

Surveillance of tuberculosis treatment prescription in Italy

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ABSTRACT: *Surveillance of tuberculosis treatment prescription in Italy. G.B. Migliori, A. Spanevello, M. Ambrosetti, M. Neri and the Varese TB Study Group.*

In industrialized countries, data on antituberculosis treatment are scanty. The aim of this study was to describe the tuberculosis (TB) treatment programme from diagnosis to drug intake in a model area of northern Italy, evaluating: 1) anti-TB regimens prescribed and their adequacy; 2) dosage of drugs; 3) side-effects; and 4) drug resistance.

Individual data on new TB cases from all the existing health facilities of the area were collected by means of a prospective surveillance system based on the systematic review of original clinical forms. Regimens were classified as adequate, potentially adequate and inadequate, based on published recommendations. Data on drug dosage, side-effects and drug resistance were analysed.

Out of 109 TB cases with regimen recorded on clinical

records, 20.2% included more than four major drugs, 63.3% three drugs and 16.5% two drugs. The regimens were classified as 1.8% adequate, 85% potentially inadequate and 12.8% inadequate. The dosages prescribed (mean \pm SD in mg·kg body weight⁻¹·day⁻¹) were: isoniazid: 6.8 \pm 2.7; rifampicin: 10.2 \pm 2.5; ethambutol: 21.3 \pm 4.5; streptomycin: 17.4 \pm 4.0; and pyrazinamide: 15.2. Twelve per cent of cases required treatment modification due to side-effects. Resistance to one single drug was found in 9% of cases, but no case with multidrug-resistant TB.

The description of the treatment programme revealed that: 1) the majority of regimens are potentially adequate; 2) they are at a proper dosage; 3) the side-effects are in agreement with the literature; and 4) drug-resistance rates are low.

Monaldi Arch Chest Dis 1998; 53: 1, 37-42.

Keywords: *Control, surveillance, treatment, tuberculosis.*

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Received: July 11 1997; accepted after revision August 11, 1997.

This study was partially supported by the Fund for Current Research, Ministry of Health, Italy, 1996.

The objective of the tuberculosis (TB) programmes is the elimination of TB by stopping the transmission of tuberculosis infection, resulting in the ultimate eradication of the disease [1, 2]. It can be achieved through the rapid identification and effective treatment of infectious cases, without at the same time creating resistance to the antimicrobials used [1, 2]. Modern anti-TB chemotherapy is based on the principle of administering properly selected therapeutic regimens at the proper dosage for a sufficient duration [3]. In Europe, data on drug prescription, usage and side-effects are scanty [4, 5].

A study was started in a model area of northern Italy (the province of Varese) based on a surveillance system (Varese Study System (VSS)) established in 1992 [6] to describe the treatment programme from diagnosis to drug intake under a public health perspective. In particular, the following parameters were evaluated: 1) anti-TB regimens prescribed and their adequacy; 2) dosage of drugs prescribed; 3) side-effects; and 4) drug resistance.

Materials and methods

Background: the province of Varese

The Province of Varese is located in the Region Lombardia, north-western Italy. In 1992, according to the Provincial Statistical Office, its average population was 807,345 inhabitants and the average number of inhabitants per square kilometre was 673 [6]. The proportion of the population working was 45.5% and the mean annual income for inhabitant US\$16,250 [6].

Study design

The study was designed as a prospective surveillance system, based on the systematic review of original clinical forms of new TB cases.

Structure and information flow of the Varese surveillance system

All the healthcare facilities available in the area surveyed agreed to participate in the surveillance assessment. A specifically designed "standard" surveillance form was proposed by the study co-ordinator (GBM), discussed with the medical officers operating in each healthcare facility and approved. The form was distributed to the medical officers in charge of each health unit (nine public health services, 10 hospitals and nine TB dispensaries). They were requested to complete the surveillance form for every new TB case diagnosed in 1992. Every month, the study co-ordinator visited each healthcare facility, reviewed the clinical records for each TB case together with the officer in charge, and collected the notification form. The 10 laboratories available in the Province were regularly surveyed to countercheck if at least all bacteriologically proven cases were enrolled into the study. Data forms were stored in a database at the co-ordinating centre, using Informix SE DBMS (Powersoft, Concorde, MD, USA), running on Compaq 486/25 PC (Compact Computer Co., Houston, TX, USA). The form consisted of 55 items, including demographic data and body weight (items 1-12), information on diagnosis [6] and treatment management (items 13-23), and clinical data (items 24-40). The last section of the form (items 41-55) investigated history of previous antiTB treatment, regimen and dosage prescribed, side-effects and compliance.

