

## Incidence of tuberculosis and the importance of treatment of latent tuberculosis infection in a Spanish prison population

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### SUMMARY

**OBJECTIVE:** To establish the incidence of tuberculosis (TB) in a prison population and its link with latent tuberculosis infection treatment (LTIT).

**METHODS:** From 1991 to 1999 a TB programme was run in a Spanish prison. A cohort study was conducted to know TB incidence and the associated variables.

**RESULTS:** Of 1050 people studied, 10% were co-infected by the human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis*. Twenty-three cases of TB were detected, an incidence rate of 6.39 per 1000 person-years of follow-up. Multivariate analysis showed HIV-infected patients (RR 4.07, 95%CI 2.61-6.35), and those infected by *M. tuberculosis* who did not undergo

LTIT (RR 10.15, 95%CI 0.90-50.59) to be at greater risk of developing TB. In TST reactors, those co-infected with HIV (RR 10.15, 95%CI 3.80-27.07) and those who had not undergone LTIT (RR 8.53, 95%CI 1.12-64.86) were shown to be at the greatest risk of developing TB.

**CONCLUSIONS:** The observed incidence of TB is much higher in prisons than in the community at large. HIV-*M. tuberculosis* co-infection appears as the main risk factor for developing TB, while LTIT significantly reduces incidence.

**KEY WORDS:** latent tuberculosis infection treatment; tuberculosis; HIV; prison

TUBERCULOSIS (TB) constitutes a serious public health problem which has led the World Health Organization (WHO) to declare a situation of world emergency.<sup>1</sup> In developing countries, where high levels of tuberculous infection exist side by side with human immunodeficiency virus (HIV) infection, the situation is especially critical.<sup>2</sup>

The estimated TB incidence for Spain is 45 new cases per 100 000 population per year, and the annual risk of infection is similar to that obtained in countries with good TB control twenty years ago.<sup>3</sup> The prison population has a higher incidence of TB than the outside world because of the risk factors for infection and developing tuberculosis of those entering prison and the special characteristics of closed institutions,<sup>4,5</sup> particularly overcrowding.<sup>6</sup> The lack of effective prevention and control programmes (PCPs)<sup>7,8</sup> facilitates the nosocomial spread of TB in prisons, and has major repercussions on the incidence of TB in the general population.<sup>5-10</sup>

The aims of the present study were to analyse the incidence of TB in a Spanish prison and assess the effectiveness of PCPs, especially latent tuberculin infection treatment (LTIT), in a social grouping with a high level of co-infection of HIV and *Mycobacterium tuberculosis*.<sup>11</sup>

### PATIENTS AND METHODS

From January 1991 to July 1999, a TB PCP consisting mainly of screening and case-finding, DOT and LTIT, was conducted in a prison in Spain.<sup>12</sup> The stable inmate population ranged from 200 to 350, with an annual rotation of about 500 admissions and about 500 releases.

For every new inmate, a case history was opened or an existing one was updated, including personal and prison records and risk factors for HIV and TB infection. HIV antibody tests were offered, for which the enzyme-linked immunosorbent assay (ELISA) technique with Western blot confirmation was used. The tuberculin skin test (TST), with 2 TUs of PPD RT-23 with Tween 80 was performed by staff trained in the Mantoux technique and readings were taken between 48 and 96 hours using Sokal's technique.<sup>13</sup> *M. tuberculosis* infection was considered proved by an induration of 5 mm or more in HIV-positive patients and in those not vaccinated with BCG (as evidenced by the vaccination scar), or by 15 mm or more in those vaccinated with BCG and not infected by HIV. The same criterion was used in the annual tuberculin monitoring of non-infected patients, with

those who had become infected being considered converted.<sup>14</sup>

Chest radiographs were taken of all inmates with an induration of 5 mm or more, of all HIV-positive patients and of those of unknown serological status with behaviour patterns indicative of risk of the virus. The radiographs were taken and interpreted by specialist staff at the Dispensario de Enfermedades del Tórax (Chest Clinic). Whenever a plate indicated possible TB (including residual forms), two serial samples of sputum were obtained and examined under the microscope by the Ziehl-Neelsen technique and in cultures grown in Löwenstein-Jensen medium.<sup>15</sup>

Patients who finished the diagnostic algorithm and who were not considered ill were given an annual TST if they were not infected with *M. tuberculosis*, or a twice-yearly radiograph if they showed the radiographic criteria stated above. Symptomatic patients who attended surgery were given the appropriate diagnostic tests.

