

# Drug resistance among tuberculosis cases in the European Union and European Economic Area, 2007 to 2012

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The European Union and European Economic Area (EU/EEA) tuberculosis (TB) surveillance system collects detailed information on resistance to TB drugs. Using this information, we provide an overview of the current TB drug resistance situation and trends in the EU/EEA by performing a descriptive analysis, including analysis of treatment outcomes, of the TB cases reported between January 2007 and December 2012. The percentages of TB cases with different drug resistance patterns have been stable with about 90% of the new laboratory-confirmed cases pan-susceptible, 6% monodrug-resistant, 2% polydrug-resistant, 2% multidrug drug-resistant (MDR) TB – excluding extensively drug-resistant (XDR) TB –, and 0.2% XDR-TB. In previously treated laboratory-confirmed TB cases, the percentage with MDR-TB excluding XDR-TB declined until 2010 to 16% and remained stable thereafter. During the study period, the percentages of cases with monodrug- and polydrug-resistant TB remained constant at about 8% and 2% whereas the percentage of XDR-TB cases increased slightly to 2.6%. Treatment outcome results for all cases have been stable with overall 77.9% of the pan-susceptible cases, 69.6% of the monoresistant cases, 68.2% of the polyresistant cases, 32.2% of the MDR-TB cases (excluding XDR-TB), and 19.1% of the XDR-TB cases treated successfully. The treatment success rate target for new pulmonary culture-positive MDR-TB cases of 70% has not been reached. In addition, drug resistance surveillance can be improved by more complete reporting of drug susceptibility results and treatment outcome.

## Introduction

Anti-tuberculosis (TB) drug resistance is a major public health challenge. Patients infected with *Mycobacterium tuberculosis* bacilli resistant to TB drugs often require longer, expensive treatment regimens, and show poorer treatment outcomes. In 2011, the global incidence of TB was estimated to be 125 cases per 100,000 population, with about 12 million prevalent TB cases [1]. Of the prevalent cases, 630,000 (5.3%) were estimated to have multidrug-resistant (MDR) TB [1]. The 53 countries

of the World Health Organization (WHO) European Region notified 380,366 TB cases in 2011. For 127,936 (33.6%), drug susceptibility testing (DST) results were available, and 29,473 (19.0%) were diagnosed with MDR-TB. In the 29 reporting European Union (EU) and European Economic Area (EEA) countries the proportion of MDR-TB was 4.5%, while in non EU/EEA countries the proportion was 25.6% [2]. Although information on MDR-TB and extensively drug-resistant (XDR) TB is systematically collected and reported by the WHO [1], less information is available on the burden of mono- and polydrug resistance, or any drug resistance.

In the EU/EEA, many countries have based their system for surveillance of anti-tuberculosis drug resistance on recommendations of a WHO and International Union Against Tuberculosis and Lung Disease (IUATLD) working group [3]. Starting with the 2007 TB cohort, TB surveillance data from the country level are reported annually to the European Surveillance System (TESSy) database, operated by the European Centre for Disease Prevention and Control (ECDC). The ECDC previously published an analysis of MDR and XDR-TB in the EU/EEA using notification data from 2008 [4]. This analysis showed that MDR-TB remained a threat and that XDR-TB had been identified within the EU/EEA borders. In the annual European tuberculosis surveillance and monitoring reports, notifications on MDR-TB and XDR-TB are provided separately from data on resistance to isoniazid or rifampicin [2]. Although information on resistance to other TB drugs is collected in the TESSy database, this information is not routinely reported. Some EU countries or regions in EU countries have published detailed information on drug resistance to individual TB drugs [5-7]. For example, the United Kingdom reported an increase of the proportion of TB cases resistant to isoniazid from 1998 to 2005 [7]. In the same period, a study from Castilla y León, Spain, indicated that the incidence of primary drug resistance and monoresistance was low [8] and this information was used to establish a new standard anti-tuberculosis treatment. Systematic analysis of drug resistance data

helps to identify strengths and remaining challenges in TB control as well as to guide actions. It can also be used to assess whether the targets set in the EU/EEA, i.e. to test 100% of the culture-positive TB cases for resistance to first-line TB drugs, are achieved [9].

Analysis of characteristics of patients with drug resistance can help to identify populations most at risk. A study in London among individuals with isoniazid monoresistance showed that cases were more likely to be young adults, born in the United Kingdom and of white or black Caribbean ethnicity, imprisoned at the time of diagnosis, unemployed, drug dealers or sex workers [10]. Another study assessed risk factors for resistance to second-line anti-tuberculosis drugs in eight countries [11]. It showed that previous treatment with second-line drugs was the strongest risk factor, and resistance to fluoroquinolones and XDR-TB were more frequent in women than in men. In addition, unemployment, alcohol abuse, and smoking were associated with resistance to second-line injectable drugs. Although some risk factors for drug resistance are study-site-specific, others seem to be general.

To assess whether TB control programmes are able to provide adequate treatment and support, an analysis of TB treatment outcomes is useful. In general, cases infected with a TB strain that is resistant to TB drugs have a worse treatment outcome [12,13]. Other patient characteristics that are reported to be related to unsuccessful treatment outcomes are being male, older age, having pulmonary TB, alcohol dependence, homelessness, unemployment and diabetes [12,14,15]. In the TESSy database, only few patient characteristics are collected, which allows for a limited risk factor analysis.

An in-depth analysis of TB drug resistance in the EU/EEA has not been performed. Therefore, we aim to provide an overview of the current TB drug resistance situation in the EU/EEA and its trend, characteristics of drug-resistant cases, and their treatment outcomes.

## Methods

### Data source and collection

Data were extracted from the TESSy database on 4 October 2013. Data from 27 EU and EEA countries reporting DST results to ECDC were analysed. France, Italy, and Spain were not included as they are not reporting case-based drug resistance data to TESSy but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. DST data had been collected for the first line drugs ethambutol, isoniazid, rifampicin, and streptomycin, and for the second line drugs amikacin, capreomycin, ciprofloxacin, gatifloxacin, kanamycin, levofloxacin, moxifloxacin, and ofloxacin.

### Data inclusion and surveillance definitions

Only confirmed TB cases according to the EU case definition [16] with data on drug susceptibility for at least isoniazid and rifampicin were analysed. Definitions and categories provided in the ECDC/WHO report on tuberculosis surveillance and monitoring in Europe 2013 were used [2]. 'Pan-susceptible' refers to a case susceptible to all drugs tested. 'Monodrug resistance' is defined as resistance to one anti-TB drug, while 'polydrug resistance' refers to resistance to two or more drugs, excluding MDR-TB. MDR-TB is defined as resistance to at least isoniazid and rifampicin. XDR-TB is a special form of MDR-TB defined as resistance to at least isoniazid and rifampicin with further resistance to a fluoroquinolone and a second-line injectable agent (amikacin, kanamycin or capreomycin). Any drug resistance refers to a case with resistance to at least one TB drug. The percentage tested for susceptibility to second-line drugs (injectable agents: amikacin, capreomycin, kanamycin; fluoroquinolones: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin) was calculated for cases for whom DST results were reported for at least one fluoroquinolone and one injectable drug. 'Previously treated TB case' means that the case has received TB treatment before the current TB episode.

