or insertion in the DNA had occurred. *S.* Urbana strains were sensitive to all antimicrobial agents tested (ampicillin, chloramphenicol, cefotaxime, imipenem, mecillinam, nalidixic acid, neomycin, sulfonamide, tetracycline, trimethoprim, streptomycin, and ciprofloxacin).

Conclusions to date

An unusual *Salmonella* serotype leading to a high rate of hospitalisation and the severe clinical picture of the cases detected in Finland and in the Czech Republic were important reasons for triggering the epidemiological investigation. According to data from the Finnish Infectious Disease Registry data base gathered between 2000 and 2009, less than 2% of all non-typhoidal salmonella findings were from blood. Similarly, in a large Spanish study, 4.5% of the patients with salmonellosis had septicaemia [1]. In the current cluster of *S.* Urbana, three cases of 14 had an invasive extraintestinal disease; two with bacteraemia and one with hematogeneous septic arthritis.

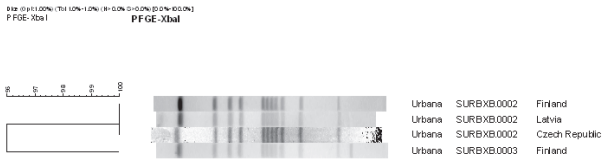
S. Urbana is rarely described in the literature. In the 1990s, a large outbreak occurred in a neonatal ward in Thailand [2] and a case of *S.* Urbana encephalopathy was reported from Japan [3]. The inquiry to the experts in the Programme on Food- and Waterborne Diseases and Zoonoses revealed that *S.* Urbana is rare in Europe in general, and mostly reported in children. Some of these cases had been associated with contacts with reptiles [4]. *S.* Urbana has also been found in sesame and equsi (melon) seeds, black pepper, animal feed and sewage sludge, according to experts in the Programme on Food- and Waterborne Diseases and Zoonoses network.

Only one of the cases (in the Czech Republic) had had contact with a reptile. According to our investigations, neither animals nor their feed seem to be the source of the current infections. Milk products appear to be less likely to be the source of infection, since one of the cases suffered from severe milk allergy. Fish, nuts, soya products and health food items were rarely consumed by the Finnish cases. Most of the cases were males, but we were not able to reveal any exposure common to the cases that could have been linked to being male.

Since the beginning of February, no further cases of *S.* Urbana have been detected in the three countries. Most of the cases had accumulated in two weeks in January in all three countries. The cases detected in the beginning of February were in a cancer patient without gastrointestinal symptoms (*Salmonella* found in blood)

Figure 1

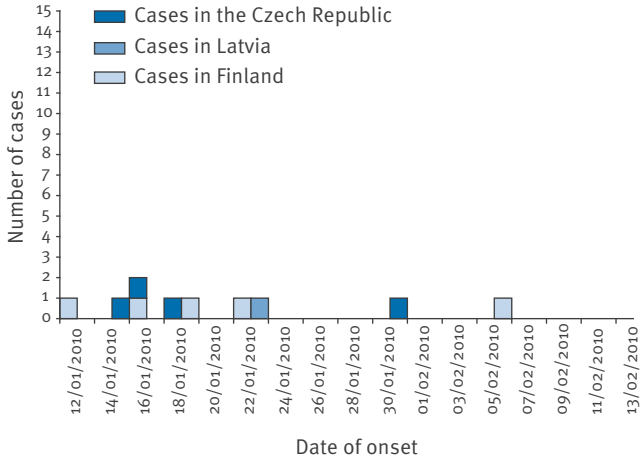
PFGE profiles of *S.* Urbana isolates from Finland, Czech Republic and Latvia when digested with *Xba*I enzyme.



PFGE; Pulsed-field gel electrophoresis

Figure 2

Cases of *S.* Urbana by date of onset of gastrointestinal symptoms and country, 12 January-7 February 2010



and an adult male who was considered a secondary case to his children that also suffered from gastrointestinal symptoms. When tested, however, the family members were negative for *Salmonella*. The accumulation of most cases with gastrointestinal symptoms in two weeks (Figure 2) suggests that the source of the infection could have been a product with a short shelf-life such as a batch of fresh produce, or a minor contamination of some other product. To date however, the source of the outbreak remains unknown.

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We thank the experts of the Programme on Food- and Waterborne Diseases and Zoonoses network for their kind response to our inquiry. The skilful assistance of the personnel of the National Salmonella Centre in Bacteriology Unit, National Institute for Health and Welfare is gratefully acknowledged for PFGE typing the strain from Latvia. Taina Niskanen and her team and Henry Kuronen and the laboratories of Finnish Food Safety Authority are thanked for organising and carrying out microbiological investigation and providing information on non-human *S*. Urbana isolates in Finland. Furthermore we are thankful to the local epidemiologists in the Czech Republic. Anita Brila and her team are acknowledged for the epidemiological investigation in Latvia. The PulseNet Europe curator Clare Maguire is thanked for providing international names for PFGE profiles.

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Surveillance of extensively drug-resistant tuberculosis in Europe, 2003-2007

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This paper describes the results of second-line drug (SLD) susceptibility tests among multidrug-resistant tuberculosis (MDR TB) cases reported in 20 European countries aiming to identify extensively drug-resistant tuberculosis (XDR TB) cases. A project on molecular surveillance of MDR TB cases was conducted by EuroTB and the National Institute for Public Health and the Environment (RIVM) from 2005 to 2007. Information on drug susceptibility testing (DST) was provided to this project and case-based data on MDR TB cases were reported on a quarterly basis by 20 countries of the World Health Organization's European Region, including 15 European Union Member States. Data included SLD susceptibility test results, enabling a retrospective description of XDR TB cases notified between 2003 and 2007. In 18 countries DST was performed for two or more of the SLD included in the XDR TB definition. The proportion of MDR TB isolates tested for SLD varied widely between countries (range 20 to 100 percent). In the 18 countries, 149 (10%) XDR TB cases were reported among MDR TB cases with available DST results for SLD. Sixteen additional MDR TB cases were reported by the MDR TB surveillance system when compared with the number of routinely reported MDR TB cases to EuroTB in ten countries with representative data reported during three consecutive years (2003-2005). To counter the threat of XDR TB in Europe, a standardised approach to XDR TB surveillance and DST for SLD is needed, as well as increased laboratory capacity across European countries.

Introduction

Extensively drug-resistant tuberculosis (XDR TB) is a worldwide threat to TB control, as XDR TB cases are extremely difficult to treat [1]. The origin of XDR TB is linked to the introduction of second-line antituberculosis drugs (SLD) for the treatment of multidrug-resistant tuberculosis (MDR TB) and the possible mismanagement of patients (including failure of compliance) under SLD treatment [2,3]. In March 2006, the term XDR TB first appeared in the literature in a United States Centers for Disease Control and Prevention (US CDC) report describing the findings of a worldwide survey on anti-TB drug resistance carried out between 2000 and 2004 [4]. Since then, a number of scientific and media reports on XDR TB have been published [5]. Although the term has emerged only recently, the occurrence of TB cases resistant to most available drugs is not new [6]. The definition of XDR TB, MDR TB plus resistance to a fluoroquinolone and at least one of three injectable SLD (amycacin, kanamycin, capreomycin) has been revised in 2006 because not all the SLD included in the original case definition were used and tested worldwide [7-9].

Epidemics of drug-resistant TB have been described in the WHO European Region since the 1990s [10]. XDR TB has been identified as a significant problem in countries of the former Soviet Union [11] and the potential threat of XDR TB for Europe has been assessed by the European Centre for Disease Centre and Prevention (ECDC) in 2006 [12]. The occurrence of XDR TB outbreaks in patients co-infected with HIV has re-enforced the public health awareness, with a particular focus on South Africa [13].

In 2005, the EuroTB network started a molecular surveillance project on MDR TB in 24 countries of the WHO European Region including 19 European Union (EU) Member States, plus Croatia, Israel, the Former Yugoslav Republic of Macedonia, Norway and Switzerland) [14]. The project was coordinated by EuroTB in France and the National Institute for Public Health and the Environment (RIVM) in the Netherlands until the end of 2007. As resistance to SLD was already a matter of concern in 2005, data on drug susceptibility testing (DST) for SLD were collected in addition to DNA fingerprint data [14,15]. The project provided an opportunity to implement case reporting of XDR TB by applying the revised XDR TB case definition of 2006

retrospectively. This article describes notification data on resistance to SLD in the EU and some neighbouring countries from January 2003 through June 2007.