Statistical analysis

Duplicated cases, reports with mention of previous antiTB treatment, cases due to Mycobacteria other than TB (MOTT) and cases receiving preventive therapy were excluded from analysis [6]. Newly notified cases were included if bacteriologically confirmed or when at least two diagnostic criteria were met [6]. All the variables were expressed as mean \pm SD. The dosage of drugs prescribed was analysed by descriptive statistics and its distribution was evaluated for normality by Shapiro-Wilks' W-test. Data were stratified by smear and culture at diagnosis (positive/negative) and clinical form (pulmonary/extrapulmonary). Expected and observed frequencies (qualitative data) were compared by uncorrected Chi-squared test, or Fisher exact test where appropriate. The mean values of two different distributions of quantitative variables were compared by Student's t-test for unpaired data. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS; Chicago, IL, USA) and Statgraphics (version 6.0; Manugistics, Rockville, MD, USA) statistical packages.

Ethical considerations

The VSS protocol was approved by the Ethics Committees of the participating centres. All but one centre approved the nominal notification on VSS forms

to facilitate removal of duplicate reports. In the one centre where nominal notification was not allowed, only patients' initials were reported. In the co-ordinating centre database, after duplicate removal, only specific codes were left. In all feedback reports only aggregated data were presented.

Determination of antiTB regimens prescribed and their adequacy

Regimens were reported on the surveillance form as they appeared on the original clinical cards. In addition to antiTB regimens, steroid adjunct therapy was recorded, if prescribed on the card. Regimens were summarized according to the World Health Organization (WHO) system [7]. In particular, the following symbols were used for the five major antiTB drugs: S = streptomycin; R = rifampicin; H = isoniazid; Z = pyrazinamide; and E = ethambutol. The following criteria were used to classify the regimens prescribed: 1) number of drugs prescribed in the intensive phase; 2) duration of the intensive phase; and 3) drugs prescribed in the continuation phase. Duration of the continuation phase and total duration of treatment were considered additional criteria. Regimens were classified as adequate, potentially adequate and inadequate, separately for smear-positive and smear-negative/extrapulmonary cases, using as reference, recommended antiTB schemes [3, 7]. 1) Smear-positive cases: A regimen was considered "adequate" if it included at least H+R+Z for two months (intensive phase) and H+R for 4 months (continuation phase); "potentially adequate" if it included three major drugs for 2 months (H+R+E, H+R+S, R+S+E) and at least two major drugs for 4 months; and "inadequate" in the remaining cases (*e.g.* fewer than three major drugs during the intensive phase or total treatment duration <6 months). 2) Smear-negative/extrapulmonary cases: A regimen was considered "adequate" if it included at least H+R+Z for the intensive phase and H+R for the 2 months of the continuation phase; "potentially adequate" if it included at least H+R for 4 months and "inadequate" in the remaining cases (*e.g.* fewer than two major drugs or total treatment duration <4 months).

Determination of the dosage of drugs prescribed

For each drug prescribed, the dosage was determined in mg·kg body weight⁻¹·day⁻¹ [4, 7, 8]. The calculation was done when both body weight and dose prescribed were specified in the clinical documents.

Evaluation of side-effects

Side-effects were monitored based on the original clinical records. They were classified according to the published literature [9, 10]. Hepatitis, for the purposes of this survey, was defined as biochemically confirmed jaundice, and abnormal liver function as elevation of the serum alanine aminotransferase (ALT) level to over five times the pretreatment level.

Evaluation of drug resistance

Drug-resistance data were collected by counter-checking clinical records and laboratory reports [6] and classified according to WHO/International Union Against Tuberculosis and Lung Disease (IUATLD) definitions [11]. Sensitivity tests were performed in the 10 laboratories available in the study area, using the absolute concentration method or the proportion method. No standardization or external quality control on laboratory procedures was performed during the survey.

Description of the treatment programme from diagnosis to drug intake

The description of the treatment programme was done adopting, as conceptual framework, an input-process-outcome evaluation, using as reference points the principles of WHO and IUATLD [2, 12-14]. The diagnostic delay was recorded, defined as the time between the first awareness of symptoms of TB and diagnosis in a healthcare facility.