If data on previous treatment were not available, information on previous TB diagnosis was used. Treatment success is defined as a treatment outcome reported as 'cured' or 'completed' within 12 months after diagnosis in non-M(X)DR-TB cases, within 24 months in MDR-TB cases and within 36 months in XDR-TB cases.

### Analysis

We performed a descriptive analysis of surveillance data to assess the burden and trends of drug resistance among TB cases in EU/EEA countries between January 2007 and December 2012. We described cases with available resistance data by previous TB treatment history and resistance type over the years covered. We analysed different resistance types by sex, age-group, origin, human immunodeficiency virus (HIV) status, site of disease and treatment success. Treatment outcome after 12 months was analysed for pan-susceptible, monoresistant, and polyresistant cases notified between 2007 and 2011, treatment outcome after 24 months for MDR-TB cases notified between 2007 and 2010 and treatment outcome after 36 months for XDR-TB cases notified between 2007 and 2009. Fisher's exact tests were used to compare categorical data. Chi-squared test for trends was used to analyse changes over time of categorical data using the `ptrend` command in STATA. A p value of <0.05 was considered significant. All data analyses were performed using STATA 12.1 (StataCorp LP, Texas, USA).

**TABLE 1**

Notified laboratory-confirmed tuberculosis cases with reported testing results for the first-line TB drugs isoniazid (H) and rifampicin (R), and multidrug-resistant TB cases with reported testing results for second-line TB drug resistance, EU/EEA, 2007–2012

Year	2007	2008	2009	2010	2011	2012
Number of countries reporting case-based data for drug susceptibility for the first-line TB drugs H and R	26 <sup>a,b</sup>	25 <sup>a,b</sup>	26 <sup>a,b</sup>	26 <sup>a,b</sup>	26 <sup>a,b</sup>	25 <sup>a,b</sup>
Number of notified laboratory-confirmed TB cases	41,943	39,628	40,220	37,401	37,577	35,279
Notified laboratory-confirmed TB cases with reported testing results for R and H resistance N (%)	26,622 (63.5)	27,688 (69.9)	28,356 (70.5)	27,831 (74.4)	28,985 (77.1)	27,694 (78.5)
Number of notified MDR-TB cases	1,511	1,556	1,499	1,382	1,421	1,310
Notified MDR-TB cases with reported testing results for resistance to second-line TB drugs N (%)	310 (20.5)	366 (23.5)	585 (39.0)	869 (62.9)	983 (69.2)	891 (68.0)
Number of notified XDR-TB cases	76	90	66	115	143	128

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

27 EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform.

<sup>a</sup> Greece is not included in 2007, 2008 and 2012.

<sup>b</sup> Liechtenstein is not included after 2008.

## Results

### Completeness of drug resistance testing reporting

In 2007, 26 EU/EEA countries reported case-based rifampicin and isoniazid susceptibility testing results for 63.5% of all laboratory-confirmed TB cases, while 25 countries reported this data in 2012. Liechtenstein reported case-based data on DST for rifampicin and isoniazid only in 2007 and Greece only from 2009 to 2011 (Table 1). The percentage of laboratory-confirmed TB cases with testing results reported increased gradually from 63.5% (26,622/41,943) in 2007 to 78.5% (27,694/35,279) in 2012. Five countries reported results for rifampicin and isoniazid susceptibility testing for 100% of the laboratory-confirmed TB cases in 2012.

Reporting of DST results for first-line TB drugs for culture-positive non-MDR-TB increased between 2007 and 2012 (Table 2), both for new and previously treated TB cases.

Reporting of testing results of MDR-TB cases for resistance to second-line TB drugs increased steeply from 20.5% (320/1,511) of the notified MDR-TB cases in 2007 to 68.0% (891/1,310) in 2012 (Table 1). In 2012, ten countries reported DST results for more than 95% of all MDR-TB cases for second-line TB drugs, while the corresponding number was six countries in 2007. The testing percentage for second-line TB drugs was largely determined by the low percentage of MDR-TB cases for which a test result for second-line drugs was reported in Romania and the high number of MDR-TB cases reported in this country, i.e. 53.6% (284/530) in 2012. Germany (8/60), Ireland (1/5), and Poland (4/31)

reported test results for second-line drugs for <50% of the MDR-TB cases. However, these countries reported a lower number of cases and thus affected the EU/EEA second-line drug susceptibility percentage to a lesser extent.

DST results to the first-line drugs ethambutol and streptomycin were reported in respectively 84.5% (1,107/1,310) and 82.9% (1,086/1,310) of the MDR-TB cases in 2012. This had increased from respectively 66.5% (1,005/1,511) and 64.2% (970/1,511) in 2007. For the most frequently tested second-line drugs, kanamycin and ofloxacin, results were reported in 22.0% (332/1,511) and 20.8% (315/1,511) of the MDR-TB cases in 2007 and in 64.6% (846/1,310) and 62.3% (816/1,310) in 2012. In 2012, 40.9% (536/1,310) of the MDR-TB cases were reported to be tested for amikacin resistance and 37.5% (491/1,310) for capreomycin resistance. Reporting on testing results for resistance to other second-line drugs was infrequent. DST results for the drugs gatifloxacin, levofloxacin, and moxifloxacin were only collected from 2013 onwards with updates for previous year data. None of the EU/EEA countries have reported susceptibility testing results for gatifloxacin or levofloxacin for the years 2007 to 2012.

### Drug resistance notification and trends

In new laboratory-confirmed TB cases, the percentage of those with any resistance reported remained stable at around 10% (Figure 1A). Also, the percentages of new laboratory-confirmed TB cases with reported monoresistance, polyresistance, MDR-TB (excluding XDR-TB), and XDR-TB remained stable at about 6%, 2%, 2%, and 0.2% respectively.

TABLE 2

Resistance to first-line tuberculosis drugs in new and previously treated culture-positive non-MDR-TB cases by year, EU/EEA, 2007–2012