Methods

Data collection

The MDR TB project included 24 countries of the WHO European Region that were able to or planning to participate in case-based reporting of molecular data on MDR TB cases at European level in 2005. Case-based data on all newly diagnosed and culture confirmed positive MDR TB cases were reported by national surveillance institutions (NSI) to EuroTB on a quarterly basis from January 2005 through June 2007. Data for 2003 and 2004 were reported retrospectively. The data were collected anonymously, according to a standardised data file specification reviewed by the members of the EuroTB advisory committee [16]. Each case had a unique record identifier. Common definitions of variables were used by the participating countries, including demographic and clinical variables and results from susceptibility testing for first and second-line anti-TB drugs. The country of origin of a case was defined as

Table 1

Reporting of anti-tuberculosis second line DST on *Mycobacterium tuberculosis* isolates of MDR TB cases in 20 European countries, 2003-2007[1]

Country	MDR TB cases	Secondline drugs tested	Injectable drugs			Fluoroquinolones	
			Amikacin	Kanamycin	Capreomycin	Ciprofloxacin	Ofloxacin
	N	N	N (%)	N (%)	N (%)	N (%)	N (%)
Five second line anti-tuberculosis drugs tested							
France[2]	152	5	148 (97)	147 (97)	135 (89)	145 (95)	149 (98)
Czech Republic[1]	38	5	25 (66)	22 (58)	25 (66)	25 (66)	25 (66)
Norway[1]	11	5	11 (100)	11 (100)	11 (100)	5 (45)	11 (100)
Ireland[1]	8	5	3 (38)	1 (13)	3 (38)	3 (38)	1 (13)
Slovenia[4]	3	5	3 (100)	1 (33)	1 (33)	3 (100)	1 (33)
Four second line anti-tuberculosis drugs tested							
Lithuania[3]	656	4	89 (14)	173 (26)	101 (15)	- -	172 (26)
Estonia[2]	248	4	245 (99)	245 (99)	244 (98)	- -	245 (99)
Israel[2]	45	4	43 (96)	- -	43 (96)	44 (98)	44 (98)
Switzerland[1]	25	4	24 (96)	- -	9 (36)	4 (16)	19 (76)
Denmark[3]	5	4	5 (100)	- -	5 (100)	5 (100)	5 (10)
Three second line anti-tuberculosis drugs tested							
Latvia[1]	712	3	- -	705 (99)	698 (98)	- -	689 (97)
Romania[3]	50	3	19 (38)	44 (88)	- -	44 (88)	- -
Belgium[1]	31	3	12 (39)	2 (6)	- -	- -	12 (39)
Poland[4]	17	3	6 (35)	- -	6 (35)	- -	6 (35)
Former Yugoslavian Republic of Macedonia[1]	15	3	8 (53)	- -	8 (53)	8 (53)	- -
Cyprus[1]	3	3	1 (33)	- -	3 (100)	- -	3 (10)
Two second line anti-tuberculosis drugs tested							
The Netherlands[2]	34	2	33 (97)	- -	- -	34 (100)	- -
Croatia[2]	5	2	1 (20)	- -	- -	2 (40)	- -
One second line anti-tuberculosis drug tested							
Spain[3]	50	1	- -	2 (4)	- -	- -	- -
Sweden[1]	21	1	15 (71)	- -	- -	- -	- -
Total	**2,129**		**691 (51)**	**1,353 (69)**	**1,292 (67)**	**322 (82)**	**1382 (71)**

DST: drug sensitivity testing; MDR TB: multidrug-resistant tuberculosis.

[1] Data reported between 2003 and 2007.

[2] Data reported between 2003 and 2005.

[3] Data reported between 2004 and 2005.

[4] Data reported in 2005 and 2006 in Poland ; 2003 and 2005 in Cyprus; 2003, 2005 and 2006 in Slovenia.

their country of birth (if available) or their country of citizenship.

Reporting of drug susceptibility testing for second-line drugs and XDR TB cases

DST results for SLD, resistant or susceptible, were collected for the following drugs: amikacin, kanamycin, capreomycin, ciprofloxacin, ofloxacin. The rationale behind the choice of the SLD tested was that they represented the most commonly used aminoglycosides (injectables) and fluoroquinolones. If no resistance is measured against the tested drugs within each of these two classes of drugs, it is unlikely that resistance can be found against other drugs from the same classes, because of cross-resistance. Data were validated by EuroTB, eventually completed by the reporting NSI and collated into a European MDR TB case database.

The revised 2006 XDR TB case definition was used for the analysis [8]. This definition refers to XDR TB as resistance to at least isoniazid and rifampicin as well as further resistance to a fluoroquinolone (ofloxacin, ciprofloxacin) and at least one second-line injectable aminoglycocide (amikacin, kanamycin and capreomycin).

The number and distribution of MDR TB isolates tested for anti-TB second-line DST as well as the number and proportion of XDR TB cases by country were calculated. The percentage of SLD tested (SLD testing percentage) for a given country was defined as the number of tests performed for a specific drug divided by the number of MDR TB cases reported in that country. The proportion of XDR TB cases was calculated using the number of MDR TB cases tested for SLD (included in the XDR TB definition) as a denominator.

As reported by EuroTB [17], anti-TB drug resistance surveillance (DRS) was performed on nationwide samples of TB cases in all 18 countries participating to the MDR TB project [14], except for Italy and Spain (partial coverage) and Poland (no information about representativeness available). Data from Romania was provided from a country-wide DST survey.

The number of MDR TB cases reported to the project was compared with the number of MDR TB cases reported to Euro-TB using drug resistance susceptibility data.

Table 2

Distribution of MDR and XDR TB cases by country reported in 18 European countries, 2003-2007[1]

Country (number of TB cases reported to EuroTB)	MDR TB cases reported to MDR TB project N	MDR TB isolates tested for 2-5 SLD N (%)	XDR TB cases N	XDR among MDR TB cases with SLD DST %
Countries with at least 88% of MDR TB cases tested for two to five SLD				
Latvia (6,107)	712	688 (97)	53	8
Estonia (1,736)	248	245 (99)	58	24
France (16,986)	152	149 (98)	1	1
Romania (60,323)	50	44 (88)	2	5
Israel (1,454)	45	44 (98)	2	5
Netherlands (3,820)	34	33 (97)	1	3
Switzerland (2,303)	25	22 (88)	0	0
Norway (1,221)	11	11 (100)	0	0
Denmark (1,200)	5	5 (100)	0	0
Slovenia (1,049)	3	3 (100)	1	33
Cyprus (102)	3	3 (100)	0	0
Total	**1,288**	**1,247 (97)**	**118**	**9%**
Countries with less than 88% of MDR TB cases tested for two to five SLD				
Lithuania (5,088)	656	173 (26)	25	14
Czech Republic (4199)	38	25 (66)	5	20
Belgium (4,187)	31	12 (39)	0	0
Poland (17,873)	17	6 (35)	0	0
Macedonia (2,662)	15	8 (53)	0	0
Ireland (1,747)	8	3 (38)	1	33
Croatia (3,931)	5	1 (20)	0	0
Total	**770**	**228 (30)**	**31**	**14%**
Total	**2,058**	**1,475 (72)**	**149**	**10%**

DST: drug sensitivity testing; MDR TB: multidrug-resistant tuberculosis, XDR TB: extensively drug-resistant tuberculosis; SLD: second line drugs.

[1] Data reported for at least one year between 2003 and 2007.

Results

Individual data on SLD testing for *Mycobacterium tuberculosis* isolates from 2,129 cases reported between January 2003 and July 2007 were available for 20 countries (population of 259,467,657) out of 24 European countries (population of 467,007,506), including 15 EU countries. Data were not reported by Germany, Italy, Finland and the United Kingdom, representing almost half of the total population covered by the surveillance project.

Sixteen additional MDR TB cases were reported by the MDR TB surveillance system when compared with the number of routinely reported MDR TB cases to EuroTB in ten countries with representative data reported during three consecutive years (2003-2005) (i.e. Belgium, Denmark, Estonia, Ireland, Israel, Latvia, Netherlands, Norway, Slovenia, Switzerland) [17].

Number of second-line anti-TB drugs tested for susceptibility by country

The number of SLD tested varied from one to five by country (Table 1).

In the five countries where SLD testing was reported for all five drugs; France, Czech Republic, Norway, Ireland, and Slovenia, the proportion of MDR TB cases tested (SLD testing percentages) varied from ≥ 13% in Ireland to ≥ 58% in the Czech Republic, and ≥ 89% in France. In countries where DST was performed for four SLD, ciprofloxacin was not tested in Lithuania and Estonia, and kanamycin was not tested in Israel, Switzerland, and Denmark. Testing percentages were very high (≥ 96%) in Estonia and Israel for all the SLD tested. In contrast, testing percentages were low in Lithuania (≤ 26%).

In the six countries where DST was performed for three drugs, amikacin was included in testing practices in all the countries, except in Latvia. DST was performed for two drugs (amikacin and ciprofloxacin) in the Netherlands (testing percentage ≥ 97%) and Croatia (testing percentage ≤ 40%). Two countries, Sweden and Spain tested for one SDL.

In six countries (Norway, Ireland, Slovenia, Denmark, Cyprus and Croatia), the numbers of MDR TB cases reported was small and therefore the results for those countries do not necessarily reflect the testing practices in these countries.

XDR TB cases reported by country

The number of XDR TB cases was calculated for the 18 countries where MDR TB isolates were tested for at least two SLD (Table 2). When considering the proportion of MDR TB cases tested for SLD, two groups of countries could be distinguished: group 1, countries with a high (≥ 88%) percentage of SLD testing and group 2, countries with a low (≤ 88%) percentage of SLD testing (Table 2). The ten countries in group 1 represented 63% (1,288/2,058) of reported MDR TB cases and 79% of the identified XDR TB cases.

XDR TB cases were detected in 10 countries, of which nine are EU Member States, and seven belonged to group 1. The overall proportion of XDR TB cases among MDR TB cases with DST for SLD was 10%. Ninety-one percent (136/149) of the XDR TB cases detected were reported in the Baltic States, where the percentage of XDR TB among MDR TB patients tested for SLD was 8% or higher (Table 2). In Estonia, 24% of MDR TB cases with DST results for SLD were XDR. This percentage is based on a highly representative sample of 99% of MDR TB patients tested for SLD. Therefore, this result indicates a relatively high prevalence of XDR TB among MDR TB cases in this country. In Latvia, where SLD results were available for 97% of MDR TB, the proportion of XDR TB was three times lower than in Estonia. In Lithuania, the proportion of XDR TB (14%) was based on a sample of 173 MDR TB cases with DST results. These 173 patients represent 26% of all reported MDR TB cases, which may not have been selected randomly meaning that only the most severe cases may have been tested for SLD. In the Czech Republic, the percentage of XDR TB cases was relatively high (20%), but the information for SLD testing was only available for 25 cases, representing 66% of the Czech MDR TB cases reported to our project.

