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Review Article

Assessment of Directly Observed Therapy for Tuberculosis - A Systematic Literature Review

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Abstract

Background: The introduction of the DOTS strategy in tuberculosis programs around the world brought a great deal of improvement in the quality of patients' results. Before their implementation, patient monitoring was very deficient, and consequently the impact of the disease on the outcome indicators was weak.

Objective: the objective of this study was to conduct a systematic literature review to assess the impact of directly observed therapy for impact and outcome indicators for tuberculosis.

Method: systematic literature review of observational and experimental studies. We searched SciELO, Lilacs, Medline, Scopus, ScienceDirect, HINARI and Pubmed for documents published between 2007 and 2017, that reported on the impact of therapy directly observed for tuberculosis in relation of performance of the impact and outcome indicators.

Results: We retrieved 627 publications from the databases. After analysis of the titles, evaluation of abstracts and reading of the text, 16 studies were included in the final review. Seven studies reported a positive impact of DOTS on tuberculosis programs, specifically on improving cure rates, dropout rates, and adherence to treatment. One study showed that low compliance was associated with poor accessibility to health care and symptomatic improvement. Another study showed that the risk of failure in treatment outcome was relatively higher among rural than urban.

Conclusion: The implementation of the DOTS strategy must obey certain basic criteria, which include the preparation of the technical team as well as the political commitment, as some studies analyzed in this review revealed a negative impact of DOTS for programs that were not prepared for its implementation.

Keywords: *Tuberculosis; Treatment; Evaluation; Impact of DOTS Strategy*

Introduction

Tuberculosis (TB) is considered one of the oldest infectious diseases of mankind. Although possible to be treated and cured, it remains a major public health problem worldwide, due to the wide geographical dispersion, emergence of multiresistant cases and co-infection with HIV [1].

The World Health Organization (WHO) recognized, in 1991, that TB continued to be a public health problem as a result of poor administration of control programs and low government commitment, coupled with population growth. Nevertheless, some countries had resources for effective disease control. A new disease control strategy called DOTS (Direct Observed Treatment, Short-course) was then proposed. This strategy is to achieve 85% treatment success, 70% case detection, and reduce treatment abandonment in 5% [2,3].

This strategy is composed of five pillars namely: smear-case detection among respiratory symptomatic persons seeking general health services; standardized treatment of short duration, directly observable and monitored in its evolution; regular supply of drugs; registration and information system to ensure the assessment of treatment; commitment of government by putting TB control as a priority among health policies [4,5].

The introduction of the DOTS strategy in tuberculosis programs around the world brought a great deal of improvement in the quality of patients' results, because before their implementation, patient monitoring was very deficient, and consequently the impact of the disease on the rates incidence was weak [6,7]. The introduction and implementation of this strategy in TB programs alone is not enough, it needs to be accompanied by policies that promote patient compliance. Adherence to the strategy is fundamental. Non-adherence to treatment may lead to therapeutic failure until a progression from simple tuberculosis to multidrug-resistant [8,9]. According to WHO, at least 30% of all patients fail to adhere to treatment in the first two or three months.

The evaluation of the impact of the DOTS strategy on TB programs is extremely important because it allows the evaluation of the performance of tuberculosis programs, based on impact and outcome indicators [10,11]. Although its evaluation in terms of impact on the treatment of tuberculosis is regular because of the nature of the strategy, the results of this strategy are not always uniform and sometimes these results diverge when is compared between countries.

The most frequent evaluation of the strategy has been more focused on the monitoring of the implementation, on the magnitude of the expansion of its coverage, on the analysis of the outcome of the treatment or on the promotion of the qualitative analysis of specific components of the program [12-15].

In the present study we use a systematic literature review to describe the evidence on the impact of the DOTS strategy in the treatment of TB, in terms of performance of indicators of outcome and of impact (adherence of treatment, rates of incidence; prevalence; abandonment of treatment; mortality and proportion of cured and of contacts).

Methods

We conducted a systematic literature review including studies published between 2007 to 2017. This time horizon was chosen because it is considered to be the period in which many countries, already have solid and well-organized data on the DOTS strategy.

No ethical approval was required because it was a systematic literature review. Nor was the request for informed consent required, as it was a secondary data analysis and did not involve humans.

