

# Characterization and evaluation of the directly observed treatment for tuberculosis in Santiago de Compostela (1996–2006)

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**Objective:** To realize a retrospective study of the characterization, results, and effectiveness of directly observed therapy, short course (DOTS) in the regional health area of Santiago de Compostela (population 453 068) between 1996 and 2006.

**Design:** Tuberculosis (TB) patient cases involved in DOTS treatment were reviewed. The studied variables included: age, sex, type of TB, TB location, microbiological studies, chest radiology, pattern and treatment duration, final status of case, and TB recurrence.

**Results:** There were 2456 diagnosed TB cases in the time period studied and 259 received DOTS. The reasons for inclusion in this treatment strategy were social dystocia in 33.2% of cases, retreatment in 30.8% of cases, alcoholism in 29.3% of cases, drug use in 17.4% of cases, HIV coinfection in 11.6% of cases, multidrug-resistant strains of TB (MDR-TB) in 3.1%, and being an immigrant in 1.9% of cases. Primary TB represented 3.5% of the instances and pulmonary TB represented 87.6%. Bacteriological confirmation was performed in 76.8% of this population. Cavitated forms in chest radiology were shown in 46.7% of patients. Standard treatment guidelines were used in 71.4% of patients. Treatment adherence was achieved in 96.1% of the cases and 86.9% cases had a successful final status. Recurrence of TB was 1.5%.

**Conclusion:** Although it is not possible to determine the exact influence of the DOTS strategy, its introduction under the conditions of the Galician Program for Prevention and Control of Tuberculosis (GPPCT)<sup>5</sup> has worked to improve the control of tuberculosis in our health area.

**Keywords:** tuberculosis, DOTS, selection criteria, drugs, recurrence

## Introduction

Tuberculosis (TB) is an infectious disease for which effective treatment has been available for more than 50 years. However, TB has neither been eradicated nor controlled globally and it remains an important public health problem.

The estimated number of cases world wide in 2006 was 9.2 million (139 cases/100,000 people).<sup>1</sup> The factors that have contributed to this situation are poverty, spread through migration, lack of disease control, the new epidemic of HIV/AIDS, and the emergence of multidrug-resistant strains of TB (MDR-TB).<sup>2,3</sup>

The current incidence of TB in Spain is not known. In 2007, a working group of experts on TB was created as a result of a proposal by the Spanish Government Health and Consumption Ministry and a “Plan for prevention and control of TB in Spain” was established.<sup>4</sup> In 1995, the Galician Program for Prevention and Control of Tuberculosis (GPPCT)<sup>5</sup> published epidemiological data on TB incidence in Galicia, in the northwest region of Spain. In 1996, the incidence of TB in Galicia was found to be about 72.3 cases/100,000 people and in 2006 about 37.7 cases/100,000 people, which indicates a 7% annual decrease.<sup>6</sup>

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Perhaps the most important action to accelerate the reduction in TB and to control it is to establish early treatment of all patients and to guarantee proper observance of the established treatment guidelines. It has been estimated that between 20% and 50% of patients do not take their treatment properly or do not complete the whole prescribed regimen. Both these situations may lead to therapeutic failure and the emergence of secondary resistance.<sup>7</sup>

A new strategy to control this disease called Stop TB was launched by the World Health Organization (WHO) in 2006.<sup>1</sup> The core of this strategy was directly observed therapy, short course (DOTS), proposed by the WHO in 1994.<sup>8</sup> The strategy involves observing patients taking their medications to ensure they are consumed in the right combination and for the correct duration.<sup>9</sup> The first component of the Stop TB strategy, DOTS expansion and enhancement, is the cornerstone. The basic components of the DOTS strategy are: political commitment to increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; systems for effective drug supply, management, monitoring and evaluation; and impact measurement.<sup>8</sup>

The GPPCT is trying to implement this DOTS method gradually, at least in those patients in whom a higher likelihood of withdrawal is expected.<sup>10</sup>

This paper reports a retrospective study of the characterization, results, and effectiveness of DOTS in relation to TB in the health area of Santiago de Compostela between 1996 and 2006.