Year	All culture positive non-MDR-TB cases <sup>a</sup>	Isoniazid		Rifampicin		Streptomycin		Ethambutol	
		Tested N (%)	R N (%)	Tested N (%)	R N (%)	Tested N (%)	R N (%)	Tested N (%)	R N (%)
New culture-positive non-MDR-TB cases									
2007	38,904	20,407 (52.5)	1,166 (5.7)	20,407 (52.5)	115 (0.6)	12,933 (33.2)	784 (6.1)	18,378 (47.2)	135 (0.7)
2008	37,104	21,034 (56.7)	1,199 (5.7)	21,034 (56.7)	87 (0.4)	12,528 (33.8)	757 (6.0)	18,321 (49.4)	143 (0.8)
2009	36,826	21,689 (58.9)	1,128 (5.2)	21,689 (58.9)	91 (0.4)	13,183 (35.8)	681 (5.2)	18,250 (49.6)	84 (0.5)
2010	35,468	21,571 (60.8)	1,185 (5.5)	21,571 (60.8)	78 (0.4)	14,801 (41.7)	879 (5.9)	17,989 (50.7)	93 (0.5)
2011	35,441	22,955 (64.8)	1,250 (5.4)	22,955 (64.8)	77 (0.3)	16,190 (45.7)	929 (5.7)	19,030 (53.7)	97 (0.5)
2012	33,182	22,061 (66.5)	1,125 (5.1)	22,061 (66.5)	89 (0.4)	15,894 (47.9)	874 (5.5)	18,717 (56.4)	77 (0.4)
Previously treated culture-positive non-MDR-TB cases									
2007	7,119	3,129 (44.0)	370 (11.8)	3,129 (44.0)	78 (2.5)	1,570 (22.1)	140 (8.9)	1,926 (27.1)	39 (2.0)
2008	6,618	3,616 (54.6)	315 (8.7)	3,616 (54.6)	54 (1.5)	1,509 (22.8)	137 (9.1)	1,950 (29.5)	42 (2.2)
2009	6,714	3,872 (57.7)	352 (9.1)	3,872 (57.7)	66 (1.7)	1,642 (24.5)	140 (8.5)	2,083 (31.0)	41 (2.0)
2010	6,256	3,671 (58.7)	348 (9.5)	3,671 (58.7)	60 (1.6)	1,706 (27.3)	153 (9.0)	1,925 (30.8)	39 (2.0)
2011	5,695	3,469 (60.9)	315 (9.1)	3,469 (60.9)	54 (1.6)	1,657 (29.1)	155 (9.4)	1,811 (31.8)	35 (1.9)
2012	5,200	3,263 (62.8)	257 (7.9)	3,263 (62.8)	57 (1.7)	1,667 (32.1)	132 (7.9)	1,871 (36.0)	23 (1.2)

EU/EEA: European Union/European Economic Area; non-MDR-TB: non multidrug-resistant tuberculosis; R: resistant; TB: tuberculosis.

27 EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Liechtenstein reported case-based data on drug susceptibility testing for rifampicin and isoniazid only in 2007 and Greece only from 2009 to 2011.

<sup>a</sup> Only TB cases with information available on previous treatment are included.

In previously treated laboratory-confirmed TB cases, the percentage with any resistance and with MDR (excluding XDR-TB) declined until 2010 (Figure 1B) and remained stable thereafter with about 30% of the previously treated cases showing any resistance. The percentage of cases with monoresistance and polyresistance did not change. The percentage of XDR-TB cases, increased from 1.4% in 2007 to 2.6% in 2012 (chi-squared (1) for trend=26.8,  $p<0.0001$ ).

In 2012, the percentage of TB cases with any resistance varied considerably across EU/EEA countries with 3.3% (6/181) showing any resistance in Slovakia and 37.7% (90/239) in Estonia (Figure 2).

The percentage of TB cases with reported rifampicin monoresistance ranged between 0% and 1.3% in 2012 in the different EU/EEA countries (Table 3). For isoniazid monoresistance the range was 0% to 6.6% and for MDR-TB 0% to 25.5%.

The total number of notified MDR-TB (including XDR-TB) cases decreased from 1,511 in 2007 to 1,310 in 2012 (Table 1). Liechtenstein did not report to TESSy in 2012, but reported 0 MDR TB cases in 2007. The number of new cases with MDR-TB (including XDR-TB) remained stable over the years, 516 in 2007 and 542 in 2012,

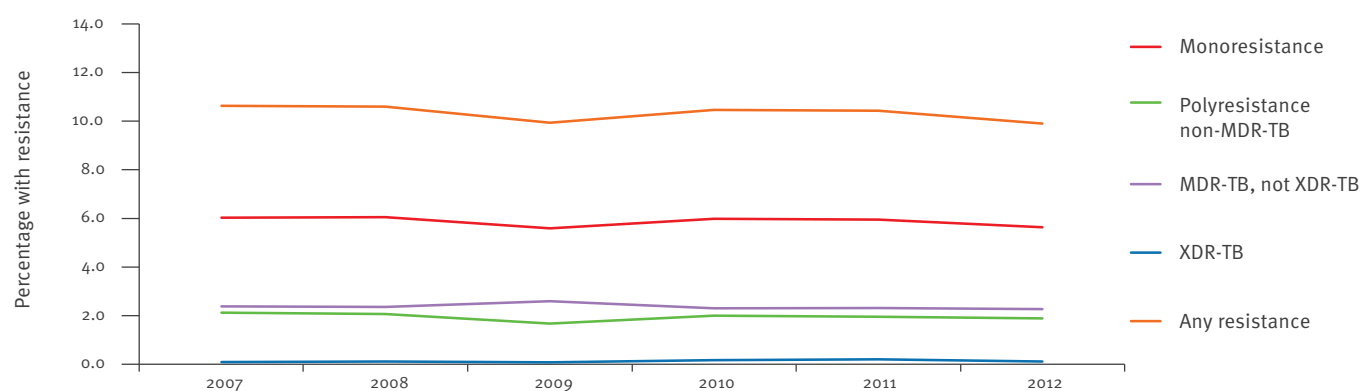
whereas the number of MDR-TB (including XDR-TB) cases that were previously treated decreased from 972 in 2007 to 727 in 2012 (Table 4). The percentage of new MDR-TB (including XDR-TB) cases of MDR-TB cases for which previous treatment was known, increased from 34.7% (516/1,488) in 2007 to (542/1,269) 42.7% in 2012 (chi-squared (1) test for trend=35.4,  $p<0.001$ ).

Of the new MDR-TB (including XDR-TB) cases,  $\geq 50\%$  were reported to be resistant to ethambutol and  $>80\%$  to streptomycin (Table 4). Among previously treated MDR-TB (including XDR-TB) cases, around 70% tested resistant to ethambutol, whereas resistance to streptomycin was comparable with the percentage in new MDR-TB cases. Resistance to kanamycin was reported in 40.7% of the new MDR-TB cases in 2007 and 23.5% in 2012. Ofloxacin resistance was less frequent in new MDR-TB cases with only 11.7% of the cases showing resistance in 2012. As expected, previously treated cases were more frequently resistant to both first-line and second-line TB drugs. Of all MDR-TB (including XDR-TB) cases tested for resistance to any of the second-line TB drugs between 2007 and 2012, 44.5% (1,782/4,004) were resistant to any of the second-line drugs.

