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Tuberculosis in migrants from 106 countries in Italy, 2008–2014

To the Editor:

Tuberculosis (TB) is a major infectious disease worldwide. Over recent years, TB caused by multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains (resistant to at least isoniazid and rifampicin) and extensively drug-resistant (XDR) strains (MDR strains resistant to any fluoroquinolone and to at least one injectable second-line drug (SLD), *i.e.* kanamycin, capreomycin or amikacin) has emerged as a public health concern in industrialised countries, due to increasing migration from regions where TB is endemic.

In Italy, while the number of TB cases decreased from 4220 in 2004 to 3153 in 2013 (7.3 and 5.3 cases per 100 000 population, respectively) [1, 2], notifications from foreign-born persons (FBPs) increased from 39.4% in 2004 to 63% in 2013. The association of MDR-TB with immigrant status was previously reported [3, 4] but a systematic study of the country of origin of migrants was not performed. The European Centre for Disease Prevention and Control (ECDC) published a report on key infectious diseases (including TB) affecting migrant populations in the European Union/European Economic Area for the years 2000–2010 [5]. Here, we conducted a retrospective analysis in Italy over the period 2008–2014 in order to estimate TB burden and MDR/XDR-TB in FBPs by country of origin, in comparison with Italian-born persons (IBPs), and to determine resistance to SLDs in MDR/XDR *M. tuberculosis* clinical isolates.

Our laboratory network, the Italian Multicentre Study on Resistance to Antituberculosis drugs (SMIRA), is composed of 35 hospital reference laboratories located in 18 out of 20 regions. All the laboratories are periodically examined by first-line drug (FLD) and SLD proficiency testing exercises by the World Health Organization (WHO) Supranational Reference Laboratory in Rome [6]. In 2013, the SMIRA network covered 74.5% of nationwide notified cases, contributing the majority of cases included in the annual ECDC/WHO TB report [2].

TB cases with positive *M. tuberculosis* cultures were routinely examined by the SMIRA laboratories for susceptibility to FLD and SLD. Table 1 shows data on drug resistance of 13 030 *M. tuberculosis* strains with known country of origin (6869 from FBPs and 6161 from IBPs) isolated from 13 030 different patients in 2008–2014. Due to difficulties in obtaining a reliable history of prior treatment in FBPs, we were not able to distinguish new cases from previously treated cases, thus the number of TB cases included both categories. MDR-TB cases decreased from 3.7% in 2008 to 3.1% in 2014.

M. tuberculosis strains were isolated from migrants coming from 106 countries, including patients with MDR strains from 37 countries and with non-MDR strains from 69 countries (table 1). Data of MDR strains from FBPs (333 out of 410) were stratified by continent (Europe, Africa, Asia and the Americas) and country of origin. Due to known differences in MDR-TB rates in European and African countries [7, 8], Europe (14 countries) was subdivided in the former Soviet Union and Eastern Europe regions, and Africa (12 countries) into North Africa and sub-Saharan regions. Migrants also came from six Asian countries and five countries in the Americas (all in South America).

Large differences were found in MDR-TB rates (MDR *M. tuberculosis*/*M. tuberculosis* strains), with the ranking (from greatest to least) being: former Soviet Union (mean±SD 29.8±9.5%, range 24.1–44.0%); the Americas (6.7±3.6%, range 2.5–11.1%); Eastern Europe (4.0±1.4%, range 2.2–5.4%); Asia (3.6±2.5%, range 1.1–6.8%) and North Africa (3.6±0.7%, range 2.9–4.3%); Sub-Sahara (3.0±2.3%, range 0.9–8.0%); IBPs (1.2%). The differences between MDR-TB percentages of the countries of a continent/region *versus* MDR-TB percentages of all other countries (excluding Italy) were statistically significant ($p<0.05$ by Student's t-test) for Europe ($p<0.001$), the former Soviet Union ($p<0.001$) and Africa ($p=0.034$). The sub-Saharan region showed a p-value of 0.067, close to cut-off for significance. No significant differences were seen for Eastern Europe, North Africa, Asia or the Americas.