## Material and methods

Data were obtained from the following sources at the Santiago de Compostela University Hospital Complex: 1) the TB unit (UTB) database, 2) patient clinical histories, 3) Microbiology Service registrations, and 4) Hospital Pharmacy Service information obtained from the unit dose dispensing program.

Informed patient consent and ethical approval were not required for this retrospective study.

The TB patients included in the study were those who received DOTS from January 1996 to December 2006. All patients belonged to the Santiago de Compostela health area (population 453,068). DOTS was established by the UTB, located in the Preventive Medicine Department of the Santiago de Compostela University Hospital. The criteria for patients to be included in DOTS were: retreatment cases (ie, treatment after default or relapse and chronic cases), evidence of HIV infection, drug use, alcoholism, psychiatric illness, social dystocia, if they were immigrants, and/or exhibited MDR-TB.

Patients were excluded from the study if they represented relapsed cases of TB diagnosed more than 15 years ago.

In order to analyze DOTS administration, two points need to be considered: the wide population dispersion in the health area analyzed and the resulting inability to centralize treatment administration. That is why, for this study, the decision on the location and selection of appropriate people to administer DOTS was individualized and conducted on the basis of a social and clinical report of the patient, with their agreement.

The variables included in the study were: age, sex, type of TB, TB location, microbiological studies, chest radiology, pattern and treatment duration, and case final status. TB type was classified according to internationally accepted recommendations.<sup>11</sup> TB location could be primary complex, pulmonary, or extrapulmonary (eg, pleural, miliar, meningal, lymph nodes).

Microbiological studies were performed in the Microbiology Department of Santiago de Compostela University Hospital, which has WHO recognition as a TB reference center in Galicia.<sup>12</sup> The studies conducted were: stains acid-fast bacilli (AFB), culture in liquid medium (using BACTEC™ MGIT™ 960 system; BD, Franklin Lakes, NJ), drug susceptibility testing (DST) to the first-line drugs (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z], streptomycin [S]) and to second-line drugs (levofloxacin, capreomycin, prothionamide, amikacin, PAS, cycloserine, ciprofloxacin, ofloxacin).

Case final status was defined following the GPPCT protocol and included the following options: bacteriological cure, completed treatment, default, death from TB, death from other causes, or transferred out.<sup>5</sup> Treatment adherence has to be ensured in all patients, which includes those patients who died or were transferred to another health area.

TB recurrence in DOTS cases was defined as rediagnosis of TB in previously treated patients who had undergone DOTS.

Data for this study was managed by MS Excel™ for Windows® XP, and analyzed with the statistical package SPSS v12 for Windows®. Associations between variables were tested using the Pearson chi-square. All tests were two-sided and *P* values < 0.05 indicated significant differences.

## Results

There were 2456 cases of TB diagnosed in the Santiago de Compostela health area between 1996 and 2006. Among these, 253 patients (10.3%) received 259 DOTS treatments. There were 58 women (22.9%) and 195 men (77.0%), with an average age of 39.9 years (range 0–83).

The distribution of total cases under DOTS by type of TB, over two time periods (1996–2000 and 2001–2006), is shown in Table 1.

**Table 1** Distribution of DOTS TB cases in Santiago de Compostela by year and type of tuberculosis

Year	New TB cases N°/% DOTS	Retreatment cases			Total N°/% DOTS/%
		Treatment after default N°/% DOTS	Relapse N°/% DOTS	Chronic N°/% DOTS	
1996–2000	1263/90.6	29/2.1	98/7	4/0.3	1394/56.8
	94	26	24	4	148
2001–2006	997/93.9	7/0.7	58/5.4	0	1062/43.2
	85	5	21	0	111
Total	2260/92	36/1.5	156/6.4	4/0.2	2456/100
	179	31	45	4	259/10.5

**Abbreviations:** DOTS, directly observed therapy, short course; TB, tuberculosis; N, number of cases.

Social dystocia and psychiatric illness met the inclusion criteria in 86 cases (33.2%), alcoholism in 76 (29.3%), drug abuse in 45 (17.4%), HIV-TB coinfection in 30 (11.6%), MDR-TB in 8 (3.1%), immigration in 5 (1.9%), and 80 (30.8%) were retreatment cases. Fifty-six patients (21.6%) presented with more than one criterion for inclusion.

