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REVISÃO
REVIEW

Effects of social protection on tuberculosis treatment outcomes in low or middle-income and in high-burden countries: systematic review and meta-analysis

Efeitos da proteção social sobre os desfechos do tratamento da tuberculose em países de renda baixa e média ou de carga alta da doença: uma revisão sistemática e meta-análise

Efectos de la protección social en los resultados del tratamiento contra la tuberculosis en países con baja o media renta y gravemente afectados: revisión sistemática y metaanálisis

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Abstract

Tuberculosis (TB) is a poverty infectious disease that affects millions of people worldwide. Evidences suggest that social protection strategies (SPS) can improve TB treatment outcomes. This study aimed to synthesize such evidences through systematic literature review and meta-analysis. We searched for studies conducted in low- or middle-income and in high TB-burden countries, published during 1995-2016. The review was performed by searching PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and LILACS. We included only studies that investigated the effects of SPS on TB treatment outcomes. We retained 25 studies for qualitative synthesis. Meta-analyses were performed with 9 randomized controlled trials, including a total of 1,687 participants. Pooled results showed that SPS was associated with TB treatment success (RR = 1.09; 95%CI: 1.03-1.14), cure of TB patients (RR = 1.11; 95%CI: 1.01-1.22) and with reduction in risk of TB treatment default (RR = 0.63; 95%CI: 0.45-0.89). We did not detect effects of SPS on the outcomes treatment failure and death. These findings revealed that SPS might improve TB treatment outcomes in lower-middle-income economies or countries with high burden of this disease. However, the overall quality of evidences regarding these effect estimates is low and further well-conducted randomized studies are needed.

Tuberculosis; Treatment Outcome; Social Welfare; Public Policy

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Introduction

Tuberculosis (TB) is still considered a major global health problem, mainly in socially vulnerable population groups living in low- and middle-income countries [1]. In 2015, 10.4 million new cases and 1.4 million deaths because of TB were estimated worldwide [2]. According to the United Nations Sustainable Development Goals (2016-2030), the World Health Organization (WHO) set a 2030 target of 90% reduction in deaths, 80% decline in TB incidence and zero TB-affected families facing catastrophic costs because of this disease [3,4,5].

Poverty is one of the most important determinants of TB and accounts for almost one third of the global burden of diseases. Besides being a poverty related illness, TB also worsens this social condition. In low-income countries, approximately 17% of TB-deaths affect the economically productive age group of 15-49 years [6]. In those countries, investments in prevention, diagnostics and treatment should consider social protection and urban planning interventions in order to improve access to TB care and treatment adherence [7,8].

Social protection strategies (SPS) enable individuals and households to protect and build their capital assets, leading them to move structurally out of poverty [7,8,9]. Their main components are social and income security, cash transfer programs, food provision, transport incentives, unemployment insurance, education, microcredit and income generation policies, as well as psychosocial support, protection against stigma/discrimination and public health systems with universal coverage, which are also included in the field of social protection [1,10,11].

Universal health coverage and social protection account for reduction of income losses and costs incurred by TB patients, leading to positive impacts on the reduction of this disease burden, measured by incidence, prevalence and mortality rates [1,2]. For these reasons, bold policies and supportive systems are among the most important pillars of the post-2015 global tuberculosis strategy [3,5].

In this context, the aim of this systematic review was to identify and assess evidences of social protection effects on TB treatment outcomes in low- and middle-income countries or in high TB-burden countries.

Methods

Following the reporting guidelines recommended in PRISMA statement [12], we conducted a systematic review to identify studies that have investigated the effects of SPS on TB treatment outcomes. The review protocol was registered in PROSPERO international database on September 17, 2015 (registration number CRD42015026305).

Eligibility criteria

Eligibility of studies followed predetermined inclusion criteria. We included interventional (randomized controlled trials — RCTs and studies with quasi-experimental design) and observational studies covering the period from 1995 to May 31st, 2016. All included studies were developed in low- and middle-income countries, according to World Bank income classification [13] or in one of the 30 high TB-burden countries listed by WHO [2].

We defined individuals under TB treatment as population of reviewed studies. The interventions of interest were SPS. Controls should be individuals under usual TB care. Primary outcome was TB treatment success rate (TSR), expressed by the proportion of all new cases that successfully completed treatment, with or without bacteriological evidences of cure [14].

Secondary outcomes were: (a) cure rate, i.e. proportion of TB cases with a negative sputum smear result recorded during the last month of treatment and in at least one previous occasion during treatment; (b) default rate, i.e. proportion of TB cases that interrupted treatment for two consecutive months or more; (c) treatment failure rate, i.e. proportion of TB cases with smear positive results five months or later after initiating treatment; (d) death rate, i.e. the proportion of TB cases that died during treatment, irrespective of cause. All these outcomes should meet WHO international definitions [14].

