Eur Respir J 1999; 13: 900–903
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European Respiratory Journal
ISSN 0903-1936

Prospective multicentre study on the evaluation of antituberculosis treatment results in Italy: comparison of the culture- *versus* the smear-based methods

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ABSTRACT: Cohort analysis of treatment outcomes is the most informative technique to evaluate the tuberculosis (TB) control programme. The aim of the study was to assess treatment outcomes comparing the smear- *versus* the culture-based methods, using data on TB patients treated under programme conditions in Italy.

This was a prospective monitoring study based on the standardized collection of forms from a representative sample of Italian TB Units. The forms, with individual data, were reviewed and analysed on a quarterly basis according to the principles of cohort analysis, using both the smear- and culture-based methods. The complete bacteriological profile of patients was analysed at diagnosis and at completion of treatment.

Nine hundred and ninety-two TB cases were notified. Among 681 pulmonary cases, 368 cases were culture-confirmed at diagnosis (333 new and 35 retreatment cases, 293 being sputum smear positive, 79.6%). At the end of treatment, out of the 333 new culture-confirmed cases, 136 (40.8%) were defined "cured" using the culture-based method and 108 (32.4%) using the smear-based method ($p<0.05$, χ^2 test).

The culture-based method is the recommended tool to evaluate pulmonary tuberculosis treatment results. Culture allows a more precise definition of a "cured" patient in both sputum smear positive and negative tuberculosis cases.

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Keywords: Culture
methodology
sputum smear
tuberculosis
treatment outcomes

Received: February 17 1998
Accepted after revision December 14 1998

Funded by the I and II TB Projects, Istituto Superiore di Sanitá, Rome, Grant N°1, 641/96 - 4,857/97 and 6,523/97

The objective of tuberculosis (TB) programmes is the elimination of TB from the society by stopping the transmission of TB infection [1–3]. It can be achieved through the rapid identification and effective treatment of infectious cases [1–3]. For programme planning and evaluation, it is necessary that adequate data on case findings and treatment results are collected and analysed systematically to quantify performance and its trend [4]. Therefore, cohort analysis of treatment outcomes is the most informative technique for evaluating the treatment programme [4]. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend a method (focused on sputum smear results) to evaluate treatment outcomes in countries with a high incidence of TB based on six mutually exclusive categories (cure, treatment completion, death, failure, treatment interruption, transfer out) [4, 5]. Recently, an adaptation of this system of treatment outcome monitoring, based on culture rather than smear results, has been proposed for Europe by the WHO and IUATLD [6, 7]. At present, no study is available in the literature which describes the methodological problems arising from cohort analysis of treatment results performed in countries with a low incidence of TB under programme conditions.

The aim of the present study was to assess treatment outcomes in a low incidence country comparing the smear-*versus* culture-based methods, using data from TB patients treated under programme conditions in Italy.

Methods

This was a prospective monitoring study based on the collection of standard recording and reporting forms from a representative sample of Italian TB units (n=41) covering about 21% of all TB cases notified every year in Italy [8].

On a quarterly basis, 9 months after enrollment, the participating units sent individual notification forms to both the co-ordinating centre (Tradate) and three area supervisors. Data forms, after the revision process, were stored in a database at the co-ordinating centre, using Powersoft Powerbuilder 5.0 (Powersoft, Concorde, MD, USA). The participating units were monitored on a monthly basis by the area supervisors and, if necessary, by the co-ordinating

unit staff. All mistakes and inconsistencies identified in the forms were corrected during the monitoring visits. The TB Units adopted the WHO recommended standardized short course chemotherapy regimens (*i.e.* for new cases two months of rifampicin, isoniazid, ethambutol and pyrazinamide followed by 4 months of isoniazid and rifampicin) [8–10]. All the definitions used were derived from published recommendations of the WHO [1, 3, 4–7, 10]. In particular, the patients were defined as: "new case", those who never had treatment for TB or who had taken anti-TB drugs for <4 weeks [10]; "retreatment case", those who had taken anti-TB drugs for >4 weeks; and "definite case", those with culture confirmed disease due to *Mycobacterium tuberculosis* complex [6]. According to the smear-based method, a patient is defined "cured" if sputum smears are negative on two occasions at the end of the treatment, and "treatment completed" if there is documented treatment completion, but no sputum smear microscopy at the end of the treatment. According to the culture-based method, a patient is defined "cured" in the presence of a documented culture conversion during the continuation phase, and "treatment completed" when treatment completion (in the absence of evidence for culture conversion) is documented. "Treatment success" is defined as the sum of patients whose outcome was "cured" and "treatment completed" divided by the total number of cases registered for treatment and expressed as a percentage [7].

