

The Situation of HIV/*M. tuberculosis* Co-Infection in Europe

Claudia Giehl^{*,1}, Robindra Basu Roy² and Anne-Laure Knellwolf³

¹European Research and Project Office GmbH, Saarbrücken, Germany

²Imperial College London, London, UK

³Italian National Institute of Health, Rome, Italy

Abstract: This article provides an overview of the situation of HIV/AIDS, tuberculosis (TB), and HIV/MTB co-infection in the 27 member states of the European Union (EU27), prepared in the context of the FP7 project EUCO-Net (European Network for global cooperation in the field of AIDS & TB). Information contained herein, together with similar reports compiled for the four other EUCO-Net partner regions Africa, India, Russia, and South America provided the basis for the development of the EUCO-Net AIDS/TB Roadmap, a document which was compiled to support and facilitate the development of national, regional, and global research priorities and health policies, and to help boost international cooperation aimed at combating the scourge of HIV/AIDS, TB, and their deadly combination.

A comprehensive overview of the national situation in all 27 EU member states is a prerequisite for effective disease management and adequate priority setting in research and development (R&D) activities in Europe. Therefore, results presented here include demographic and epidemiological data on HIV and MTB infection, both separately and combined, as well as information concerning disease management such as diagnostics, resistance testing, treatment, and associated economic costs. Results of the primary data collection were presented at the “AIDS/TB workshop on research challenges and opportunities for future collaboration” at the University of Stellenbosch, South Africa, in July 2009, which brought together more than 60 scientists from Europe and all EUCO-Net target regions to discuss future joint AIDS/TB research. In this context, intercultural aspects that may hamper cross-national cooperation and research in these fields such as language barriers, different ethical regulations, or operational challenges were also taken into account.

The article concludes by summarizing the jointly identified key areas to improve disease management within the EU and by recommending priority areas for future AIDS/TB research in Europe.

Keywords: Europe, AIDS/TB, HIV/*M. tuberculosis* co-infection, epidemiology.

BACKGROUND

Tuberculosis and HIV/AIDS represent a global public health problem with considerable mutual interaction: HIV suppresses parts of the immune system rendering patients more vulnerable to acquiring TB infection or reactivation, and TB is a leading cause of mortality for people living with HIV/AIDS. In addition, the diagnosis of TB in HIV-infected patients is particularly challenging.

The burden of morbidity and mortality without doubt lies heaviest upon areas of the world such as sub-Saharan Africa, Russia, and the Indian subcontinent. Nevertheless, the EU cannot afford to be complacent as it faces its own crisis from HIV/MTB infection. The greatest threat is conferred by the high rate of multidrug-resistant (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). These forms of TB that are resistant to first-line (MDR-TB) and second-line (XDR-TB) medications require early diagnosis to prevent further spread, prolonged hospital stays, and protracted courses of expensive treatment with no guarantee of cure. Groups particularly at risk for MDR-TB and XDR-TB include those from countries of the former USSR, central Asia, and institutionalized populations such as prisoners [1].

The predominant transmission mode of HIV infection varies by area, illustrating the wide diversity in the epidemiology of HIV in Europe. In the East, injecting drug use is still the main mode of transmission and incidence is increasing, while in central Europe HIV transmission predominantly occurs between men who have sex with men (MSM) followed by heterosexual contact. This also holds true for Western Europe, when cases originating from countries with generalized epidemics are excluded [2]. In all EU countries, sex workers and migrant populations from high prevalence areas are particularly at risk. Although mother-to-child transmission (MTCT) may represent a further concern, effective antenatal, delivery, and postnatal interventions can decrease its risk to <1% [3].

Co-infection with both HIV and MTB is a serious and, in some areas, growing health issue within Europe [4]. In 2008, 5.6% (23,800) of all reported new TB cases in the WHO European Region[§] were estimated to be associated with HIV co-infection [5].

*Address correspondence to this author at the European Research and Project Office GmbH, Saarbrücken, Germany; Tel: +49 681 95923378; Fax: +49 681 95923370; E-mail: c.giehl@eurice.eu

[§]The WHO European Region includes the EU together with 26 other countries, including the Russian Federation, Turkey, and some Central Asian states.

DEMOGRAPHIC DATA

Demographic data for each European country were collected from the WHO Annual Report or National Statistics Institutes, with the year of reference of available data varying from 2004 to 2010.

The combined population of the EU member states is provisionally estimated at 501 million people for 2010 [6]. In comparison to some of the EUCO-Net partner regions, the age distribution within the EU is weighted towards older members of society, with those aged greater than 64 years constituting 12.7% of the total population, and children under 14 years constituting 15.8% [6]. In 2008, the predicted life expectancy at birth in the EU for males was 76.3 years and 82.4 for females, again in striking contrast to some of our partner regions [7]. Overall, population growth remains relatively static for the EU with estimated growth of 0.098% for 2010.

Within the EU, there is significant variation between the member states on key demographic variables (Table 1). All but one of the 11 countries whose life expectancy for males falls below the average for the EU are former Eastern European countries who joined the EU in 2004 or 2007 (Lithuania, Latvia, Estonia, Romania, Bulgaria, Hungary, Slovakia, Poland, Czech Republic, and Slovenia). Nine of these countries also have the lowest gross national product (GNP) of the EU countries (Fig. 1) and show the largest net decrease in population (Fig. 2).

HIV/AIDS AND TB IN EUROPE

The **HIV epidemiological** data collection was mainly based on the UNAIDS 2008 Report on the global AIDS epidemic, the HIV/AIDS surveillance in Europe 2008 report by the European Centre for Disease Prevention and Control

(ECDC) and the WHO Regional Office for Europe, and the UN General Assembly Special Session (UNGASS) country progress reports.

The **TB epidemiological** data collection was mainly based on data from the ECDC or the WHO report "Global tuberculosis control: a short update to the 2009". Data which could not be obtained from these sources were retrieved by accessing national statistical data or data from national TB programmes.

HIV/AIDS Epidemiological Data

The EU has an estimated HIV incidence of 5.4 cases per 100,000, with an AIDS incidence of 1.4 cases per 100,000 [7]. The highest prevalence (Fig. 3) and incidence (Fig. 4) is found in Estonia and Latvia, as is the calculated associated mortality (Table 2). Of note, in contrast to the TB epidemiological data below, several Western European countries such as Spain, Portugal, Italy, and France are amongst those with the highest HIV prevalence. The highest incidence of AIDS is found in Estonia, followed by Latvia, Spain, Portugal and Italy. A similarly diverse picture is seen with the proportions of HIV positive patients on treatment with Latvia, Lithuania, Cyprus and Ireland all reporting less than 30% of patients being on antiretroviral treatment. Availability of data on transmitted drug resistant HIV was limited (Table 3).

