Eur Respir J 2003; 21: 129–134
DOI: 10.1183/09031936.03.00047402
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European Respiratory Journal
ISSN 0903-1936

Monitoring the quality of laboratories and the prevalence of resistance to antituberculosis drugs: Italy, 1998–2000

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ABSTRACT: In 1998 a network of 20 regional tuberculosis (TB) laboratories (the Italian Multicentre Study on Resistance to Antituberculosis drugs (SMIRA) network) was established in Italy to implement proficiency testing and to monitor the prevalence of drug resistance nationwide. The network managed 30% of all TB cases reported in Italy each year.

The aim of the present report is to describe: 1) the accuracy of drug-susceptibility testing in the network; 2) the prevalence of drug resistance for the period 1998–2000.

Data were collected from the network laboratories. Sensitivity to streptomycin and ethambutol increased from the first survey (1998–1999) to the second survey (2000) from 87.7 to 91.9%. Specificity, predictive values for resistance and susceptibility, efficiency and reproducibility were consistent in both surveys. In previously untreated cases, the prevalence of multidrug-resistance was the same in both surveys (1.2%), while a slight decrease from the first to the second survey was observed for monoresistance to rifampicin (from 0.8 to 0.4%) and isoniazid (from 2.9 to 2%).

The significant association found between isoniazid resistance and immigration is a useful indicator for both clinicians managing individual tuberculosis cases and public health services planning control strategies.

Eur Respir J 2003; 21: 129–134.

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Keywords: Drug, immigrant, prevalence of resistance, proficiency testing, susceptibility testing, tuberculosis

Received: June 3 2002
Accepted after revision: September 25 2002

This study was supported by grants from Istituto Superiore di Sanità, Rome, (National Tuberculosis Project), from the WHO and from AIPO, Grant No. TBC1.

Multidrug resistance is a substantial threat both in terms of public health (tuberculosis (TB) control) [1] and in the clinical management of individual cases. Multidrug-resistant TB is difficult to cure as the drugs required for treatment are more expensive and frequently cause severe side-effects [2].

A global project on antituberculosis drug-resistance surveillance, aimed at measuring the prevalence of anti-TB drug resistance using standardised methods, was launched by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) [3]. The project was based on three main principles: 1) adequate sample representative of the population under study; 2) discrimination of drug resistance between never and previously treated cases; 3) proper laboratory performance. In order to adhere to the international recommendations [4, 5], the Italian Ministry of Public Health established a network of regional laboratories (Italian Multicentre Study on Resistance to Antituberculosis drugs (SMIRA) Project) to fulfil all requirements for participation to the WHO/IUATLD Global Project on Drug Resistance Surveillance.

The aim of the present report is to describe: 1) the

accuracy of drug susceptibility testing in the established network of TB laboratories [6]; 2) the prevalence of drug resistance for the period 1998–2000.

Methods

Proficiency testing

Study design. All definitions were derived from the WHO/IUATLD Global Project on Drug Resistance Surveillance [3, 6]. Multidrug resistance was defined as resistance to at least isoniazid and rifampicin. Drug resistance among new cases (or previously untreated cases or cases with no history of previous treatment) is defined as the presence of resistant strains of *Mycobacterium tuberculosis* in TB cases where TB drugs have never been given or have been administered for <1 month of treatment. An immigrant is defined as a person born in another country [3–6].

In 1998 the Dept of Bacteriology and Medical Micology of Istituto Superiore di Sanità in Rome, was appointed as the Supranational Reference Laboratory and Istituto Villa Marelli in Milan, as the National Reference Laboratory. The same batch of strains provided by the WHO/IUATLD coordinating centre in Ottawa, Canada, was used for proficiency testing. The Supranational Reference Laboratory sent the strains to the national Reference Laboratory, and the National Reference Laboratory to the 20 regional laboratories. As an official register of the laboratories and TB units performing the drug susceptibility testing does not exist in Italy, a convenience sampling was done. The network of 20 regional mycobacteriology laboratories and 46 clinical units (SMIRA), covering 30% of the confirmed TB cases notified every year [7], was used to reach the sample size planned (n=750 patients) [6]. Two surveys of proficiency testing were organised in 1998 and 1999, preceding the prevalence study, performed in 1998–1999 (the first survey from April 1st, 1998–April 1st, 1999) and in 2000 (second survey from January 1st–December 31st). Human immunodeficiency virus (HIV) serology was performed (with informed consent) in the presence of a risk behaviour and/or signs and symptoms suggestive of HIV infection (including low-grade fever, weight loss, presence of oral thrush, *etc.*).

