



A Meta-Analysis of Directly Observed Treatment vs. Self-Administered Therapy Outcomes in Pulmonary Tuberculosis Patients

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Abstract

A systematic review and meta-analysis were conducted in order to compare the effectiveness of directly observed therapy, short-course (DOTS) with self-administered treatment (SAT) in people with pulmonary tuberculosis. PubMed, Embase, ISI Web of Science, and the Scielo/Lilacs were searched for studies published between 1 January 1965 and 31 December 2013. Eleven studies were selected, including 14390 people with the following outcomes: cure, treatment completion or abandonment, and death. Results showed that approximately 22% more healing and completed treatment occurred among patients who underwent SAT (OR 1.22, 95% CI 1.07 to 1.40), while a lower treatment dropout rate was found in the group receiving DOTS (OR 0.68, 95% CI 0.56 to 0.83). Results did not detect a significant difference in the risk of death when comparing SAT and DOTS (OR 0.82, 95% CI 0.64 to 1.05). In the discussion, a reflection is made on what kind of treatment regimen is best suited to those infected by *Mycobacterium tuberculosis* and a discussion ensues on how to achieve better cure rates and less abandonment and mortality. It is concluded that when choosing a treatment regimen for patients, public programs are key to considering the dynamics of health services as well as the conditions and lifestyle of patients. The latter must also provide prevention, treatment and monitoring of infection, and have sufficient funding to train a health team and ascertain follow up of patients and families in order to attain the best success rates possible.

Keywords

Tuberculosis, Pulmonary tuberculosis, Treatment

Introduction

Tuberculosis (TB) still represents a serious problem in public health, expressed by approximately nine million new cases and 1.5 million deaths each year [1-3]. Studies also point to the fact that TB cure and disease control are seriously compromised by drop-out rates, as can be deduced by statistics on re-treatment, relapse, treatment dropout, drug resistance and death by TB [4-6]. Such to better TB treatment and control its spread, especially in countries with a high incidence, the WORLD HEALTH ORGANIZATION (WHO) has recommended a strategy since 1993 called Directly Observed Treatment Short-Course (DOTS). The latter involves four components: politically committed governments, improvement of laboratory diagnosis, supervised treatment with continuous supply of drugs and an information system to monitor and record appropriate treatment progress of patients and programs [2].

Treatment administered under the supervision or direct observation of a trained professional from initiation of treatment to cure, has become a key element leading to successful DOTS [3]. Studies show that by adopting DOTS more than 30 million TB patients have been treated, resulting in cure rates above 80% as well as reducing dropout rates by about 10% [4].

In 2006 the Global Plan to Stop TB recommended that DOTS become "standard treatment" under appropriate conditions. This treatment method has been shown to reduce the risk of drug resistance as well as support patients, thus resulting in increased adherence to treatment, and consequently, the possibility of cure [1]. Several studies support this statement [7-14].

This being said, the systematic review conducted by Volmink and Garner [15] showed no significant evidence supporting the routine use of DOTS over SAT when aiming to cure patients or at least complete the chosen treatment. In a recent meta-analysis, Karumbi and Garner [16] concluded that DOTS did not provide a solution to poor adherence in TB treatment. Several studies have not found DOTS to be the most efficient regimen for TB management [17,18]. DOTS has recently been questioned because its resulting completion rates seem equivalent to those of SAT. DOTS has been criticized as a passive model within public health services since it often only delivers the appropriate drugs without taking into account some important social components of the disease which may lead to a low success rate, social stigma, and lack of moral support by family members unwilling to modify living conditions and habits [18].