Discussion

This surveillance-based project provides baseline data on XDR TB in a large number of European countries at the time of the establishment of the XDR TB case definition. Although four western European countries with a large population were not included in this project, results show that at least one XDR TB case was reported in 10 out of 18 European countries. The overall proportion of XDR TB among 1,475 (72%) MDR TB patients tested for SLD was approximately 10%. Ninety-one percent of the reported 149 XDR TB cases were notified by the three Baltic countries (Estonia: 248 cases, Latvia: 712 cases, Lithuania: 656 cases), which belonged to the former Soviet Union until 2004. This confirms the finding of a worldwide survey conducted by WHO and the US CDC, showing that the proportion of XDR TB among TB patients originating from former Soviet Union countries is high. [18].

These data have to be interpreted in a broader scope of the establishment of TB surveillance and control in the WHO European Region [19,20]. The number of XDR TB cases detected can partly be affected by differences in surveillance systems between countries for case definitions, the possibility of linking laboratory and notification data, and by data quality (completeness and validity). The revision of the XDR TB definition had an impact on the determination of the number of XDR TB cases in European countries [8]. According to the previous case definition, the proportion of XDR among MDR TB cases was estimated to be higher in 17 countries [12].

The fact that 20 out of 24 participating countries reported SLD test results for at least one drug, and that

DST for SLD was performed but not available for reporting in at least one other country, the United Kingdom, is a positive indicator for the availability of DST for SLD at European level. However, the number of XDR TB cases reported could be underestimated because of the limited number of SLD susceptibility testing in some countries or over-estimated due to lack of standardisation.

The number and type of SLD tested varied considerably between countries. A lack of standardisation and homogeneity in drug susceptibility testing practices for SLD has been identified by a panel of laboratory experts [21]. However, susceptibility testing of SLD has yielded reliable and reproducible results for some of the SLD [22]. Cross-resistance is common among aminoglycosides and absolute among fluoroquinolones, however, not all isolates exhibit the same resistance profile. Despite issues related to cross-resistance, it remains important to test a broad panel of SLD [23]. At the time of reporting, SLD DST methods had not been standardised or recommended, and External Quality Assurance (EQA) was not available, but since 2007 EQA for SLD has begun and since 2008 policy guidance has been published, which should help in standardising testing practices [21]. Therefore, it is expected that SLD DST practices and standardisation of these will improve significantly within the coming years.

The findings of this project and previous ones [14,18] concerning the relatively high rate of 10% XDR among MDR TB cases, should have an impact on clinical management of individual patients and TB control, especially in eastern European countries. There is a need for new drugs and treatment strategies. However, while new drugs will only be available in a number of years, the utility of derivates of current drugs and also alternative drugs like meropenem should be explored [24]. Serious consequences for TB control may be related to increased travel and migration, as this can lead to imported cases MDR TB from eastern Europe to western Europe, and transmissible forms of MDR and XDR TB are a fearsome scenario [14]. If transmission of XDR TB is diagnosed in western European countries, new strategies on monitoring risks associated with immigration from and travel to high-incidence settings should be developed.

Our surveillance project has some limitations that should be taken into account in future MDR and XDR TB surveillance in Europe. It would be of considerable value if data from the four missing countries could be added. In countries with a low proportion of patients tested for SLD, (Lithuania, Czech Republic), additional data is needed to better interpret the XDR TB prevalence. In countries with low numbers of XDR TB cases reported (e.g. Ireland and Slovenia), XDR TB percentages can be biased and therefore should not be compared to other countries.

Conclusion

Further research are conducted on the occurrence of transmitted MDR and XDR TB strains to investigate whether they pose a new evolutionary development of *M. tuberculosis*, or an extend of the current problem. Both scenarios would highlight consequences of a long lasting, uncontrolled problem and demonstrate the need for enhanced efforts in TB control in the regions where this problem develops. The capacity for SLD testing should be upgraded, especially in areas with high numbers of drug-resistant TB cases, such as in eastern Europe. As identified in a previous survey [25], standardisation and quality assurance of laboratory methods for DST of SLD should be improved across Europe. An EU reference laboratory network has been established with EU Member States to support their activities [26]. Surveillance data on MDR and XDR TB with improved quality are essential to determine the magnitude of this threat to TB control. In addition, surveillance data is needed to monitor TB control activities, and as a basis for implementing appropriate treatment and care and to prioritise laboratory resources.

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Analysis of tuberculosis treatment outcomes in the European Union and European Economic Area: efforts needed towards optimal case management and control

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An analysis of surveillance data was performed to assess treatment outcomes of patients belonging to selected calendar year cohorts. Twenty-two countries in the European Union (EU) and European Economic Area (EEA) reported treatment outcome monitoring data for culture-confirmed pulmonary tuberculosis (TB) cases reported in 2007. The overall treatment success rate was 73.8% for all culture-confirmed pulmonary cases and 79.5% for new culture-confirmed pulmonary cases. For the cohort of new culture-confirmed TB cases, only three countries achieved the target of 85% success rate. This underachievement appears to be a result of relative high defaulting and unknown outcome information. Case fatality remains high particularly among cases of national origin. This factor appears attributable to advanced age of the national cohort. Treatment outcomes for multidrug-resistant tuberculosis were reported by 15 countries, with a range of 19.8% to 100% treatment success at 24 months. The data underline the urgent need for strengthening treatment outcome monitoring in the EU and EEA in order to ensure an effective programme implementation and case management that will ultimately contribute to TB elimination.

Background

Tuberculosis (TB) remains a global emergency with estimates of 1.8 millions deaths worldwide in 2008 and over nine million cases. In 2008, the estimated global incidence rate fell to 139 cases per 100,000 population after reaching its peak in 2004 at 143 per 100,000. However, this decline was not homogeneous throughout the World Health Organization (WHO) regions, with Europe failing to record a substantial decline, but rather appearing to have reached a stabilisation of rates [1].

The 30 Member States of the European Union (EU) and European Economic Area (EEA) present a peculiar and highly heterogeneous situation in terms of TB epidemiology and control. Three broad epidemiological areas are distinguished within the borders of the EU/EEA: low incidence countries (below 20 notified cases per 100,000 population) with cases aggregating in vulnerable populations and only occasional increased notification rates; countries with moderate-to-high, but declining notification rates and with a low proportion of multidrug-resistant (MDR) TB; and finally, countries with relatively high notification rates (over 100 notified cases per 100,000) and high levels of MDR TB, but again with declining overall TB rates [2-4].

Attention to TB control in the EU and EEA has been raised in recent years through a number of initiatives, including the launching of a Framework Action Plan to Fight Tuberculosis in the EU [5]. Among the key issues underlined in the Action Plan is the need to achieve and sustain acceptable levels of treatment success among all TB patients.

Treatment success measured by a standardised process of treatment outcome monitoring (TOM) is one of the pillars of TB control and, along with case detection, is recognised as a key programmatic output. It is against this rationale that a World Health Assembly (WHA) resolution was passed in 1991, adopting two targets for global TB control: to detect at least 70% of new infectious cases and to cure at least 85% of those detected. These targets were linked to the Millennium Development Goals, and the Stop TB Partnership set the year 2005 as the deadline for achievement [6-8].

Globally, the treatment success rate has exceeded the 85% target for the first time in 2008 since the target was set in 1991, with a percentage of 87% for patients starting treatment in 2007. Furthermore, treatment success rates were maintained or improved between 2006 and 2007 in all WHO regions with the exception of the European Region which recorded the lowest success rate globally at 67% [1].

The importance of strengthening treatment outcome monitoring in Europe has long been recognised. A statement put forward by the WHO and the International Union against Tuberculosis and Lung

Disease underlined in 1998 the need for standardisation and evaluation of treatment results for TB patients in the WHO European region, including those in low and intermediate incidence countries [9].

In this study we aimed to analyse treatment outcomes and progress towards the targets specifically for the EU/EEA region as a whole and its Member States separately.

Since 1 January 2008, the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe have jointly coordinated the TB surveillance in Europe. Designated national surveillance institutions or individuals are responsible for providing the data, which is reported to a central joint database. Furthermore, historical data are available from the former EuroTB project for TB surveillance activities in Europe from 1996 to 2007. These data represent a valuable source for an in-depth analysis of treatment outcome monitoring and were used in our study.