Laboratory methods. Participating laboratories used the drug-susceptibility testing (DST) method with which they were most familiar within the four methods recommended by WHO in both proficiency testing surveys [3, 6]: 1) the absolute concentration method [8]; 2) the resistance-ratio method [8, 9]; 3) the proportion method and its variants [3, 8]; 4) the BACTEC 460® radiometric method (Becton Dickinson, Towson, MD, USA) [9, 10]. In addition, the Mycobacteria Growth Indicator Tube (MGIT) method (Becton Dickinson) was used [11, 12]. Among the laboratories reporting results by the proportion method, all used Lowenstein-Jensen medium either self-prepared or purchased from commercial sources [6]. Ten pairs of cultures of *M. tuberculosis* were sent to the regional laboratories by the National Reference Laboratory. The sample size was calculated to yield a significance level of α=0.05 to be able to detect a true difference between laboratory methods with a power of 90% [13]. In order to maintain confidentiality, each laboratory was identified by a letter of the alphabet.

Data analysis. The standardised WHO forms for recording and reporting data were used [3, 14]. Cultures were classified as resistant or susceptible [3, 14]. Results were compared to the gold standard, represented by the judicial results of the WHO/IUATLD Global Network of Supranational Laboratories (agreement of the majority of Supranational Reference Laboratories) [13]. A laboratory was considered validated for any given drug when no more than two results were different from the gold standard. The results were evaluated by the following parameters: sensitivity (ability to detect true resistance), specificity (ability to detect true susceptibility), predictive values for resistance (the rate of true resistances to total resistance) and for susceptibility (the rate of true susceptibility to total susceptibility) and efficiency (fraction of the number of correct results and the total number of results) and the overall intralaboratory reproducibility (or reliability) between duplicate cultures expressed as per cent agreement [13, 14].

Prevalence survey

All consecutive confirmed (culture positive) cases diagnosed in the TB laboratories in the two periods mentioned above were enrolled. When the previous treatment status was unknown or dubious, patients were excluded. Resistant cases with and without a previous treatment history were stratified using the following categories: any resistance; monoresistance; isoniazid plus rifampicin resistance; isoniazid plus other nonrifampicin resistance; rifampicin and other nonisoniazid resistance; other multiresistance; any isoniazid and rifampicin resistance. The pattern of drug resistance was also stratified by age, sex, country of birth and HIV status. The 95% confidence intervals (CI) were calculated.

Results

Proficiency testing

Twenty-two laboratories participated in the first survey and 20 in the second. In the first survey, nine (41%) laboratories used the proportion method, nine (41%) used the BACTEC 460® radiometric and four (18%) the MGIT method. In the second survey, seven (35%) laboratories used the proportion method, 10 (50%) the BACTEC 460® radiometric and three (15%) the MGIT method. In the first survey, 19 of 22 (86%) laboratories were validated for isoniazid and rifampicin and 15 (68%) achieved validation for all four drugs tested. In the second survey, 18 out of 20 laboratories (90%) were validated for isoniazid and rifampicin and 13 (65%) for all drugs tested. The

Table 1. – First and second survey of proficiency testing in Italy (1998–1999 and 2000 respectively)

Drug	First survey, 1998/1999			Second survey, 2000		
	Value	Min	Max	Value	Min	Max
INH						
Sensitivity	93.2	29	100	96.3	56	100
Specificity	98.5	100	100	98.8	75	100
PVR	99.0	93	100	99.7	94	100
PVS	91.0	38	100	92.5	36	100
Efficiency	94.8	50	100	96.8	65	100
Reproducibility	95.0	80	100	96.5	80	100
RMP						
Sensitivity	94.9	70	100	94.0	50	100
Specificity	98.6	89	100	96.5	50	100
PVR	98.6	89	100	97.4	67	100
PVS	96.2	77	100	95.2	67	100
Efficiency	96.7	85	100	95.3	75	100
Reproducibility	95.1	70	100	95.5	90	100
SM						
Sensitivity	87.7	20	100	91.9	75	100
Specificity	96.3	78	100	89.2	58	100
PVR	96.2	82	100	87.5	58	100
PVS	91.4	56	100	94.8	83	100
Efficiency	91.7	60	100	90.3	70	100
Reproducibility	90.6	75	100	90.5	60	100
EMB						
Sensitivity	85.5	0	100	88.8	17	100
Specificity	93.8	75	100	97.5	75	100
PVR	91.4	67	100	98.5	86	100
PVS	94.1	70	100	90.6	44	100
Efficiency	91.3	70	100	92.3	50	100
Reproducibility	86.9	60	100	93.0	70	100