The inclusion criteria were observational or experimental studies, published in Portuguese, English or Spanish as original articles, and communications that focused on the impact of directly observed therapy for tuberculosis, specifically in adherence of treatment and in performance of indicators of outcome and of impact. We searched the databases SciELO (www.scielo.org), Lilacs (bases.bireme.br), Medline (www.ncbi.nlm.nih.gov/pubmed), Scopus (www.scopus.com), ScienceDirect (http://www.sciencedirect.com/science?), HINARI Research in Health (http://www.who.int/hinari/en/) and Google scholar. The search terms used in this systematic review were obtained through consultation with the Descriptors in Health Sciences (decs.bvs.br). In the bibliographic research, the combination of the descriptors used was: "avaliação da terapia diretamente observada para tuberculose" e "impacto" in Portuguese, "assessment of directly observed therapy for tuberculosis" and "impact" in English and "evaluación de la terapia directamente observada para la tuberculosis" y "impacto" in Spanish.

For assessment of eligibility of the publications found, two authors participated. Both assessed independently the abstracts, arriving at a consensus whenever there were discordant cases. After selecting the documents for full-text analysis, an electronic form, designed for the purpose of this review, was used to extract of the following informations: author, title, year of publication, objective, type of study, data collection instruments and main results.

Due to the heterogeneity of the studies included and results a qualitative synthesis of the results was done.

Results

A total of 627 publications were identified of which 571 were excluded after assessing titles and abstracts since they were not related with the theme of the systematic literature review. Of the 28 publications that addressed the theme of the systematic literature review, 16 met all inclusion criteria and were submitted to the data collection (Figure 1).