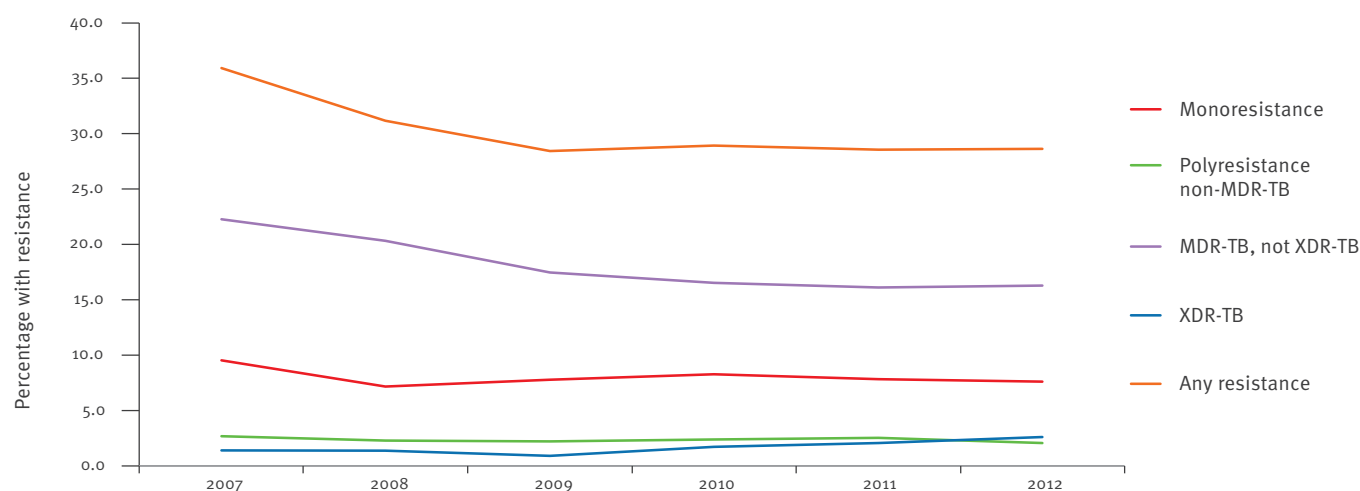
**FIGURE 1**

Resistance pattern among new (a) and previously treated (b) laboratory-confirmed TB cases tested for at least isoniazid and rifampicin resistance by year, EU/EEA, 2007–2012

A. New laboratory-confirmed TB cases



B. Previously treated laboratory-confirmed TB cases



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

27 EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Of the 27 EU/EEA countries included in the study, Liechtenstein reported case-based data on drug susceptibility testing for rifampicin and isoniazid only in 2007 and Greece only from 2009 to 2011.

For 143 of the 183 (78.1%) MDR-TB cases (including XDR-TB) with ciprofloxacin resistance, no cross resistance with other fluoroquinolones was reported. Of the 815 MDR-TB cases (including XDR-TB) with ofloxacin resistance, for 727 (89.2%) no resistance to other fluoroquinolones was reported, and of the 55 cases resistant to moxifloxacin, for three (5.5%) no other resistance to fluoroquinolones was reported. Thirty-six MDR-TB cases (including XDR-TB) were reported with resistance to both ciprofloxacin and ofloxacin and 48 showed resistance to both ofloxacin and moxifloxacin. Only

four MDR-TB (including XDR-TB) cases were reported with resistance to all three fluoroquinolones.

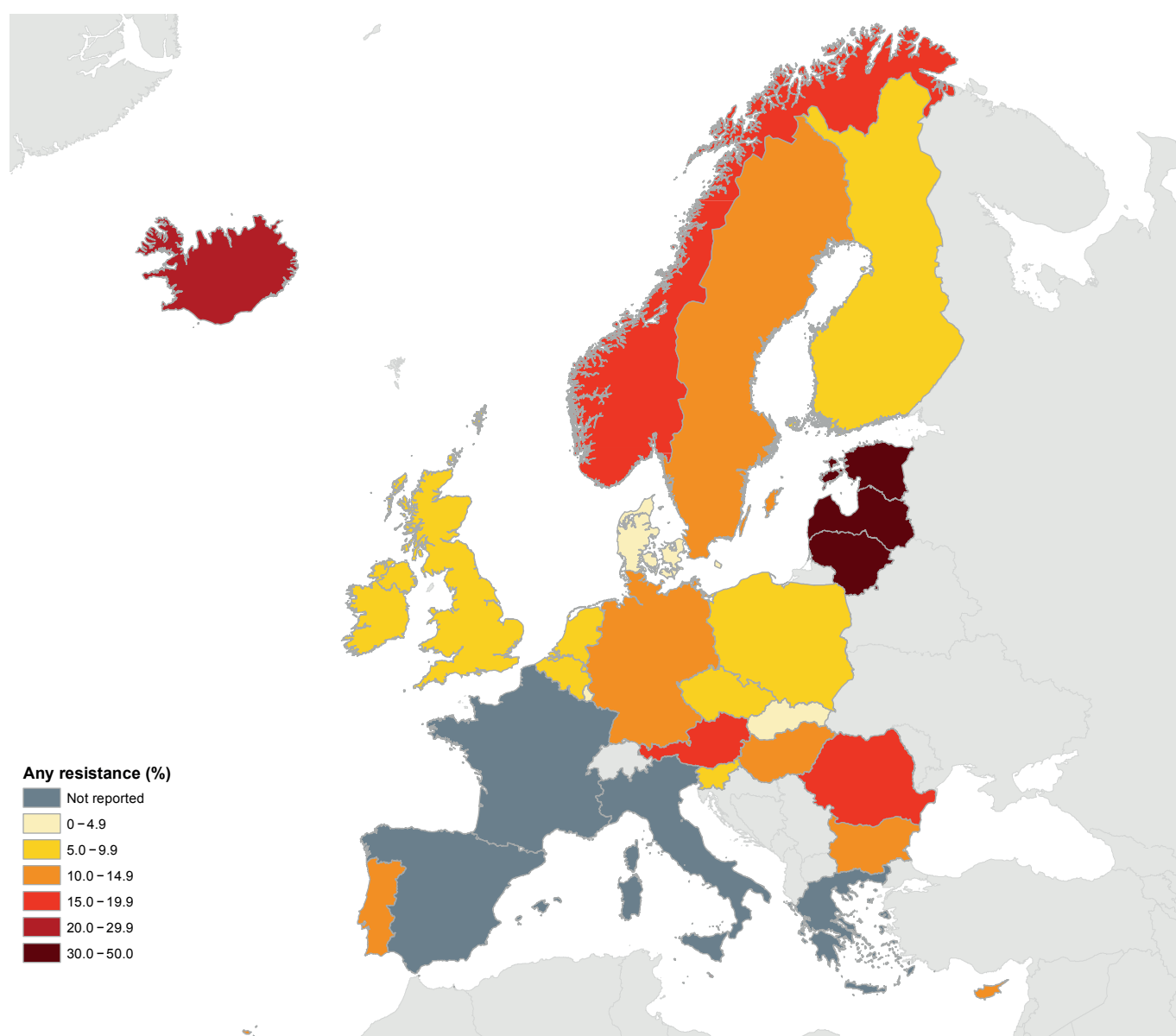
### Characteristics of tuberculosis cases with drug resistance

In 2012, 32.6% of all laboratory-confirmed TB cases tested for at least isoniazid and rifampicin resistance were female (Table 5). In the groups with MDR-TB (excluding XDR-TB), and XDR-TB, females accounted for a lower proportion compared to the other groups, 25.6% and 21.9% of all cases, respectively ( $p < 0.001$  and  $p = 0.008$ , respectively).