All data are presented as per cent. PVR: positive value of a resistant result; PVS: positive value of a susceptible result; INH: isoniazid; RMP: rifampicin; SM: streptomycin; EMB: ethambutol.

results of the proficiency testing exercises are summarised in table 1. All parameters concerning the key drugs (rifampicin and isoniazid) remained constantly high or even improved from the first to the second survey. Furthermore, sensitivity for streptomycin and ethambutol increased, respectively, from 87.7 to 91.9%, and from 85.5 to 88.8%, with a minimum value increasing from 20 to 75% for streptomycin and from 0 to 17% for ethambutol.

Prevalence survey

The prevalence of drug resistance detected in 1998–1999 and 2000 is summarised in table 2. In subjects with no history of previous treatment, the prevalence of resistance to isoniazid was 2.9% in the first and 2.0% in the second survey, to rifampicin 0.8% and 0.4% respectively, while that to isoniazid plus rifampicin (multidrug resistance) was 1.2% in both

Table 2. – Prevalence of drug resistance among tuberculosis (TB) cases never or previously treated for TB

	No history of previous treatment				History of previous treatment			
	First survey, 1998/1999		Second survey, 2000		First survey, 1998/1999		Second survey, 2000	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Total tested	683 (100)		688 (100)		115 (100)		108 (100)	
Fully sensitive	599 (87.7)	85.1–90.0	610 (88.7)	86.1–90.9	44 (38.3)	29.7–47.3	57 (52.8)	43.4–62.1
Any resistance	84 (12.3)	10.0–14.9	78 (11.3)	9.1–13.9	71 (61.7)	52.6–70.3	51 (47.2)	37.9–56.6
Mono resistance	65 (9.5)	7.5–11.9	48 (7.0)	5.2–9.1	16 (13.9)	8.4–21.2	18 (16.7)	15.5–24.6
INH	20 (2.9)	1.8–4.4	14 (2.0)	1.2–3.3	6 (5.2)	2.1–10.5	6 (5.6)	2.3–11.2
RMP	6 (0.8)	0.3–1.8	3 (0.4)	0.1–1.2	5 (4.3)	1.6–9.4	6 (5.6)	2.3–11.2
SM	36 (5.3)	3.8–7.1	27 (3.9)	2.6–5.6	5 (4.3)	1.6–9.4	5 (4.6)	1.7–10.0
EMB	3 (0.4)	0.1–1.2	4 (0.6)	0.2–1.4	0 (0.0)	0.0–2.5	1 (0.9)	0.0–4.5
INH+RMP resistance	8 (1.2)	0.5–2.2	8 (1.2)	0.5–2.2	42 (36.5)	28.1–45.6	26 (24.1)	16.7–32.8
Any INH resistance	38 (5.6)	4.0–7.5	44 (6.4)	4.7–8.4	53 (46.1)	36.8–55.6	39 (36.1)	27.5–45.5
Any RMP resistance	15 (2.2)	1.3–3.5	11 (1.6)	0.8–2.8	55 (47.8)	38.8–56.9	32 (29.6)	21.6–38.7

INH: isoniazid; RMP: rifampicin; SM: streptomycin; EMB: ethambutol.

surveys. The decrease in prevalence of rifampicin and isoniazid resistance observed between the first and the second survey was not statistically significant. The results obtained by stratifying TB cases by country of birth are summarised in table 3. In the second survey, the prevalence of resistance to mono-isoniazid (relative risk (RR) 1.89; 95% CI 1.34–2.67; p=0.01) and to any isoniazid (RR 1.52; 95% CI 1.16–2.01; p<0.01) but not to rifampicin, was higher in immigrants than in native Italians (as observed in the first survey). No difference was found when stratifying prevalence data by age, sex and HIV status. In cases with previous treatment, a statistically significant decrease was observed from the first to the second survey for multidrug resistance (from 36.5 to 24.1%; RR 0.72; 95% CI 0.52–1.01; p<0.05), for any resistance (from 61.7% to 47.2%; RR 0.74; 95% CI 0.57–0.97; p=0.029) and for any rifampicin resistance (from 47.8% to 29.6%; RR 0.66; 95% CI 0.48–0.90; p<0.01).