TB Epidemiological Data

Overall, the EU has an estimated prevalence of TB of 18.3 per 100,000, an estimated incidence of 19.5 per 100,000, and an estimated mortality of 2.4 per 100,000 [7]. The burden of TB infection and disease is distributed unevenly within the EU27 (Table 3). Former Eastern European countries bear the brunt of its impact. Five

European Union Gross National Product per capita in US\$

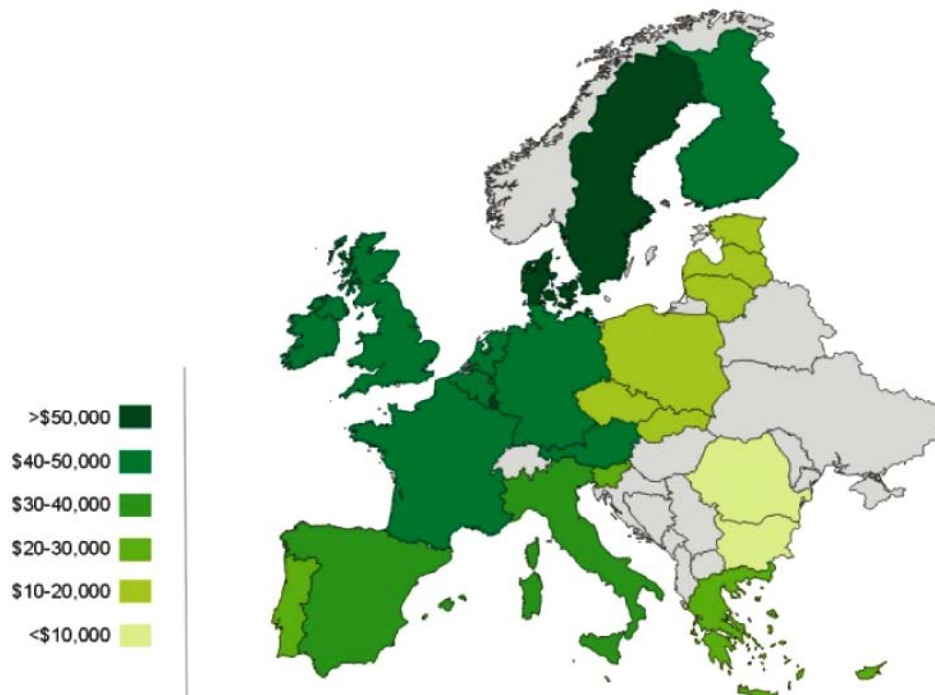


Fig. (1). EU GNP per capita.

Population change % (2010 estimates)

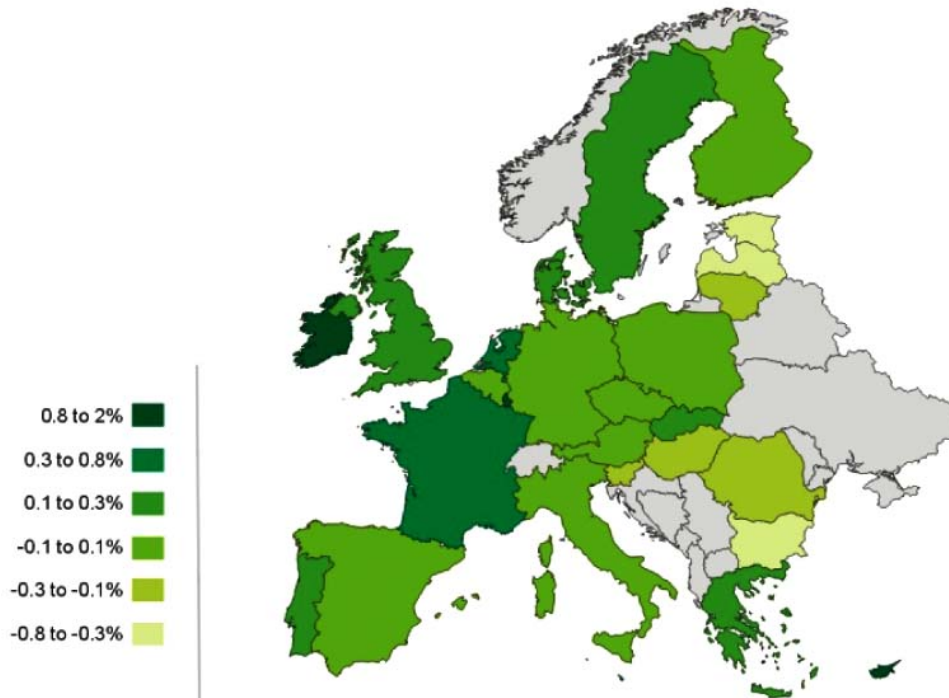


Fig. (2). Population change.

countries share the highest TB prevalence (Fig. 5), TB incidence (Fig. 6), and calculated mortality attributable to TB. These countries are Romania, Lithuania, Bulgaria, Latvia, and Estonia (in descending order for incidence and attributable mortality). The same five countries have the highest prevalence (Fig. 7) and incidence (Fig. 8) of MDR-TB, with the three Baltic states being most severely affected. Latvia, Lithuania and Estonia also have the highest XDR-TB prevalence and incidence of those countries for which estimates were available.

HIV/MTB Co-Infection Epidemiological Data

Data on HIV/MTB co-infection were limited, with no data available for 14 out of the 27 EU member states. Of those countries for whom information was accessible, Spain and Portugal had the largest numbers of TB/HIV co-infected patients in absolute terms. In these countries, the percentage of TB patients for whom the HIV status was known ranged from 0% (Poland) to 93% (Estonia). At present, the data suggest that TB and HIV co-infection is still a relatively low cause of mortality within the EU. All member states have a mortality of one or less than one per 100,000 population attributable to HIV/MTB co-infection (Table 4).

A recent study summarizing prevalence data for 23 European countries over several years also reports findings on the development of co-infection, showing that in England, for example, the prevalence of HIV co-infection among TB patients rose from 5% in 2000 to 8% in 2005, with a peak at 9% in 2003–2004.

France, Iceland and Portugal (11–15%) had higher co-infection levels, while similar levels were found for Estonia and Malta (9%), and very low levels were reported from central European countries (0–1%).

A rise in co-infection levels was seen in Estonia, Latvia, Lithuania, the UK and Belgium, while decreases were seen in Spain and Portugal [4].

HIV - Country Standards and Availability of Standard Diagnostic Tests

There were limited data from countries on the availability, cost, and frequency of use of different diagnostic tests for HIV infection.

Available data show that HIV screening is performed in 17 countries, 16 of which use enzyme-linked immunosorbent assay tests (ELISA), whilst one country uses a “fourth generation” combined ELISA with p24 antigen assay. Confirmatory tests were reported for 19 countries, of which 16 countries reported commonly using a Western blot to confirm diagnosis, whilst one reported ELISA, one a “fourth generation” combined ELISA with p24 antigen assay, and one country PCR for children less than 18 months old. For viral load measurements, 18 countries report using polymerase chain reactions (PCR) to confirm viral load at diagnosis and follow-up. The level of CD4 cells is quantified by flow cytometry in eighteen countries once diagnosis is confirmed and at follow-up. Phenotypic resistance testing was reported by 17 countries which use cell culture-based viral replication assays to assess for phenotypic resistance. For 18 countries, the use of gene sequencing of HIV to detect mutations for genotypic resistance was reported.

MTB/TB - Country Standards and Availability of best Possible Diagnostic Tests

As with HIV testing, only limited data could be retrieved on the availability, cost, and frequency of use of different diagnostic tests for MTB infection/TB disease across countries.