Treatment outcomes were reported individually. The denominator for all treatment outcomes was the total number of consecutive patients registered for treatment between January 1, 1995 and March 31, 1996 (n=992) [5, 7]. Treatment outcomes were stratified into new and retreatment cases, and into pulmonary (sputum smear positive (SSP) and negative (SSN)) and extrapulmonary cases (EP) [10]. Out of all pulmonary cases (n=681), a core data set of culture confirmed pulmonary TB cases was identified for further analysis (n=368). Within this data set, treatment outcomes were assessed using both the smear-based [5] and culture-based methods [7]. The denominator was the total number of consecutive culture positive pulmonary patients registered for treatment in the study period. As it was expected that a certain proportion of cases would have no bacteriological monitoring at the end of treatment, the individual form included a field for information on reasons for lack of bacteriological confirmation at the end of treatment. An additional analysis was performed to obtain further information on the issue.

Observed and expected frequencies were compared by means of 2×2 contingency tables using uncorrected Chi-squared test. A p-value <0.05 was considered statistically significant.

Results

TB cases notified

Out of 992 TB cases notified, 897 (90.4%) were new cases and 95 (9.6%) were retreatment cases. The bacteriological confirmation of these cases is shown in figure 1. No significant difference with national data was found for the relevant variables available (bacteriologically confirmed cases, age and sex distribution of cases).

New definite pulmonary cases

Out of 368 definite pulmonary cases, 333 (90.5%) were new cases. Among them, 265 (79.6%) were SSP, 51 (15.3%) were SSN and 17 (5.1%) were not tested by sputum smear at diagnosis. At the end of treatment, 139 (41.7%) out of all 333 new definite pulmonary cases were tested by culture and 136 (97.8%) of them were culture negative. Out of 265 new definite pulmonary SSP cases, sputum smear examination at the end of treatment was performed in 114 (43%) cases, 109 (95.6%) of them being SSN. Treatment outcome of new definite pulmonary cases is summarized in figure 2. Out of 333 new definite pulmonary cases, 136 (40.8%) were defined "cured" using the culture-based method and 108 (32.4%) using the

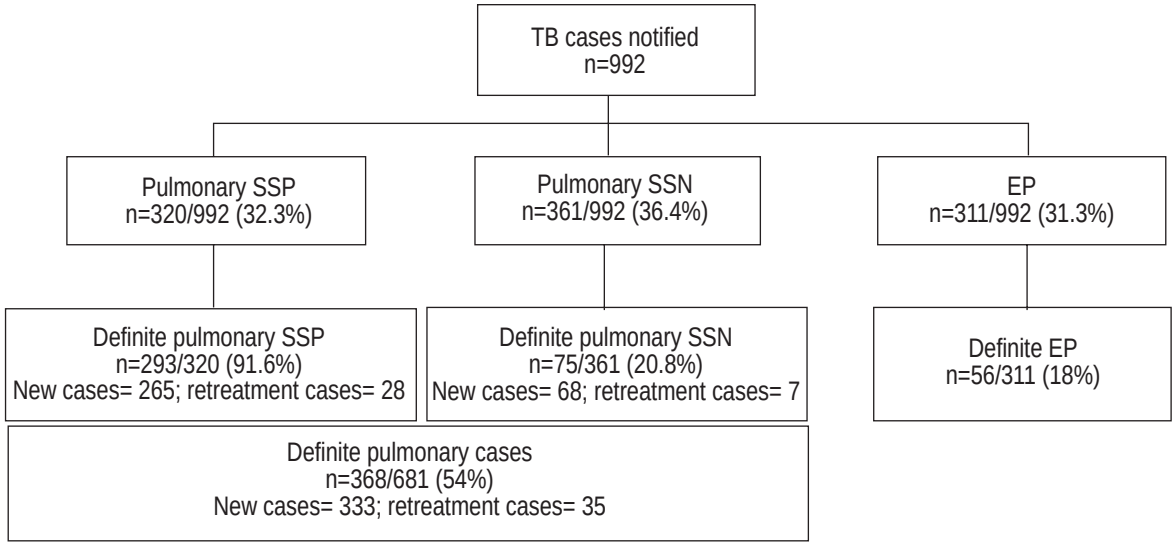

Fig. 1. – Bacteriological confirmation of 992 tuberculosis (TB) cases notified. SSP: sputum smear positive; SSN: sputum smear negative; EP: extrapulmonary; Definite cases: culture confirmed cases.

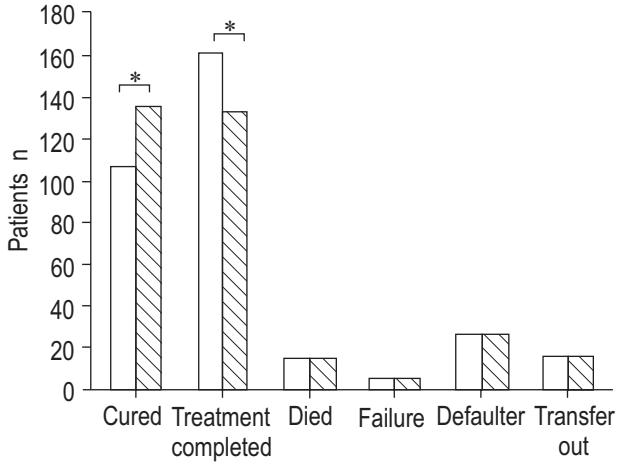

Fig. 2. – Treatment outcomes of 333 new definite pulmonary tuberculosis cases based on smear (□) and culture (▨) results. *: p<0.05, uncorrected χ^2 test.

smear-based method (p<0.05, χ^2-test). Among SSN cases, a radiological improvement at the end of treatment was reported in 83.3% of them.