Results

Determination of anti-TB regimens prescribed and their adequacy

In 1992, 143 cases were detected by VSS. Twenty two cases were removed from VSS (eight duplications, six MOTT and eight preventive therapy). Out of 121 cases detected by VSS, 109 (90.1%) had their regimen recorded in the clinical records and 12 were transferred out without specifying the regimen prescribed in the clinical documents. Twenty two regi-

mens (20.2%) included more than four major drugs in the intensive phase, 69 regimens (63.3%) three drugs and 18 (16.5%) two drugs (table 1). Out of 56 smear-positive cases whose regimen was recorded, 1 (1.8%) was prescribed adequate, 47 (83.9%) potentially adequate and 8 (14.3%) inadequate treatment. Out of 53 smear-negative/extrapulmonary cases whose regimen was recorded, one (1.9%) was prescribed adequate, 46 (86.8%) potentially adequate and six (11.3%) inadequate treatment ($p=0.89$, uncorrected Chi-squared test). Fixed-dose combination of H+R was prescribed to 55 patients (45%) and of H+E to five patients (4%). Prednisolone was prescribed to 17 patients (14%).

Determination of the dosage of drugs prescribed

The dosage by anti-TB drug and its distribution are summarized in table 2 and figure 1. The dosage distribution of H and R fitted significantly the normal distribution ($p<0.0001$ and $p=0.014$; respectively, Shapiro-Wilks' W-test). Prednisolone was prescribed for a period of 23 ± 7 days at the total dose of 35 ± 0.06 mg.

Table 2. - Dosage of drugs prescribed in Varese Province, 1992

Drug recorded	Regimen recorded	Body weight recorded	Dosage mg·kg body weight ⁻¹ ·day ⁻¹
H	101 (92.7)	84 (95.5)	6.8±2.7
R	106 (97.2)	83 (94.3)	10.2±2.5
E	51 (83.5)	74 (84.1)	21.3±4.5
S	29 (26.6)	29 (33.0)	17.4±4.0
Z	4 (3.7)	1 (1.1)	15.2
Total	109 (100)	88 (100)	

Values are absolute number, with percentage in parenthesis, or mean±sd. For definitions see legend to table 1.

Table 1. - Drug regimens prescribed in Varese province, 1992

Regimen		Patients n	Smear positive n	Culture positive n	Total duration months	Treatment outcome		
Intensive phase*	Continuation phase*					Adequate	Potentially adequate	Inadequate
4-5 Drugs								
2 H+R+S+E+Z	4 H+R+E	1	0	0	6	1	0	0
2 H+R+S+E	2 H+R+E	1	1	0	4	0	0	1
1 H+R+S+E	4-5 H+R+E	6	6	4	5-6	0	5	1
1 H+R+S+E	5 H+R	1	0	1	6	0	1	0
1 H+R+S+E	5 H+R+E	12	9	4	6	0	12	0
2 H+R+E+Z	4 H+R	1	1	1	6	1	0	0
3 Drugs								
1 H+R+S	8 H+R	5	3	1	9	0	5	0
H+R+E	-	57	29	23	4-9	0	57	0
6 H+R+E	3 H+R	1	1	1	9	0	1	0
H+R+Z	4 H+R	2	0	1	5	0	2	0
2 R+S+E	2 R+E	4	2	0	4	0	0	4
2 Drugs								
3 H+R+CPX	4 H+R	1	0	1	7	0	1	0
H+R	-	10	1	2	6-11	0	9	1
H+E	-	3	3	2	4	0	0	3
R+E	-	3	0	0	4	0	0	3
R+E+CPX	-	1	0	0	4	0	0	1
Total		109	56	41		2	93	14

*: numbers in these columns refer to the treatment duration in months (where no number is given, the treatment was given for the whole duration). H: isoniazid; R: rifampicin; S: streptomycin; E: ethambutol; Z: pyrazinamide; CPX: ciprofloxacin.