Table 1. Demographic Data for the 27 EU Member States, in Order of Increasing Life Expectancy for Males

	Population (Millions)	Median Age	% 0-14 Years	% 15-64 Years	% >64 Years	Life Expectancy at Birth (Yrs) [‡]		Population Change (%) 2010 Estimates [*]	Gross National Product Per Capita [^] (US\$)
						M	F		
Lithuania	3.6	39.3	14.2	69.6	16.2	66.3	77.6	-0.28	11,870
Latvia	2.2	39.9	13.4	69.7	16.9	67	77.8	-0.61	11,860
Estonia	1.3	39.9	14.9	67.5	17.6	68.7	79.5	-0.63	14,570
Romania	22.2	38.4 ⁺	18	68	14	69.7	77.2	-0.15	8,280
Bulgaria	7.8	41.6 ⁺	14	68.9	17.1	69.8	77	-0.79	5,490
Hungary	10.1	40.0 ⁺	17	68	15	70	78.3	-0.26	12,810
Slovakia	5.4	35.8	18.9	63.1	18	70.8	79	0.14	16,590
Poland	38.5	37.9	15	71.6	13.4	71.3	80	-0.05	11,730
Czech Republic	10.2	40.1	13.6	71	15.5	74.1	80.5	-0.09	16,650
Slovenia	2	42.1 ⁺	14	70.6	15.4	75.5	82.6	-0.11	24,230
Portugal	10.7	39.4	16.3	66.1	17.6	76.2	82.4	0.28	20,680
Finland	5.3	42.1	16.4	66.8	16.8	76.5	83.3	0.1	47,600
Denmark	5.5	40.3	18.4	65.9	15.7	76.5	81	0.28	58,800
Belgium	10.4	41.7	16.1	66.3	17.6	77.1 [‡]	82.6 [‡]	0.09	44,570
Malta	0.4	39.5	16.1	69.4	14.5	77.1	82.3	0.4	16,680
Ireland	4.2	34.6	20.9	67.1	12	77.5	82.3	1.12	49,770
Germany	82.3	43.8	13.7	66.1	20.3	77.6	82.7	-0.05	42,710
UK	61.1	40.2	16.7	67.1	16.2	77.7 [‡]	81.9 [‡]	0.28	46,040
Greece	11.3	42.2 ⁺	14.3	66.6	19.1	77.7	82.4	0.13	28,400
Austria	8.2	42.2	14.5	67.5	18	77.8	83.3	0.052	45,900
France	64.1	39.4	18.6	65	16.4	77.8	84.9	0.55	42,000
Spain	40.5	41.1	14.5	67.4	18.1	78	84.3	0.07	31,930
Luxembourg	0.5	39.2	18.5	66.7	14.8	78.1	83.1	1.17	69,390
Netherlands	16.7	40.4	17.4	67.7	14.9	78.4	82.5	0.41	49,340
Cyprus	0.8	35.5	19.1	68.5	12.3	78.5	83.1	1.69	26,940
Italy	59.1	43	14	66	20	78.7 [‡]	84.2 [‡]	-0.05	35,460
Sweden	9.1	41.3	15.7	65.5	18.8	79.2	83.3	0.16	50,910

[‡]Life expectancy at birth in 2008, Eurostat, European Commission, http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/main_tables#, [‡]Life expectancy at birth in 2007, Eurostat, European Commission, ^{*} <https://www.cia.gov/library/publications/the-world-factbook/index.html>, [^] 2008 figures, European Health for All Database, WHO Europe.

In all 27 EU member states chest x ray is used to diagnose TB and the tuberculin skin test (TST) is employed to support the diagnosis. All countries have access to microscopy with appropriate staining for *Mycobacterium tuberculosis* and culture. 16 countries reported use of polymerase chain reactions (PCR) either to distinguish between *Mycobacterium tuberculosis* and other mycobacteria, to detect clonal relatedness, or to detect resistance mutations (see below). However, nine of these 15 countries only rarely use PCR. When testing contacts of patients with TB, all 27 EU member states report using TST followed by chest X-ray where indicated. 17 countries have access to interferon- γ release assays (IGRA) to detect latent *Mycobacterium tuberculosis* infection. However, for ten

countries its use was categorized as 'rare'. Of those who specified which IGRA was utilized, three had access to the T-SPOT.TB test (Oxford Immunotec, Abingdon, UK), and six utilized the Quantiferon TB Gold assay (Cellestis, Carnegie, Australia). 18 countries test for phenotypic resistance through drug susceptibility testing. Genotypic resistance testing is commonly performed in five countries, whilst 12 use such methods only rarely. The methods of genotypic resistance testing used in the EU include techniques such as DNA sequencing, and line-probe assays. 19 of the EU states for whom data were available provide TB diagnostic tests free of charge for all suspected cases through national TB treatment programmes. Three also provide free diagnostic testing based on other criteria. 20 of

HIV prevalence - patients per 100,000 population

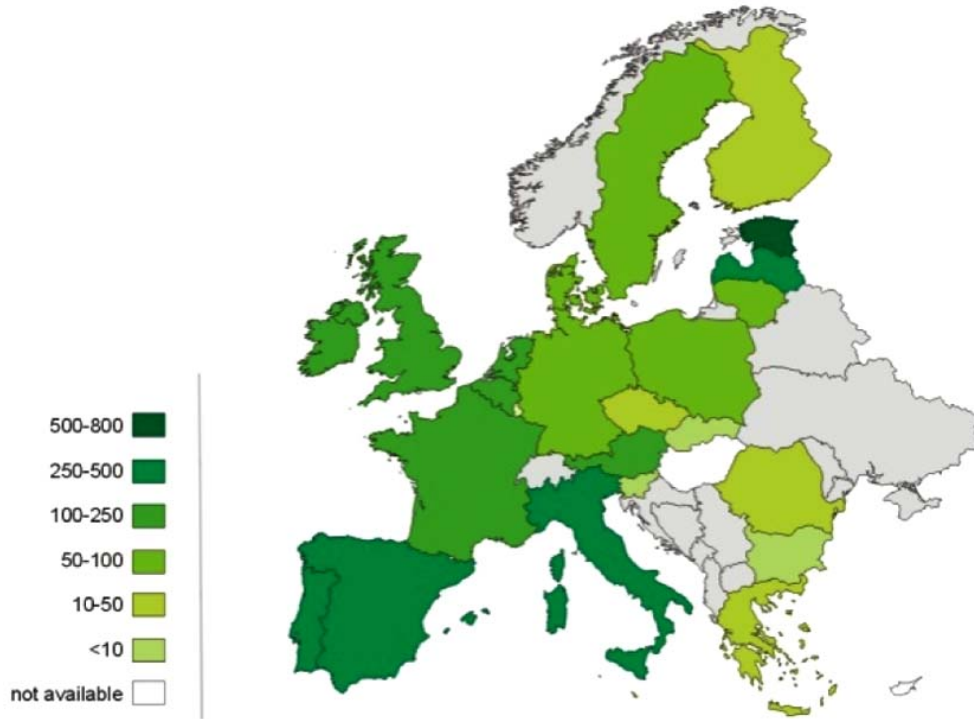


Fig. (3). HIV prevalence.

HIV incidence - new cases per 100,000 population per year

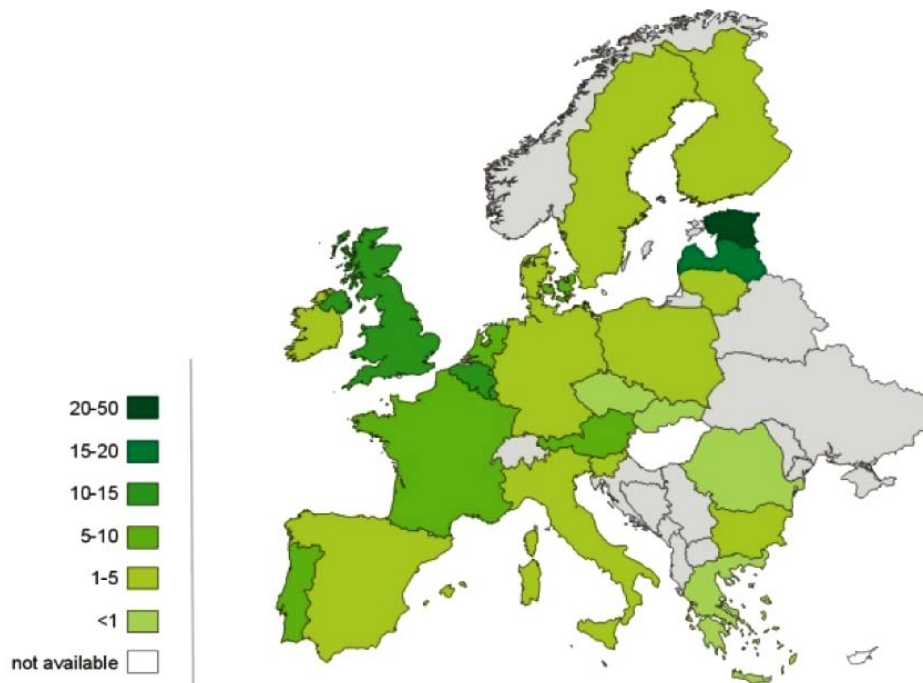


Fig. (4). HIV incidence.

the 27 EU member states routinely perform first-line drug susceptibility testing on all new cases. 19 countries have access to second line drug susceptibility testing within the country, and another four have access to such tests through another country (Table 5).