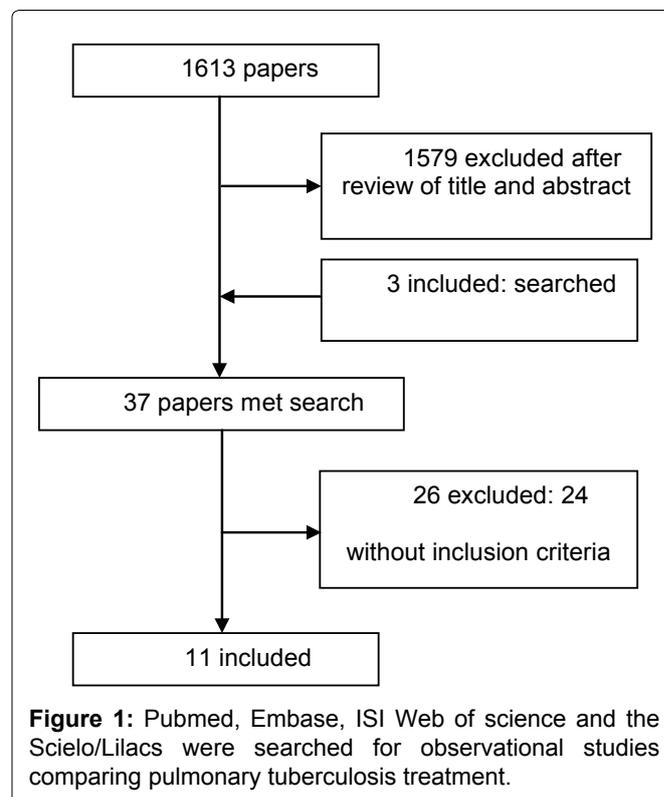
The fact that the literature boasts few studies or meta-analyses which result in significant levels of evidence to prove that one type of TB therapy is more effective than any other also leads to the importance of further investigating the comparative effectiveness of DOTS and other pulmonary TB management strategies. This systematic review and meta-analysis intends to compare the effectiveness of DOTS with SAT in the fight against pulmonary TB.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. We searched PubMed, Embase, ISI Web of Science, and the Scielo/Lilacs for studies published between 1 January 1965 and 31 December 2013. There was no exclusion of articles by language. Bibliographies of original articles, key reviews, and consensus statements were also searched for additional relevant studies. The following Medical Subject Heading terms and strategy was used: directly observed therapy or supervised therapy or directly observed treatment strategy or DOT or DOTS and self-administered therapy or self-supervised therapy OR unsupervised therapy and tuberculosis.

Inclusion criteria

Three researchers (AAC, EWB and EMNF) began the process of selecting relevant studies by examining titles and abstracts using the following inclusion criteria: the studies were observational studies comparing pulmonary TB patients following the DOTS, or SAT regimens until the treatment was concluded or interrupted, the patients were healed, or died of TB. Studies that exclusively



addressed extra pulmonary tuberculosis as well as qualitative studies were excluded. After evaluating titles and abstracts, 1579 articles were excluded (Figure 1). The outcomes cited above were classified according to the WHO definitions [20]:

- Healed: Patient whom completed TB treatment which resulted in negative culture at the end of the treatment.
- Treatment completed: Patient completed treatment but did not meet the criteria for cure or failure. This definition applies to patients with pulmonary TB smear-positive and smear-negative cultures.
- Abandonment: Patient who took anti TB drugs for one month or more and interrupted treatment for two months or more.
- Death: Patient who died for any reason during anti TB treatment.

Thirty seven articles were read by the following researchers, AAC, PHL and SACU. It was determined that only studies which followed adult patients with pulmonary TB under DOTS or SAT with the following regimens would be considered: the first two months daily doses of four drugs were administered (isoniazid (INH), rifampin (RMP), pyrazinamide and ethambutol) followed by a four month maintenance phase of INH and RMP during which individuals were followed by a health professional. The outcomes included in the review were treatment completion, abandonment, cure and death.

Data extraction

The data was extracted independently by three researchers (AAC, PHL and SACU). In case of disagreement between the authors, a fourth researcher (RNOC)

Table 1: Characteristics of studies selected for meta-analysis.