Methods

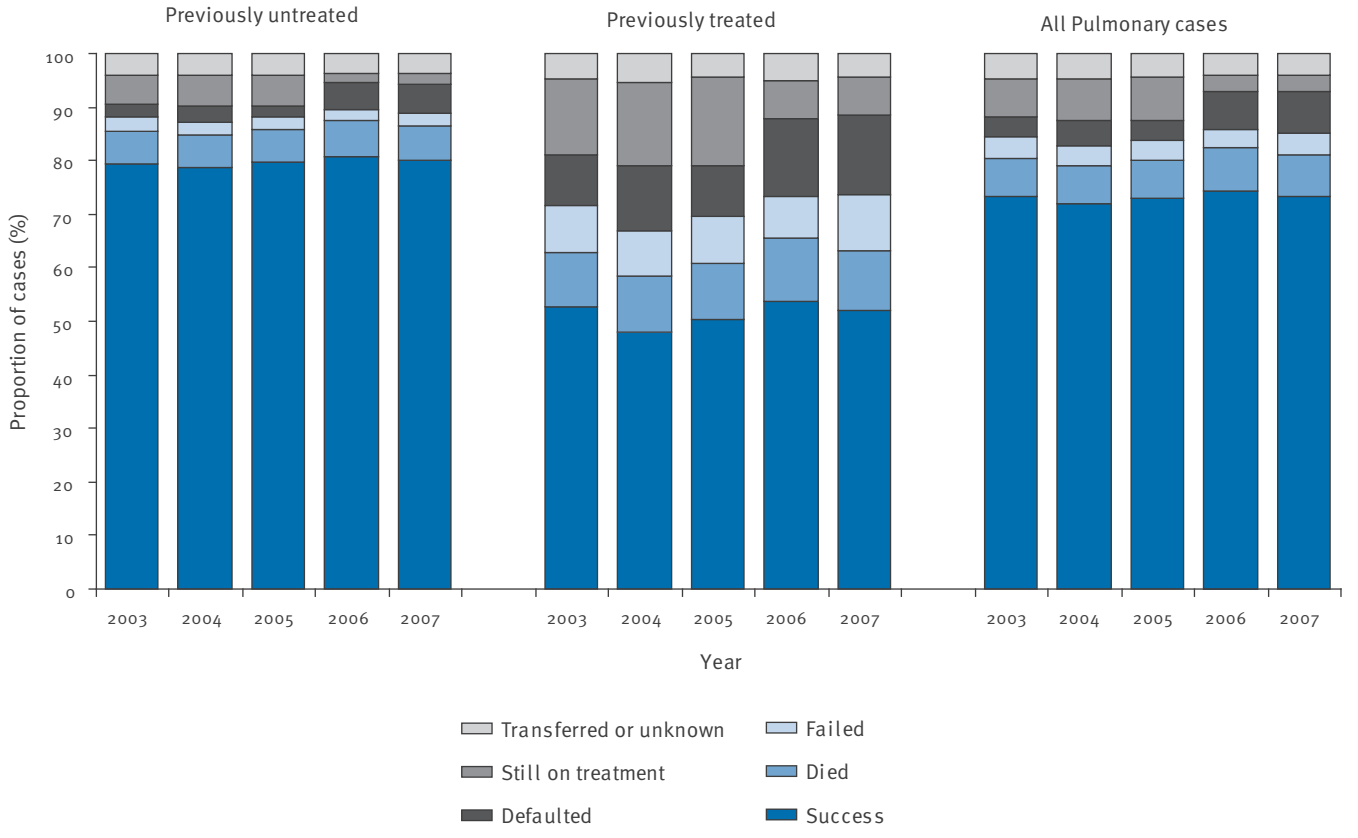
A descriptive analysis of surveillance data was performed to assess treatment outcomes of patients belonging to selected calendar year treatment cohorts.

Data were extracted from The European Surveillance System (TESSy) and from the former EuroTB historical database for the 30 EU and EEA countries reporting data to the ECDC. Since the reporting year 2002, outcome data are collected for all individual cases by submission of an individual dataset for the 12 months before the year for which notification data are reported to TESSy, and since 2008 also for MDR treatment outcome for cases reported 24 months before the year for which notification data are reported to TESSy. The cases eligible for outcome analysis (cohorts) include all the culture-confirmed pulmonary TB cases notified in the calendar year of interest, after exclusion of cases with final diagnosis other than TB.

Country-specific data were extracted for 2007 for both new and retreatment laboratory-confirmed pulmonary TB cases for the analysis of 12 months of treatment outcome data. For 2006, country-specific data were extracted for laboratory-confirmed MDR TB cases (combined new and retreatment) for the analysis of 24 months of treatment outcome data. Aggregated EU/EEA data were extracted for the period 2003 to 2007 for trend analysis of treatment outcome for new, retreatment and combined laboratory-confirmed pulmonary

Figure 1

Treatment outcome of laboratory-confirmed pulmonary cases, EU/EEA countries[1] 2003-2007



EEA: European Economic Area; EU: European Union.

[1] Excluding countries that did not or not in all years report cases: Austria, Bulgaria, Finland, France, Greece, Liechtenstein, Luxembourg, and Spain.

Table 1

Treatment outcome in new and retreatment culture-confirmed pulmonary tuberculosis cases, by country, EU/EEA countries, 2007 (n=36,377)

	Cases notified in 2007	Success		Died		Failed		Defaulted		Still on treatment		Transferred or unknown	
Country	**N**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
New cases													
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium[1]	499	342	(68.5)	42	(8.4)	0	(0.0)	44	(8.8)	12	(2.4)	59	(11.8)
Bulgaria	1,233	972	(78.8)	85	(6.9)	4	(0.3)	96	(7.8)	41	(3.3)	35	(2.8)
Cyprus	-	-	-	-	-	-	-	-	-	-	-	-	-
Czech Republic	459	331	(72.1)	86	(18.7)	4	(0.9)	32	(7.0)	4	(0.9)	2	(0.4)
Denmark[1]	213	169	(79.3)	11	(5.2)	2	(0.9)	3	(1.4)	11	(5.2)	17	(8.0)
Estonia	302	185	(61.3)	41	(13.6)	2	(0.7)	29	(9.6)	45	(14.9)	0	(0.0)
Finland	181	126	(69.6)	35	(19.3)	1	(0.6)	2	(1.1)	7	(3.9)	10	(5.5)
France	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	2,421	1,863	(77.0)	277	(11.4)	3	(0.1)	36	(1.5)	69	(2.9)	173	(7.1)
Greece	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	612	311	(50.8)	74	(12.1)	86	(14.1)	34	(5.6)	84	(13.7)	23	(3.8)
Iceland	7	6	(85.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)
Ireland[1]	181	127	(70.2)	10	(5.5)	0	(0.0)	3	(1.7)	8	(4.4)	33	(18.2)
Italy	-	-	-	-	-	-	-	-	-	-	-	-	-
Latvia	772	634	(82.1)	54	(7.0)	1	(0.1)	32	(4.1)	51	(6.6)	0	(0.0)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	1,209	860	(71.1)	144	(11.9)	18	(1.5)	89	(7.4)	94	(7.8)	4	(0.3)
Luxembourg	-	-	-	-	-	-	-	-	-	-	-	-	-
Malta	12	9	(75.0)	0	(0.0)	0	(0.0)	1	(8.3)	1	(8.3)	1	(8.3)
Netherlands[1]	397	314	(79.1)	18	(4.5)	0	(0.0)	8	(2.0)	0	(0.0)	57	(14.4)
Norway[1]	114	89	(78.1)	2	(1.8)	0	(0.0)	0	(0.0)	4	(3.5)	19	(16.7)
Poland	4,502	3,444	(76.5)	269	(6.0)	12	(0.3)	448	(10.0)	16	(0.4)	313	(7.0)
Portugal	1,694	1,467	(86.6)	90	(5.3)	5	(0.3)	52	(3.1)	56	(3.3)	24	(1.4)
Romania	11,245	9,508	(84.6)	453	(4.0)	442	(3.9)	533	(4.7)	95	(0.8)	214	(1.9)
Slovakia	304	260	(85.5)	36	(11.8)	1	(0.3)	5	(1.6)	1	(0.3)	1	(0.3)
Slovenia	150	123	(82.0)	16	(10.7)	0	(0.0)	4	(2.7)	0	(0.0)	7	(4.7)
Spain	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweden[1]	237	157	(66.2)	17	(7.2)	0	(0.0)	2	(0.8)	8	(3.4)	53	(22.4)
United Kingdom[1]	2,241	1,733	(77.3)	145	(6.5)	0	(0.0)	15	(0.7)	128	(5.7)	220	(9.8)
Total New cases	**28,985**	**23,030**	**(79.5)**	**1,905**	**(6.6)**	**581**	**(2.0)**	**1,468**	**(5.1)**	**735**	**(2.5)**	**1,266**	**(4.4)**
Retreatment cases													
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium[2]	49	27	(55.1)	6	(12.2)	0	(0.0)	4	(8.2)	8	(16.3)	4	(8.2)
Bulgaria	146	52	(35.6)	38	(26.0)	2	(1.4)	23	(15.8)	27	(18.5)	4	(2.7)
Cyprus	-	-	-	-	-	-	-	-	-	-	-	-	-
Czech Republic	44	30	(68.2)	7	(15.9)	0	(0.0)	4	(9.1)	2	(4.5)	1	(2.3)
Denmark[2]	18	8	(44.4)	3	(16.7)	0	(0.0)	1	(5.6)	1	(5.6)	5	(27.8)
Estonia	66	31	(47.0)	5	(7.6)	3	(4.5)	13	(19.7)	14	(21.2)	0	(0.0)
Finland	7	7	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
France	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	178	114	(64.0)	25	(14.0)	3	(1.7)	8	(4.5)	13	(7.3)	15	(8.4)
Greece	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	130	51	(39.2)	26	(20.0)	26	(20.0)	12	(9.2)	13	(10.0)	2	(1.5)
Iceland	1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(100.0)
Ireland[2]	28	16	(57.1)	4	(14.3)	0	(0.0)	0	(0.0)	3	(10.7)	5	(17.9)
Italy	-	-	-	-	-	-	-	-	-	-	-	-	-
Latvia	167	96	(57.5)	14	(8.4)	2	(1.2)	17	(10.2)	36	(21.6)	2	(1.2)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	423	130	(30.7)	119	(28.1)	21	(5.0)	89	(21.0)	63	(14.9)	1	(0.2)