Cases considered to be TB-incident were those with sputum smears positive for *M. tuberculosis* and those with symptoms and bacteriology compatible with the disease.

Those who were not monitored and those who did not reach the end of the diagnostic algorithm were considered lost to follow up.

For those infected by the tubercle bacillus, LTIT was recommended once it was ruled out that they had developed the disease. For those who agreed to begin treatment, the most appropriate dosage and timing

were chosen by consensus: 300 mg isoniazid per day or 900 mg twice-weekly for 6 months for HIV-negative patients with normal radiographs, and 12 months for HIV-positive patients and HIV-negative patients whose plates showed residual or fibrotic forms. Optionally, in daily therapy, administration could be directly observed.

For work management purposes, a programme was specially designed using Epi-Info<sup>16</sup> along with its 'eped', 'enter' and 'check' sub-programmes.

Incidence was calculated on the basis of new cases detected during the total period of monitoring per 1000 person-years of follow-up (p-y). Monitoring was considered complete in incident cases at the time when antituberculosis chemotherapy was begun, and in the remaining patients, at the time of the last available test, provided that the diagnostic algorithm had been completed.

For the study of factors associated with the manifestations of TB, relative risks (RRs) were calculated using 95% confidence intervals (95%CI) and the Kaplan-Meier method, and a comparison was made between the different probability curves for TB manifestation by means of the Log-rank test. At multivariate level we used Cox regression (enter method). For this the SPSS-Win programme was used (SPSS Inc. Chicago, IL).

## RESULTS

Over the period under study, 3081 inmates entered the prison, and active screening for cases reached