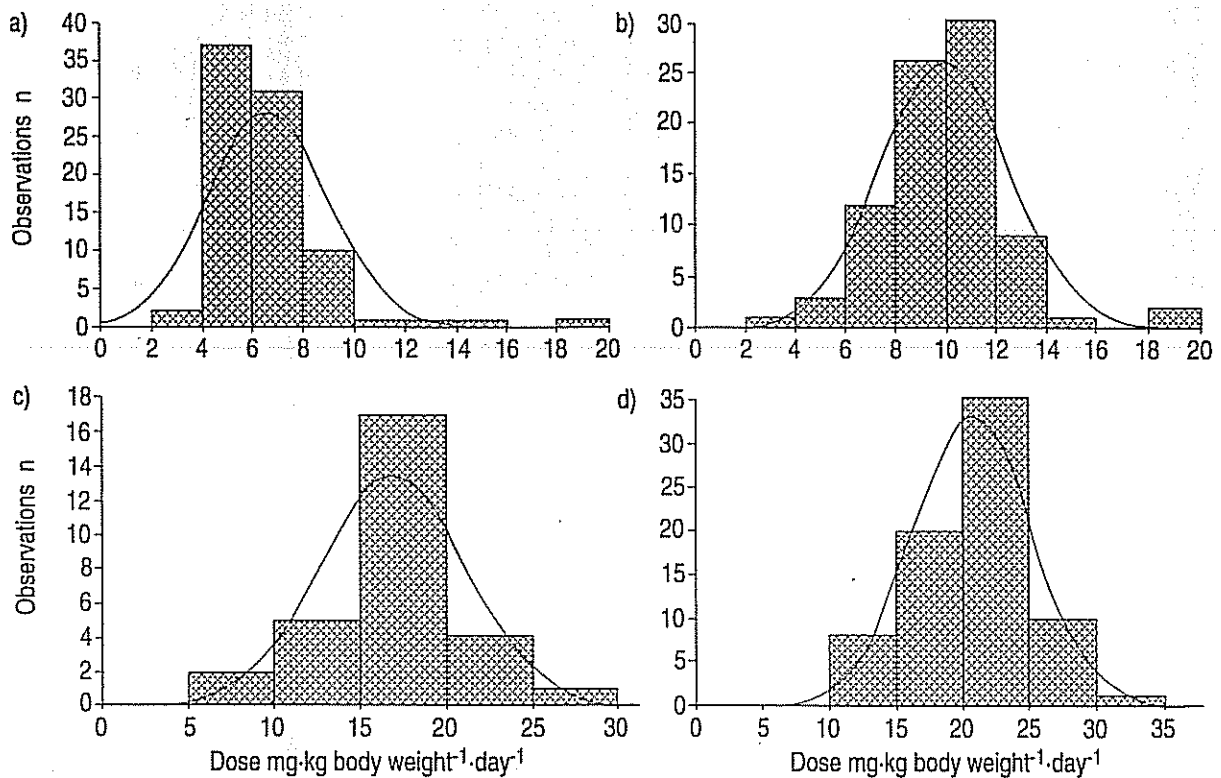


Fig. 1. — Doses of: a) isoniazid; b) rifampicin; c) streptomycin; and d) ethambutol prescribed in the study area. —: expected normal.

Evaluation of side-effects

Adverse reactions were reported in 17 (14.0%) of 121 cases. In 14 of them (11.6%) modification of treatment was required, stopping the drug in nine cases (7.4%) and reducing its dosage in five cases (4.1%). The side-effects observed were the following: hepatitis in nine cases (7.4%); abnormal liver function in five (4.1%); neurological disturbances in two (who also had hepatitis); and ocular, haematological and cutaneous problems in one case.

Evaluation of drug resistance

Sensitivity testing was performed in 44 new culture positive cases. Four cases (9%) had single drug resistance, three to S and one to H. No case with combined or multiple drug resistance was observed.

Description of the treatment programme

One hundred and fifteen cases out of 121 were hospitalized (80 out of 88 pulmonary *versus* 27 out of 33 extrapulmonary cases; $p=0.16$, uncorrected Chi-squared test). The duration of hospitalization was 63.2 ± 57.1 days, significantly longer for pulmonary cases (67.2 ± 57.1 *versus* 31.8 ± 35.6 ; $p=0.001$, Student's *t*-test for unpaired data). The diagnostic delay was 70.3 ± 70 days, without significant differences between pulmonary and extrapulmonary cases ($p=0.17$). Five cases died during hospitalization (4.1%), two from TB and three from concomitant cancer. Three cases (2.5%) were diagnosed by postmortem examination. Data on treatment monitoring were available on 41 out of 60 smear-positive cases (68.3%) and 10 out of 44 culture-positive patients (22.7%). Smear conversion was as follows: after 1 month, 16 (39.0%); after

