

## Current status of treatment completion and fatality among tuberculosis patients in Spain

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### SUMMARY

**OBJECTIVES:** To determine treatment completion among patients with tuberculosis (TB), and to analyse factors associated with treatment default and fatality.

**METHODS:** A prospective cohort study of patients who began treatment between 1 June 1999 and 31 May 2000 in areas where members of the SEPAR Tuberculosis and Respiratory Infections Group work. Factors associated with treatment default and fatality were studied using logistic regression, calculating odds ratios (OR) and their 95% confidence intervals (95%CI).

**RESULTS:** The study involved 142 physicians from 76 different hospitals who provided information on 1515 cases. Eighty-two per cent of the patients completed treatment correctly, 14% defaulted, 5% died, 0.5% failed, and 8.7% interrupted treatment due to transfer or other reasons. The variables associated with default were intravenous drug use (IVDU) (OR 6.00, 95%CI

2.59–13.89) and immigration (OR 8.57, 95%CI 3.78–19.45); sex, age, homelessness, incarceration, directly observed treatment (DOT) or hospitalisation were not associated with default. Variables found to be predictive of fatality were alcoholism (OR 6.38, 95%CI 2.09–19.48), human immunodeficiency virus (HIV) infection (OR 7.08, 95%CI 2.08–29.15) and age >64 years (OR 10, 95%CI 2.9–34.07), whereas sex, IVDU, homelessness, DOT and hospitalisation were not.

**CONCLUSIONS:** In industrialised countries, IVDU patients and immigrants should be targeted for DOT, while to reduce fatality rates stricter monitoring is required for patients who are alcoholic, HIV-infected, or aged >64 years.

**KEY WORDS:** tuberculosis; Spain; cure; treatment; completion; case-fatality ratio; predictors

TUBERCULOSIS (TB) is a health problem that is on the increase worldwide.<sup>1</sup> In 2001, an incidence rate of 54 per 100 000 population was recorded in the 51 member states of the World Health Organization (WHO) European Region, and it was estimated that there were over 8 million cases worldwide.<sup>2</sup> Unfortunately, data on completion of the long tuberculosis treatments are not available for the majority of countries.

Since the beginning of the 20th century a decline had been observed in TB incidence in industrialised countries due to improvements in social conditions, health measures, and adequate treatment. Since the mid-1980s, however, this trend has altered slightly in many industrialised countries. The first evidence of change was observed in the United States, and was attributed to immigration, the human immunodeficiency virus (HIV) epidemic and deterioration in tuberculosis control programmes.<sup>3</sup> Similar tendencies have been reported in Europe in the last few years.<sup>4,5</sup>

In Spain, TB is still an important public health problem. In 2001, 17 cases per 100 000 were notified, although the true incidence could have been double this figure.<sup>6</sup> Although recent results are better than expected due to improvements in control programmes and a decline in the impact of the acquired immunodeficiency syndrome (AIDS), TB incidence in Spain is still higher than in many other industrialised countries<sup>6</sup> with whom it is comparable in terms of other health indicators. The distribution of TB has changed as a result of the HIV epidemic, immigration and the emergence of multidrug-resistant strains.<sup>3</sup>

Cure of TB cases, and especially smear-positive cases, is without doubt the most effective measure for interrupting the chain of transmission of *Mycobacterium tuberculosis*.<sup>7,8</sup> We know how to diagnose it, we know how to treat it, and yet TB is far from being eradicated anywhere in the world. Failure to adhere to treatment is the main reason for these difficulties in

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controlling a disease that is far from new. For these reasons, determination of the level of treatment completion, particularly the percentage of patients who are cured or who default, is the most important public health indicator for evaluating the current situation and the possible future of TB in a community. Nevertheless, this indicator has rarely been analysed and very few programmes have data available on completion.

The aim of the present study was to determine the true cure and fatality rates among TB cases treated by pulmonologists in Spain, and to determine the factors associated with treatment default and death, to define those population groups for which intervention is a priority.

## MATERIALS AND METHODS

A multicentric prospective cohort study was designed. All patients diagnosed with TB by a member of the Tuberculosis and Respiratory Infections Group of the Sociedad Española de Neumología y Cirugía Torácica (SEPAR), and who started treatment between 1 June 1999 and 31 May 2000, were included. A total of 142 pulmonologists were involved who worked in 76 different hospitals. All of Spain's Autonomous Regions were represented, and all researchers provided information on cases that had been diagnosed by themselves or by collaborators. As criteria for inclusion into the cohort, two requirements had to be met: to have been diagnosed with TB, and to have initiated tuberculosis treatment. Any of the following were acceptable for inclusion as a case: 1) a smear-positive organic sample with visible acid-fast bacilli and/or culture with evidence of growth of *M. tuberculosis* colonies; 2) a pathology result from an organic sample suggestive of TB; or 3) decision by the physician in charge to initiate tuberculosis treatment. Cases diagnosed with TB but who had not begun treatment and those diagnosed after death were excluded from the study.