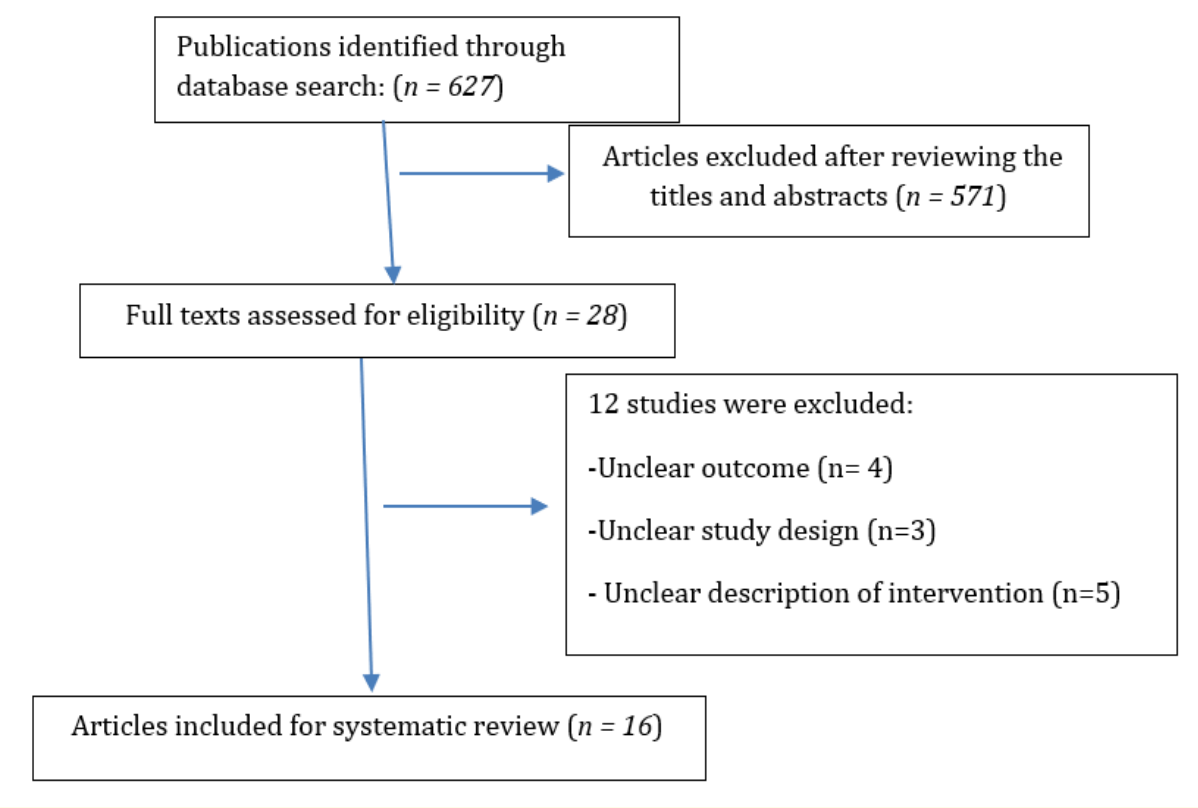

Figure 1: *Flowchart of selection of references.*

Table 1 shows the general characteristics of the studies included in the analysis. Of the 16 studies included, 6 were cross-sectional studies, 7 cohort studies, 1 case-control and 2 community trials.

Author	Title	Year of publication	Objectives
Cláudia Eli Gazetta., *et al.* [26]	[A descriptive study on the implementation of the short-term treatment strategy directly observed in the control of tuberculosis in São José do Rio Preto and its impacts (1998-2003)]	2007	To describe treatment outcomes (cure, noncompliance or death) after the implementation of the Directly Observed Treatment.
Sharma S., *et al.* [18]	The DOTS strategy for treatment of paediatric pulmonary tuberculosis in South Delhi, India	2008	To evaluate the outcome of the DOTS strategy for paediatric pulmonary tuberculosis
R Subramani., *et al.* [33]	Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South India	2008	To assess the epidemiological impact of the DOTS strategy on the prevalence of pulmonary tuberculosis
Hubert Barennes., *et al.* [22]	Survival and health status of patients in rural Lao PDR	2010	To assess the outcome of and compliance with directly observed treatment (DOTS) of TB patients over a 3 year period in rural Lao PDR
SC Cavalcante., *et al.* [34]	Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil	2010	To compare the impact of routine DOTS vs. enhanced DOTS (DOTS-Ampliado or DOTS-A) on tuberculosis (TB) incidence
Sean P Fitzwater., *et al*. [35]	Prolonged Infectiousness of Tuberculosis Patients in a Directly Observed Therapy Short-Course Program with Standardized Therapy	2010	To quantifies time to conversion from smear and culture positivity to negativity in unselected tuberculosis patients receiving standardized therapy in a directly observed therapy short-course (DOTS) program.
Lenilde Duarte de Sá., *et al*. [19]	[Implantation of the DOTS strategy in the control of Tuberculosis in Paraíba: between the political commitment and the involvement of the teams of the family health program (1999-2004)]	2011	To analyze the political commitment of the managers in the the DOTS strategy, from the point of view of the coordinators of Tuberculosis control program in the six priority municipalities from Paraíba.
Matsumoto K., *et al*. [17we analyzed the association between the performance of directly observed treatment short course (DOTS]	Evaluation of the effect of DOTS on treatment outcomes in patients with smear-positive pulmonary tuberculosis in Osaka City	2012	To analyze the association between the performance of directly observed treatment short course (DOTS) and treatment outcomes in patients with tuberculosis.

Adegoke AO and Orokotan OA [20"page":"952-959","volume":"6","issue":"12","source":"PubMed","abstract":"OBJECTIVE: To evaluate the success rate of tuberculosis intervention programme at a specialist hospital in Ibadan, Nigeria through a retrospective study as well as carry out physicochemical evaluation of anti-tuberculous agents as a way of eliminating drug-related failure.\nMETHODS: The retrospective study involved the use of quarterly tuberculosis central register at the Government Chest Hospital, Ibadan between 1st quarter (2003]	Evaluation of directly observed treatment short courses at a secondary health institution in Ibadan, Oyo State, Southwestern Nigeria.	2013	To evaluate the success rate of tuberculosis intervention programme at a specialist hospital in Ibadan, Nigeria
Charokopos., *et al*. [16]	Modified directly observed treatment for tuberculosis versus self-administered therapy: an observational study in rural Greece.	2013	To evaluate a modified DOT program (MDOT) by a general practitioner (GP) in a rural area of southwest Greece.
JY Chien., *et al*. [28]	Direct observation therapy with appropriate treatment regimens was associated with a decline in second-line drug-resistant tuberculosis in Taiwan	2014	To evaluate the associations between the appropriateness of treatment for tuberculosis (TB) and the directly observed treatment, short course (DOTS)/ DOTS-plus programs and their impact on the prevalence of SLD-resistant MTB.
Gebremedhin Gebrezgabiher., *et al*. [8]	Treatment Outcome of Tuberculosis Patients under Directly Observed Treatment Short Course and Factors Affecting Outcome in Southern Ethiopia: A Five-Year Retrospective Study	2016	To determine the treatment outcome of TB patients and investigate factors associated with unsuccessful outcome at Dilla University Referral Hospital, southern Ethiopia.
Mohammadzadeh KhA, Ghayoomi A and Maghsoudloo D [36]	Evaluation of factors associated with failure of tuberculosis treatment under DOTS in northern Islamic Republic of Iran.	2016	To identify the risk factors associated with failure of tuberculosis treatment under the DOTS strategy in two cities of Golestan province.