First author/ year of publication	Country	Period	People	Loss	Regimen		Outcomes	
					DOT	SAT	DOT	SAT
Waley, et al. [21]	Pakistan	1996-1999	497	0	335	162	Cure/treatment completed: 64.47% (216/335) Default: 29.55% (99/335) Death: 3.88% (13/335)	Cure/treatment completed: 64.81% (105/162) Default: 32.71% (53/162) Death: 1.85% (3/162)
Zwarenstein, et al. [22]	South Africa	1994-1995	156	0	112	44	Cure/treatment completed: 65% (73/112) Default: 29% (33/112) Death: 1.7% (2/112)	Cure/treatment completed: 59% (26/44) Default: 25% (11/44) Death: 2.7% (1/44)
Zwarenstein, et al. [23]	South Africa	2004-2005	216	0	111	105	Cure/treatment completed: 54.05% (60/111) Default: 28.8% (32/111) Death: 0.9% (1/111)	Cure/treatment completed: 60% (63/105) Default: 28.57% (30/105) Death: 0.95% (1/105)
Kamolratanakul, et al. [24]	Thailand	1996-1997	836	0	415	422	Cure/treatment completed: 75.9% (315/415) Default: 6.5% (27/415) Death: 6.2% (26/415)	Cure/treatment completed: 67% (283/422) Default: 13% (55/422) Death: 4.9% (21/422)
Falcão [25]	Brazil	1998-2004	1548	84 (DOT); 161(SAT)	218	1085	Cure/treatment completed: 76.5% (167/218)	Cure/treatment completed: 61% (666/1085)
Gabardo [26]	Brazil	2003	159	0	113	46	Cure/treatment completed: 86.7% (98/113) Default: 9.8% (11/113) Death: 3.5% (4/113)	Cure/treatment completed: 87% (40/46) Default: 10.9% (5/46) Death: 2.2% (1/113)
Vieira, et al. [27]	Brazil	2003-2005	301	0	153	148	Cure/treatment completed: 93% (143/153) Default: 7% (10/153)	Cure/treatment completed: 86,5% (128/148) Default: 13.5% (20/148)
Okanurak, et al. [28]	Thailand	2004-2005	931	0	432	300	Cure/treatment completed: 78.4% (339/432) Default: 5.3% (23/432) Death: 3.7% (16/432)	Cure/treatment completed: 84% (252/300) Default: 3% (9/300) Death: 3.6% (11/300)
Anuwatnonthakate, et al. [29]	Thailand	2004-2006	8031	0	6625	1406	Cure/treatment completed: 67% (1369/6625) Default: 7% (509/6625) Death: 12% (805/6625)	Cure/treatment completed: 53% (748/1408) Default: 23% (332/1408) Death: 5% (67/1408)
Egwaga, et al. [30]	Tanzania	2006	1032	0	484	548	Cure/treatment completed: 64.5% (312/484) Default: 2.7% (13/484) Death: 12.2% (59/484)	Cure/treatment completed: 60.9% (334/548) Default: 5.1% (28/548) Death: 16.8% (92/548)
Moosazade, et al. [31]	Iran	2004 -2010	683	0	362	321	Cure/treatment completed: 92% (333/362) Default: 0.8% (3/362) Death: 3.6% (13/362)	Cure/treatment completed: 83,2% (267/321) Default: 4.7% (15/321) Death: 5.3% (17/321)

was consulted. The following data was extracted from the eleven selected studies (Figure 1): first author, year of publication, country where the study was conducted, period, the number of patients with pulmonary TB, number of losses, type of treatment and outcome (Table 1).

Analysis

The odds ratio (OR) was calculated by means of the Mantel-Haenszel method, using a confidence interval of 95%, while a chi-square test with a significance level of 5% was used to determine the heterogeneity between studies. All calculations were made with Review Manager 4.2.

Results

Eleven studies met the inclusion criteria [21-31]. The characteristics of the selected studies are listed in table 1. The outcome measures for comparison between DOTS and SAT were: cure, treatment completion or abandonment and death.

Cure and treatment completion

Of all the TB patients considered for this review, 2716 were followed within the DOTS regimen to measure cure rate and treatment completion, while 2096 were followed