All participating researchers adhered to the follow-up protocol of their own hospital. This usually includes four to five supervisory visits for a 6-month course of treatment. All researchers participating in the project were actively followed to ensure that the epidemiological questionnaire administered at the start of treatment was filled out and sent again when treatment was completed. DOT (directly observed treatment) was favoured in cases where default seemed likely, although this type of programme is only available in large cities (methadone programmes, specialised clinics, out-patient departments) and in prisons. A patient was considered to be on DOT if treatment was taken under supervision.

At the end of the follow-up period, it was requested that all patients be assigned to one of the following categories:

- Cured: a patient for whom there was proof that treatment had been followed (supervised, or with periodic controls) and who had negative microbiological results. A negative microbiological result was taken to mean a minimum of one negative culture at the end of the 4th month of treatment and a negative smear after the end of the 6th month. With longer treatment courses the requirement was for a negative culture 2 months before the end of treatment, and a negative smear at the end of treatment.
- Completed treatment: a patient for whom there was proof that treatment had been followed (supervised or with periodic controls) and who did not have microbiological results at the end of treatment. This included patients who could not produce sputum or from whom other samples could not be obtained.
- Defaulted: a patient for whom it was known, through supervised treatment or periodic controls, that they had not received tuberculosis treatment for over 1 month, or who had not attended follow-up appointments prescribed by the physician in charge.
- Transferred: a patient included in the cohort at a given hospital, who moved during treatment, and who was then followed by another hospital.
- Died: a patient diagnosed with TB who died during the course of treatment. Such cases were classified as having died from TB or from some other cause.
- Failure: a patient who, although there was proof that treatment had been correctly followed, presented positive cultures after the 4th month of treatment.

Any patient born outside Spain was classified as an immigrant. Men consuming over 280 g of alcohol per week, or women over 168 g, were considered alcoholics. Users of illegal drugs (heroin and cocaine) were classified as intravenous drug users (IVDU); the majority were injecting heroin addicts.

The percentage of treatment completion was calculated as patients who completed treatment (including cured category) in relation to the sum of those who completed and those who defaulted from treatment. The percentage of treatment success was calculated as the sum of those cured plus those who completed treatment in relation to the total.

### Statistical analysis

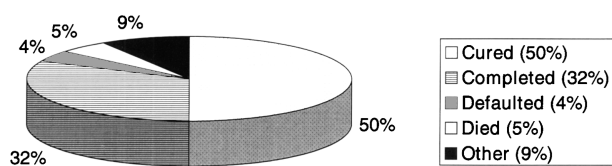
Information collected using the questionnaire was incorporated into a database and processed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA). At bivariate level, we analysed factors associated with non-completion of treatment using  $2 \times 2$  contingency tables and factors associated with fatality. Measures of association were obtained using the  $\chi^2$  test and calculation of odds ratios (OR), with their 95% confidence intervals (95%CI). Those variables significantly ( $P < 0.15$ ) related to non-completion or

fatality were studied further, at multivariate level, using logistic regression.

## RESULTS

Of 1520 TB cases included in the study, the final outcome was determined for 1515 (99%). All regions provided cases: Catalonia provided the most (25.3%), followed by the Basque Country (15%), Andalusia (10.3%), and Galicia (9.5%); the other regions provided the remaining 39.9%.

In the descriptive analysis of cases followed to the end of treatment, 64.5% were men, and 93.5% were aged over 18 years. Of these, 7.7% were drug addicts, 8.1% were HIV-positive, 14.1% had a history of alcoholism, 7.6% were immigrants, 2.4% were homeless, and 1.9% were in prison. Pulmonary TB was diagnosed in 75% of cases, 18% had extra-pulmonary TB, and 7% both pulmonary and extra-pulmonary TB. A total of 67.4% of the patients were hospitalised. Of the total cases followed through to the end of treatment, 50% were cured, 32% were recorded as having completed treatment, 4% defaulted, and 5% died during treatment, while 0.5% failed treatment. Patients were transferred, or treatment was otherwise interrupted for a variety of reasons in 8.7% (Figure). The



**Figure** Information on tuberculosis treatment outcome in the 1515 study patients.

completion rate was 95%, while the treatment success rate was 82%.