Tauseef Ahmad., *et al*. [37]	Treatment Outcome of Tuberculosis Patients Under Directly Observed Treatment Short Course and its Determinants in Shangla, Khyber. Pakhtunkhwa, Pakistan: A retrospective Study	2017	To determine treatment outcome and factors affecting treatment outcome of TB
Tanu Anand., *et al*. [29]	Decadal impact of Directly Observed Treatment Short course program on age and gender among New Infectious Tuberculosis cases in Delhi	2017	To assess the decadal impact of DOTS strategy on some epidemiological factors such as age and gender of new sputum positive (NSP) TB patients in Delhi.
Olusola Adedeji Adejumo., *et al*. [21]	Evaluation of outcomes of tuberculosis management in private for profit and private-not-for profit directly observed treatment short course facilities in Lagos State, Nigeria	2017	To compare the treatment outcomes of patients managed at private for profit (PFP) and private not for profit (PNFP) directly observed treatment short course (DOTS) facilities.
Type of study	**Data collection instruments**	**Main results**	
Cross-sectional [26]	Questionnaire	After the implementation of the DOTS strategy there was a decrease in dropout rates and case detection and an increase in cure and death rates. The increase in the number of deaths due to tuberculosis may have occurred due to three factors: the prevalence of the disease in individuals older than 50 years; tuberculosis/HIV co-infection and the presence of associated diseases.	
Cross-sectional [18]	Questionnaire	The cure rate was 92.4% (302/327) for new and 92% (80/87) for retreatment cases (chi(2)(1) = 0.02, P = 0.901), but the treatment completion rate was significantly higher for new cases (97%, 636/656) than retreatment cases (53.6%, 15/28) (chi(2)(1) = 100.8, P < 0.001). The overall success rate was 95.4% and 82.6% for new and retreatment cases, respectively (chi(2)(1) = 30.35, P < 0.001). Overall, the rates for default, failure and death in the study were respectively 3%, 1.9% and 1%.	
Community Essay [33]	Questionnaire	TB prevalence declined by about 50% in 5 years, from 609 to 311 per 100 000 population for culture-positive TB and from 326 to 169/100 000 for smear-positive TB. The annual rate of decline was 12.6% (95%CI 11.2–14.0) for culture-positive TB and 12.3% (95%CI 8.6–15.8) for smear-positive TB. The decline was similar at all ages and for both sexes.	
Retrospective Cohort 22[]	Interview script	The study enrolled 172 patients with tuberculosis, of which 26 (15.1%) died. Low compliance was associated with poor accessibility to health care (p = 0.01) and symptomatic improvement (p = 0.02). The survivors had a persistently weak state of health. They were underweight (54.7%) and still had clinical symptoms (53.5%), including dyspnoea (28.8%) and hemoptysis (9.5%).	
Community Essay [34]	Questionnaire	Among the contacts of DOTS-A communities, 26 (4%) had active TB diagnosed and treated, 429 (61.3%) were detected with infectious latent tuberculosis and 258 (60.1%) started preventive therapy. Incidence of tuberculosis increased by 5% in communities with routine DOTS and decreased by 10% in DOTS-A communities, for a 15% difference after 5 years (P = 0.04).	