Luxembourg	-	-	-	-	-	-	-	-	-	-	-	-	-
Malta	1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(100.0)
Netherlands[2]	40	27	(67.5)	3	(7.5)	0	(0.0)	1	(2.5)	0	(0.0)	9	(22.5)
Norway[2]	17	13	(76.5)	1	(5.9)	0	(0.0)	0	(0.0)	1	(5.9)	2	(11.8)
Poland	698	429	(61.5)	69	(9.9)	4	(0.6)	141	(20.2)	8	(1.1)	47	(6.7)
Portugal	182	140	(76.9)	13	(7.1)	0	(0.0)	11	(6.0)	12	(6.6)	6	(3.3)
Romania	4,933	2,462	(49.9)	479	(9.7)	683	(13.8)	767	(15.5)	325	(6.6)	217	(4.4)
Slovakia	42	35	(83.3)	1	(2.4)	1	(2.4)	1	(2.4)	4	(9.5)	0	(0.0)
Slovenia	13	10	(76.9)	3	(23.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Spain	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweden[2]	13	7	(53.8)	2	(15.4)	0	(0.0)	1	(7.7)	1	(7.7)	2	(15.4)
United Kingdom[2]	196	141	(71.9)	22	(11.2)	0	(0.0)	0	(0.0)	14	(7.1)	19	(9.7)
Total retreatment	**7,392**	**3,826**	**(51.8)**	**840**	**(11.4)**	**745**	**(10.1)**	**1,093**	**(14.8)**	**545**	**(7.4)**	**343**	**(4.6)**
Total for all	**36,377**	**26,856**	**(73.8)**	**2,745**	**(7.5)**	**1,326**	**(3.6)**	**2,561**	**(7.0)**	**1,280**	**(3.5)**	**1,609**	**(4.4)**

EEA: European Economic Area; EU: European Union.

[1] Not previously diagnosed cases.

[2] Previously diagnosed cases.

Table 2

Treatment outcome in culture-confirmed pulmonary TB cases by geographic origin and by country, EU/EEA countries, 2007 (n=37,160)

	Cases	Success		Died		Failed		Defaulted		Still on treatment		Transferred or unknown	
Country	**N**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
National origin													
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium	327	224	(68.5)	42	(12.8)	0	(0.0)	14	(4.3)	8	(2.4)	39	(11.9)
Bulgaria	1,379	1,024	(74.2)	123	(8.9)	6	(0.4)	119	(8.6)	68	(4.9)	39	(2.8)
Cyprus	-	-	-	-	-	-	-	-	-	-	-	-	-
Czech Republic	407	306	(75.2)	84	(20.6)	3	(0.7)	9	(2.2)	5	(1.2)	0	(0.0)
Denmark[1]	113	89	(78.8)	10	(8.8)	1	(0.9)	1	(0.9)	4	(3.5)	8	(7.1)
Estonia	312	184	(59.0)	38	(12.2)	3	(1.0)	36	(11.5)	51	(16.3)	0	(0.0)
Finland	146	99	(67.8)	35	(24.0)	1	(0.7)	1	(0.7)	5	(3.4)	5	(3.4)
France	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	1,680	1,214	(72.3)	292	(17.4)	6	(0.4)	28	(1.7)	47	(2.8)	93	(5.5)
Greece	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	719	345	(48.0)	100	(13.9)	113	(15.7)	43	(6.0)	94	(13.1)	24	(3.3)
Iceland	1	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ireland	149	103	(69.1)	14	(9.4)	0	(0.0)	3	(2.0)	2	(1.3)	27	(18.1)
Italy	-	-	-	-	-	-	-	-	-	-	-	-	-
Latvia	887	691	(77.9)	66	(7.4)	3	(0.3)	44	(5.0)	82	(9.2)	1	(0.1)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	1,593	971	(61.0)	258	(16.2)	36	(2.3)	172	(10.8)	151	(9.5)	5	(0.3)
Luxembourg	-	-	-	-	-	-	-	-	-	-	-	-	-
Malta	5	4	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(20.0)
Netherlands	198	148	(74.7)	19	(9.6)	0	(0.0)	6	(3.0)	0	(0.0)	25	(12.6)
Norway	26	21	(80.8)	3	(11.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)
Poland	5,178	3,863	(74.6)	338	(6.5)	16	(0.3)	586	(11.3)	24	(0.5)	351	(6.8)
Portugal	1,622	1,397	(86.1)	93	(5.7)	5	(0.3)	48	(3.0)	56	(3.5)	23	(1.4)
Romania	16,178	11,970	(74.0)	932	(5.8)	1,125	(7.0)	1,300	(8.0)	420	(2.6)	431	(2.7)
Slovakia	346	296	(85.5)	38	(11.0)	2	(0.6)	6	(1.7)	4	(1.2)	0	(0.0)
Slovenia	128	106	(82.8)	17	(13.3)	0	(0.0)	4	(3.1)	0	(0.0)	1	(0.8)
Spain	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweden	66	37	(56.1)	12	(18.2)	0	(0.0)	1	(1.5)	1	(1.5)	15	(22.7)
United Kingdom	915	673	(73.6)	113	(12.3)	0	(0.0)	7	(0.8)	44	(4.8)	78	(8.5)

Total Nationals	**32,380**	**23,765**	**(73.4)**	**2,628**	**(8.1)**	**1,320**	**(4.1)**	**2,428**	**(7.5)**	**1,066**	**(3.3)**	**1,173**	**(3.6)**
Foreign origin													
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium	288	190	(66.0)	17	(5.9)	0	(0.0)	39	(13.5)	13	(4.5)	29	(10.1)
Bulgaria	1	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cyprus	-	-	-	-	-	-	-	-	-	-	-	-	-
Czech Republic	96	55	(57.3)	9	(9.4)	1	(1.0)	27	(28.1)	1	(1.0)	3	(3.1)
Denmark[2]	118	88	(74.6)	4	(3.4)	1	(0.8)	3	(2.5)	8	(6.8)	14	(11.9)
Estonia	56	32	(57.1)	8	(14.3)	2	(3.6)	6	(10.7)	8	(14.3)	0	(0.0)
Finland	42	34	(81.0)	0	(0.0)	0	(0.0)	1	(2.4)	2	(4.8)	5	(11.9)
France	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	1,157	914	(79.0)	66	(5.7)	1	(0.1)	24	(2.1)	37	(3.2)	115	(9.9)
Greece	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	24	14	(58.3)	0	(0.0)	3	(12.5)	4	(16.7)	3	(12.5)	0	(0.0)
Iceland	7	5	(71.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(28.6)
Ireland	95	62	(65.3)	3	(3.2)	0	(0.0)	0	(0.0)	9	(9.5)	21	(22.1)
Italy	-	-	-	-	-	-	-	-	-	-	-	-	-
Latvia	52	39	(75.0)	2	(3.8)	0	(0.0)	5	(9.6)	5	(9.6)	1	(1.9)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	43	21	(48.8)	7	(16.3)	3	(7.0)	6	(14.0)	6	(14.0)	0	(0.0)
Luxembourg	18	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	18	(100.0)
Malta	9	5	(55.6)	0	(0.0)	0	(0.0)	1	(11.1)	1	(11.1)	2	(22.2)
Netherlands	285	216	(75.8)	10	(3.5)	0	(0.0)	4	(1.4)	0	(0.0)	55	(19.3)
Norway	121	90	(74.4)	2	(1.7)	0	(0.0)	0	(0.0)	5	(4.1)	24	(19.8)
Poland	22	10	(45.5)	0	(0.0)	0	(0.0)	3	(13.6)	0	(0.0)	9	(40.9)
Portugal	249	208	(83.5)	8	(3.2)	0	(0.0)	15	(6.0)	12	(4.8)	6	(2.4)
Romania	0	0	-	0	-	0	-	0	-	0	-	0	-
Slovakia	4	2	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	1	(25.0)
Slovenia	35	27	(77.1)	2	(5.7)	0	(0.0)	0	(0.0)	0	(0.0)	6	(17.1)
Spain	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweden	184	127	(69.0)	7	(3.8)	0	(0.0)	2	(1.1)	8	(4.3)	40	(21.7)
United Kingdom	1,874	1,467	(78.3)	82	(4.4)	0	(0.0)	11	(0.6)	106	(5.7)	208	(11.1)
Total Foreigners	**4,780**	**3,607**	**(75.5)**	**227**	**(4.7)**	**11**	**(0.2)**	**151**	**(3.2)**	**225**	**(4.7)**	**559**	**(11.7)**

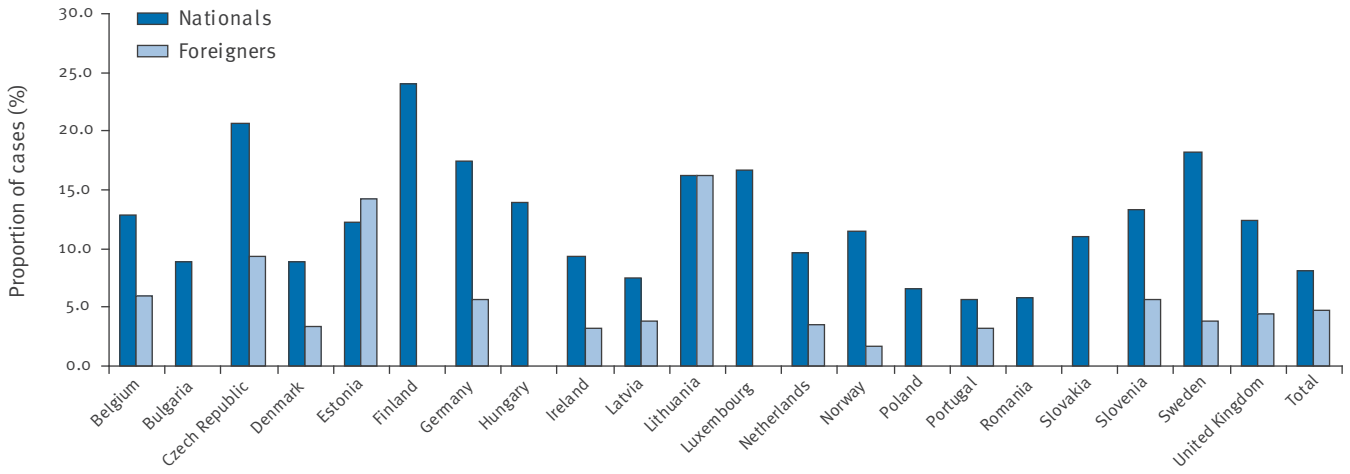
EEA: European Economic Area; EU: European Union.