Medical Treatment Standards for HIV

There were very limited data available from the survey of EU countries on the use of antiretroviral therapy for treatment of HIV/AIDS. The annual progress report “Towards universal access: scaling up priority HIV/AIDS

Table 2. HIV Epidemiological Data in Order of Decreasing HIV Prevalence

	HIV Prevalence Per 100,000 Population (Min;Max)	HIV Incidence Per 100,000 Population Per Year	% of Transmitted Drug Resistant HIV	% of HIV Patients on Treatment	Number of New HIV Infections 2008	Number of New Infections in Men who have Sex with Men 2008	Number of New Hetero-Sexually Transmitted Infections 2008	Number of New HIV Infections in Intravenous Drug Users 2008	Number of New Infections Transmitted from Mother-to-Child	AIDS Cases 2008	AIDS Incidence Per 100,000 Population 2008	Mortality Attributable to HIV Per 100,000 Population (Min;Max)
Estonia	760 (410; 1460)	48.7	NA	38 (19-81)	545	NA	3	36	8	61	4.55	<38.4
Latvia	430 (320; 650)	15.22	NA	2.2	358	22	163	100	8	99	4.36	53
Spain	340 (200; 570)	3.96	3.8	92	1583	614	675	146	4	1170	2.91	5.7 (<2.5; 16.3)
Portugal	320 (180; 590)	8.36	8.4	NA	1124	196	670	220	6	387	3.64	<4.7 (<1.9; 10.3)
Italy	300 (150; 430)	2.1	NA	NA	1958	566	911	152	5	977	1.72	7.6
France	220 (120; 370)	8.97	12.3	80	4068	996	1644	96	17	624	0.98	2.5 (<1.6; 6.4)
Luxemburg	<200	13.6	NA	30-40	47	22	21	4	0	6	1.24	5
Belgium	140 (80; 280)	0.01	10.8	61	1079	332	350	16	7	100	0.94	<0.96
Ireland	130 (100; 180)	4.86	NA	29.1	405	100	284	36	7	28	0.64	<2.4
United Kingdom	120 (60; 260)	14.61	7.1 (8)	>62	7298	2433	3717	152	92	611	1	<0.8 (<0.16-1.9)
Netherlands	110 (60; 190)	6.41	6.9	61 (36; 95)	1361	843	364	9	9	206	1.26	<1.2
Austria	100 (90; 150)	5	NA	NA	NA	NA	NA	NA	NA	65	0.78	<1.22
Denmark*	90 (70; 120)	4.45	3.9	NA	306*	142*	130*	21*	7*	32*	0.59*	<1.8
Germany	70 (70; 80)	3.41	NA	NA	2806	1555	699	123	11	246	0.3	NA
Sweden	68 (38; 120)	4.14	12.9	76.5	359	96	176	22	8	62*	0.68*	<1.1
Lithuania	60 (30; 130)	2.95	NA	18 (8;31)	95	9	26	42	0	55	1.63	<5.5
Poland	50 (28; 88)	1.88	NA	31	804	52	52	46	6	114	0.3	<0.52
Finland	45 (26; 80)	3.68	NA	>90	154	46	64	7	0	29	0.55	<1.9
Czech Republic	14 (<9; 27)	0.91	6	56 (30; 95)	148	92	45	8	0	29	0.28	<0.98
Romania	30	0.83	NA	100	179	25	93	1	5	224	1.04	21.6
Malta	16	6.5	NA	100	28	0	24	2	0	8	1.95	16.2
Greece	13	0.8	NA	33.2	543	235	119	7	1	89	0.79	2.5
Bulgaria	8	1	NA	<80	122	7	28	52	0	29	0.38	<1.28
Slovakia	3	0.5	NA	53	53	33	8	3	0	1	0.02	0.53
Slovenia	1.6	1.7	NA	49.7	48	34	5	0	0	11	0.55	3.8
Cyprus	NA	NA	NA	29.1	37	9	21	1	0	6	0.76	10.6
Hungary	NA	NA	NA	NA	145	93	17	2	0	23	0.23	NA

* = 2007 data. NA = data not available.

TB prevalence - patients per 100,000 population

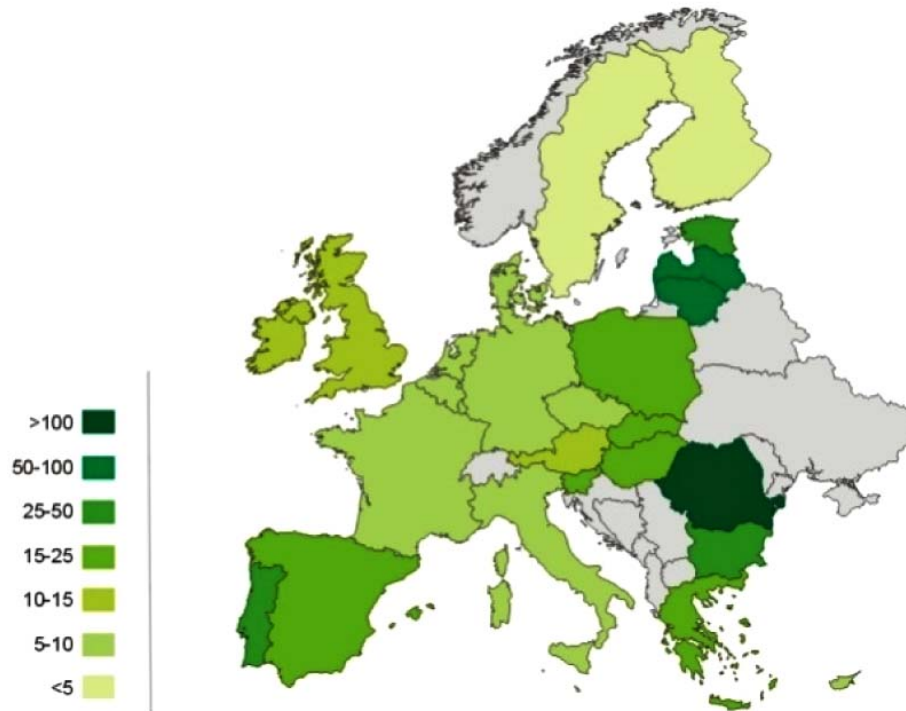


Fig. (5). TB prevalence.