2 months, 33 (80.5%); after 3 months, 37 (90.2%); and after 4 months, 41 patients (100%). Culture conversion was observed in four patients after 1 month and six patients after 2 months. Information on negative sputum performed at the end of the treatment is available in 14 cases (duration of treatment: 5 months in six cases; 6 months in one; 7 months in one; 8 months in two; 9 months in four). No clinical information was available on two patients (1.6%). They were not notified, were detected by VSS by means of laboratory registers and treated by private physicians. Four cases were treated from the beginning on an ambulatory basis. Since no centralized order for drug procurement is available, all hospitals purchased drugs directly from companies. All hospitalized patients received drugs from the hospital pharmacy, and from local pharmacies after discharge. Patients treated on an ambulatory basis received their drugs from local pharmacies. Directly observed therapy (DOT) (every pill swallowed under observation) was ensured in all hospitals during admission, but it was never provided after hospital discharge, self-administered free-cost treatment being the standard procedure.

Discussion

The aim of the present study was to describe the TB treatment programme from diagnosis to drug intake in a model area. In particular we: 1) described the regimens selected, observing that 1.8% were adequate, 85.3% potentially adequate and 12.9% inadequate; 2) realized that the dosages prescribed met the published recommendations; 3) evaluated the side-effects requiring modification of the regimen (11.6%); and 4) found resistance to one single drug in 9% of cases and no case with multidrug-resistant TB.

In most low-prevalence countries a complete TB treatment programme is not yet implemented on a routine basis, with the notable exception of the Netherlands [4, 15]. In several studies, the treatment programme was evaluated by means of questionnaires and notification data derived from routine surveillance systems [9, 16]. In industrialized countries, few studies based on the systematic review of all original clinical records, are available in the literature [17, 18]. Due to the study design, it was also possible to obtain information on 45 cases (37%) not notified by the official surveillance system [6]. Data on smear conversion were available in 68% of smear-positive cases and on cure in 23% of them. Due to the varying accuracy in the original clinical records, a lack of information was noticed concerning clinical data [6]. For example, 12 patients were transferred to a specialized TB hospital outside the model area immediately after diagnosis without mentioning the regimen prescribed, and in 21 clinical records reporting the regimen prescribed, the body weight was not recorded, as described in a previous study performed in Italy [17].

The representativeness of the study design, which presents possible limiting factors, deserves discussion. The study area was small and not representative of the general Italian situation [19], but the methodology may be applied easily in other areas of the country. The results of our study indicate that patients are hospitalized for the initial intensive phase of treatment. Additional data on follow-up are not complete enough to evaluate treatment outcomes, due to the nonstandardized approach to treatment monitoring, and smear conversion rate is the only reliable indicator. In Italy, as in other European countries, the surveillance system is hampered by problems, such as low coverage, limited validity of data and diagnosis, and significant underreporting [6]. Since in the country cohort analysis of treatment results is not available, it is necessary to search for other solutions to evaluate the treatment programme. *Ad hoc* studies in model areas may be designed to evaluate both the routine surveillance system and the treatment programme. Towards the development of guidelines for rapid review of national TB control programmes, a comprehensive approach was recently suggested by the WHO [14, 20]. Since most of the studies on programme effectiveness were unidimensional, a multiple-method approach was proposed, based on a range of components of the TB programme, indicators used to represent these components, and methods used to measure these indicators [14]. In this study, 15 components categorized in three groups, and 33 indicators were proposed. The study is part of the rapid evaluation method (REM), developed by WHO, consisting of a set of observation- and survey-based diagnostic activities, carried out mainly in health facilities, to identify operational problems and take managerial action within a few weeks time [14, 20]. Although our study was organized as a comprehensive surveillance system, it utilized in the evaluation REM components (initial curative care, case-holding, case-finding, policy, implementation, planning, evaluation) and indicators (diagnostic profile, diagnostic delay, treatment regimens, length of hospitalization, outcome, notification rates, drugs).

A problem arose in the evaluation of the national policy, since in 1992 no national guidelines were available except on surveillance [5]. The results of the present study stimulated the proposal of comprehensive guidelines on TB control suitable nationwide, including treatment standardization, which is presently under implementation at regional level [5, 21]. A recent study performed in Croatia found consumption of S and Z to be approximately 10 times lower than H, R and E, using the defined daily dose (DDD = average maintenance dose of the drug recommended on its major indication) as a measure of drug utilization [22]. Although anti-TB drugs represent an almost ideal group of drugs for the measurement of drug utilization using the DDD methodology, we preferred a direct approach for our study. In fact, in Italy, R is often used for indications other than TB and reliable data on drug cost are difficult to obtain from hospital administrations. Furthermore, data obtained through DDD are less informative in evaluation of the treatment programme because the dosage is stated as an *a priori* hypothesis.