**FIGURE 2**

Percentage of laboratory-confirmed tuberculosis cases tested for at least isoniazid and rifampicin resistance with any drug resistance, EU/EEA, 2012<sup>a</sup>



EU/EEA: European Union/European Economic Area.

The 'Not reported' legend indicates that case-based drug susceptibility results are not reported to the European Surveillance System (TESSy).

<sup>a</sup> France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Liechtenstein and Greece did not report to TESSy in 2012.

Most notified TB cases were between 25 and 64 years-old. The percentages of 25 to 64 year-olds were higher compared to those aged younger or older for XDR-TB (85.2%) and MDR-TB (excluding XDR-TB) (82.2%) cases when compared to pan-susceptible (70.1%) or monoresistant (74.4%) cases (comparison XDR-TB vs pan-susceptible, chi-squared (1)=13.8  $p<0.001$ ; comparison MDR-TB (excluding XDR-TB) vs pan-susceptible, chi-squared (1)=79.8  $p<0.001$ ; comparison XDR-TB vs monoresistant, chi-squared (1)=7.4  $p=0.007$ ;

comparison MDR-TB (excluding XDR-TB) vs monoresistant, chi-squared (1)=24.4  $p<0.001$ ). Cases aged  $\geq 65$  years were significantly more frequent among pan-susceptible cases (17.3%,  $p<0.001$ ) when compared to all other age groups (7.3–10.8%).

Of the pan-susceptible TB cases, 28.1% were recorded with a foreign origin. While monoresistant cases were more frequently of foreign origin, 34.6% ( $p<0.001$ ), MDR-TB (excluding XDR-TB), and XDR-TB cases were

TABLE 3

Rifampicin monoresistance, isoniazid monoresistance, and multidrug-resistant TB in EU/EEA countries, 2012

Country	Number of TB cases with reported susceptibility testing results to at least isoniazid and rifampicin	Rifampicin monoresistant N (%)	Isoniazid monoresistant N (%)	MDR-TB N (%)
Austria	392	0 (0.0)	14 (3.6)	27 (6.9)
Belgium	735	5 (0.7)	37 (5.0)	20 (2.7)
Bulgaria	829	9 (1.1)	27 (3.3)	49 (5.9)
Cyprus	49	0 (0.0)	1 (2.0)	0 (0.0)
Czech Republic	397	1 (0.3)	4 (1.0)	4 (1.0)
Denmark	298	0 (0.0)	8 (2.7)	1 (0.3)
Estonia	239	3 (1.3)	3 (1.3)	61 (25.5)
Finland	222	0 (0.0)	8 (3.6)	3 (1.4)
France <sup>a</sup>	–	–	–	–
Germany	2,794	5 (0.2)	96 (3.4)	60 (2.1)
Greece <sup>b</sup>	–	–	–	–
Hungary	449	2 (0.4)	17 (3.8)	11 (2.4)
Iceland	5	0 (0.0)	0 (0.0)	1 (20.0)
Ireland	265	0 (0.0)	10 (3.8)	5 (1.9)
Italy <sup>a</sup>	–	–	–	–
Latvia	766	0 (0.0)	28 (3.7)	106 (13.8)
Liechtenstein <sup>b</sup>	–	–	–	–
Lithuania	1,368	10 (0.7)	56 (4.1)	271 (19.8)
Luxembourg	29	0 (0.0)	0 (0.0)	0 (0.0)
Malta	14	0 (0.0)	0 (0.0)	0 (0.0)
Netherlands	656	1 (0.2)	23 (3.5)	11 (1.7)
Norway	280	1 (0.4)	7 (2.5)	6 (2.1)
Poland	4,659	9 (0.2)	104 (2.2)	31 (0.7)
Portugal	1,321	1 (0.1)	21 (1.6)	17 (1.3)
Romania	5,966	75 (1.3)	232 (3.9)	530 (8.9)
Slovakia	181	0 (0.0)	4 (2.2)	1 (0.6)
Slovenia	126	0 (0.0)	2 (1.6)	0 (0.0)
Spain <sup>a</sup>	–	–	–	–
Sweden	503	1 (0.2)	33 (6.6)	14 (2.8)
United Kingdom	5,151	8 (0.2)	196 (3.8)	81 (1.6)
Total EU/EEA	27,694	131 (0.5)	931 (3.4)	1,310 (4.7)

EU/EEA: European Union/European Economic Area; MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis.

<sup>a</sup> No case-based reporting to the European Surveillance System (TESSy) of drug susceptibility testing results but aggregated results were reported to the World Health Organization's Tuberculosis Monitoring and Evaluation platform.<sup>b</sup> No reporting to TESSy in 2012.

less frequently of foreign origin, respectively 18.7% and 12.5% ( $p < 0.001$  for both comparisons).

Previous treatment was reported for 14.4% of all laboratory-confirmed cases, but it was much more common in cases with MDR-TB (excluding XDR-TB), and XDR-TB, accounting for 53.1% ( $p < 0.001$ ) and 77.3% ( $p < 0.001$ ), respectively compared to all other cases (pan-susceptible, monoresistant and polyresistant cases). Surprisingly, only 15.3% of the TB cases with a polyresistant pattern had previously received TB treatment. This is a bit more than the 11.9% ( $p = 0.022$ ) of

the pan-susceptible that had previously received TB treatment, and comparable to the 18.0% ( $p = 0.168$ ) of monoresistant TB cases.

Fifteen countries reported case-based HIV testing results. Overall, only 28.1% of the TB cases had HIV status reported, but this percentage was much higher for MDR-TB (excluding XDR-TB), and XDR-TB cases, i.e. respectively 52.7% and 65.6%. Also, the percentage testing positive for HIV was higher for MDR-TB (excluding XDR-TB) cases (10.4%,  $p < 0.001$ ), and XDR-TB cases (13.1%,  $p < 0.001$ ), when compared to all other cases

TABLE 4

Anti-tuberculosis drug resistance in new and previously treated multidrug-resistant TB cases<sup>a</sup> (including extensively drug resistant tuberculosis) by year, EU/EEA, 2007–2012