Longitudinal cohort [35]	Questionnaire	The mean time of conversion of culture positivity to negativity was 38.5 days and was not affected by smear status. Patients with fully susceptible tuberculosis had a mean culture conversion time of 37 days; 10% remained positive cultures for up to 60 days.
Cross-sectional [19]	Interview script	Five of the six municipalities analyzed, achieved a cure rate of 90%. In the political dimension, there was a discontinuity of the coordinators of the tuberculosis control program, lack of preparation of the local staff, poor technical and administrative structure and insufficient laboratory network.
Retrospective Cohort [17]	Questionnaire	Four percent of the 377 patients who had partial DOTS failed treatment compared to 15.2% of the 33 patients who fulfilled DOTS, which meant a significant difference (P <0.01). The absence of a support partner in DOTS was considered a risk factor for discontinuation of treatment in 31 (56.4%) of the 55 patients who did not respond to treatment in 2009 and 2010.
Retrospective Cohort [20]	Questionnaire	A general cure rate of 80.24% was achieved over the 7 years, which is below the WHO recommended target of 85%. Cure rates were better in women than in men. Results of treatment failure were recorded as positive (1.51%); deaths (8.73%); (3.33%) and transferred (5.95%), although they were not statistically significant (P> 0.05). Failure rates in all categories were higher in males than in females (P> 0.05).
Control case [16]	Questionnaire	The implementation of modified DOTS revealed that 11 cases (84.6%) were successfully treated, one (7.7%) died and one (7.7%) was lost at follow-up. None of the contacts close to new cases of tuberculosis were infected with active TB.
Retrospective Cohort [28]	Questionnaire	There was a significant reduction (all values of p <0.01) in the prevalence of MTB isolates that were resistant to oral fluoroquinolones and injectables. The implementation of DOTS/DOTS-plus programs with appropriate regimens was associated with a decrease in the prevalence of resistance of second line and XDR drugs.
Retrospective Cohort [8]	Questionnaire	Of the total of the 1537 patients analyzed, 544 (35.4%) were positive samples and 816 (53.1%) were smear negative pulmonary and 177 (11.5%) were extra pulmonary tuberculosis samples. Of the 1537 patients, 181 (11.8%) were cured, 1129 (73.5%) completed the treatment, 171 (11.1%) abandoned, 52 (3.4%) died and 4 (0.3%) failed treatment. The risk of failure in treatment outcome was relatively higher among rural than urban patients (AOR = 1.63, 95% CI: 1.21-2.20).
Retrospective Cohort [36]	Questionnaire	The multivariate regression analysis found that the strongest predictors of tuberculosis treatment failure were: being infected with other diseases (OR 9.35, 95% CI: 3.01-29.1), male (OR 5.03 , 95% CI: 1.58-16.1), Turkmen ethnicity (OR 11.0, 95% CI: 2.00-60.1), family history of tuberculosis (OR 0.21, 95% CI: 0 , 05-0.96) and household size (OR 1.21, 95% CI: 0.99-1.48).
Cross-sectional [37]	Questionnaire	There was a high rate of treatment success. The DOTS strategy is not effective, as there is no effective management and diagnosis of cases of extrapulmonary tuberculosis.

Cross-sectional [29]	Questionnaire	The case detection rate has shown a considerable increase from 196/100,000 population in 2001 to 306/100,000 population at the end of Quarter 3 of 2011. The number of NSP male and female patients have increased in all age groups from 2001 to 2011 except in 25–34 years age group. NSP male patients on DOTS aged 15–44 years showed a left ward shift in increase, a significant right ward shift was noted in increase in female NSP patients of similar age group.
Cross-sectional [21]	Questionnaire	The treatment success rate was higher among patients who were privately administered (PFP) (89.4%) with DOTS than those privately administered non-profit (PNFP) (81.3%) also with DOTS (P = 0.04). The privately administered patients were 4 times more likely to be cured than those privately administered non-profit (p = 0.05), controlling for other variables.

Table 1: *General characteristics of the analyzed studies.*

As for data collection instruments, 12 studies used questionnaires, 2 used interview scripts and 2 studies used questionnaires and interview scripts. The majority of the studies (n = 14) were published in English and 2 in Portuguese. Three studies were carried out in Brazil, three in India, two in Nigeria, one in Vientiane, one in Peru, one in Japan, one in Greece, one in Taiwan, one in Ethiopia, one in Iran and one in Pakistan.