When treatment adherent patients were compared in the bivariate analysis with those who defaulted (Table 1), factors predictive of treatment default included being of male sex, aged between 18 and 64 years, HIV-infected, homeless, immigrant, drug addict, in prison, on DOT, and having been hospitalised. At multivariate level, the only variables associated with defaulting were drug addiction and being an immigrant (Table 1).

In the analysis of fatality (Table 2) at bivariate level, variables predictive of death included being male, aged >64 years, drug addict, alcoholic, on DOT, and being hospitalised. Statistically significant predictors of fatality at multivariate level were being alcoholic, HIV-infected and aged >64 years (Table 2).

**Table 1** Predictors of tuberculosis treatment default in a cohort of 1515 patients

Variable	Defaulted n (%)	Bivariate analysis			Multivariate analysis		
		P	OR	95%CI	P	OR	95%CI
Sex							
M	55/833 (66)	<0.001	3.17	1.54–6.68	0.17	—	—
F	10/458 (2.2)		1				
Age, years							
≤17	4/83 (4.8)		1				
18–64	60/985 (6.1)	<0.001	1.28	0.43–4.26	0.07	—	—
>64	1/216 (0.5)	<0.001	0.09	0–0.89	0.96	—	—
HIV							
Y	11/90 (12.2)	<0.001	3.17	1.48–6.66	0.28	—	—
N	43/1021 (4.2)		1				
Drug addict							
Y	22/93 (23.7)	<0.001	9.85	5.25–18.42	0.00	6.00	2.59–13.89
N	34/1115 (3.0)		1			1	
Homeless							
Y	6/29 (20.7)	<0.001	6.46	2.23–17.80	0.09	—	—
N	45/1159 (3.9)		1				
Prison							
Y	3/23 (13.0)	0.07	3.55	0.81–13.21	0.9	—	—
N	47/1158 (4.1)		1				
Immigrant							
Y	16/92 (17.4)	<0.001	5.37	2.75–10.39	0.00	8.57	3.78–19.45
N	42/1114 (3.8)		1			1	
Hospitalised							
Y	44/813 (5.4)	0.05	1.99	0.98–4.13	0.24	—	—
N	11/393 (2.8)		1				
DOT							
Y	22/234 (9.4)	<0.001	2.56	1.44–4.52	0.74	—	—
N	40/1025 (3.9)		1				

Not statistically significant: alcohol, symptoms, prior history of TB.

OR = odds ratio; CI = confidence interval; M = male; F = female; HIV = human immunodeficiency virus; Y = yes; N = no; DOT = directly observed treatment.

**Table 2** Predictors of death in a cohort of 1515 tuberculosis patients

Variable	Deaths n (%)	Bivariate analysis			Multivariate analysis		
		P	OR	95%CI	P	OR	95%CI
Age, years							
≤17	0/83 (0)		1			1	
18–64	13/1002 (1.3)	<0.001	1.09	0.15–22.61	0.9	0.0016	0.0–3.53
>64	13/232 (5.6)	<0.001	4.93	0.66–102.4	<0.001	10.00	2.9–34.07
Sex							
M	20/858 (2.3)	0.13	1.83	0.69–5.12	—	—	—
F	6/466 (1.3)		1				
HIV							
Y	7/97 (7.2)	<0.001	6.14	2.16–17.0	0.002	7.08	2.08–29.15
N	13/1040 (1.3)		1			1	
Drug addict							
Y	4/97 (4.1)	0.112	2.41	0.68–7.67	0.58	—	—
N	20/1141 (1.8)		1				
Alcoholic							
Y	10/182 (5.5)	<0.001	4.31	1.75–10.50	<0.001	6.38	2.09–19.48
N	14/1051 (1.3)		1			1	
Homeless							
Y	3/32 (9.4)	0.02	6.02	1.34–23.12	0.13	—	—
N	20/1185 (1.7)		1				
DOT							
Y	13/248 (5.2)	<0.001	5.18	2.15–12.57	0.27	—	—
N	11/1042 (1.1)		1				
Hospitalised							
Y	24/842 (2.9)	0.002	11.67	1.68–232.8	0.016	—	—
N	1/396 (0.3)		1				

Not statistically significant: the symptoms being in prison, being an immigrant, or prior history of tuberculosis. OR = odds ratio; CI = confidence interval; M = male; F = female; HIV = human immunodeficiency virus; Y = yes; N = no; DOT = directly observed therapy.

## DISCUSSION

TB treatment has two important negative characteristics: its length predisposes patients not only to stigmatisation, but also to default from treatment.<sup>9,10</sup> Non-completion of TB treatment has for decades been considered one of the greatest problems faced by public health in TB control.