With regards to TB type, 179 (69.1%) of these patients were newly diagnosed cases and 80 (30.8%) were being retreated for TB. Among the latter, 31 (38.7%) were classified as treatments after default, 45 (56.2%) were relapse cases and 4 (5%) had chronic illness. Of the 179 patients with newly diagnosed TB, 16 (9%) met more than one criterion to be included in the DOTS program, while there were 40 patients in this situation among the 80 (49.4%) retreatment cases ( $P < 0.01$ ).

The distribution of TB cases according to location and microbiology was as follows: 1) there were 9 (3.5%) primary complex TB cases, with only 1 case confirmed bacteriologically. Microbiological study was not performed in 8 cases; 2) there were 227 (87.6%) pulmonary TB cases, 170 (74.9%) of which had a positive AFB stain. Bacterial presence because of positive culture growth was confirmed in 191 (84.1%) patients. Bacteria were not isolated in 9 cases with positive AFB. Microbiological studies were negative in 28 (12.3%) cases; 3) there were 23 (8.8%) extrapulmonary TB cases, 5 (21.7%) of which were AFB positive, 7 (30.4%) had bacteriological confirmation, 4 (17.4%) had negative bacteriology, and no microbiological studies were carried out in 12 (52.2%) patients; 4) bacteriological confirmation was performed in 199 (76.8%) DOTS cases and of the 227 patients with pulmonary TB, 106 (46.7%) presented cavitated forms in their chest radiology while 114 (50.2%) had noncavitated images.

The physical locations where DOTS administration was conducted are shown in Table 2. Table 3 shows the pattern of and treatment regimens for this therapy, classified as: standard and internationally accepted patterns, extended regimens, and other guidelines. The latter include not only

the treatment of resistant and MDR cases, but changes in the therapy because of intolerance and/or drug toxicity.

Treatment adherence was achieved in 249 (96.1%) cases. The final case status is described in Table 4. Of those patients who took the treatment, 225 (86.8%) cases were cured or completed treatment.

No relationship was found between the final case status and the place of treatment ( $P > 0.05$ ) or treatment regimen followed ( $P > 0.05$ ).

Among the 253 patients who were successfully treated, 5 (1.9%) were rediagnosed with active TB in the observation period (1996–2006), one of them twice and another who had not completed the DOTS. The time of recurrence ranged between 1 and 6 years. There was no statistically significant relationship found between new cases TB or retreated TB and final status ( $P > 0.05$ ).

## Discussion

The foremost strategy of the WHO to achieve TB control is to apply DOTS to every single TB patient.<sup>13</sup> As this recommendation addresses mainly the poorest countries of the world, every country needs to adapt this WHO proposal to its own social, epidemiologic, and economic situation.

In our health area, 259 DOTS, according to the criteria set out in GPPCT, were conducted by the UTB during the years of this study, representing 10.5% of all registered cases.

**Table 2** DOTS treatment locations

Place of treatment	N° DOTS	%
UTB	97	37.5
Health center	72	27.8
Social services	42	16.2
Family	31	12
Drugs unit	13	5
School	3	1.2
Hospital	1	0.4

**Abbreviation:** DOTS, directly observed therapy, short course; UTB, tuberculosis unit at Santiago de Compostela University Hospital, Spain.