Regarding the main results found in the studies analyzed, the cure rate showed considerable improvements (above 80%) after implementation of the strategy, in the various studies conducted in Greece, Japan, India, Brazil and Nigeria [16-21]. In relation to the abandonment rate, a cohort and a cross-sectional study carried out in Ethiopia and Greece, found a considerable reduction of dropout rate of 11.1% and 7.7%, respectively, following the implementation of the strategy [8,16]. Two cohort and one cross-sectional studies conducted in Ethiopia, Japan, and Greece, showed that the mortality rate declined from 3.4 to 8.73% after implementation of the strategy [8,16,17]. Treatment failure also reduced, between 3 to 4% in studies conducted in Ethiopia, Japan, and Nigeria [8,17,20]. A study showed that service performance is influenced by availability of human/material resources, internal organization of services, absence of the patient at home, socio-cultural and economic context of the patient [14] while another study showed that low compliance was associated with poor accessibility to health care and improvement in the symptoms presented by the patients [22]. One study showed that the risk of failure in treatment outcome was relatively higher among rural than urban patients [8], although other authors have found that residing in the countryside, having tuberculosis symptoms, and having support in treatment were associated with DOTS satisfaction [23].

Discussion

The World Health Organization (WHO) and the International Union against TB and Lung Disease (IUATLD) promote universal adoption of Directly Observed Treatment, Short-Course (DOTS) for TB treatment as a means to improve TB treatment outcomes [24].

In the majority of the studies included in this systematic literature review, the cure rate increased considerably, after the implementation of DOTS which seems to underline the relevance of implementing the strategy in targeted population.

At the same time, dropout rates, mortality and treatment failure also seems to decrease after adoption of the strategy. In view of these results, it is important to consider that the implementation of the DOTS strategy in TB control programs, generally adds value to the improvement of tuberculosis program indicators, especially in developing countries where the consequences of this disease are most severe [25-27].

Several studies have shown that TB control programs implemented the DOTS strategy have considerably improved their indicators. It is believed that this is linked to the fact that, with this strategy, it is possible to better and more efficiently monitor the patient at all stages of treatment, either in the health unit or in its community [8,17,28-30]

For a successful implementation of the strategy and good performance of the program, it is necessary to train technical and administrative teams [20,31]. This became evident in a case study carried out in Rio de Janeiro in which compliance with DOTS actions were compared between two health units. It was described that health professionals' engagement with the strategy was dependent on their daily routine activities which points out that not every health professional is suitable to do DOTS [32]. Unpreparedness associated with turnover of program managers and a weak political commitment may negatively influence DOTS strategy [19]. On the other hand, the integration of DOTS strategy into TB control programs, especially in developing country, where resources are scarce and patients often face socio-economic hardship, has shown to improve the results [14].

The success in treatment depends greatly on patients' uninterrupted treatment adherence. DOTS has been seen as one of the best strategies to ensure adherence to treatment by patients, but in many countries the absence of donors that guarantee the effective functioning of the strategy may result in an increase in the drop-out rates for TB treatment. A study conducted in Osaka City, where the effect of DOTS on treatment outcomes was evaluated in patients with smear-positive pulmonary TB, showed that the absence of a DOTS supporting partner was a risk factor for dropping out of treatment in the majority of the patients who did not respond to treatment in 2009 and 2010 [17]. This fact once again reinforces the need to maximize scarce resources, as well as to strengthen collaborative activities with other entities working on the health focus, especially in developing countries.

Socio-economic factors, access to health services and place of residence can influence the performance of DOTS programs. Individuals with low income have few options for accessing health services. People in rural areas have less access to health facilities, particularly in developing countries. This was demonstrated in a study in Ethiopia that examined the outcome of treatment of tuberculosis patients under DOTS supervision and factors associated with treatment failure, in which the authors found a relatively greater risk of failure in treatment outcomes in patients living in rural areas than urban [8].

Conclusion

Most of the studies included in this systematic review were cross-sectional and cohort, and used mostly questionnaires and interview scripts as data collection instruments.

Integration of DOTS strategy in TB control programs was a positive milestone, as it brought an improvement in the performance and outcome indicators of TB programs.

The implementation of the strategy must obey certain basic criteria, which include training of the technical team as well as the political commitment, as some studies in the review revealed a negative impact of DOTS on programs that were not prepared for its implementation. The regular assessment of the impact of the DOTS strategy is extremely important as it allows to identify possible gaps in the system that may interfere with poor health service performance.

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