New MDR-TB cases (including XDR-TB)												
Tuberculosis drugs <sup>b</sup>	2007 (N MDR-TB=516)		2008 (N MDR-TB=533)		2009 (N MDR-TB=596)		2010 (N MDR-TB=547)		2011 (N MDR-TB=593)		2012 (N MDR-TB=542)	
	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)
Ethambutol <sup>c</sup>	439	268 (61.0)	460	269 (58.5)	498	249 (50.0)	480	264 (55.0)	529	337 (63.7)	487	292 (60.0)
Streptomycin <sup>c</sup>	397	355 (89.4)	384	321 (83.6)	456	392 (86.0)	466	411 (88.2)	514	454 (88.3)	470	403 (85.7)
Amikacin <sup>d</sup>	124	21 (16.9)	169	47 (27.8)	219	48 (21.9)	245	57 (23.3)	308	55 (17.9)	293	56 (19.1)
Capreomycin <sup>d</sup>	140	34 (24.3)	163	48 (29.4)	219	51 (23.3)	251	63 (25.1)	292	58 (19.9)	278	51 (18.3)
Ciprofloxacin <sup>d</sup>	8	0 (0.0)	40	6 (15.0)	30	5 (16.7)	33	5 (15.2)	58	7 (12.1)	32	2 (6.3)
Kanamycin <sup>d</sup>	140	57 (40.7)	151	47 (31.1)	236	71 (30.1)	355	98 (27.6)	406	97 (23.9)	358	84 (23.5)
Moxifloxacin <sup>d</sup>	0	0 (–)	0	0 (–)	1	0 (0.0)	47	7 (14.9)	69	16 (23.2)	102	8 (7.8)
Ofloxacin <sup>d</sup>	151	23 (15.2)	197	31 (15.7)	247	32 (13.0)	373	60 (16.1)	410	77 (18.8)	375	44 (11.7)
Previously treated MDR-TB cases (including XDR-TB)												
Tuberculosis drugs <sup>b</sup>	2007 (N MDR-TB=972)		2008 (N MDR-TB=1,003)		2009 (N MDR-TB=873)		2010 (N MDR-TB=817)		2011 (N MDR-TB=792)		2012 (N MDR-TB=727)	
	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)	Tested N (%)	Resistant N (%)
Ethambutol <sup>c</sup>	543	400 (73.7)	652	472 (72.4)	606	396 (65.3)	545	342 (62.8)	604	416 (68.9)	580	411 (70.9)
Streptomycin <sup>c</sup>	561	523 (93.2)	616	478 (77.6)	607	539 (88.8)	559	498 (89.1)	614	534 (87.0)	582	507 (87.1)
Amikacin <sup>d</sup>	96	23 (24.0)	111	38 (34.2)	139	34 (24.5)	209	50 (23.9)	208	47 (22.6)	218	56 (25.7)
Capreomycin <sup>d</sup>	108	27 (25.0)	113	38 (33.6)	150	40 (26.7)	204	47 (23.0)	201	43 (21.4)	189	54 (28.6)
Ciprofloxacin <sup>d</sup>	11	8 (72.2)	159	68 (42.8)	103	16 (15.5)	106	18 (17.0)	136	27 (19.9)	101	21 (20.8)
Kanamycin <sup>d</sup>	192	128 (66.7)	172	112 (65.1)	319	133 (41.7)	470	170 (36.2)	526	193 (36.7)	480	208 (43.3)
Moxifloxacin <sup>d</sup>	0	0 (–)	0	0 (–)	1	0 (0.0)	11	3 (27.3)	15	6 (40.0)	56	15 (26.8)
Ofloxacin <sup>d</sup>	162	72 (44.4)	221	45 (20.4)	231	56 (24.4)	399	113 (28.3)	422	128 (30.3)	418	134 (32.1)

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

<sup>a</sup> EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Liechtenstein reported case-based data on drug susceptibility testing for rifampicin and isoniazid only in 2007 and Greece only from 2009 to 2011.

<sup>b</sup> MDR-TB cases (including XDR-TB) with information available on previous treatment are included.

<sup>c</sup> Drug susceptibility testing results for the drugs levofloxacin, gatifloxacin, and moxifloxacin were only collected from 2013 onwards with updates for previous year data. None of the EU/EEA countries has reported susceptibility testing results for levofloxacin or gatifloxacin.

<sup>d</sup> First line drugs.

<sup>e</sup> Second line drugs.



**TABLE 5**

Characteristics of all laboratory-confirmed TB cases tested for at least isoniazid and rifampicin resistance by drug resistance pattern, EU/EEA, 2012

Characteristics	Pan-susceptible N (%)	Monoresistant N (%)	Polyresistant non-MDR-TB N (%)	MDR-TB not XDR-TB N (%)	XDR-TB N (%)	Total N (%)
<b>Total</b>	<b>24,199 (100.0)</b>	<b>1,648 (100.0)</b>	<b>537 (100.0)</b>	<b>1,182 (100.0)</b>	<b>128 (100.0)</b>	<b>27,694 (100.0)</b>
<b>Sex</b>						
Female	7,968 (32.9)	536 (32.5)	180 (33.5)	303 (25.6)	28 (21.9)	9,015 (32.6)
Male	16,227 (67.1)	1,112 (67.5)	356 (66.3)	879 (74.4)	100 (78.1)	18,674 (67.4)
Unknown	4 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	5 (0.0)
<b>Age groups (years)</b>						
0–14	356 (1.5)	34 (2.1)	7 (1.3)	13 (1.1)	0 (0.0)	410 (1.5)
15–24	2,687 (11.1)	210 (12.7)	64 (11.9)	111 (9.4)	9 (7.0)	3,081 (11.1)
25–44	9,125 (37.7)	685 (41.6)	246 (45.8)	515 (43.6)	62 (48.4)	10,633 (38.4)
45–64	7,843 (32.4)	541 (32.8)	174 (32.4)	457 (38.7)	47 (36.7)	9,062 (32.7)
≥65	4,186 (17.3)	178 (10.8)	46 (8.6)	86 (7.3)	10 (7.8)	4,506 (16.3)
Unknown	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
<b>Origin</b>						
Foreign	6,805 (28.1)	570 (34.6)	174 (32.4)	221 (18.7)	16 (12.5)	7,786 (28.1)
Native	17,060 (70.5)	1,057 (64.1)	356 (66.3)	959 (81.1)	112 (87.5)	19,544 (70.6)
Unknown	334 (1.4)	21 (1.3)	7 (1.3)	2 (0.2)	0 (0.0)	364 (1.3)
<b>Previous treatment</b>						
No	20,343 (84.1)	1,288 (78.2)	430 (80.1)	517 (43.7)	25 (19.5)	22,603 (81.6)
Yes	2,885 (11.9)	296 (18.0)	82 (15.3)	628 (53.1)	99 (77.3)	3,990 (14.4)
Unknown	971 (4.0)	64 (3.9)	25 (4.7)	37 (3.1)	4 (3.1)	1,101 (4.0)
<b>HIV status</b>						
HIV tested	6,431 (26.6)	470 (28.5)	173 (32.2)	623 (52.7)	84 (65.6)	7,781 (28.1)
HIV infected <sup>a</sup>	282 (4.4)	41 (8.7)	15 (8.7)	65 (10.4)	11 (13.1)	414 (5.3)
Unknown	17,768 (73.4)	1,178 (71.5)	364 (67.8)	559 (47.3)	44 (34.4)	19,913 (71.9)
<b>Site of disease</b>						
Pulmonary	20,450 (84.5)	1,368 (83.0)	461 (85.8)	1,126 (95.3)	127 (99.2)	23,532 (85.0)
Extra-pulmonary	3,699 (15.3)	280 (17.0)	75 (14.0)	55 (4.7)	1 (0.8)	4,110 (14.8)
Unknown	50 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	52 (0.2)

EU/EEA: European Union/European Economic Area; HIV: human immunodeficiency virus; MDR-TB: multidrug resistant tuberculosis; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

<sup>27</sup> EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Liechtenstein and Greece did not report to TESSy in 2012.