In a recent study on the outcomes of anti-tuberculosis treatment in six Autonomous Regions in Spain, it was observed that results still do not reach levels recommended by the WHO (85% treatment success in smear-positive patients), and non-completion of TB treatment continues to be an important problem for public health in Spain.<sup>11</sup> In the present study the treatment success rate was 82%, close to the recommended target. This may be explained by the fact that fatality of AIDS cases with TB has fallen, thanks largely to the new antiretroviral treatments, and as a consequence the number of deaths among patients with TB has also decreased.

When DOT is not used it is more difficult to be sure that treatment has indeed been completed. In Spain, however, a number of factors aid in treatment completion. For all TB cases, anti-tuberculosis drugs are combined in the same tablet (isoniazid, rifampicin and pyrazinamide [HRZ] during the initial phase, and HR in the continuation phase), and treatment is easily accessible for all. The low rates of primary resis-

tance, probably due to the use of combined formulations over several decades, also suggest high completion rates. We can therefore assume that, among cases finishing treatment, even with poor adherence, it is difficult for treatment to fail, as most relapse cases respond well to all drugs. The 95% treatment completion rate is also much higher than that observed in other studies in urban settings, with or without DOT.<sup>12–14</sup>

The results of the present study of 1520 cases cannot be extrapolated to the totality of cases in Spain (an estimated 12 000 annually, incidence 30/100 000 in the period under study). Our figures are representative only of cases seen by members of the scientific society undertaking the study. Unfortunately there is significant undernotification of TB cases in Spain, and there are no mechanisms in place for determining the final outcomes of those patients who are notified. For these reasons the present study represents an important step in learning more about, and being able to improve, TB control in Spain. Studies in the US, where the treatment completion target is 90% at 12 months, show that there are still many difficulties to overcome before such rates can be reached.<sup>15,16</sup> The completion figures reported in the present study, which are higher than in other reports,<sup>11</sup> may in fact be higher than the true values, as it is probable that the participating researchers were highly motivated. It must also be recognised that there could be some bias

in data collection, as there is no gold standard for measuring completion. The present study used diverse techniques (appointment attendance, physician estimation, patient confirmation . . .), but none are 100% reliable. There is therefore room for confusion of treatment failure with default, and it cannot be assured with certainty that treatment was in fact completed in all cases thus classified.

This study identified two risk factors significantly associated with non-completion: being a drug addict and being an immigrant. Other reports have noted a similar relationship between non-completion and drug addiction.<sup>17-19</sup> This is an additional concern for TB control, as the behaviour of this group facilitates transmission. In addition to drug addiction, other studies outside Spain have found non-completion to be associated with alcoholism, homelessness and being HIV-infected.<sup>12,14,20</sup>

In the study mentioned previously,<sup>11</sup> as in our study, it was the immigrant group who had the worst outcomes in terms of completion. This can be explained by the differing beliefs regarding health, communication difficulties, changes of domicile or expectations of treatment that can affect patients' behaviour.<sup>21,22</sup>

From the point of view of resource planning and distribution, drug addicts and immigrants should be considered in priority for DOT. There are no data to determine at precisely what moment adherence begins to fail, although this generally seems to happen during the first 3 months of treatment. This information would be useful to decide whether DOT is needed only in the initial phase, or during the entire course of treatment.<sup>23,24</sup>

It may seem surprising that in the present study patients who received DOT did not obtain better rates of completion than those who self-administered. One limitation of the study with regard to completion is that some patients could have reported better adherence than was actually true, although it must be remembered that in our case DOT is only offered to 'likely defaulters'. This is not the case, however, in other studies in which attempts have been made to assess the effectiveness of DOT.<sup>25</sup> Spain has a good health system, with universal free coverage; TB patients pay only a small amount for treatment, and the more needy receive free treatment. Our results and those of other studies in Spain show that, in contrast to recommendations for developing countries, it is possible to obtain good completion rates without resorting to DOT in all patients.

In analysing fatality, it is noteworthy that higher risks are found among patients who are alcoholic, HIV-infected, or aged >64 years, as in other studies.<sup>11,26,27</sup> This fact would justify closer monitoring of these patients. Due to the fact that we included deaths where cause was not specified (often, as for AIDS patients, it is difficult to ascertain underlying cause), it is possible that some deaths were not due to TB, but

rather to AIDS, and in some cases even to other risk factors in these groups (e.g., drug overdose among IVDUs).

It must be underlined that the study was carried out by a scientific society, and that it managed to include cases from all the Spanish Autonomous Regions. The study has enhanced the motivation of the Working Group on Completion of Tuberculosis Treatment in Spain, and may serve as an example for other scientific societies in other countries.

