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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