<sup>a</sup> The denominator for the calculation of percentage of HIV infected was the number of HIV-tested cases.

(pan-susceptible, monoresistant and polyresistant cases).

Over 95% of the MDR-TB (excluding XDR-TB), and XDR-TB cases had pulmonary TB. For the other resistance patterns, around 85% were reported to have pulmonary TB.

### Treatment outcome of tuberculosis cases with drug resistance

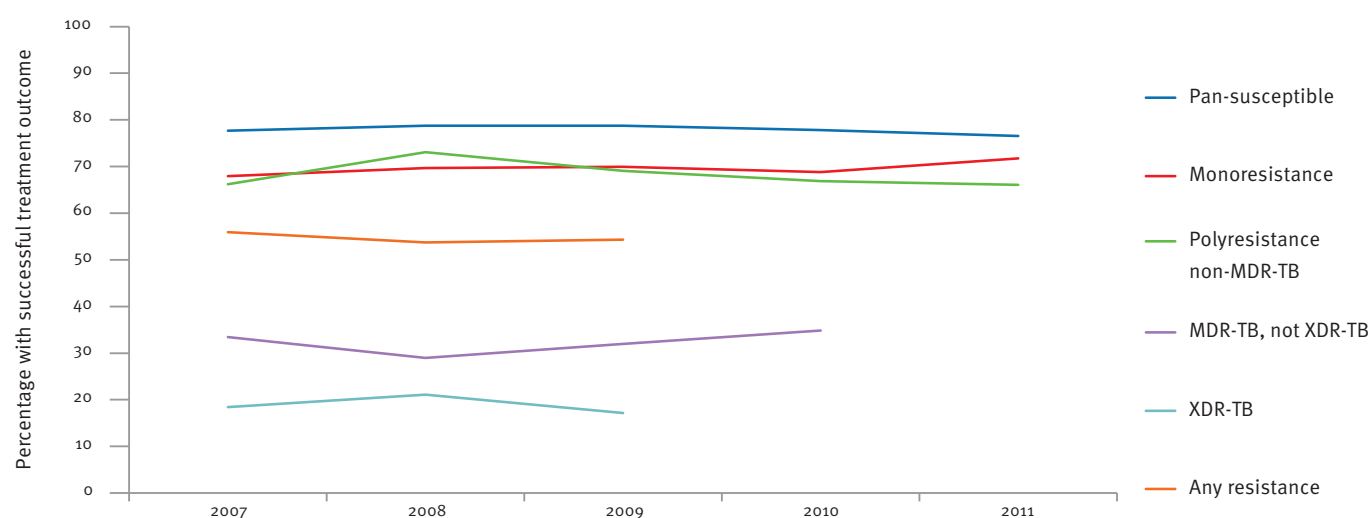
In period from 2007 to 2011, 77.9% of the pan-susceptible laboratory-confirmed TB cases with a test result for at least isoniazid and rifampicin resistance had a

successful treatment outcome. Cases with a monoresistant or polyresistant non-MDR-TB drug resistance pattern showed slightly lower (69.6% and 68.2%, respectively) treatment success rates. For MDR (excluding XDR-TB) reported in period from 2007 to 2010 and XDR-TB cases reported in period between 2007 and 2009, the treatment success rates were 32.2% and 19.1%, respectively (Figure 3). Trends in successful treatment outcome were relatively stable over the years.

The treatment success rate of new pulmonary MDR-TB (excluding XDR-TB) cases was 48.2% and 21.4% for

**FIGURE 3**

Successful treatment outcome of laboratory-confirmed tuberculosis (TB) cases tested for at least isoniazid and rifampicin resistance, by drug resistance pattern, EU/EEA, 2007–2011



EU/EEA: European Union/European Economic Area.

27 EU/EEA countries provided case-based data. France, Italy, and Spain do not report case-based drug susceptibility results to the European Surveillance System (TESSy) database but report aggregated results to the World Health Organization's Tuberculosis Monitoring and Evaluation platform. Of the 27 EU/EEA countries included in the study, Liechtenstein reported case-based data on drug susceptibility testing for rifampicin and isoniazid only in 2007 and Greece only from 2009 to 2011.

previously treated pulmonary MDR (excluding XDR-TB) cases in the period between 2007 and 2010. For new pulmonary XDR-TB cases the treatment success rate was 49.2% in the period from 2007 to 2009 and for previously treated pulmonary XDR-TB cases it was 13.3%.

Of all MDR-TB cases (including XDR-TB) diagnosed between 2007 and 2009, 32.4% had a successful treatment outcome. Of all MDR-TB cases (including XDR-TB) that had an unsuccessful treatment outcome, 21.4% died, 24.5% failed treatment and 19.8% defaulted from treatment, 0.6% transferred out and for 1.4% outcome was unknown (Figure 4). Treatment outcomes did not show any improvement in the years 2007 to 2009.

In period between 2007 and 2009, Romania reported a treatment success rate of 20.5% for 2,089 MDR-TB (including XDR-TB) cases. Since this significantly influences the overall picture for the EU/EEA, we provide treatment outcome results without the data reported by Romania. Without these data, 49.1% successfully finished treatment, 20.7% died, 7.5% failed treatment, 18.1% defaulted, 1.3% were transferred out, and 3.3% were reported as unknown.

## Discussion

The percentage of laboratory-confirmed TB cases with different drug resistance patterns, i.e. pan-susceptible, mono-, and polydrug resistance, MDR-TB (excluding XDR-TB), and XDR-TB, has been stable for new cases during the period of the study, from 2007 to 2012. In

new TB cases, drug resistance does not seem to be a significant problem with only 2% being diagnosed with MDR-TB. However, in previously treated TB cases, a much higher percentage, i.e. 16% is diagnosed with MDR-TB. The observed decline in the percentage of previously treated TB cases with MDR-TB from 22.3% in 2007 to 16.5% in 2010 can partly be explained by less selective testing. In 2007, 37.2% of all previously treated TB cases were tested for isoniazid and rifampicin resistance and in 2010 this had increased to 46.6%.

Our analysis also showed that treatment outcome results have been stable over the years with an acceptable treatment success rate in pan-susceptible TB cases, though below the target of 85% of the monitoring framework of the Framework Action Plan to Fight Tuberculosis in the European Union [9]. Measured against the set target of 70% in the monitoring framework of the Framework Action Plan to Fight Tuberculosis in the European Union [9], the treatment success rate of new pulmonary culture-positive MDR-TB was unacceptably low at only 48.2% in the period from 2007 to 2010.