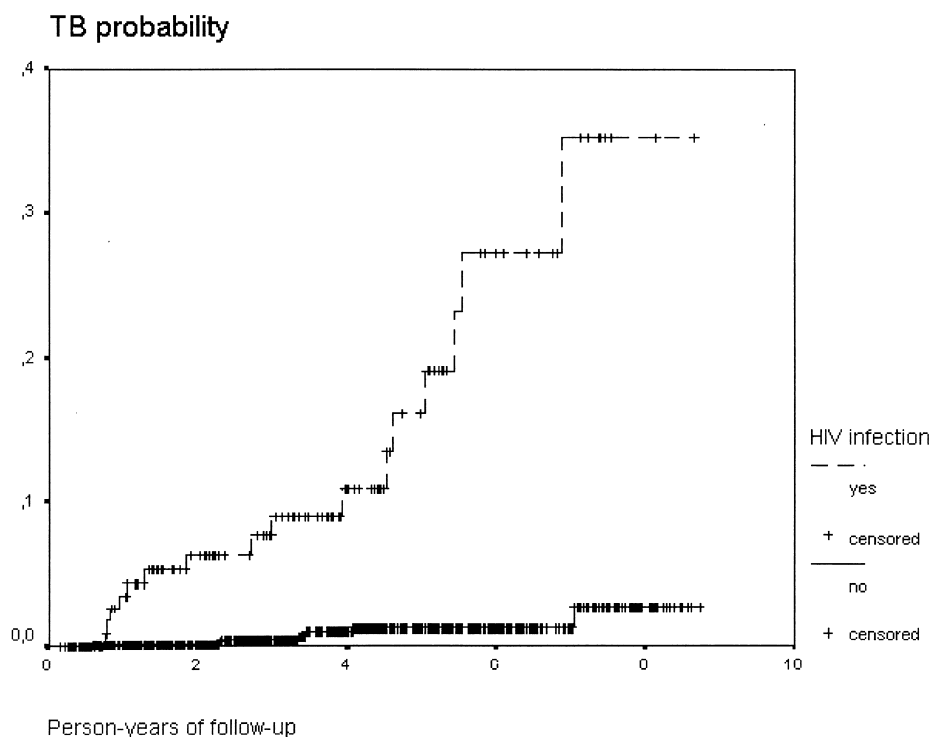
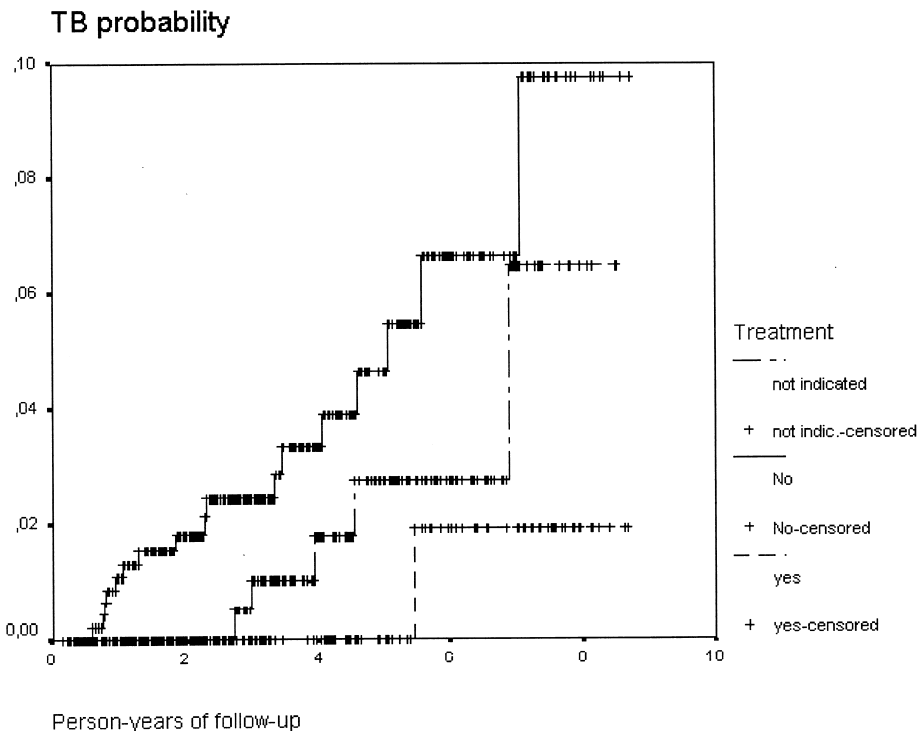


Figure 1 Probability of developing tuberculosis according to HIV infection.



**Figure 2** Probability of developing tuberculosis according to treatment of latent tuberculosis infection.

2541 (82.5%), most of the losses being due to the non-reading of the tuberculin test owing to release before 48 hours. Six new cases of TB were diagnosed on entry, a rate of 2.36 cases/1000. A total of 1050

people (41.3%) were monitored. Total monitoring time was 3597 years (average 3.4 years, standard deviation [SD] 2.1 years).

The population under study was mainly male

**Table 1** Distribution of TB according to different variables. Uni- and multi-variate analyses

Variable	n	Cases	Years	Incidence	RR	95%CI	P	Adj RR	95%CI
Sex									
Male	79	1	233	4.29	1		0.72		
Female	971	22	3364	6.54	1.52	0.21–11.31			
Age-group (years)									
16–24	357	4	1316	3.04	1				
25–34	471	14	1546	9.06	2.98	0.98–9.05	0.03		
>34	222	5	735	6.80	2.24	0.60–8.33	0.58		
Chemotherapy history									
No	1019	20	3517	5.69	1		0.0003		
Yes	31	3	80	37.50	6.59	1.96–22.19			
Time in prison									
0–11 months	648	7	2124	3.30	1		0.008		
>11 months	402	16	1473	10.86	3.30	1.36–8.01			
IDUs									
No	636	5	2144	2.33	1		0.0003		
Yes	414	18	1452	12.40	5.32	1.97–14.32			
HIV infection									
No	900	7	3118	2.25	1			1	
Yes	127	16	420	38.10	16.97	6.98–41.25	<0.001	4.19*	2.68–6.55
LTIT									
Yes	149	1	677	1.48	1			1	
No	498	17	1666	10.20	6.91	0.92–51.91	0.02	8.32†	1.09–63.49
Not necessary	397	5	1247	4.01	2.71	0.32–23.24	0.20	3.42‡	0.39–29.59

\* Log-rank =  $P < 0.0001$ .