Discussion

In the context of consistent results in the two proficiency testing surveys, the prevalence results indicate a stable prevalence of anti-TB drug resistance in the country, over the 3-yr study period.

Under a methodological perspective, the sample size was reached correctly in both surveys. Furthermore, the consistency of the results among newly diagnosed cases being an indicator of "low result variability", the estimates obtained were reliable, although a convenience sampling was used. In fact, due to the lack of a national list of laboratories and TB units, it is not currently feasible to randomise the units involved in the survey [6, 7].

Proficiency testing

The proficiency test results, achieved by regional laboratories of a single country, are similar to those achieved by the Global Network of Supranational Reference Laboratories [3]. A relevant issue discussed elsewhere [6] was the low sensitivity results for ethambutol and streptomycin, due to the different critical concentrations used for BACTEC and proportion methods [6]. The second survey results indicate that the decision of the Supranational Reference Laboratory and National Reference Laboratory to standardise the concentration country-wide was correct. In the second survey, the specificity values were higher than the sensitivity ones for all drugs except streptomycin (table 2). The panel of strains used, had more resistant than susceptible strains to isoniazid (16 resistant, four susceptible), rifampicin (10 resistant) and ethambutol (12 resistant), while streptomycin had more sensitive than resistant strains (eight resistant, 12 sensitive). This was apparently the opposite that could be expected [6]. Efficiency values were consistently higher for rifampicin and isoniazid than for streptomycin and ethambutol. With the exception of the predictive value for resistance of streptomycin, the predictive values for resistance and susceptibility were

Table 3. – Main findings obtained stratifying tuberculosis (TB) cases by country of birth in Italy

	No history of previous treatment								History of previous treatment							
	First survey 1998/1999					Second survey 2000				First survey 1998/1999				Second survey 2000		
	n (%)#	N (%)¶	p-value	RR	95% CI	n (%)#	n (%)¶	p-value	RR	95% CI	n (%)#	N (%)¶	p-value	RR	95% CI	n (%)#	n (%)¶	p-value	RR	95% CI
Total tested	207 (100)	476 (100)				265 (100)	423 (100)				18 (100)	97 (100)				41 (100)	67 (100)			
Mono INH	13 (6.3)	7 (0.2)	0.0014	2.22	1.58–3,13	10 (3.8)	4 (0.9)	0.01	1.89	1.34–2.67	1 (5.6)	7 (7.2)	NS	0.79	0.12–5.18	3 (7.3)	3 (4.5)	NS	1.34	0.58–3.11
Any INH resistance	16 (0.1)	15 (3.2)	0.01	1.76	1.23–2.53	25 (9.4)	19 (4.5)	0.01	1.52	1.16–2.01	10 (55.6)	43 (44.3)	NS	1.46	0.62–3.44	15 (36.6)	24 (35.8)	NS	1.02	0.62–1.68
Any INH resistance (not RMP)	15 (0.1)	10 (2.1)	0.001	2.06	1.46–2.89	23 (8.7)	13 (3.1)	0.001	1.71	1.31–2.23	1 (5.6)	9 (9.3)	NS	0.62	0.09–4.17	6 (14.6)	7 (10.5)	NS	1.25	0.66–2.38

RR: relative risk; CI: confidence interval; INH: isoniazid; RMP: rifampicin. #: immigrants; ¶: Italians.

consistently higher than 90% in the second survey, suggesting that the Italian Network is presently generating reliable drug susceptibility testing results, in terms of capacity of detecting true resistance and susceptibility to the four first line anti-TB drugs.

Prevalence survey

From the public health prospective, the study results indicate a consistently low prevalence of resistance to isoniazid, rifampicin and of multidrug resistance among new cases in the period evaluated and a statistically significant downward trend in the prevalence of multidrug-resistant tuberculosis among previously treated cases [15]. Resistance to isoniazid was significantly associated with immigration from high prevalence countries where isoniazid has been extensively used in the past. This finding is relevant to practicing physicians, as it will help with the identification of subjects at high risk of isoniazid resistance hence allowing for the prescription of the proper treatment regimen. It is also useful for public health planners, as immigrants from endemic areas contribute significantly to the fraction of new tuberculosis cases in the country (28.2% in 1998) [5, 7]. Last, but not least, the finding that multidrug-resistant tuberculosis is still observed in 36.5% (first survey) and 24.1% (second survey) of previously treated tuberculosis cases, calls for immediate public action on treatment result control.