Finally, it should also be emphasised that studies on treatment completion are of primary importance for planning health strategies for TB control, not only to decide which patients should be given priority for DOT,<sup>28-30</sup> but also in devising new strategies to improve completion rates and in evaluating the effectiveness of control programmes.<sup>31,32</sup>

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**OBJECTIFS :** Déterminer le niveau d'adhésion au traitement parmi les patients atteints de tuberculose (TB) et analyser les facteurs associés à l'abandon du traitement et à la létalité.

**MÉTHODES :** Une étude prospective de cohorte de patients commençant le traitement entre le 1er juin 1999 et le 31 mai 2000 dans les zones d'action où travaillent les membres du Groupe Tuberculose et Infections Respiratoires de la SEPAR. Les facteurs associés à l'abandon du traitement et à la létalité ont été étudiés par régression logistique en calculant les odds ratios (OR) et leurs intervalles de confiance (IC) à 95%.

**RÉSULTATS :** L'étude a impliqué 142 médecins provenant de 76 hôpitaux différents, qui ont fourni des informations sur un total de 1.515 cas. Le traitement a été correctement terminé par 82% des patients. Il y a eu 14% d'abandons, 5% de décès, 0,5% de cas classés comme échecs et 8,7% d'interruptions du traitement en raison de transferts ou d'autres causes variées. Les vari-

ables associées à l'abandon ont été le fait d'être un utilisateur de drogues par voie intraveineuse (IVDU) (OR 6,00 ; IC95% 2,59–13,89) et le fait d'être immigrant (OR 8,57 ; IC95% 3,78–19,45), alors qu'aucun des facteurs suivants n'était associé à l'abandon : sexe, âge, absence de domicile fixe, incarcération, traitement directement observé (DOT) ou admission à l'hôpital. En ce qui concerne la létalité, les variables prédictives ont été l'alcoolisme (OR 6,38 ; IC95% 2,09–19,48), l'infection par le VIH (OR 7,08 ; IC95% 2,08–29,15) ou un âge de plus de 64 ans (OR 10,00 ; IC95% 2,29–34,07), alors qu'aucun des facteurs suivants n'était associé à la létalité : IVDU, absence de domicile fixe, DOT ou admission à l'hôpital.

**CONCLUSIONS :** Dans les pays développés, les patients IVDU et les immigrants doivent être ciblés pour le DOT alors qu'un suivi plus strict s'impose pour les patients alcooliques, infectés par le VIH ou âgés de plus de 64 ans afin de tenter de limiter les taux de létalité.

**OBJETIVOS :** Determinar el grado de cumplimentación del tratamiento en los pacientes con tuberculosis (TB), y analizar los factores asociados al abandono del mismo y a la letalidad.

**MÉTODOS :** Estudio de cohortes prospectivo de los pacientes que iniciaron tratamiento entre el 1 de junio 1999 y el 31 de mayo 2000 y que fueron atendidos por los médicos del grupo de Tuberculosis e Infecciones Respiratorias (TIR) de la SEPAR. En el estudio de factores asociados al abandono y a la letalidad se analizaron las variables usuario de drogas por vía parenteral (UDVP), inmigrante, sexo, edad, virus del inmunodeficiencia humana (VIH), indigente, estar ingresado en prisión, seguir tratamiento directamente observado (TDO) y ingreso en hospital. Se utilizó regresión logística, calculándose la odds ratio (OR) y los intervalos de confianza del 95% (IC).

**RESULTADOS :** Participaron 142 médicos de 76 centros diferentes que aportaron 1515 casos. El 82% de los pacientes acabó correctamente el tratamiento, el 4% lo abandonó, el 5% falleció, el 0,5% fracasó y el 8,7% fueron trasladados o interrumpieron el tratamiento por diversos motivos. Las variables asociadas al abandono fueron ser UDVP (OR 6,00 ; IC95% 2,59–13,89) y ser inmigrante (OR 8,57 ; IC95% 3,78–19,45). En cuanto a la letalidad fueron variables predictoras el ser alcohólico (OR 6,38 ; IC95% 2,09–19,48), estar infectado por VIH (OR 7,08 ; IC95% 2,08–29,15) y tener más de 64 años (OR 10 ; IC95% 2,9–34,07).

**CONCLUSIONES :** En los países desarrollados, los pacientes UDVP o inmigrantes deberían ser poblaciones diana para TDO, mientras que habría que monitorizar más minuciosamente a los pacientes alcohólicos, VIH positivos o más de 64 años, con el fin de disminuir la letalidad.