† Log-rank = 0.04.

‡ Log-rank = 0.26.

RR = risk ratio; CI = confidence interval; Adj RR = adjusted risk ratio; IDUs = intravenous drug users; HIV = human immunodeficiency virus; LTIT = latent TB infection treatment.

**Table 2** Distribution of TB in TST-positive patients according to different variables. Uni- and multivariate analyses

Variable	n	Cases	Years	Incidence	RR	95%CI	P	Adj RR	95%CI
Sex									
Male	32	1	28	10.20	1		0.76		
Female	600	17	2208	7.70	0.75	0.10–5.67			
Age-group (years)									
16–24	160	1	623	1.61	1				
25–34	308	13	1106	11.75	7.32	0.96–55.98	0.02		
>34	164	4	578	6.92	4.31	0.48–38.58	0.15		
Chemotherapy history									
No	601	15	2227	6.74	1		0.002		
Yes	31	3	80	37.50	5.57	1.61–19.23			
Time in prison									
0–11 months	342	6	1188	5.05	1		0.14		
>11 months	290	12	1118	10.73	2.13	0.80–5.66			
IDUs									
No	344	4	1259	3.18	1		0.006		
Yes	288	14	1047	13.37	4.21	1.39–12.79			
Co-infection with HIV									
No	530	6	1913	3.14	1			1	
Yes	102	12	393	30.53	9.74	3.65–25.94	<0.001	10.15*	3.80–27.07
LTIT									
Yes	146	1	677	1.50	1			1	
No	486	17	1639	10.37	6.92	0.92–51.99	0.02	8.53 <sup>†</sup>	1.12–64.86

\* Log-rank  $P < 0.0001$ .<sup>†</sup> Log-rank  $P = 0.038$ .

TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; Adj RR = adjusted risk ratio; IDUs = intravenous drug users; HIV = human immunodeficiency virus; LTIT = latent TB infection treatment.

(92.5%), white (85%) and young, with an average age of 29 years (SD 8.5 years). At the beginning of the study, 12.4% of the 1027 patients were known to be HIV-infected, and fresh analyses were carried out on 674 patients, revealing 28 seroconverted. At the end of the study, 15.1% of the population were known to be infected with HIV; 39% of the inmates were intravenous drug users (IDUs) or ex-IDUS, and these showed an HIV infection rate of 37%.

On admission to prison, 41.3% were classified as infected with *M. tuberculosis* and 216 patients were considered converted. At the end of monitoring, 62% of the patients were infected. Co-infection by tuberculosis and HIV was 5.7% at the start and 10% at the end of monitoring.

The total number of cases of TB detected in monitoring was 23 (a case rate of 6.39/1000/year; binomial 95%CI 4.01–9.56 cases/1000/year). No differences were observed in the appearance of the disease based on sex or ethnic background. The greatest risks of developing TB were shown by patients aged 25–34 years, those with a history of TB, those who had previously been in prison for a year or more, IDUs, HIV-infected patients (Figure 1) and those who did not submit to LTIT despite recommendation (Figure 2) (Table 1).

After multivariate analysis, HIV infection and LTIT were the only TB risk factors (Table 1). LTIT of 6 months or more proved to be a protecting factor against the development of TB, when those receiving it were compared to those who did not or who did so over less than 6 months (Table 1).

Of *M. tuberculosis* infected patients, those who did not submit to LTIT showed a greater probability of developing TB, both among the total sample (10.20 vs 4.01 cases/1000 p-y; RR 2.54; 95%CI 0.94–6.90;  $P = 0.08$ ) and among HIV-negative cases (4.88 cases/1000 p-y vs. 0;  $P = 0.02$ ). Among the HIV-infected, TB incidence was not connected with response to tuberculin (49.02 vs. 36.76/1000 p-y; RR 1.33, 95%CI 0.46–3.90;  $P = 0.6$ ).