The SMIRA Network based in Italy is composed of: C. Piersimoni (Ancona), A. De Santis (Bari), V. Giorgio (Bari), P. Vinciguerra (Bari), G. Angarano (Bari), L. Petrozzi (Bari), D. Costa (Bari), F. Gozzellino (Biella), A. Perboni (Biella), D. Marchetti (Bologna), M.L. Moro (Bologna), A. Pascali (Bologna), F. Falcone (Bologna), V. Mariano (Bologna), F. Rizza (Bolzano), P. Pretto (Bolzano), A. Turano (Brescia), A. Matteelli (Brescia), G.P. Carosi (Brescia), S. Tedoldi (Brescia), G. Pinsi (Brescia), A.G. Farris (Cagliari), B. Farris (Cagliari), A. Spanevello (Cassano Murge), C. Foschi (Cesena), G. Trucco (Costarainera), S. Aiolfi (Crema), T. Ceruti (Cremona), M. Parpanesi (Cremona), S. Calabro (Feltre), G. Felisatti (Ferrara), E. Tortoli (Firenze), S. Nutini (Firenze), G. Montini (Forlì), F. Fiorentini (Forlì), V. D′Ambrosio (Gallarate), A. Ceraminiello (Lodi), S. Bernorio (Lodi), L. Buono (Matera), P. Montesano (Matera), E. Vinci (Mesagne), E. Sabato (Mesagne), S. Gamba (Miazzina), P. Crepaldi (Miazzina), A. Gori (Milano), LR Codecasa (Milano), F. Mandler (Milano), V. Penati (Milano), P. Vaccarino (Milano), C. Saltini (Roma), G. Bertoli (Modena), F. Rupianesi (Modena), M. Losi (Modena), L. Richeldi (Modena), G. Ferrara (Modena), E. Minuccio (Napoli), G. Napolitano (Napoli), G.L. Molinari (Novara), L. Saini (Novara), A. Garzone (Novara), C. Vertuccio (Nuoro), S. Marcias (Oristano), M. Menozzi (Palermo), P. Marone (Pavia), V. Peona (Pavia), C. Nascimbene (Pavia), A. Pasi (Pavia), A. Cascina (Pavia), L. Casali (Perugia), A. Monaco (Perugia), S. Pauluzzi (Perugia), O. Penza (Perugia), M.B. Pasticci (Perugia), F. Bistoni (Perugia), T. Sposini (Perugia), V. Colorizio (L′Aquila), P. Bottrighi (Piacenza), A. Orsi (Piacenza), L. Schiavi (Piacenza), G. Macor (Pinerolo), G. Moretti (Pinerolo), R. Fatigante (Potenza), A. Barbaro (Reggio Calabria), G. Agati (Reggio Calabria), F. Zaccara (Rho), S. Viola (Rho), R. Le Donne (Rieti), G. Farinelli (Rieti), D. Mancini (Rieti), M. Ermeti (Rimini), G. Orefici (Roma), E. Iona (Roma), M. Tronci (Roma), A. Bisetti (Roma), A. Altieri (Roma), A. Cassone (Roma), L. Fattorini (Roma), L. Ortona (Roma), F. Diamare (Salerno), G. Lauriello (Salerno), G. Besozzi (Sondalo), P. Troupioti (Sondalo), G. Cicchitto (Sondalo), G. Di Pisa (Sondalo), S. De Lorenzo (Sondalo), P. Ferranti (Terni), L. Fabbro (Torino), M. Cavallero (Torino), M. Bugiani (Torino), D. Cirillo (Torino), G. Castiglioni (Tradate), R. Centis (Tradate), L. D′Ambrosio (Tradate), G.B. Migliori (Tradate), M. Neri (Tradate), A. Mottola (Treviso), M. Confalonieri (Trieste), C. Scarparo (Vicenza), O. Armignacco (Viterbo), L. Barelle (Vittorio Veneto), S. Nardini (Vittorio Veneto), G. Bazzerla (Vittorio Veneto).

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