MDR-TB prevalence - patients per 100,000 population

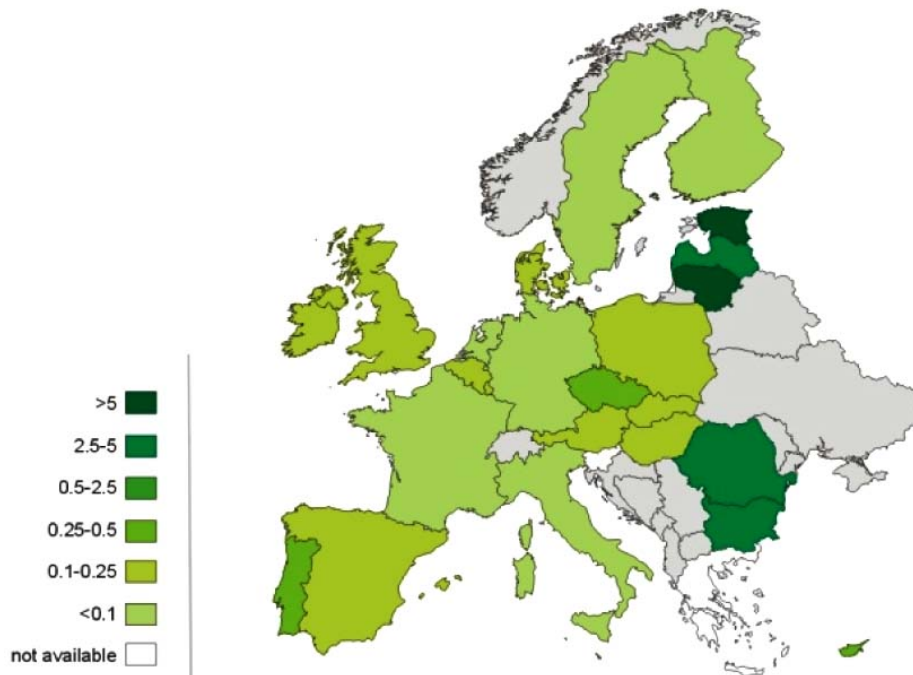


Fig. (6). TB incidence.

interventions in the health sector” by WHO, UNAIDS, and UNICEF which provides information on antiretroviral therapy primarily focuses on low- and middle-income countries and does not contain individual data on most European countries (Table 6). Of note, where data were available, HIV testing in pregnancy had an estimated coverage of as low as 8% of pregnant women, and antiretroviral therapy for infants of mothers living with HIV to prevent MTCT was as low as 44%.

Medical Treatment Standards for TB

Treatment success for TB across the EU member states remains a target for improvement with 18 of the 22 countries for whom data were available failing to attain the WHO target of >85%. Of note, poor treatment success rates do not necessarily mirror MDR-TB rates. Many low TB and MDR-TB prevalence countries also fail to reach the WHO target. These findings reflect those of previous publications [8, 9].

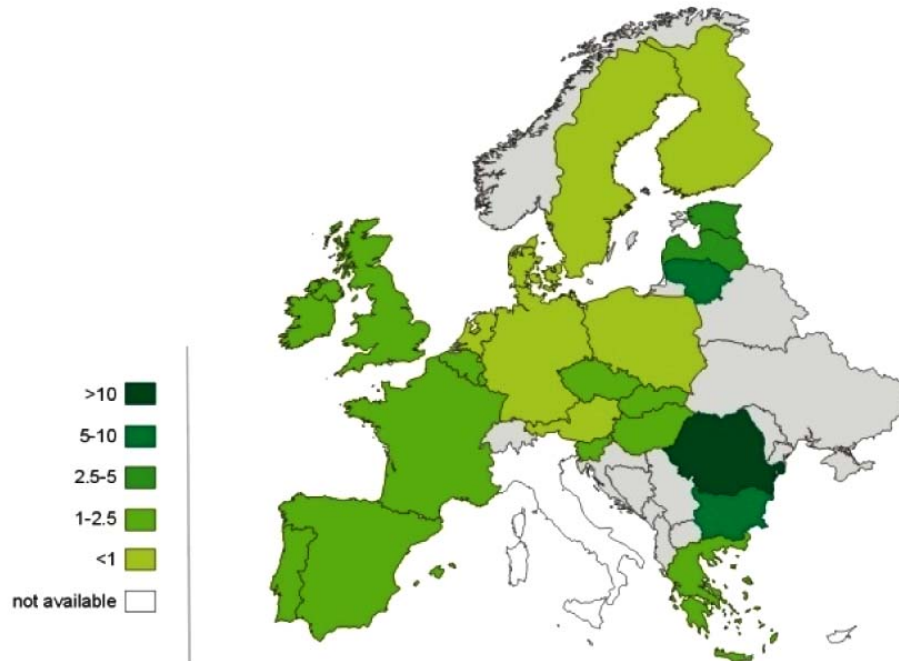
TB incidence - new cases per 100,000 population per year

Fig. (7). MDR-TB prevalence.

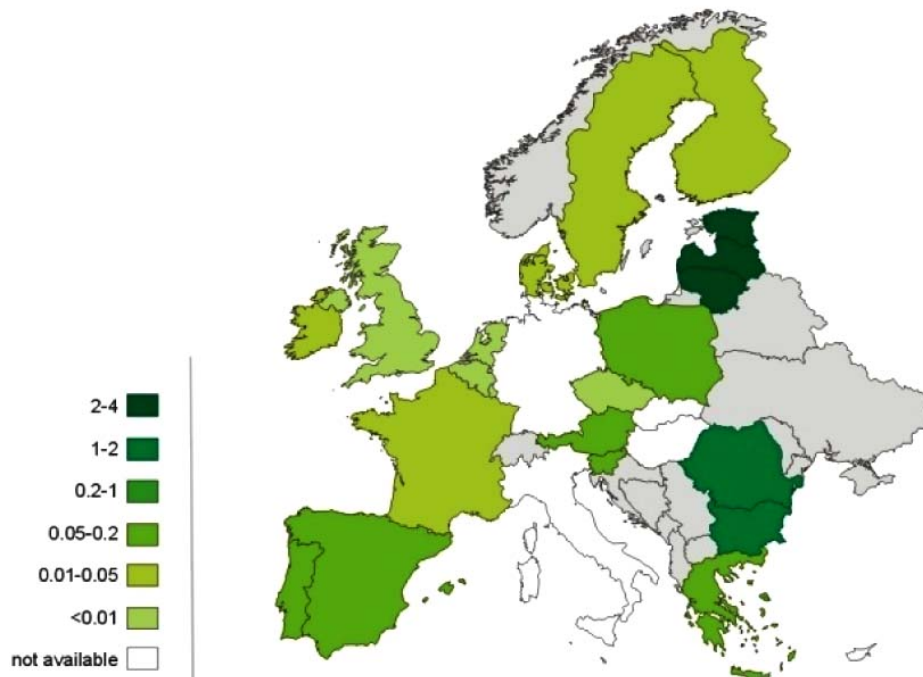
MDR-TB incidence - new cases per 100,000 population per year

Fig. (8). MDR-TB incidence.

12 of the 21 countries for whom data were available did not have formulations for anti-TB drugs procured specifically for children (WHO Global Tuberculosis Control Report Short Update, 2009). Of the 22 countries for whom data were available, seven did not have a national surveillance system to measure the prevalence of drug resistance among TB cases. There is also variability in the policies on screening immigrants for TB, with nine of the 21 countries for whom data were available routinely screening all immigrants (Tables 7 and 8).

SCIENTIFIC CHALLENGES FOR THE FUTURE

Based on the description of the situation of HIV/AIDS, TB, and HIV/MTB co-infection in Europe and subsequent discussions among all EUCO-Net experts at the “AIDS/TB Workshop on Research Challenges and Opportunities for Future Collaboration” in Stellenbosch [10], the group agreed that European research would largely benefit from joint open-access facilities for data collection and statistical analysis, and emphasized the need for centralized facilities for biobanking and immunomonitoring.