Among those who were HIV-infected at the beginning of the study, the incidence of TB was significantly higher among those with a history of TB (37.04 vs. 1.63 cases/1000 p-y; RR 22.70; 95%CI 4.40–117;  $P = 0.006$ ).

The incidence of TB among cases co-infected with HIV and *M. tuberculosis* was significantly greater than among the others at the beginning and during the study (30.53 vs. 3.47/1000 p-y; RR 8.79, 95%CI 3.88–19.92;  $P < 0.0001$ ). Apart from patients submitting to LTIT, the risk of developing TB in co-infected cases was greater than for the rest (41.98 vs. 4.19 cases/1000 p-y; RR 10.02, 95%CI 4.34–23.10;  $P < 0.0001$ ).

Of those infected by *M. tuberculosis*, co-infected patients and those who did not submit to LTIT were shown by multivariable analysis to be at a greater risk of TB (Table 2).

## DISCUSSION

The observed incidence of TB, 6.39 cases/1000 p-y, is about 14 times higher than that estimated for the gen-

eral population,<sup>17</sup> but lower than those reported by other authors for Spanish prison populations, which ranged from 27.75 to 10.40 cases/1000 p-y.<sup>18–20</sup> Studies of the prison population in the USA have given incidences ranging from 20.40 to 1.84 cases/1000 p-y,<sup>21–23</sup> between 5 and 11 times higher than for the outside population.<sup>24</sup> These differences may be explained by the different situations of endemic tuberculosis in the USA and Spain and also by the possibly different levels of effectiveness of PCPs in the prison population.<sup>25–27</sup> Reported incidences higher than those observed in this study are due to epidemics breaking out at centres with ineffective PCPs. The same reasons may explain why the incidences observed are much lower than those recorded in Russia, Azerbaijan and Ivory Coast, where there may be as many as 58 smear-positive cases/1000 p-y.<sup>28–30</sup>

The incidence of TB observed among the HIV-infected is lower than that reported in most published literature,<sup>31–37</sup> which may be due to a better preserved immune state among our population than in groups studied in hospitals, the active search for infection in patients with risk-linked behaviour, and the prescription and completion of LTIT in a greater percentage of cases. The lower incidence observed among HIV-infected patients who did not undergo LTIT may be due to a lower exposure to re-infection, attributable, at least partly, to a relatively efficient TB control programme in our population.<sup>38,39</sup>

The higher incidence found among patients with a history of chemotherapy may be due to non-compliance with anti-tuberculosis treatment, with a consequent risk of relapse,<sup>40</sup> although in an environment of high prevalence of uncontrolled sources of bacilli re-infection cannot be ruled out,<sup>41</sup> nor can infection by different strains appearing at different times.<sup>42</sup>

As regards factors associated with a greater probability of TB, the multivariable analysis ruled out the influence of the time spent in prison, age and IDUs. This is probably due to these variables being associated with HIV, given that the HIV-positive are usually IDUs, young (25–34 years) and usually spend longer in prison.<sup>43</sup>

The strong association of TB incidence with HIV infection is a known fact in that it is the main factor predisposing patients to the development of the illness after infection.<sup>28,35</sup>

Apart from patients undergoing LTIT, the TST response was effective in ruling out the disease and is undeniably useful in the active and passive search for TB, especially among the HIV negative.<sup>35</sup> In the case of those infected by HIV, the tuberculin test did not appear to be a predictive factor, perhaps because of the fast development of TB after recent infection or re-infection with *M. tuberculosis*, especially in an environment or group exposed to a high incidence of tuberculosis infection, rather than the development of TB after endogenous reactivation.<sup>44</sup>

From the clinical point of view, more interest possibly lies in the fact that reaction to the tuberculin test while HIV-infected, i.e., co-infected, is the main risk factor for developing TB, as is the fact that LTIT was an important protecting factor against the development of TB in the case of TST-positive patients (Table 2). It is known that isoniazid treatment is important to avoid the transition from infection to symptomatic disease.<sup>35</sup> In the case of the TST-positive patients not infected with HIV, no cases were observed among those who were undergoing LTIT, although perhaps because of a problem of statistical power the differences between these and those who were not were not significant. In those co-infected with HIV and *M. tuberculosis*, LTIT was strongly protective against TB development and was near to statistical significance, as recent meta-analyses show.<sup>45,46</sup> The same studies show that the administration of LTIT to HIV-positive tuberculin-negative patients is of no benefit when compared with non-administration. In our prison, no cutaneous anergy tests were carried out, so LTIT was recommended for those who showed no response to the tuberculin test as a simple matter of resource assignment.<sup>47</sup>