[1] Excluding native cases < 26 years old whose parents were born outside Denmark

[2] Including native cases < 26 years old whose parents were born outside Denmark

Figure 2

Proportion of tuberculosis deaths by geographic origin, EU/EEA countries[1], 2007 (of n=37,160 cases)



EEA: European Economic Area; EU: European Union.

[1] Excluding countries that did not or not in all years report cases.

TB cases. The following case classification was used for the purpose of the analysis:

- A ***laboratory-confirmed TB case*** was a patient with culture-confirmed disease due to *Mycobacterium tuberculosis* complex.
- A ***new case*** was any case who had not received drug treatment for active TB in the past, or who received anti-TB drugs for less than one month.
- A ***retreatment case*** was a case diagnosed with TB in the past and who received treatment with anti-TB drugs (excluding preventive therapy) for at least one month.
- A ***pulmonary case*** was any case with TB affecting the lung parenchyma, the tracheo-bronchial tree or the larynx.
- ***Multi-drug resistance*** was defined as resistance to at least isoniazid and rifampicin.
- ***Foreign/national origin*** for comparison of treatment outcome by geographical origin of TB cases was classified according to place of birth: born in the country (national origin) or born outside the country (foreign origin). For countries reporting citizenship rather than place of birth, the former was used as a proxy of national/foreign origin. In Denmark, the place of birth of parents was also used to classify geographical origin.

For the purpose of this analysis, internationally recommended outcome categories where used with two additional categories [9]: 'still on treatment' after 12 months of treatment, and 'unknown'. Adopted definitions in our study were:

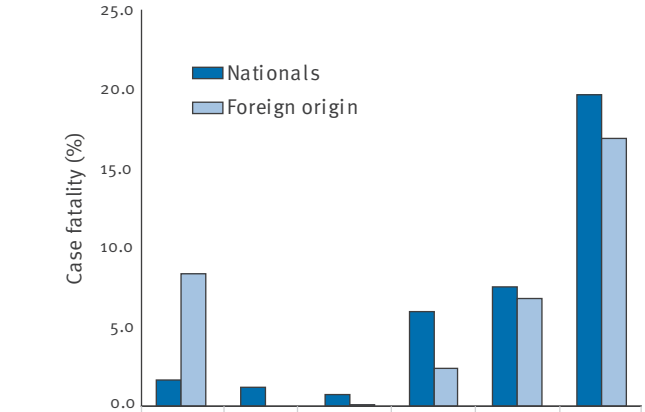
- ***Cured:*** The treatment has been completed and culture has become negative on samples taken at the end of treatment and on at least one previous occasion.
- ***Completed:*** The treatment has been completed but the case does not meet the criteria for cure or treatment failure.
- ***Failed:*** Culture or sputum smear remain positive or become positive again five months or later into the course of treatment.
- ***Died:*** Death, irrespective of cause, occurred before the patient was cured or treatment was completed.
- ***Defaulted:*** The treatment was interrupted for two months or more, not resulting from a decision of the care provider; or the patient was lost to follow-up for two months or more before the end of treatment, except if transferred.
- ***Transferred:*** The patient was referred to another clinical unit for treatment, and information on outcome is not available.
- ***Still on treatment:*** The patient is still on treatment at 12 (24 when applicable) months after the start of treatment and did not meet any other outcome during treatment. This category includes patients whose initial treatment was changed due to poly-resistance (i.e. resistance to at least two first-line drugs) of the isolate taken at the start of treatment, whose treatment was prolonged because of side effects/complications, whose initial regimen had been planned for more than 12 months, or patients for whom information on the reasons for being still on treatment was not available.
- ***Unknown:*** Information on outcome is not available, for cases not known to have been transferred.
- ***Success:*** This refers to the combined number of patients belonging to the treatment categories 'cured' and 'completed'. The ***success rate target*** (established by the WHA as 85% of new smear-positive cases) has been adapted to the EU/EEA setting where bacteriological confirmation of cases is done by culture. Thus for the purposes of this study, a success rate target of 85% applies to new laboratory-confirmed cases.
- ***Cohort:*** This includes all cases eligible for outcome analysis (cohorts); i.e. all the culture-confirmed pulmonary TB cases notified in the calendar year of interest, after exclusion of cases with final diagnosis other than TB.

For the purpose of calculating the outcome variables, culture-confirmed pulmonary TB cases notified in the calendar year of interest were used as denominators. Data for one country were considered to be complete if the cohorts used as denominators included all culture-confirmed pulmonary TB cases notified in the year selected for analysis and if the combined total of 'defaulted, transferred and unknown' cases did not exceed 35% of cases notified in that year.

Proportions of deaths by geographic origin were stratified by age to allow comparability.
Adjustments to account for how countries with high numbers of cases influence the EU/EEA average were not performed as the study aimed at presenting overall figures for EU/EEA patients.

Figure 3

Age-stratified case fatality by geographic origin, EU/EEA countries, 2007 (of n=25,391 cases)



Age group (years)	0-4	05-14	15-24	25-44	45-64	>64
Nationals	1.6	1.2	0.7	6.0	7.6	19.7
Foreign origin	8.3	0.0	0.1	2.4	6.8	16.9

EEA: European Economic Area; EU: European Union.

Results

Twenty-two countries reported TOM data at 12 months for culture-confirmed pulmonary TB cases reported in 2007. Data were considered to be complete as per study definition in all reporting countries. The overall treatment success rate for all laboratory-confirmed pulmonary cases was 73.8%. Of these patients, 7.5% died while being treated for TB, 3.6% failed treatment, 7.0% defaulted, 3.5% were still on treatment at the end of the 12-month observation period and 4,4% had an outcome recorded as unknown or transferred (Figure 1, Table 1).

Among new laboratory-confirmed pulmonary cases, 79.5% had a successful outcome, 6.6% died, 2% failed, 2.5% were still on treatment, and 4.4% were transferred or had an unknown outcome (Table 1). Among countries with more than 20 new culture-confirmed pulmonary cases, success rates varied widely from 50.8% in Hungary to 86.6% and 85.5% in Portugal and Slovakia respectively. Three countries achieved treatment success in 85% or more of this category of cases: Iceland, 85.7%, Portugal, 86.6% and Slovakia, 85.5%. The percentage of cases that died while undergoing TB treatment ranged from 1.8% in Norway to 18.7% in the Czech Republic. Overall treatment success rates below 75% were associated with a high loss to follow-up (defaulted and transferred or unknown) ranging from 6.6% to 25.7%.

Treatment outcomes for retreatment culture-confirmed pulmonary TB cases were reported from 22 EU/EEA Member States (Table 1). For seven countries, information about previous treatment was not distinguished and reported as previously diagnosed cases (Belgium, Denmark, Ireland, the Netherlands, Norway, Sweden and United Kingdom). Among these retreatment cases the overall success rate was lower (51.8%; range: 0%–100%) than among new cases. Death (11.4%), treatment failure (10.1%), default (14.8%) and still on treatment (7.4%) were more frequently reported in this group than among new cases. Only six countries achieved a treatment success of at least 70% among retreatment cases (Table 1).

Analysis of data by geographic origin revealed similar proportions of successfully treated cases of national origin (73.4%) and those of foreign origin (75.5%). However, marked differences were observed in the proportion of deaths, with higher percentages among cases of national origin (8.1%) compared with those of foreign origin (4.7%). Similarly, differences were found in the percentages of failed cases (4.1% in nationals versus 0.2% in cases of foreign origin) and transferred/unknown (3.6% in nationals versus 11.7% in cases of foreign origin) (Table 2, Figure 2).

With regards to the differences in proportion of deaths between foreign origin and national cases, the stratification of case fatality by age group (Figure 3) reveals that age acts as an effect modifier, where the proportion of deaths increased with increasing age. The highest case fatality was in the age group of over 64-year-olds, regardless of geographical origin. The high case fatality in 0-4-year-old children in the group of foreign origin is a doubtful interpretation as there was only one death in this group.

Fifteen countries (12 of which provided complete data as per study definition) reported the treatment outcome at 24 months for culture-confirmed MDR TB cases (new and retreatment). The overall treatment success in the 15 countries ranged from 19.8% to 100%. Of the entire cohort, 16.6% died while on treatment, 17.0% failed treatment and 13.2% defaulted. 17.0% of registered cases were still on treatment at the end of the 24 months observation period and 5.3% had been transferred or had an unknown outcome (Table 3).