Not all notified laboratory-confirmed TB cases had a result reported for rifampicin and isoniazid sensitivity testing. In 2010, the EU/EEA target for testing culture-confirmed TB cases for susceptibility to first-line TB drugs was set at 100% [9]. Even though a higher percentage of TB cases was tested in 2012 (78.5%)

compared to 2007 (63.5%), the target was far from being reached for the EU/EEA overall. However, five EU/EEA countries have reached and nine are close to reaching the target, reporting DST results including for rifampicin and isoniazid for 95% or more of the laboratory-confirmed TB cases. The low percentage of notified laboratory-confirmed TB cases with a result reported for rifampicin and isoniazid drug sensitivity testing is mainly explained by the low percentage of testing results reported by Romania, the country that reported the highest number of laboratory-confirmed TB cases in the EU/EEA, and reported rifampicin and isoniazid DST results for less than half of their cases. In addition, several EU countries do not report case-based DST results to TESSy but report aggregated results to the WHO's Tuberculosis Monitoring and Evaluation platform.

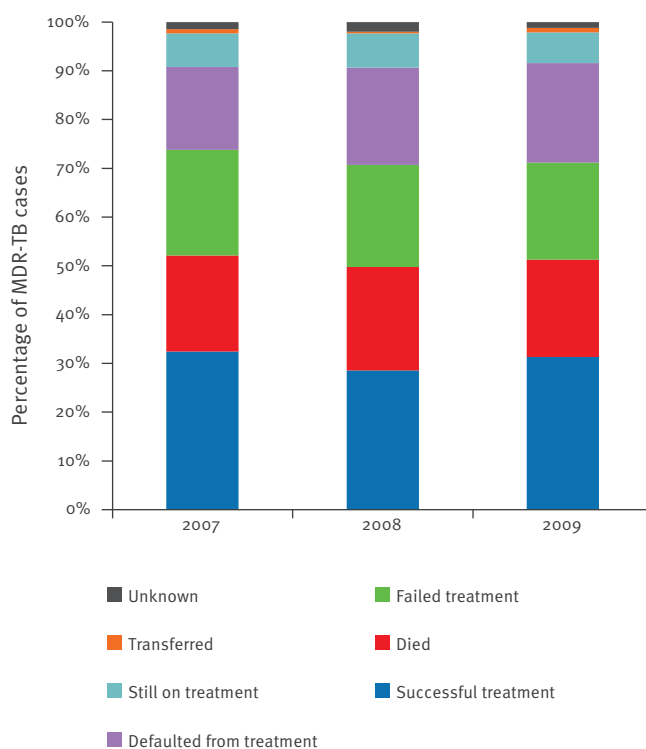
Information on the drug susceptibility pattern for second-line TB drugs is likely to be beneficial for the treatment outcome of MDR-TB patients as drug susceptibility results allow for adequate choice of treatment. The EU/EEA surveillance data showed that in 2012, for 68.0% of MDR-TB cases, a testing result for susceptibility to second-line TB drugs was reported and between 2008 and 2010 there was a sharp increase. ECDC started collection of drug susceptibility results for second line drugs in 2008. Few countries provided second line drug susceptibility data for the years before 2008. After 2008 the number of countries reporting second line drug susceptibility data increased and also the completeness of reporting improved.

TB patient characteristics differed across resistance patterns. Characteristics of cases with mono- and poly-drug resistance were largely similar to those of pan-susceptible cases whereas MDR- and XDR-TB cases seemed to differ from cases with other resistance patterns. Of the limited number of risk factors that we could evaluate, we found that male sex, native origin, previous TB treatment, and HIV infection were more frequent in MDR-TB (excluding XDR-TB) and XDR-TB. Of note is the low percentage of TB cases for which HIV status was reported. Other studies have shown similar results [17-21]. Especially a history of previous treatment is frequently identified as a strong risk factor for MDR-TB [17, 18, 21]. Other reported risk factors are a history of imprisonment, alcohol abuse, smoking, and hospitalisation for more than 14 days [17,18,20].

Treatment outcome results of TB cases with a mono- or polydrug resistance (not MDR-TB) were only slightly less favourable compared to those of pan-susceptible TB cases. The reported treatment success rates for MDR-TB and XDR-TB cases were significantly below the EU/EEA target of 70% [9]. In a recently published meta-analysis, using individual MDR-TB patient data, the pooled treatment success rate was 54% and ranged between 11 and 89% in the different studies that were included [22]. Surveillance data reported in the Global Tuberculosis Report 2012 showed that MDR-TB

**FIGURE 4**

Treatment outcome of all MDR-TB cases (including XDR-TB) after 36 months, EU/EEA countries<sup>a</sup>, 2007–2009



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

<sup>a</sup> Countries reporting treatment outcome for the different cohorts are provided in [27].

treatment success rates ranged between 44% and 58% for the 2009 treatment cohort in the different WHO regions [1]. Since 58.5% of the MDR-TB patients in the EU/EEA were notified by Romania between 2007 and 2009, the treatment outcomes achieved in this country have a considerable effect on the overall MDR-TB treatment outcomes in the EU/EEA.

In the analysis we included confirmed TB cases according to the EU case definition with available data on drug susceptibility for at least isoniazid and rifampicin. These inclusion criteria may potentially underestimate the percentage of TB cases with any resistance as well as polydrug resistance.

This study is based on the TB surveillance data submitted to ECDC by the EU/EEA countries. As listed above, this limits the information available on risk factors. Also, not all reported information is complete and the quality of the reported information is the responsibility of the individual country. However, the substantial amount of data available allows for obtaining a rather adequate picture of the drug resistance situation in the EU/EEA.

The EU/EEA TB surveillance system does not contain information on drug susceptibility data for the drug pyrazinamide. This is because of the technical complexity of achieving reliable and reproducible results. Also, there is no external quality assurance for pyrazinamide available [23]. Pyrazinamide is important in the treatment of tuberculosis and is included in many of the new TB regimens that are currently evaluated [24].

## Conclusion and recommendations

The available data show that the number of TB cases with drug resistance is stable in the EU/EEA, but not declining. Patients having drug resistant TB need to sustain longer treatment with more drugs, and they have worse treatment outcomes, especially if diagnosed with MDR-TB or XDR-TB. Also, treatment costs of MDR-TB are at least five times higher compared to treatment costs of drug susceptible TB [25]. Health systems in EU/EEA countries should be prepared to adequately diagnose and treat drug-resistant TB, and test all TB cases for drug susceptibility in a quality-assured laboratory [26]. Monitoring of drug resistance data at national and EU/EEA level should be continued to support identification of risk groups and areas where improvement may be needed.

## Conflict of interest

None declared.

## Authors' contributions

Marieke J. van der Werf designed and drafted the manuscript and coordinated the input from the other authors. Csaba Ködmön performed the data extraction and analysis and provided input for specific parts of the manuscript, reviewed the draft manuscript, and gave final approval of the version to be published. Vahur Hollo checked the data provided in the manuscript, reviewed the draft manuscript, and gave final approval of the version to be published. Andreas Sandgren checked the data provided in the manuscript, performed the statistical testing, reviewed the draft manuscript, and gave final approval of the version to be published. Phillip Zucs provided input for specific parts of the manuscript, reviewed the draft manuscript, and gave final approval of the version to be published.

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