The highest MDR-TB rates were observed in FBPs from the former Soviet Union (Ukraine, Moldova, Russia, Georgia, Armenia, Belarus, Chechnya, Kyrgyzstan and Lithuania), in accordance with the fact that these countries, with the exception of Chechnya, belong to the WHO list of 27 high MDR-TB burden countries [7]. Indeed, MDR-TB levels were consistent with those of their native countries (*e.g.* in 2013: Ukraine, 26.0%; Moldova, 33.8%; Russia, 28.5%; Georgia, 16.6%; Armenia, 15.1%; Belarus, 39.7%;

TABLE 1 Geographic distribution of 13 030 *Mycobacterium tuberculosis* strains isolated in Italy in 2008–2014 from 6869 foreign-born persons (FBPs) and 6161 Italian-born persons (IBPs) with tuberculosis

Group (% total strains)	Strains n			MDR *M. tuberculosis*/ *M. tuberculosis*[#]	MDR strains tested for SLD resistance				
	M. tuberculosis	MDR	XDR		Strains n	SLD-resistant strains n (%)			
						Km	Ak	Cm	Ofl
Europe (19.3)				p<0.001					
Former Soviet Union (2.6)				p<0.001					
Ukraine	165	44	13	26.7	28	11 (39)	10 (36)	11 (39)	17 (61)
Moldova	123	30	2	24.4	23	9 (39)	5 (22)	4 (17)	6 (26)
Russia	25	11	1	44.0	5	2 (40)	0	1 (20)	2 (40)
Georgia, Armenia, Belarus, Chechnya, Kyrgyzstan and Lithuania[¶]	29	7	1	24.1	4	1 (25)	1 (25)	0	2 (50)
Eastern Europe (16.7)				p=0.201					
Romania	1904	103	8	5.4	66	23 (35)	20 (30)	22 (33)	15 (23)
Albania	137	4	0	2.9	4	2 (50)	2 (50)	2 (50)	1 (25)
Bulgaria	62	3	0	4.8	2	1 (50)	1 (50)	1 (50)	0
Poland	45	1	0	2.2	0	0	0	0	0
Serbia	21	1	0	4.8	0	0	0	0	0
Africa (12.8)				p=0.034					
North Africa (5.8)				p=0.244					
Morocco	653	24	1	3.7	12	2 (17)	3 (25)	2 (17)	3 (25)
Tunisia	70	3	0	4.3	1	0	0	0	0
Algeria	34	1	0	2.9	0	0	0	0	0
Sub-Saharan Africa (7.0)				p=0.067					
Senegal	352	3	0	0.9	2	0	0	0	0
Nigeria	168	3	0	1.8	1	0	0	0	0
Somalia	102	1	0	1.0	0	0	0	0	0
Ethiopia	85	2	0	2.4	2	0	0	0	0
Eritrea	79	3	0	3.8	0	0	0	0	0
Ghana	60	2	0	3.3	0	0	0	0	0
Cameroon	38	1	0	2.6	0	0	0	0	0
Congo and Angola[+]	25	2	0	8.0	2	0	0	0	2 (100)
Asia (11.8)				p=0.143					
Pakistan	427	6	0	1.4	4	0	0	0	2 (50)
India	396	11	0	2.8	3	0	0	0	1 (33)
China	265	18	0	6.8	7	0	0	0	1 (14)
Philippines	268	3	0	1.1	3	0	0	1 (33)	1 (33)
Bangladesh	156	4	1	2.6	2	1 (50)	0	1 (50)	1 (50)
Sri Lanka	30	2	1	6.7	1	1 (100)	1 (100)	1 (100)	1 (100)
The Americas (4.6)				p=0.429					
Peru	364	26	2	7.1	21	10 (48)	10 (48)	9 (43)	5 (24)
Brazil	121	3	0	2.5	3	1 (33)	2 (66)	2 (66)	0
Ecuador	81	9	0	11.1	1	0	0	0	1 (100)
Colombia and Argentina[§]	34	2	0	5.9	2	0	0	0	0
69 countries with non-MDR strains (4.2)	550	0	0	0	0	0	0	0	0
FBPs (52.7)	6869	333	30	4.8	199	64 (32)	55 (27)	57 (29)	61 (31)
IBPs (47.3)	6161	77	3	1.2	39	12 (31)	7 (18)	10 (26)	6 (15)
FBPs and IBPs (100)	13 030	410	33	3.1	238	76 (32)	62 (26)	67 (28)	67 (28)