According to our study, 87.1% of patients were prescribed a treatment classified as adequate or potentially adequate. Inadequate treatment is due to direct or indirect monotherapy [4]. Direct monotherapy is a treatment with, or intake of, a combination of drugs resulting in a minimal inhibitory concentration (MIC) of only one drug for which the strain concerned is sensitive. Inadequate treatment is considered to be mostly due to indirect monotherapy [4]. Both direct and indirect monotherapy may be doctor-, drug- or patient-related. In our study, doctor-related monotherapy is mainly evaluated. In Italy, only drugs of proven bioavailability are used, and drug-related monotherapy is not a problem. We do not have the possibility, at present, to prevent patient's monotherapy since DOT is not a recommended policy [5]. In spite of their common use (50% of cases were prescribed associations of R+H or H+E), drug associations are not presently recommended in governmental documents and the H+R+Z triple combination is not presently included in the list of essential drugs. To develop a correct approach to selection of drugs, regimens and dosage, fixed-dose combinations should be supported by the national programme and distributed directly from selected clinical units [6]. Two criteria used to classify regimens as other than adequate, namely the limited duration of the intensive phase (1 month: three regimens) and the absence of a third drug in the same phase (11 regimens), should be discussed. All those regimens were prescribed to smear-negative patients. Considering their sufficient duration (table 1), the absence of multiple drug resistance and the accurate dosages, these regimens have probably cured the patients. Moreover, the nonstandardized approach to regimen selection is a serious problem to face. The regimen most frequently prescribed (H+R+E, table 1) is not recommended by any of the existing guidelines [8, 23, 24]. The finding of a low use of Z-containing regimens is consistent with other surveys performed in Italy [17, 25]. The importance of disseminating guidelines at national level is evident. From this perspective, the recent adoption at regional level of standardized regimens according to WHO guidelines represents a

significant improvement [5]. Our results are also consistent with those of the above-mentioned survey reporting, in 1986, deviations from established therapeutic regimens in terms of drug selection (27%), duration (37%) and, less frequently, dosage (18%) [18]. Finally, 14% of TB cases are treated with corticosteroids in the model area and, according to the published literature, their use does not appear justified [26].

Our study described the treatment programme from prescription to drug intake. Based on our results we conclude as follows: 1) patients are treated within public health services. Official guidelines, not available when the study was performed, have been proposed more recently and a process of regional adoption is under implementation; 2) drugs are supplied from hospital or local pharmacies. Drugs are easily available, of proven bio-availability and no specific control exists for the supply of drugs; and 3) compliance with treatment is not routinely promoted outside follow-up visits. Treatment is cost-free and not supervised. The fixed-dose triple combination is not available in the country.

According to the parameters evaluated (majority of regimens potentially adequate and at proper dosage; side-effects in agreement with the literature and low drug resistance rates) the treatment programme in the study area, though not standardized, is reasonably able to cure patients starting antituberculosis treatment. Since poor treatment engenders drug resistance and chronic cases, resulting in increased cost of cure and rehabilitation, standardization of treatment and implementation of evaluation of treatment outcomes on a routine basis must become public health priorities at a national level.

Acknowledgements: The authors wish to thank M.C. Raviglione, Global Tuberculosis Programme, and L. Clancy, President IUATLD-ER, for their useful comments on the manuscript and the Executive Committee of the IUATLD, Europe Region, for the contribution in the study design.

Members of the Varese TB Study Group: V. D' Ambrosio (Gallarate Hospital); M. Della Rossa, C. Tiso (Tradate Local Health Unit); F. Riva, M. Merlo (Varese Dispensary); R. Adami (Saronno Hospital); A. Scorti (Busto Arsizio Hospital); C. Cerra (Cuasso al Monte Hospital); A. Larghi, C. Gambarini (Varese Circolo Hospital); C.V. Landoni, M. Grandi, G. Mazzucchelli, A. Satta, G. Vocaturo (Pneumology Dept, Fondazione S. Maugeri, Tradate); L. Ballardini (Bioengineering Dept, Fondazione S. Maugeri, Tradate).

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