Analysis of trends for the cohorts 2003 to 2007 did not reveal any significant difference in the proportions of cases belonging to any of the treatment outcome categories. Treatment success remained in the range of 78% to 80% in the new laboratory-confirmed pulmonary cases. Minimal improvement from 48% to 52.2% was recorded between the 2006 and 2007 cohorts of retreatment culture-confirmed pulmonary cases (Figure 1).

Discussion and conclusions

This analysis of treatment outcome monitoring within the EU and EEA Member States revealed significant findings concerning TB control in the region. Firstly, it is a matter of concern that there has been only a marginal improvement in the number of countries reporting treatment outcomes to the EU-wide database, which increased by only one Member State compared with the 2006 cohort reporting (22 versus 21 countries). Similarly, the number of cases with an unknown treatment outcome because of transfer or 'outcome unknown', remained high with an average of 4.4% of all pulmonary culture-confirmed cases belonging to this category and with six of 22 countries reporting more than 10% of unknown outcomes. This represents a programmatic weakness in one of the pillars of TB control and highlights the importance of the monitoring and evaluation process [2,3,10].

More disturbing is the fact that there has been no significant improvement in the percentage of cases successfully treated over the past five years, with 79.5% of new laboratory-confirmed pulmonary cases successfully treated and 51.8% in retreatment cases. This is reflected at the level of the individual Member States: only three countries achieved the target of 85% success rate in 2007 compared with seven countries for the 2006 cohort.

The authors would have wished to extend the analysis of completeness of treatment to all notified cases to gain further insight in the distribution and quality of outcomes; however data proved insufficient to pro-

ceed with this approach since only few countries report treatment completion for all cases.

Achieving high success rates becomes particularly important in a setting like the EU and EEA where the decline in incidence that was typical of the past few decades is becoming slower in most countries [2]. This trend is certainly influenced by many factors including importation of cases from high-burden countries, outbreaks among vulnerable populations, persisting MDR TB, and in some cases a lack of adequate TB control measures. In this setting it is essential to achieve optimal treatment success in all TB patients.

The need for reaching the success rate target is justified by its potential epidemiological impact. Several epidemiological models have shown [11-14] that achieving the 85% success target coupled with a case detection of at least 70% would cause a decline in the annual TB incidence rate of 5-10% in the absence of co-infection with human immunodeficiency virus (HIV). These theoretical assumptions are further corroborated by empirical findings, particularly in the European context. In fact, the TB incidence has been declining rapidly all over Europe over the past century, but the decline has more than doubled following the introduction of effective treatment.

The analysis of the data by geographical origin (national versus foreign) revealed a similarity in the two groups in terms of overall success rate. Differences exist in the distribution of negative outcomes with regard to geographic origin. However, stratifying case fatality by age showed that the excess proportion of deaths

Table 3

Treatment outcome of multidrug-resistant tuberculosis cases after 24 months of treatment, EU/EEA countries, 2006 cohort (n=1,190)

Country	Total number of MDR cases	TOM after 24 months											
		Success		Died		Failed		Defaulted		Still on treatment		Transferred or unknown	
		N	%	N	%	N	%	N	%	N	%	N	%
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium	18	10	(55.6)	1	(5.6)	0	(0.0)	0	(0.0)	3	(16.7)	4	(22.2)
Bulgaria	-	-	-	-	-	-	-	-	-	-	-	-	-
Cyprus	0	-	-	-	-	-	-	-	-	-	-	-	-
Czech Republic	12	3	(25.0)	4	(33.3)	0	(0.0)	3	(25.0)	2	(16.7)	0	(0.0)
Denmark	3	2	(66.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)	0	(0.0)
Estonia	53	24	(45.3)	12	(22.6)	2	(3.8)	14	(26.4)	1	(1.9)	0	(0.0)
Finland	-	-	-	-	-	-	-	-	-	-	-	-	-
France	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	83	42	(50.6)	4	(4.8)	1	(1.2)	10	(12.0)	14	(16.9)	12	(14.5)
Greece	-	-	-	-	-	-	-	-	-	-	-	-	-
Hungary	17	9	(52.9)	1	(5.9)	5	(29.4)	1	(5.9)	1	(5.9)	0	(0.0)
Iceland	0	-	-	-	-	-	-	-	-	-	-	-	-
Ireland	4	1	(25.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	2	(50.0)
Italy	-	-	-	-	-	-	-	-	-	-	-	-	-
Latvia	142	87	(61.3)	34	(23.9)	6	(4.2)	15	(10.6)	0	(0.0)	0	(0.0)
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithuania	-	-	-	-	-	-	-	-	-	-	-	-	-
Luxembourg	0	-	-	-	-	-	-	-	-	-	-	-	-
Malta	2	2	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Netherlands	-	-	-	-	-	-	-	-	-	-	-	-	-
Norway	3	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(66.7)
Poland	32	11	(34.4)	4	(12.5)	3	(9.4)	4	(12.5)	0	(0.0)	10	(31.3)
Portugal	25	16	(64.0)	6	(24.0)	1	(4.0)	2	(8.0)	0	(0.0)	0	(0.0)
Romania	788	156	(19.8)	130	(16.5)	184	(23.4)	107	(13.6)	178	(22.6)	33	(4.2)
Slovakia	7	3	(42.9)	2	(28.6)	0	(0.0)	0	(0.0)	2	(28.6)	0	(0.0)
Slovenia	1	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Spain	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweden	-	-	-	-	-	-	-	-	-	-	-	-	-
United Kingdom	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal EU/EEA	**1,190**	**368**	**(30.9)**	**198**	**(16.6)**	**202**	**(17.0)**	**157**	**(13.2)**	**202**	**(17.0)**	**63**	**(5.3)**

EEA: European Economic Area; EU: European Union; MDR: multidrug-resistant; TOM: treatment outcome monitoring.

among nationals was attributed to older age. These findings are not unexpected, and the similarities in terms of success rate, evident also at country level, seem to suggest that foreign-born patients are not at a higher risk of unfavourable outcome.

The analysis also revealed a potential for worsening of the M/XDR TB epidemic in the EU and EEA, resulting from the high default rates recorded among retreatment and MDR TB cases (14.8% and 13.2%, respectively). Despite the data limitations with respect to the MDR TB analysis (with regards to data representativeness completeness and quality assurance of laboratory methods) a clear need for strengthening case holding and treatment monitoring among these two populations (retreatment and MDR TB) emerges. As widely shown in the literature, defaulting and previous unsuccessful treatment represent the biggest risk factor for the emergence of drug resistance, in particular M/XDR TB [15-18].

The role that surveillance of TB treatment outcomes can and ought to play in strengthening TB control needs to be highlighted. Reporting of outcomes allows close monitoring of the ability of TB programmes to support and ensure completion of patients' treatment. It also allows tailoring control activities to high-risk groups defined in terms of their inability to comply with treatment and achieve successful outcomes.

The claim that an unknown or unreported treatment outcome does not necessarily represent a negative one should be balanced against the argument that lack of knowledge about treatment outcomes deprives the programme of essential information to guide TB control.

Finally it should be noted that the importance of achieving the highest possible treatment success rate goes beyond its programmatic and epidemiological impact. Achieving universal success in treating individual patients remains a fundamental point in case management and patient care.

The importance of treatment outcome monitoring needs to be further stressed and mechanisms explored to maximise progress towards achievement of the targets. Clinicians, public health experts and policy makers must be convinced of the importance of a standardised approach to monitoring of treatment including a proper evaluation of its implementation. Only by recognising the key position that treatment outcome monitoring holds in TB control can progress towards elimination be pursued.

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Risk of developing tuberculosis from a school contact: retrospective cohort study, United Kingdom, 2009

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To quantify the risk of developing tuberculosis (TB) following school contact with a student with smear positive respiratory TB in a population with a high background rate of tuberculosis, a retrospective cohort study was conducted. This study included all students and staff (n=1,065) at an inner city secondary school in Birmingham, United Kingdom (UK). Being in the same school year as the index case resulted in a significantly higher risk of being diagnosed with active TB (odds ratio (OR) 6.11) and either active or latent TB (OR 10.52) compared to the risk for pupils in other school years. Neither lower level classroom exposure in tutoring groups nor being a staff member resulted in significantly increased risk of infection. The number of cases detected in the school was significantly higher than compared with the TB notification rate for the respective age groups in the population in the area. This study is consistent with the small body of evidence that already exists suggesting that greater levels of classroom contact with a student with smear positive active TB significantly increases the risk of contracting active and latent TB. It also suggests that staff may be at a lower risk of active TB than students. It does not appear that being in an area with high TB incidence substantially alters the epidemiology of the outbreak or risk of transmission between students in comparison to other populations.

Introduction

Historically tuberculosis (TB) has been a major cause of premature death in the United Kingdom (UK). It remains a serious disease and active TB can lead to death if not treated. An outbreak of TB in a school often causes major concern for children and parents and generates significant volumes of work for health-care organisations. In these situations it is important that action is based on robust scientific evidence to ensure that the correct response is being applied. However, the current evidence base for the management of a school-based outbreak of TB is small and increasing the size of this will ensure that screening strategies are both safe and effective in identifying those with infection.

The evidence base for the United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommendations for management of TB in schools [1] refers to five analytical studies [2-6] none of which are UK based, nor conducted in areas of high local prevalence of TB or where the majority of students are from black or minority ethnic (BME) groups. Of these studies only three have provided estimates of the relative risk to children and staff within the school following a case of smear positive (open) TB in a school pupil.