We may conclude that a high incidence of TB was observed, basically linked to high HIV infection and co-infection with *M. tuberculosis*. This incidence is lower, however, than expected, and may be due to the effectiveness of the prevention and control programmes including DOT, early diagnosis and LTIT. Monitoring bacillary foci may explain the lower incidence in those who did not submit to LTIT, but LTIT also proved effective in reducing the incidence of TB, mainly in HIV-*M. tuberculosis* co-infected patients, which leads us to recommend its use in centres where such co-infection is common.

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## R É S U M É

**OBJECTIF :** Etablir l'incidence de la tuberculose (TB) dans la population d'une prison ainsi que ses liens avec le traitement d'une infection tuberculeuse latente (LTIT).

**MÉTHODES :** Un programme de tuberculose a été conduit entre 1991 et 1999 dans une prison espagnole. On a mené une enquête de cohorte visant à connaître l'incidence de la TB et les variables associées.

**RÉSULTATS :** Parmi les 1.050 sujets étudiés, 10% étaient co-infectés par le virus de l'immunodéficience humaine (VIH) et *Mycobacterium tuberculosis*. On a détecté 23 cas de TB correspondant à un taux d'incidence de 6,39 pour 1.000 personne/années de suivi. L'analyse multivariée a démontré que les sujets infectés par le VIH encouraient un risque plus important de développer la TB

(RR = 4,07 ; IC95% 2,61–6,35) et ceux infectés par *M. tuberculosis* un risque de non-adhésion au LTIT supérieur (RR = 10,15 ; IC95% 0,90–50,59). Chez les sujets tuberculino-positifs, ceux co-infectés par le VIH et ceux qui n'avaient pas subi le LTIT s'avèrent avoir le risque le plus élevé de développement d'une tuberculose, respectivement (RR = 10,15 ; IC95% 3,80–27,07 et RR = 8,53 ; IC95% 1,12–64,86).

**CONCLUSIONS :** L'incidence observée de la TB est beaucoup plus élevée que dans la collectivité en général. La coinfection VIH-*M. tuberculosis* est le facteur de risque le plus important pour le développement d'une TB, alors que le LTIT en diminue l'incidence de façon significative.

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## R E S U M E N

**OBJETIVO :** Establecer la incidencia de tuberculosis (TB) y su relación con el tratamiento de la infección tuberculosa latente (TITL) en la población de una prisión española.

**MÉTODOS :** Desde 1991 a 1999 se llevó a cabo en una prisión española un programa de prevención y control de la TB. Se realizó un análisis de cohortes para conocer la incidencia de TB y las variables asociadas.

**RESULTADOS :** Fueron estudiadas 1050 personas, el 10% co-infectadas por el virus de la inmunodeficiencia humana (VIH) y *Mycobacterium tuberculosis*. Fueron detectados 23 casos de TB, lo que supuso una tasa de incidencia de 6,39 casos por mil personas y año de seguimiento. El análisis multivariado desveló que los pa-

cientes infectados por VIH tenían un mayor riesgo de desarrollar TB (RR 4,07, IC95% 2,61–6,35), y los infectados por *M. tuberculosis* que no realizaron TITL (RR 10,15, IC95% 0,90–50,59). Entre los reactivos a la prueba de la tuberculina los coinfectados con VIH (RR 10,15, IC95% 3,80–27,07) y aquellos que no realizaron TITL (RR 8,53, IC95% = 1,12–64,86) mostraron un mayor riesgo de desarrollar TB.

**CONCLUSIONES :** La incidencia de TB observada es mayor que la de la población no reclusa. La coinfección VIH-*M. tuberculosis* aparece como el principal factor de riesgo para desarrollar TB, mientras que el TITL reduce significativamente la incidencia.

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