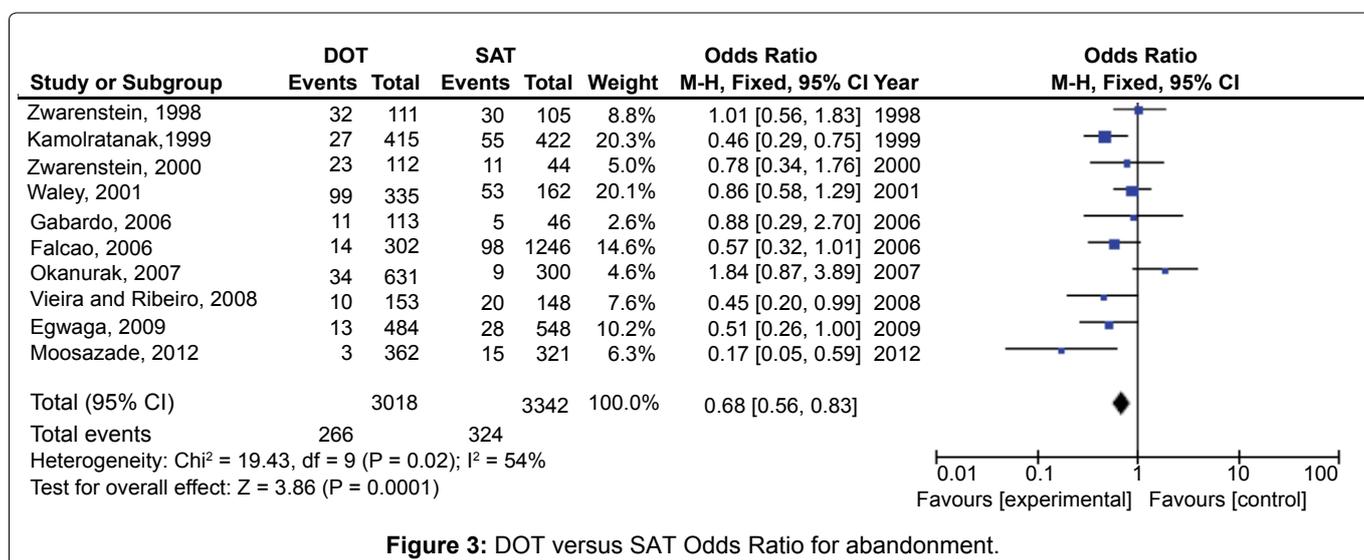
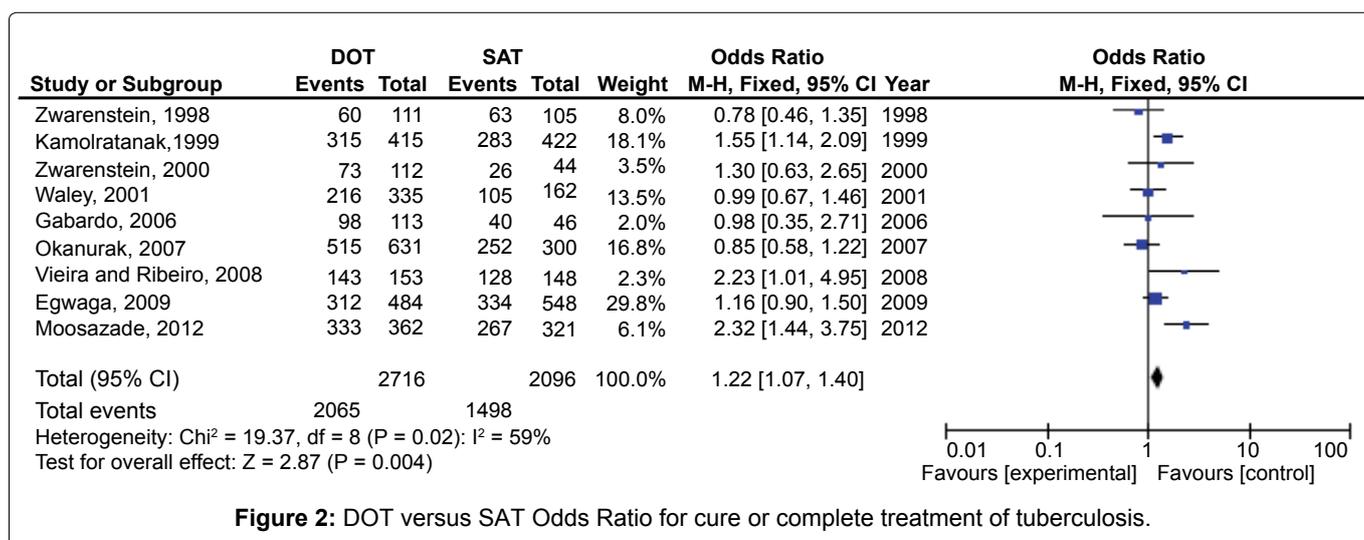
within the SAT regimen. From the DOTS group 2065 patients were considered cured or had completed the treatment, while in the SAT group 1498 subjects were assigned the same outcome. Data analysis revealed that approximately 22% more of the SAT patients were considered healed and completed treatment (OR 1.22, 95% CI 1.07 to 1.40) (Figure 2).

Abandonment

From the subjects included in this review, 3018 were followed within the DOTS regimen to measure the treatment abandonment rate and 3342 were followed within the SAT regimen. Results showed that 266 patients dropped out of DOTS while 324 left SAT. By comparison, the group receiving DOTS had a lower dropout rate, approximately 32% lower (OR 0.68, 95% CI 0.56 to 0.83) (Figure 3).