Search strategy

We searched the electronic databases PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and LILACS, without language restriction. The search terms were defined according to Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS). Search strategy applied the terms: social protection, public policy, social welfare, income, food assistance, food supply, transportation, reimbursement, financial support, government financing, social work, social security, public assistance, motivation. We used the operator "OR" to connect synonyms and the operator "AND" to combine them with the term *tuberculosis*. We applied filters to humans and publication dates. The searches occurred in October 2015 and were rerun in May 2016.

We hand searched in clinical trials registries (Clinical Trials.gov and Brazilian Clinical Trials Registry – ReBEC). Google Scholar was also screened in order to access grey literature (e.g. non-indexed journals, official documents, government reports), abstracts published in annals of scientific meetings, theses and dissertations digital libraries. The full search strategy is available in the supplemental material – cf. Appendix 1: https://www.4shared.com/web/preview/pdf/B-Gv6byoca.

One reviewer (K.V.F.A.) conducted the literature search based on the strategy developed by all the review team. Then, two reviewers (K.V.F.A., R.A.S.) independently examined titles and abstracts. Cohen's Kappa coefficient (k) was used as a measure of inter-rater agreement. Disagreements were resolved by consensus or by consulting a third reviewer (S.M.P.) to adjudicate.

We extracted and summarized data from the fully reviewed studies using a form to list study characteristics, including: author, publication year, study design and location, criteria for inclusion and exclusion of participants, randomization approach (if applicable), description of interventions, and TB treatment outcomes.

Quality assessment

We adapted Downs & Black [15] checklist to assess the methodological quality of non-randomized studies (NRS). The original version of this tool contains 27 items that assess internal (bias and confounding) and external validity (sample representativeness). Two reviewers (K.V.F.A., J.S.N.) performed the quality assessment applying 21 "yes"-or-"no" questions (using the scores 1 for yes and 0 for no) and another one with three answer options in order to check the description of confounding in each study, with these answer options: described (2 points), partially described (1 point) or not described (0 points). The total maximum score was 23.

The reviewers excluded five questions of the original version [15] for considering them inadequate or not applicable for our quality assessment. These questions addressed the following features: reporting of random variability estimates in the data for the main outcome, reporting of adverse events associated with study interventions, presence of unplanned analyses, adequacy of statistical tests and study power. Some of these excluded questions have limitations in their answer options. The scores profile provided a summary of methodological strengths and weakness of each study. However, we did not exclude studies based on it.

We performed a specific quality assessment for RCTs using *The Cochrane Risk of Bias Tool* [16]. In addition, quality of evidence across studies was evaluated with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [17] approach. *GRADEpro Guideline Development Tool* (GDT) [18] was used to visualize evidences profile and generate the summary of findings (SoF) table.

Data analysis

All studies retained for systematic review were described in qualitative synthesis. Only RCTs were submitted to meta-analysis. TB treatment outcomes were analyzed using risk ratios (RR) and their 95% confidence intervals (95%CI), recalculated from the data provided by RCTs, using the Mantel-Haenszel method. Meta-analyses were performed according to each outcome. Data from cluster-RCTs were adjusted based on the intracluster (or intraclass) correlation coefficient (ICC) provided by these studies [16].

To conduct these meta-analyses, a random effects model was fitted. This choice was based on the diversity of interventions and studies characteristics (e.g. participants and methods). The I^2 statistic was used to quantify the heterogeneity, categorized as not important (I^2 value between 0-40%), moderate (I^2 value between 30-60%), substantial (I^2 value between 50-90%) and considerable (I^2 value of 75% or more) [16]. Visual inspection of funnel plots contributed to assess the likely presence of publication bias. Meta-analyses were developed in the software Review Manager (RevMan; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) version 5.3.