Retreatment definite pulmonary cases

Out of 368 definite pulmonary cases, 35 (9.5%) were retreatment cases. Among them, 28 (80%) were SSP, 3 (8.6%) SSN and 4 (11.4%) not tested by sputum smear at diagnosis. At the end of treatment, 10 (28.6%) out of all retreatment definite pulmonary cases were tested by culture and 8 (80%) of them were culture negative. Out of 28 retreatment definite pulmonary SSP cases, sputum smear examination at the end of treatment was performed in 9 (32.1%) cases, 7 (77.7%) of them being SSN. Treatment success was achieved in 18 (51.4%) cases, while 7 (20%) cases died, 2 (5.7%) failed and 8 (22.9%) defaulted. No significant difference was found comparing cases "cured" obtained by the smear-based and the culture-based method (7 (20%) *versus* 8 (22.9%) respectively; NS).

Reasons for absence of sputum result at end of treatment

As no compulsory report of comments at the end of treatment was established, the reason for absence of sputum result was available in 83 cases out of 170 (49%): in 13 of them the laboratory did not stain the sputum because it was deemed as saliva, while in 70 cases the patient was unable to produce sputum because of the clinical improvement.

Discussion

According to the WHO, high cure rate, low level of acquired drug resistance and high detection rate define an effective TB control programme [10]. As a high cure rate of infectious patients is the main target of TB control, the evaluation of treatment outcomes is a relevant indicator of programme performance [4, 7]. Although data on treatment results from high incidence countries are often available, few industrialized low incidence countries in Europe (*e.g.* the Netherlands, the Czech Republic and Slovakia) have implemented such a procedure [11, 12]). The methodology to evaluate treatment outcomes through cohort analysis has been validated in high incidence countries, focusing on smear results [4, 5]. The present study compared treatment outcomes of TB patients in a low incidence country applying the smear- *versus* culture-based methods with the aim of defining which of the two methods is more reliable. No significant difference was found in treatment outcomes according to the smear- *versus* culture-based methods for SSP cases. A significant difference was found for SSN cases, which, by definition, cannot be defined as cured (but only treatment completed).

Under a public health perspective, a methodology including a double cohort analysis (sputum smear- and culture-based) of culture confirmed cases may be proposed in low incidence countries, allowing the comparison of treatment outcomes among "definite" cases in these countries with those of high incidence countries (where the available smear-based approach focuses on infectious cases). Under the clinician′s perspective, treatment monitoring is important in patients undergoing anti-TB chemotherapy in order to evaluate the response to treatment and rapidly identify and manage drug-induced toxicity [10]. Bacteriological monitoring is possible only in patients who are culture positive and/or SSP. Using the smear-based method one should rely on sputum smear results, performed at the end of the intensive phase of treatment (2nd month for new cases) and at the end of treatment (5th and 6th month for new cases). Using the culture-based method, one has the option to rely on culture only or to use sputum smear to obtain additional (and readily available) information. According to the proposed definitions, a "definite" case is defined cured when culture conversion is achieved during the continuation phase [7]. While a negative sputum smear after two months of treatment in a definite case allows the clinician to wait for the final culture, an SSP result suggests the need for medical action (to prolong the intensive phase, to ask for a culture, *etc.*).

In addition the results of this study show that, in Italy: 1) only 54% of pulmonary TB cases are culture confirmed at diagnosis (368/681) and only 21.9% monitored by culture at the end of treatment (149/681); 2) in a relevant proportion of cases, the sputum was not performed at the end of treatment because the patient was unable to produce sputum or because a salivary sample was obtained; and 3) the proportion of patients other than SSP (SSN and sputum not done) is higher than expected (388/681, 57%). The observation that 83 pulmonary patients SSP and/or culture positive at diagnosis were not monitored at the end of treatment because of lack of sputum suggests that, in Europe, according to the present definitions [8], a relevant proportion of patients being really "cured" might be classified as treatment completed [6, 8].

The results of this study underline the importance of further disseminating guidelines among physicians diagnosing, reporting and treating tuberculosis at national level and within scientific societies. The proportion of bacteriologically unconfirmed patients ("other than definite cases" [6]) might reflect early diagnosis (cases with a negative bacteriological examination), or for patients without bacteriological examination performed, a pitfall of the programme (overemphasis on chest radiographs and clinical

presentation for diagnosis) and the difficulty of obtaining sputum samples (cases unable to produce sputum or merely producing saliva). Based on the consideration that some cases diagnosed as "minimal tuberculosis" (sputum smear negative) might be affected by diseases other than tuberculosis, the final and more reliable analysis was performed on culture confirmed cases only, as recommended by a World Health Organization/International Union Against Tuberculosis and Lung Disease task force [7].

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