FBP strains were isolated from people coming from 106 countries, including patients with multidrug-resistant (MDR) strains from 37 countries and with non-MDR strains from 69 countries. XDR: extensively drug-resistant. SLD: second-line drug; Km: kanamycin; Ak: amikacin; Cm: capreomycin; Ofl: ofloxacin. [#]: p-values (Student's t-test) for percentages of MDR *M. tuberculosis*/*M. tuberculosis* of the countries of a continent/ region (in bold) *versus* percentages of MDR *M. tuberculosis*/*M. tuberculosis* of all other countries, excluding Italy. [¶]: MDR *M. tuberculosis*/ *M. tuberculosis* Georgia, 2/22; Armenia, 1/1; Belarus, 1/2; Chechnya, 1/1; Kyrgyzstan, 1/1; Lithuania 1/2. [+]: MDR *M. tuberculosis*/*M. tuberculosis* Congo 1/20; Angola, 1/5. [§]: MDR *M. tuberculosis*/*M. tuberculosis* Colombia, 1/24; Argentina, 1/10.

Kyrgyzstan, 36.8%; Lithuania, 19.2%) [2]. Among the Eastern European countries, Romania was the largest TB group and showed the highest MDR-TB rate (5.4%). As for Asia and the Americas, the highest rates were observed in migrants from China (6.8%) and Ecuador (11.1%), respectively.

The lowest MDR-TB rates were observed in FBPs from sub-Sahara (3.0±2.3%), in keeping with the knowledge that MDR-TB in new cases in African countries is <3% [7]. Values ranged from 0.9% (Senegal) to 8% (Congo and Angola, pooled for low case numbers). Nigeria and Ethiopia, also belonging to the 27 WHO countries group [7], showed 1.8% and 2.4% MDR-TB, respectively. MDR-TB from North Africa was 2.9–4.3%. A recent meta-analysis [8] reporting low MDR-TB in new cases and previously treated cases in 21 sub-Saharan countries (including Ethiopia, Somalia, Ghana and Cameroon) is in agreement with our observations. Some investigators also found low levels of MDR-TB in Sub-Sahara/Africa [9, 10] while others reported increasing MDR-TB in five African countries other than those of table 1 [11]. Low MDR-TB rates in sub-Sahara/Africa were ascribed to several factors including poor diagnostic and surveillance [9], wide use of fixed-dose combinations [8], and the fact that for many years Africa was neglected and TB was not treated [10].

The ranking of XDR-TB rates (XDR *M. tuberculosis* strains/*M. tuberculosis* strains) in 33 XDR strains isolated from 10 countries (including Italy) was as follows: former Soviet Union (17 strains, 4.97%); Eastern Europe (eight strains, 0.37%); the Americas (two strains, 0.33%); Asia (two strains, 0.13%) and North Africa (one strains, 0.13%); IBPs (three strains, 0.05%); sub-Sahara (no strains, 0%); reflecting the MDR-TB trend.

Among 238 MDR strains tested for susceptibility to SLDs (199 from FBPs and 39 from IBPs), resistance in FBPs and IBPs was similar for kanamycin (32% and 31%, respectively) and capreomycin (29 and 26%, respectively), while it was higher in FBPs than in IBPs for amikacin (27% and 18%, respectively) and ofloxacin (31% and 15%, respectively), which is likely to be due to the large use of amikacin and fluoroquinolones for treatment of MDR-TB in FBPs. Indeed, resistance to fluoroquinolones and other drugs is increasing in high TB burden countries with weak healthcare systems [12, 13]. Only some of the MDR strains (238 out of 410) were tested for SLD resistance because in the SMIRA network, the first SLD proficiency testing was performed in 2010 [6], thus only MDR strains isolated in 2011–2014 were considered.

Overall, a consistent migration of TB patients from 106 countries occurred in Italy in 2008–2014, with MDR- and XDR-TB being very high in FBPs from the former Soviet Union and low from sub-Sahara. Our data show that the MDR-TB rates in migrants reflects those in the countries of origin. These findings should guide clinicians in their approach to TB in migrants, using all available diagnostic tools to rapidly start with treatment of the populations at high risk of MDR/XDR-TB. In addition, monitoring drug resistance rate in migrants in low-incidence countries can provide information on the rate in the countries of origin, in the framework of the WHO vision to eliminate TB as a public health problem by 2035 [14, 15].

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