**Table 3** Patterns and treatment regimen for tuberculosis

Standard treatment	Treatment after				
	Regimen	New	Default	Relapsed	Chronic
2HRZ + 4HR	Daily	85	8	4	–
	Twice/week	2	1	–	–
2HRZE + 4HR	Daily	32	10	16	–
	Twice/week	3	–	–	–
2RbhZ + 4RbH	Daily	–	1	–	–
2HRE + 7RH	Daily	8	1	1	–
2HRZES + 1HRES + 5HRE	Daily	5	–	8	–
<b>Prolonged standard treatment</b>					
2HRZ + 10 HR	Daily	2	1	–	–
2HRZ + 7HR	Daily	4	2	1	–
2HRZE + 10HR	Daily	8	1	1	–
2HRZE + 7HR	Daily	1	1	–	–
2HRE + 10HR	Daily	7	2	2	–
2HRSZ + 10HR	Daily	–	–	2	–
<b>Other treatments</b>					
<b>Resistant TB/multiresistant or intolerances</b>					
2HRZE + 10RE	Daily	2	1	1	–
2HRZ + 10RE	Daily	4	–	–	–
2HZE + 16HE	Daily	1	–	–	–
2REZS + 10RE	Daily	–	–	1	–
Treatment with first-line drugs + quinolones	Daily	8	1	2	–
Treatment with first-line drugs + quinolones + other second line drugs	Daily	5	1	6	3
Other treatments with first- and second-line drugs	Daily	2	–	–	1

**Abbreviations:** TB, tuberculosis; H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; S, streptomycin; Rb, rifabutin.

Treatment supervision was achieved in all of the diagnosed chronic patients as well as in all the MDR-TB cases. Among the patients treated after default, DOTS was performed in 86.1% of the cases. Supervision was carried out in 28.8% of the relapsed cases and in 7.9% of the new TB cases. The low percentage among relapsed cases could be explained by the majority of these patients having a very old TB episode (more than 15 years prior). The analysis of the results shows a statistically significant ( $P < 0.05$ ) decrease in the number

of treatments after default relapse and the elimination of chronic cases in the last 6 years of the studied period.

The most recent WHO report shows that DOTS has a very different distribution throughout Europe, ranging from 0% to 100% (67% average). The statistics in this report emphasize that Western European countries, with low TB incidence, do not use the DOTS strategy.<sup>1</sup>

The patient profile described in the WHO report is very similar to the one shown in our patients where most were male and the average age was 39.9 years. This is consistent with the classical studies performed on populations in high TB incidence areas, which show men are in the majority and that there is a bimodal curve with a first high peak for young patients.<sup>14</sup>

Cases of pulmonary TB cases probably take priority when a TB control program is conducted because of their potential to infect others if left untreated.<sup>15</sup> In our study, 87.6% of the cases undergoing DOTS presented with pulmonary TB. Cavitated forms in chest radiology were shown in 46.7% of patients, 74.9% of whom had a positive AFB result on diagnosis. From positive AFB smears, the TB

**Table 4** Final status of tuberculosis cases after DOTS

Final status of the case	New TB/%	Retreatment TB/%	Total/%
Bacteriological cure	7/3.9	5/6.2	12/4.6
Treatment completed	151/84.4	62/77.5	213/82.2
Defaulted	8/4.5	2/2.5	10/4
Death from TB	0	2/2.5	2/0.8
Death from other causes	6/3.4	5/6.3	11/4.2
Transferred out	7/3.8	4/5	11/4.2
Total	179/69.1	80/30.8	259

**Abbreviations:** DOTS, directly observed therapy, short course; TB, tuberculosis.

rate was 27.1 cases/100,000 people in 1996 which fell to 9.2 cases/100,000 people in 2006. Despite this reduction, the rates are higher than expected if we consider the social and economic status of our area, and, more alarmingly, too high when compared to the rates in other Western European countries such as Germany (6.5 cases/100,000 people) or the United Kingdom (14 cases/100,000 people). Fortunately the figures are lower than the ones in Eastern European countries such as Russia (106.3 cases/100,000 people) or Georgia (143.1 cases/100,000 people).<sup>16</sup>

HIV infection has a high impact on TB epidemiology in Spain because our country has the highest incidence of HIV-TB coinfection in Europe.<sup>17</sup> However, in Galicia, from the very beginning of the GPPCT, it has been demonstrated that TB continues to show a classical epidemiologic distribution, without the influence of HIV.<sup>6</sup> The statistics reveal a coinfection rate of about 4.3% in 1996 and 3.3% in 2006. In none of the years of the study was this coinfection rate higher than 10%.