Table 3. TB Epidemiological Data in Order of Decreasing Prevalence

	TB Prevalence Per 100.000 Population (Min;Max)	TB Incidence Per 100.000 Population Per Year	MDR-TB Prevalence Per 100.000 Population	MDR-TB Incidence Per 100.000 Population Per Year	XDR-TB Prevalence Per 100.000 Population	XDR-TB Incidence Per 100.000 Population Per Year	Mortality Per 100.000 Population Attributable to TB
Romania	117	16.3	3.52	1.44	NA	NA	15.8
Lithuania	66.9	6.8	8.72	3.44	0.69	0.28	6.8
Latvia	57	4.3	4.45	2.63	0.45	122	4.3
Bulgaria	40.8	5.26	2.85	1.605	NA	NA	5.1
Estonia	36.5 (36; 37)	3.31	6.15	4	0.154	0.307	3.3
Portugal	29	1	0.32	0.196	0	0.0093	1
Poland	22.4	0.8	0.13	0.073	0	0.0026	0.8
Slovakia	20.4	1.85	0.13	NA	NA	NA	1.8
Spain	19.2	1.17	0.14	0.052	0.01	NA	1.2
Hungary	19	2	0.11	NA	NA	NA	2
Greece	16.2	2.7	NA	0.126	NA	NA	2.6
Slovenia	15	1.9	NA	0.05	NA	NA	1.9
UK	11.7	1	0.12	0.0016	0	NA	1
Ireland	10.83	1	0.19	0.024	0.024	NA	1
Austria	10.7 (10.6; 10.8)	0.94	0.11	0.097	0	0	0.9
Belgium	9.5	1	0.2	0.0096	0	NA	1
Czech Republic	9.3	1	0.25	0.001	0.049	NA	1
Malta	9.25	NA	0.25	NA	NA	NA	0
Luxembourg	8.8	1	0.2	<0.05	NA	NA	1
France	8.7	1.32	0.031	0.022	NA	NA	1.3
Italy	7.6	NA	0.093	NA	NA	NA	0.5
Denmark	6.4	<1	0.13	0.036	0	NA	<1.0
Germany	6.1	0.169	0.08	NA	NA	NA	0.17
Netherlands	5.69	<1	0.06	0.006	0.006	NA	<1.0
Cyprus	5	NA	0.375	NA	NA	NA	0
Sweden	4.6	<1	0.066	0.011	0.011	NA	<1.0
Finland	4.5	<1	0.07	0.019	NA	NA	<1.0

The experts furthermore identified a number of scientific challenges as of particular importance for their region and of special interest to researchers in Europe.

Specifically, they agreed that more basic research is needed. An improved understanding of HIV/MTB pathogenesis is a pre-requisite for the urgently needed development of better treatments and treatment strategies for both adults and children, as well as for the prediction of TB latency/progression.

The experts stated that further research should lead to improved diagnostics (in adults and in children) of active and latent TB, improved smear-negative TB diagnostics (especially in HIV+ patients), and the development and dissemination of rapid, simple and cheap diagnostic tools including rapid drug-

resistance testing. Despite recent advances such as the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA), an automated real-time PCR test that simultaneously identifies *M. tuberculosis* and detects rifampicin resistance directly from clinical sputum specimens within hours [11], offering great potential in TB diagnostics and endorsed by the World Health Organization [12], critical factors such as expense, the need for a power supply, and limitations for paediatric populations remain a concern. Biological approaches aiming at the improvement of TB diagnostics from blood, urine, and saliva still need to be further investigated.

In addition, a joint European strategy on when and how to start therapy for co-infected patients needs to be developed.

Table 4. TB/HIV Co-Infection Epidemiological Data in Order of Decreasing Absolute Number of Co-Infected Patients

	Number of TB/HIV Patients	Number of TB Patients with Known HIV Status	Patients Notified (New and Re-Treatment)	% of TB Patients with Known HIV Status	% HIV-Positive of TB Patients with Known HIV Status	TB-HIV Mortality Absolute Numbers [†]	TB-HIV Positive Mortality Rate Per 100,000 Population [†]
Spain	507	3937	8,214	48	13	122	<1
Portugal	438	2350	2,871	82	19	81	<1
Romania	202	6149	23,457	26	3	129	<1
Latvia	72	910	1,065	85	8	12	<1
Belgium	56	913	1,006	91	6	5	<1
Estonia	44	400	429	93	11	18	1
Netherlands	37	261	983	27	14	3	<1
Ireland	15	54	463	12	28	2	<1
Denmark	13	158	391	40	8	2	<1
Czech Republic	7	174	872	20	4	<1	<1
Malta	5	45	50	90	11	<1	<1
Cyprus	2	36	50	72	6	NA	NA
Bulgaria	0	520	2,998	17	0	9	<1
Austria*	NA	NA	874	NA	NA	3	<1
Finland	NA	5	350	1	NA	<1	<1
France	NA	NA	5,812	NA	NA	57	<1
Germany	NA	NA	4,350	NA	NA	11	<1
Greece	NA	NA	663	NA	NA	12	<1
Hungary	NA	NA	1,469	NA	NA	4	<1
Italy	NA	NA	4,418	NA	NA	43	<1
Lithuania	NA	NA	2,247	NA	NA	9	<1
Luxembourg	NA	NA	28	NA	NA	<1	<1
Poland	NA	35	7,825	0	NA	34	<1
Slovakia	NA	633	597	106	NA	NA	NA
Slovenia	NA	NA	212	NA	NA	NA	NA
Sweden	NA	NA	552	NA	NA	1	<1
UK	NA	NA	8,655	NA	NA	30	<1
WHO European region [‡]	11,410	357,473	455,315	79	3	8,096	<1

All data from 2008 from WHO Global tuberculosis control: a short update to the 2009 report, unless otherwise specified. *Data from 2007, †2007 Data from WHO REPORT 2009, Global Tuberculosis Control – Epidemiology, strategy, financing. ‡ The WHO European Region includes the EU together with 26 other countries, including the Russian Federation, Turkey, and some Central Asian states.

Varied and low rates of TB treatment success highlight the need for increased efforts to develop new short-course TB treatments and to further investigate HIV/MTB drug interactions in order to avoid toxicity. Particular attention should be paid to the improved diagnosis and management of immune reconstitution inflammatory syndrome (IRIS).

With regards to disease management, the experts stated that increased and improved capacity building, training, and education programs for the management of HIV/MTB co-infection are needed, specifically addressing health care workers, communities, schools, policymakers, and patient organizations.

LIMITATIONS

Methodological Issues

Attributable mortality (Tables 3 and 4): The rates are expressed differently from one country to another (absolute rate with or without confidence interval vs approximative rate). The classical way of recording mortality rate is absolute rate with confidence interval. We were unable to calculate the confidence interval because global mortality data were not always available.

Prevalence and Incidence rates (Tables 3 and 4): The results presented in Tables 3 and 4 should be interpreted very

Table 5. Access to TB Diagnostics and Surveillance within the EU

	Is Diagnosis Provided Through the TB National Treatment Programme Free-of-Charge?	Was there a National Reference laboratory?	Is there a National Surveillance System to Measure the Prevalence of HIV in TB Patients?	Was there a National Surveillance System to Measure the Prevalence of Drug Resistance Among TB Cases?	Is First-Line Drug-Susceptibility Testing Routinely Performed for New Cases?
Austria	NA	NA	NA	NA	No
Belgium	Yes (other criteria)	Yes	No	Yes	Yes
Bulgaria	Yes (all suspects)	Yes	No	No	No
Cyprus	Yes (all suspects)	Yes	Yes	Yes	Yes
Czech Republic	Yes (all suspects)	Yes	No	Yes	Yes
Denmark	Yes (all suspects)	Yes	No	Yes	Yes
Estonia	Yes (all suspects)	Yes	Yes	Yes	Yes
Finland	Yes (all suspects)	Yes	No	Yes	Yes
France	Yes (all suspects)	Yes	No	Yes	Yes
Germany	Yes (all suspects)	Yes	No	No	Yes
Greece	NA	NA	NA	NA	No
Hungary	Yes (all suspects)	Yes	No	Yes	Yes
Ireland	Yes (all suspects)	Yes	No	Yes	Yes
Italy	Yes (other criteria)	Yes	No	No	Yes
Latvia	Yes (all suspects)	Yes	Yes	Yes	Yes
Lithuania	NA	NA	NA	NA	No
Luxembourg	NA	NA	NA	NA	No
Malta	Yes (all suspects)	No	Yes	Yes	Yes
Netherlands	Yes (all suspects)	Yes	No	No	Yes
Poland	Yes (all suspects)	Yes	No	Yes	Yes
Portugal	Yes (all suspects)	Yes	Yes	Yes	Yes
Romania	Yes (all suspects)	Yes	Yes	Yes	Yes
Slovakia	Yes (all suspects)	Yes	No	No	Yes
Slovenia	Yes (if TB is confirmed)	Yes	NA	NA	No
Spain	Yes (other criteria)	Yes	No	No	No
Sweden	Yes (all suspects)	Yes	No	No	Yes
United Kingdom	Yes (all suspects)	Yes	No	Yes	Yes