Death

Of all the TB patients making up the sample, 2563 received the DOTS regimen and were followed to measure mortality rate, while 1948 received the SAT regimen under the same conditions. We found that among the DOTS group 133 deaths occurred, while 147



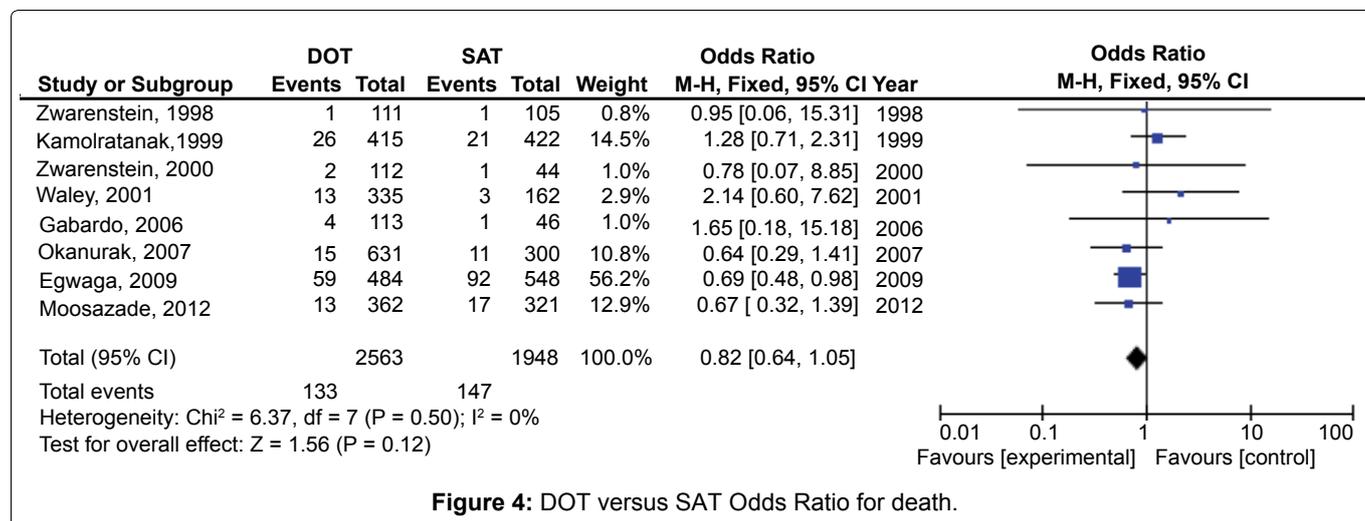


Figure 4: DOT versus SAT Odds Ratio for death.

were counted in the SAT group. No significant difference was found in risk of mortality when both regimes were compared (OR 0.82, 95% CI 0.64 to 1.05) (Figure 4).

Discussion

DOTS, has long been defended as a highly effective strategy in the cure of pulmonary TB. It is said that patients adhere more easily to the regimen which consequently increases success rates in treatment [3,6].

However, DOTS has not clearly shown an increase in cure rates, reduced dropout rates or lower mortality, factors which would prove the efficiency of this type of therapy. Furthermore, few studies compare DOTS to SAT, blurring the picture even more.

The findings of this meta-analysis showed that treatment success, found only in the healed and completed treatment group, was more significant among patients under the SAT regimen (OR 1.22, 95% CI 1.07 to 1.40). Similar findings were also published by Volmink and Garner [15], who did not find that DOTS was significantly more effective than SAT, regarding cure or completed treatment (OR 1.06, 95% CI 1.00 to 1.13). Karumbi and Garner [16] showed that TB cure was low with SAT across all studies and direct observation did not substantially improve this (OR 1.08, 95% CI 0.91 to 1.27), while treatment completion showed a similar pattern, ranging from 59% to 78% in the self-treatment groups, and DOTS did not improve this (RR 1.07, 95% CI 0.96 to 1.19).

Even though these meta-analyses, has shown DOTS not to be more effective than SAT, several studies have done so. Charokopos, et al. [32], compared both regimens and found that patients receiving DOTS had the higher cure rate of the two. Elkomy, et al. [33], also published results supporting DOTS as the most effective treatment ($P < 0.005$). Steffen, et al. [34] supported DOTS as well by finding that DOTS treatments were completed more frequently than SAT. The favorable findings for DOTS in these studies may be explained by small sample sizes. Other factors may help increase the cure rate and treatment completion in the groups that received supervised

therapy. It is important to note that treatment supervision is one of the pillars of the DOTS strategy; there may be differences in the quality of the supervision provided, considerably influencing the result represented by complete healing.