Since the development of the GPPCT, the UTB has overcome serious problems in order to instigate DOTS, particularly in the very early days. Implementing DOTS is difficult. In addition to this, population dispersion around the health area makes it even more complicated to provide treatment to patients.

WHO firstly recommends the use of internationally accepted guidelines for TB treatment. This universally standard treatment (2RHZ + 4RH, 2RHZE + 4RH) was used in 71.4% patients who newly presented with TB without complications in their illness. WHO endorses 6-month regimens based on rifampicin, isoniazid, and pirazinamide in areas where primary resistance to isoniazid is lower than 4%.<sup>18</sup> This resistance rate has never been exceeded in our study and, more importantly, primary resistance reached only 2.9%.<sup>19,20</sup> Second-line drugs such as capreomycin and prothionamide were the drugs selected for 11.1% patients who developed resistance and/or drug intolerance. The DOTS strategy is critical for this kind of drug management; 90.3% of the cases after default received standard treatments, while the percentage decreased to 77.8% in relapse cases. Drug regimens for chronic patients were individualized according to their anti-biograms results and their history of previous drug use.

Quinolone use in TB treatment is now a controversial topic. Ten percent of the patients from our study received quinolones. Ciprofloxacin was the option used at the very beginning of the study time period, but it was replaced by levofloxacin in recent years. This third generation quinolone, as well as moxifloxacin (fourth generation drug), are both reported to be

better treatment options for complicated TB cases.<sup>21,22</sup> A recent study showed that the use of moxifloxacin was associated with culture conversion and the authors suggest that moxifloxacin, in combination with other first-line anti-TB drugs, could shorten the time needed to cure TB by several months.<sup>23</sup>

Most patients in our study had a once-daily regimen and only 2.3% received an intermittent drug administration schedule. Intermittent regimens have shown to be as effective as the ones based on once-daily administration and are, as well, the less costly option.<sup>24</sup> Studies have also shown that intermittent regimens do not increase the rate of TB drug resistance.<sup>25</sup> Now that some of these infrastructure problems have been solved, it would be very interesting to implement this kind of regimen.

In our health area, social and familial problems are the major inclusion criteria in DOTS programs. Drug use and alcoholism, for instance, can lead to inadequate compliance in drug therapy. It should be noted that the retreated group had a statistically significant multifactor risk.

Few studies carried out under routine program conditions have reported disease recurrence. Published values range from 0% to 14%.<sup>26</sup> TB recurrence is a useful indicator of treatment efficacy under the DOTS strategy. In our series, recurrence under DOTS was low (1.9%), indicating the efficacy of the treatment. DOTS results were potentially unsatisfactory in 13.1% of patients. Even so, we think this is a good result given the historical difficulty in achieving drug compliance in many TB patients.

Recently, new and original DOTS systems have been developed. In the Valencian Region of Spain, a pilot program based on DOTS administration by pharmaceutical chemists has begun. First results show that it is a good alternative for the future.<sup>27</sup>

The introduction of the DOTS strategy under the GPPCT, together with strict control and follow-up of all TB diagnoses in our health area, has combined to reduce the illness incidence rate of TB, which ranged from 72.7 cases/100,000 people in 1996 to 27.1 cases/100,000 people in 2006. Even so, we are far from achieving total TB control. A re-evaluation of the situation is needed, as is a deep analysis of the causes of the delay in diagnosis, which naturally leads to a delay in the start drug therapy.<sup>28</sup> Decisions on new approaches to the problem should be made according to the DOTS strategies.

## Conclusions

Patient selection criteria for DOTS administration were very important for TB control in our region. The group of retreated patients often had more than one risk factor for inclusion in DOTS ( $P < 0.01$ ). Standard treatment guidelines

recommended by WHO were used in 71.4% patients, 87.1% of whom achieved a satisfactory final status. The level of TB recurrence in patients under the DOTS strategy was low.

Although it is not possible to determine the exact influence of the DOTS strategy, its introduction under the conditions set up by the GPPCT has helped to improve the control of TB in our health area.

## Disclosures

The authors report no conflicts of interest in this work.

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