We conducted a retrospective cohort study following a large school-based TB outbreak in a state funded secondary school in the inner city of Birmingham, UK. Over 95% of the school's students were from BME groups and all were aged 10-16 years. The school was located in an area of central Birmingham with a high proportion of residents from a BME group (68%) [7] and one of highest incidence rates of tuberculosis in England [8]. In 2006 and 2007 it had a direct standardised incidence rate for TB of 109.6 and 99.4 cases per 100,000 population, respectively [9] compared with the UK average of 13.8 per 100,000 [10]. In both the 10-14 and 15-19-year-old age groups in the school uptake area the TB incidence was 105.7 per 100,000 in 2007 [8].

The index case for the outbreak was a 16-year-old male who was diagnosed with smear positive respiratory TB in December 2008. He had been increasingly unwell with cough and weight loss since September 2008. He had attended the school as usual for the majority of this time after which he received antimicrobial therapy and became smear negative. Initially the students in the same school year as the index case were screened for TB in February 2009. As a result of this screening which yielded several secondary cases of active TB, the whole school population was offered screening as advised by national guidance [1]. Screening of the whole school was carried out in April 2009.

This study aims to:

- Identify the risks of developing tuberculosis following different types of school contact with a child with smear positive respiratory TB.
- Quantify the magnitude of these risks.

Methods

Study population

The study population comprised all students (886) and staff members (179) who attended or worked at the school between September 2008 and April 2009 (n=1,065). The student population was evenly split between five school years (173-189 pupils in each year). Students in the same school year were all of a similar age.

Outcome measures and case ascertainment

The primary outcome measure was the diagnosis of active TB infection requiring full antimicrobial treatment by a physician specialising in infectious or respiratory diseases. The secondary outcome measure was the diagnosis of active or latent TB requiring chemoprophylaxis according to local TB screening protocols.

Students were screened by Mantoux testing. All students with a positive Mantoux result (greater than 15 mm if Bacillus Calmette-Guérin (BCG) vaccinated, greater than 5 mm if unvaccinated) were referred for further clinical assessment. All staff were over 18 years of age and were offered screening by chest radiograph or Mantoux testing if pregnant. All staff with an abnormal chest radiograph or a positive Mantoux result were referred for clinical assessment.

All patients referred were assessed for TB infection by at least clinical history, clinical examination, chest radiograph and gamma interferon test (T-spot), plus microscopic examination of sputum if coughing. More invasive diagnostic testing was carried out as clinically indicated. Diagnosis of latent or active tuberculosis was made by a consultant respiratory physician.

Measurement of exposure

Data were collected for each subject during the co-ordinated health service response to the outbreak, including information on date of birth, address, history of BCG vaccination and for students, school year and tutoring group.

Students from different school years did not mix for lessons but there was significant mixing of students within a school year for lessons. Class sizes varied from approximately 20-35 students. The only formal mixing of students between years was as part of a tutor

Table 1

Outcomes of tuberculosis exposure groups under study, United Kingdom, 2009 (n=1,065)

	Pupils	Staff	Same school year as index case	Other school year	Same tutor group as index case	Other tutor group
Active tuberculosis	12	0	7	5	0	12
Latent tuberculosis	55	0	37	18	1	54
No evidence of tuberculosis	698	172	103	595	15	683
Did not attend screening	121	7	23	98	2	119
Total	**886**	**179**	**170**	**716**	**18**	**868**

Table 2

Results of logistic regression analysis of exposure factors to the risk of being diagnosed with active or latent tuberculosis, United Kingdom, 2009

Risk of being diagnosed with active tuberculosis			
Exposure	**Odds ratio**	**95% Confidence interval**	**p-value**
Staff member (versus pupil)	0	0	0.99
Male	0.89	0.28-2.84	0.85
Previous BCG vaccination	2.83	0.36-22.09	0.32
Same tutor group as index case	0	0	0.99
Same school year as index case	6.11	1.91-19.48	0.002
Risk of being diagnosed with active or latent tuberculosis			
Exposure	**Odds ratio**	**95% Confidence interval**	**p-value**
Staff member (versus pupil)	0	0	0.99
Male	1.12	0.68-1.85	0.66
Previous BCG vaccination	1.32	0.68-2.58	0.41
Same tutor group as index case	0.71	0.09-5.45	0.75
Same school year as index case	10.52	6.14-18.03	<0.0001

BCG: Bacillus Calmette-Guérin

group where a total of 18 students from different years shared a classroom weekly for 1.5 hours per week.

For students, two measures of increased exposure were used; being in the same school year with the index case (three 30 hours of classroom exposure per week) and being in the same tutoring group (tutor groups included students from all school years, sharing a tutoring group equated to 1.5 hours classroom exposure per week). Students not in the same tutor group or school year were classified as having low school exposure (less than 1.5 hours per week). For staff substantial exposure was defined as those who had prolonged and direct contact with the index case. This exposure was assessed clinically by interview as part of a risk assessment for each staff member.

Statistical analysis

Standard descriptive statistics were used to summarise the data. The relationship between exposure and outcomes was analysed using logistic regression which allowed the effect of interactions between exposure categories on outcomes to be assessed. Reported p-values are all two-sided. Except where stated otherwise, the control group was all students classified as the low exposure group. Comparisons of risk were made with (i) those in the same school year as the index case, and (ii) those in the same tutor group as the index case and staff. The chi-square test was used to assess differences in the rate of TB infection between the school population and the overall rate seen in school uptake area population [8] All analysis was carried out using SPSS version 15.

Results

All students at the school were aged between 10 and 16 years at the time of investigation, all of which were included in the study. The study also included all staff members employed at the school during the study period.

All students and staff were offered screening. Staff numbered 179 and of these 172 participated (96.1%). There were 886 students and of these 765 (86.3%) participated. The remainder, 121 pupils and seven staff, declined screening. Complete data are available for all participants. The outcomes for the different groups under study are presented in Table 1.

Being in the same school year as the index case resulted in a significantly higher risk of having active TB (OR 6.11) and either active or latent TB (OR 10.52) (Table 2). The lower level of classroom exposure of those attending the same tutoring groups did not result in any significantly increased risk. No staff member was diagnosed with active or latent TB.

Previous BCG vaccination did not significantly reduce the risk of being diagnosed with active or latent TB.

Multiple logistic regression analysis showed no significant interaction between exposure categories on outcomes.

Applying the age specific rate of TB infection of the school uptake area population [8] to the school population it would be expected that there would be 0.94 cases of TB diagnosed per year. This is significantly lower than the actual number seen in our outbreak investigation (chi-square p=0.002).

Discussion

The study supports current recommendations for management of TB cases in schools. The highest level of risk of being diagnosed with active or latent TB and therefore priority area of concern is children in the same school year as the index case. The increased level of exposure seen in other groups did not translate to substantially increased risk of infection. While we would not suggest that teachers with substantial levels of exposure should not be tested for TB in school based outbreaks, these results suggest they can be reassured they are unlikely to be at higher levels of risk for contracting active TB.

It is possible that the high numbers of students diagnosed with active TB in our study were due to the high incidence rate in the population. However, the large and significant difference between the expected number of cases in the school and the number actually found makes it unlikely that the majority of cases detected by screening were due to previously undiagnosed TB acquired in the wider community. In addition, three cases with active TB had their *Mycobacterium tuberculosis* strains molecularly typed by DNA fingerprinting. All of them were indistinguishable from one another and identical to the strain found in the index case which strongly supports the school being the place of transmission.

This study adds to the small evidence base related to school based TB outbreaks. A particular strength of the study is the size of the population, which is larger than most of the other published studies [2,3,6] and the relatively low proportion of the population that did not attend screening which increases the reliability of the results.

The most significant limitation of this study is the sole use of chest radiograph in the screening of non-pregnant staff members. UK guidance recommends that this is satisfactory for those aged over 35 years and have had previous BCG vaccination [1]. However, those that do not satisfy these criteria should ideally be screened by Mantoux testing. Due to the limitation of the data available we were unable to estimate what proportion of staff should ideally have had Mantoux testing. Therefore caution should be used when interpreting the prevalence of latent TB in the staff population. However, the results for the prevalence of active TB in the staff group should still be reliable since all subjects

had either normal chest radiographs or TB excluded by a physician if the radiograph was abnormal.

Current NICE guidance quotes a relative risk for existing high school pupils compared to new school entrants of 2.3 (95% CI 1.7-3.2) [3]. Only two other studies examined the risk of classroom versus non-classroom exposure (relative risk (RR) 2.3 95% CI 1.4-3.8) [2], (RR 10.9 95% CI 8.7-13.4) [4]. We have reported OR because of the use of logistic regression and although not the same as RR their values become increasingly similar as the ratio of subjects without disease to those with disease increases above 6:1. This study's main finding of the risk of students in the same school year developing active TB has a ratio of approximately 24:1. Therefore we can be confident that the values of the OR presented here can be directly compared to the RR reported in previous studies without the need for statistical correction.

A number of other papers have discussed the epidemiology of school outbreaks but have not formally quantified risk. No studies were found that quantified the risk to staff of contracting TB from students although studies exist that examined risks to students taught by staff with open TB [11].

The results of this study are consistent with other studies published on school-based TB outbreaks and confirm that higher levels of classroom exposure to people with open TB significantly increase the risk of being diagnosed with active or latent TB. It also suggests that the risk to staff may be very small when teaching children who have open TB although more research is required to confirm this. It does not appear that being in an area of high background TB incidence substantially alters the epidemiology of the outbreak or risk of transmission between students in comparison to other populations and that there is no evidence that alternative screening strategies are required in this situation.

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