2008 data from WHO Global Tuberculosis Control Report Short Update, 2009.

carefully. As far as **prevalence** was concerned, the **annual** prevalence was only taken into account in the analysis and not the cumulative prevalence on a period of time as usually given in WHO reports. When only cumulative cases on a period of time were available, we tried to calculate an annual prevalence rate considering the **same year** from all countries.

When the **annual reference year** for demographic data was different from the prevalence and incidence year of reference, we took as a reference the data published by OECD [13].

Where data were unavailable in our survey on issues of relevance to this report, existing data from the European Union and World Health Organization were utilized.

Comments on Results

The variation of HIV prevalence rates between countries may be due to the difficulty to assess HIV/AIDS prevalence. It is not clear if the prevalence data are collected from HIV registry (mandatory declaration of HIV+) or registry of AIDS disease. The very high prevalence of TB in Romania is questionable, as well as the number of treated patients (higher than the number of HIV patients).

An estimation of treatment success for HIV patients is poorly documented and raises the question how treatment success is best evaluated with regard to existing national and international guidelines).

Table 6. Antiretroviral Therapy within the EU

	Reported Number of People Receiving ART	Reported Number of Adults Receiving ART	Reported Number of Children Receiving ART	Number of Pregnant Women Living with HIV who Received ART for Preventing MTCT	Reported Number of Pregnant Women Tested for HIV	Percentage Estimated Coverage of Pregnant Women Tested for HIV	Reported Number of Infants Born to Women Living with HIV Receiving ART for Preventing MTCT	Estimated Coverage of Infants Born to Women Living HIV Receiving ART for Preventing MTCT
Austria	2,250	NA	NA	NA	NA	NA	NA	NA
Belgium [*]	6,928	NA	NA	NA	NA	NA	NA	NA
Bulgaria	251	248	3	1	NA	NA	NA	NA
Cyprus	170	NA	NA	NA	NA	NA	NA	NA
Czech Republic [*]	570	NA	NA	NA	NA	NA	NA	NA
Denmark	3,000	NA	NA	NA	NA	NA	NA	NA
Estonia	1,004	NA	NA	NA	NA	NA	NA	NA
Finland [†]	450	NA	NA	NA	NA	NA	NA	NA
France	79,680	NA	NA	NA	NA	NA	NA	NA
Germany	36,500	NA	NA	NA	NA	NA	NA	NA
Greece	4,236	NA	NA	NA	NA	NA	NA	NA
Hungary	500	443	7	1	8,357	8%	NA	NA
Ireland [‡]	1,600	NA	NA	NA	NA	NA	NA	NA
Italy	95,000	NA	NA	NA	NA	NA	NA	NA
Latvia	334	311	23	37	14,152	61%	NA	NA
Lithuania	127	126	1	11	28,614	91%	11	>95%
Luxembourg	344	NA	NA	NA	NA	NA	NA	NA
Malta	91	NA	NA	NA	NA	NA	NA	NA
Netherlands	9,272	NA	NA	NA	NA	NA	NA	NA
Poland	3,822	3,705	117	70	NA	NA	69	44%
Portugal	12,366	NA	NA	NA	NA	NA	NA	NA
Romania	7,434	7,218	216	109	100,168	47%	161	88%
Slovakia	97	97	0	NA	NA	NA	NA	NA
Slovenia [*]	157	NA	NA	NA	NA	NA	NA	NA
Spain	82,710	NA	NA	NA	NA	NA	NA	NA
Sweden [†]	2,800	NA	NA	NA	NA	NA	NA	NA
United Kingdom [*]	39,556	NA	NA	NA	NA	NA	NA	NA

2008 data from Towards universal access: scaling up priority HIV/AIDS interventions in the health sector Report 2009, WHO, UNICEF, UNAIDS. ^{*}=data from 2007. [†]2006 data. [‡]2005 data.

INTERCULTURAL CHALLENGES AND SENSITIVITIES

Given the fact that the EU combines 27 countries with different languages and cultures, EU wide, harmonized HIV/AIDS and TB treatment and care and related research naturally face a number of particular challenges that were also discussed at the “AIDS/TB Workshop on Research Challenges and Opportunities for Future Collaboration”.

Even though a high risk group, migrants to and within the EU from high prevalence TB and HIV regions struggle with

limited understanding of the language of the country they now live in, which may negatively impact their access to healthcare and/or health awareness. For instance, in Belgium, of those people living with HIV whose nationality is known (70% of all cases), 63% are not Belgian nationals. Fear of contact with the authorities by immigrants with uncertain legal status was raised as an issue by experts from several Western European countries, with corresponding concerns of infectious patients presenting advanced disease to health services, with risks both to their own health, and that of the population through ongoing spread of disease.

Table 7. TB Treatment Data in Order of Increasing TB Treatment Success

	% of TB Treatment Success	% of TB Patients in Treatment
Hungary	33	NA
Cyprus	62	NA
Sweden	63	NA
Estonia	66	68
Ireland	66	100
Lithuania	67	71.9
Austria	69	56.2
Czech Republic	69	100
Romania	70	NA
Spain	70.4	NA
Latvia	71	76.1
Poland	72	57.9
Belgium	73	82
Denmark	77	25
Slovakia	78	NA
UK	79	93
Bulgaria	80	NA
Germany	80.5	92.3
Portugal	86	65.5
Netherlands	90	95
Slovenia	92	94
Italy	100	NA
Malta	100	NA
Finland	NA	NA
France	NA	NA
Greece	NA	NA
Luxembourg	NA	NA

Grey shading denotes countries not meeting WHO target of >85% treatment success). NA=data not available.

Also, prevention strategies are influenced on a country-by-country basis by cultural and religious customs, and on national level are usually tailored to the demographic groups at highest risk.

While the demographics of different marginalized groups vary within the EU as described in Section 4, intravenous drug users, migrants, sex workers, institutionalized citizens, and MSM are all at greater risk for HIV and/or MTB infection than the general population. For several of these groups and again varying among different cultural environments there is again a fear of involvement with authorities, with corresponding public health consequences.

Despite greater awareness and public visibility of HIV/AIDS, many patients still fear the stigma associated with such a diagnosis, with a concomitant impact upon

presenting to health services when at risk or symptomatic, and engaging with care thereafter.

Disease registration and epidemiological data collection, as highlighted throughout this report, are fundamental for assessing the extent, impact, and trends of these diseases. There is a clear and urgent need for improved data collection systems to record factors relevant to clinical, epidemiological, and resistance variables for HIV and TB.

Lastly, both within and between EU countries, there is a perceived lack of integration and co-ordination between governmental agencies involved in dealing with AIDS and TB disease management and research funding.