All countries where the studies included in this review were conducted have high incidence rates of TB. Two studies in particular observed better results in relation to healing when comparing DOTS with SAT [24,25], which leads us to seek an explanation for the increased success in the two countries Brazil and Thailand. The Brazilian Health System (Unified Health System - SUS) ensures universal access and public funding of health programs and services. Regarding TB control, a government program called the Family Health Strategy has decentralized diagnosis and supervised treatment in order to facilitate access and encourage patient adherence to TB treatment. In Thailand, the government invested in the public health system through disease prevention programs. Among these, the TB Control Program is well organized and effective. These results may be explained by the fact that the DOTS regimen has been efficiently implemented in these two countries, reinforcing the importance of government involvement. Studies carried out in Pakistan [21] and South Africa [22] showed no difference between SAT and DOTS regimens in terms of efficiency. Thus, it can be said that DOTS is only the most effective method when government funding is sufficient, casting a slight shadow over the WHO recommendation. This makes the DOTS regimen an expensive choice, especially in developing countries where government funding doesn't usually permit such extensive health programs. Quite possibly, DOTS is not economically feasible for developing countries, casting a favorable light on SAT, and a less expensive alternative.

A likely explanation for the limited effectiveness of DOTS is its lack of routine execution in regular health services in developing countries. Unlike the SAT, in which the patient takes responsibility for their treatment, implementation of DOTS depends on the commitment of the health professionals involved in the supervision

of the TB patient. Often, there is lack of preparation, interest, and professionalism in health staff supervising the intake of drugs, due to work overload in the clinic and insufficient number of employees [35]. These situations contribute to undermine DOTS, neither prioritizing it nor making it effectively systematic, especially when performed in the patient's home. In addition, hardship can often reduce the possibility that patients will go to the clinic on a daily basis for DOTS, which does not favor adherence to treatment.

The higher rate of cure and complete treatment under unobserved regimen found in this meta-analysis suggests that SAT is more effective than DOTS. The factors mentioned above may explain this finding, even though WHO has recommended treatment under supervision as the best option for TB control.

In this study, a lower dropout rate for TB treatment was observed for the DOTS group (OR 0.68, 95% CI 0.56 to 0.83), confirming the findings of other studies that have shown reduced dropout treatment among patients with pulmonary TB and supervised therapy [36-38].

Treatment dropout is still one of the barriers to the effectiveness of TB treatment, especially in unsupervised patients [37]. Studies report the following risk factors associated with non-adherence in patients under supervised treatment: being of male gender, unaware of the importance of regular treatment, uses illicit drug, and of low economic status [36-38].

No significant difference in mortality was found when TB deaths between the two treatment groups (DOTS versus SAT) were analyzed (OR 0.82, 95% CI 0.64 to 1.05). However, the heterogeneity between studies was significant, possibly resulting from the inclusion of deaths from other causes in the calculation of mortality rates from TB.

A study in Taiwan [39], showed a reduction in all causes of mortality among patients with TB from 2006 to 2008, a period that corresponds to the increase of the DOTS regimen in Taiwan, and after controlling for confounding factors, the odds ratio of death among patients who received DOTS was 40% lower (OR 0.60, 95% CI 0.5 to 0.80) than for SAT. Bloss, et al. [40], contradicted the results of this systematic review when his 2012 study analyzed the risk of TB death during observed and unobserved treatment, and showed that in the unobserved group the risk of death increased significantly when compared to the observed group, OR 53.9, 95% CI 43.0-67.4 and OR 10.9, 95% CI 8.7-13.6 respectively. Again, these types of results are inconclusive since the inclusion of deaths from other causes entered in the calculation of mortality rates from TB, obscuring the picture, and preventing any definitive conclusion from being drawn.

We understand that DOTS is a relevant strategy for TB control, however, its relevance and effectiveness is

greatly diminished if not implemented in a government program as WHO originally intended. Investment becomes necessary to train health professionals involved in the supervision of treatment as well as from their training of thought about TB treatment. Clinic and hospital staff should use common sense when considering the dynamics of health services as well as patient style and quality of life to give good advice on the most appropriate treatment regimen. Furthermore, the technical and financial health care resources allotted to TB control, together with the effective participation of the community and patients, can make a difference regardless of the treatment regimen used.

Our results incite reflection about whether we should simply be focusing on the type of therapy to be adopted by those infected with *Mycobacterium TB* to obtain better cure rates and less abandonment and mortality. However, further studies are needed, controlling for these potential biases, to determine the best strategy to increase patient adherence to treatment and achieve the effective results promised by DOTS, as recommended by WHO.

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