CONCLUSIONS AND RECOMMENDATIONS

The data presented underline that HIV/AIDS and TB are major and urgent health problems within the EU. However, reliable and consistent epidemiological, demographic, treatment, and resistance data for HIV-, MTB-, and especially for co-infection are not easily accessible across the EU member states. There is an urgent need for appropriate resources to co-ordinate harmonized and comprehensive data collection relevant to public health and clinical management at national and EU levels.

With regards to **HIV/AIDS**, a high awareness and a low threshold for testing for HIV are key to prevent late presentation with attendant immune deterioration. Much remains to be done to prevent spread of HIV infection through transmission between MSM, heterosexual intercourse, intravenous drug use, and mother-to-child transmission.

To prevent the spread of **TB infection**, early and appropriate initiation of treatment and infection control procedures is a key prerequisite. Until recently, diagnosis of TB however has relied primarily on clinical assessment, microscopy, and culture and confirmation of active TB by culture, which can take several weeks. The GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA) marks a major advance in this area, and can provide a diagnosis within hours, including of MDR-TB [11]. Investigation of host biomarkers and urinary tests for mycobacterial-specific substances remain key areas for research.

The reasons behind the suboptimal and varied **treatment success rates for TB** within the EU require exploration. Resistance and failures in reporting are likely to play a role, although these and other factors need further elucidation.

MDR- and XDR-TB are a serious threat to public health within the EU. There are significant morbidity, mortality, and health care costs associated with these conditions due to lengthy lag times before drug susceptibility results are available, limited therapeutic options, and the need for inpatient treatment and isolation. The failure to meet WHO treatment success targets for TB across many of the EU member states contributes to development of further resistance.

Management of patients with **HIV/MTB co-infection** should take into account the increasing movement of people between EU member states, and from high prevalence areas outside of the EU.

Table 8. Access to TB Treatment, National Guidelines on Drug Resistance, and Immigrant Screening Policy within the EU Member States

	Were TB Drugs Provided Free-of-Charge to All TB Patients Treated with First-Line Drugs Under the National Treatment Programme?	Were Paediatric Formulations of Anti-TB Drugs Procured Specifically for Children?	Have National Guidelines for Management of Drug-Resistant TB been Developed?	Are Immigrants Routinely Screened for TB?
Austria	NA	NA	NA	NA
Belgium	Yes	No	NA	Yes
Bulgaria	Yes	No	No	No
Cyprus	Yes	No	NA	No
Czech Republic	Yes	No	NA	No
Denmark	Yes	No	NA	No
Estonia	Yes	No	Yes - including XDR	No
Finland	Yes	Yes	NA	Yes
France	Yes	Yes	NA	Yes
Germany	Yes	Yes	NA	NA
Greece	NA	NA	NA	NA
Hungary	Yes	No	NA	No
Ireland	Yes	Yes	NA	No
Italy	Yes	NA	NA	No
Latvia	Yes	No	Yes - not including XDR	Yes
Lithuania	NA	NA	NA	NA
Luxembourg	NA	NA	NA	NA
Malta	Yes	Yes	NA	Yes
Netherlands	Yes	No	NA	Yes
Poland	Yes	Yes	Yes - including XDR	No
Portugal	Yes	No	NA	No
Romania	Yes	Yes	Yes - including XDR	No
Slovakia	Yes	No	NA	Yes
Slovenia	NA	No	NA	NA
Spain	NA	NA	NA	No
Sweden	Yes	Yes	NA	Yes
United Kingdom	Yes	Yes	NA	Yes

There is a need to implement prevention strategies for TB infection and intensify TB case-finding among people living with HIV. Appropriate implementation of international recommendations on treatment should be monitored and evaluated.

Collaboration between agencies, researchers, and governments involved in management of HIV and MTB infection is key to a coordinated approach to these fundamentally interwoven diseases [14] and joint research into HIV/MTB co-infection needs to be better represented in international funding programs.

ACKNOWLEDGEMENTS

We would like to thank Romano Arcieri, Daniela Arias, Massimiliano Bugarini, Paloma Cuchi, Jan Dirks, Lucia Palmisano, Carlo Torti, Enrico Tortoli, Heike Uhlmann-

Schiffler and Pascal Vignally for their participation in data collection, and Hagen von Briesen, Andreas Meyerhans, Juan Carlos Palomino, Martina Sester and Laure Sonnier for critical reviewing of the manuscript and valuable feedback.

The work presented in this manuscript is derived from the EUCO-Net project funded by the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n°223373.

ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
DOTS	Directly Observed Treatment, Short course

ECDC	European Centre of Disease Prevention and Control
EU	European Union
EU27	The 27 EU member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom
EUCO-Net	European Network for global cooperation in the field of AIDS & TB
GNP	Gross National Product
HCW	Health Care Workers
HIV	Human Immunodeficiency Virus
IDU	Intravenous Drug User
IGRA	Interferon Gamma Release Assays (blood tests aimed to determine whether a person has been exposed to tuberculosis)
MDR-TB	Multidrug Resistant Tuberculosis (resistant to at least rifampicin and isoniazid)
MSM	Men who have Sex with Men
MTB	<i>Mycobacterium tuberculosis</i> (the causative agent of tuberculosis)
MTCT	Mother-to-child transmission
NA	Data not available
PCR	Polymerase Chain Reaction
TB	Tuberculosis
TB/HIV	Denoting co-infection with MTB and HIV.
TST	Tuberculin skin test
WHO	World Health Organization

XDR-TB	Extensively Drug Resistant Tuberculosis (MDR-TB with <i>additional</i> resistance to a quinolone <i>and</i> a second-line injectable drug namely kanamycin, amikacin or capreomycin)
UNAIDS	Joint United Nations Programme on HIV/AIDS

REFERENCES

- [1] Plan to Stop TB in 18 High-priority Countries in the WHO European Region 2007–2015, WHO Regional office for Europe 2007.
- [2] HIV/AIDS surveillance in Europe 2008, Stockholm: European Centre for Disease Prevention and Control/WHO Regional Office for Europe 2009.
- [3] Townsend CL, Cortina-Borja M, Peckham CS, de Ruyter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS* 2008; 22: 973–81
- [4] Kruijshaar ME, Pimpin L, Ködmön C, *et al.* TB-HIV co-infection: how does the UK compare to Europe? *Thorax* 2010; 65: Suppl 4 A150 doi:10.1136/thx.2010.151043.21
- [5] Global tuberculosis control: a short update to the 2009 report, World Health Organization, 2009
- [6] Eurostat, European Commission, <http://ec.europa.eu/eurostat>, retrieved 27.9.2010
- [7] European Health for All Database, WHO Regional Office for Europe, <http://data.euro.who.int/hfad/>, retrieved 27.9.2010
- [8] Global Tuberculosis Control. Surveillance, Planning, Financing. WHO Report. WHO 2003.
- [9] Faustini A, Hall AJ, Perucci CA. Tuberculosis treatment outcomes in Europe: a systematic review. *Eur Respir J* 2005; 3: 503–10.
- [10] Sester M, Giehl C, McNerney R, *et al.* Challenges and perspectives for improved management of HIV/Mycobacterium tuberculosis co-infection. *Eur Respir J* 2010; 36(6): 1242–7.
- [11] Boehme CC, Nabeta P, Hillemann D, *et al.* Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; 363: 1005–15.
- [12] Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB, WHO (2010) http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf, retrieved 02.03.2011
- [13] Monitoring and Evaluation Toolkit, Tools for monitoring programs for HIV, tuberculosis, malaria and health systems strengthening The Global Fund Third Edition February 2009 <http://www.theglobalfund.org>
- [14] A guide to monitoring and evaluation for collaborative TB/HIV activities. WHO 2009.

Received: November 26, 2010

Revised: March 7, 2011

Accepted: March 10, 2011

© Giehl *et al.*; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.