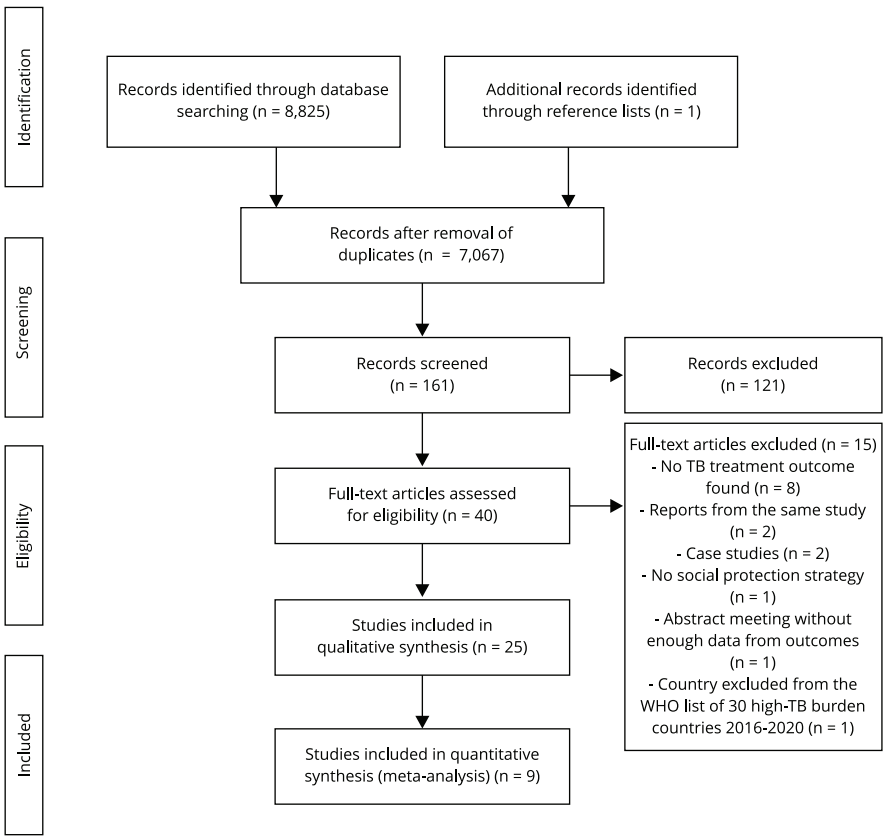
Results

In total, we identified 8,825 articles. After removal of 1,758 duplicates, two reviewers (K.V.F.A., R.A.S.), working independently, screened 7,067 titles with k = 0.1907. Subsequently, 161 abstracts of the selected titles were independently screened by the same reviewers (with k = 0.4385), retaining 40 articles for full-text review.

In hand searches, the reviewers did not find eligible articles. One additional article was added from the reference lists examined in the full-text review. Finally, 25 articles were retained for qualitative synthesis and nine RCTs for meta-analysis (Figure 1).

Figure 1

PRISMA flow diagram for systematic review and meta-analysis.



WHO: World Health Organization.

Description of studies included in qualitative synthesis (n = 25)

Nineteen studies were conducted in middle-income countries (13 in upper-middle and six in lower-middle). Four studies were developed in three low-income countries: Ethiopia [19,20], Malawi [21] and Nepal [22]. Two studies [23,24] were developed in Russia, which is not in low- and middle-income categories, but it is listed between the high TB-burden countries [2].

Seventeen studies were performed in high TB-burden countries. The other studies (n = 8) occurred in countries out of this category, but referred to as low-income: Malawi [21] and Nepal [22] or middle-income countries: Ecuador [25], Mexico [26], Republic of Moldova [27], Peru [28], Swaziland [29] and Timor-Leste [30].

Quasi-experimental designs (n = 11) accounted for most of the reviewed studies, followed by RCTs (n = 9) and observational studies (n = 5). Seventeen studies (among then eight RCTs) presented evidences on effects of non-financial interventions for TB patients (lay community health workers or social workers [19,28,31,32,33,34,35], food assistance [23,27,28,30,36,37], counselling [22], "TB clubs" [20], training programs [26], social franchising [38], socio-educational approaches [21]).

Twelve studies presented patient or treatment supporters directed financial interventions (among then seven quasi-experimental studies), including monetary incentives [22,24,25,27,28,29,35,39,40,41], a conditional cash transfer program [42] and economic support by voucher delivery [43]. Some studies [22,27,28,35] combined financial and non-financial interventions.

Sixteen studies were prospective with primary data collection and nine studies used secondary data sources. Seventeen studies did not include TB vulnerable populations. Eleven studies only included individuals with pulmonary TB and eight did not restrict TB clinical forms. See Table 1 for details of this section.

Description of TB treatment outcomes

- **Treatment success rates (TSR)**

Twenty-two controlled studies showed TSR for TB patients. In quasi-experimental studies (n = 10), TSR ranged from 69.3 to 96.9% in intervention groups and from 31.1 to 96.9% in controls. In RCTs (n = 9), TSR ranged from 70 to 97.7% in intervention groups and from 57.5 to 84.1% in controls. In observational studies (n = 3), TSR ranged from 68.7 to 95.8% in individuals exposed to social protection and from 46.9 to 92.9% in non-exposed individuals. The largest difference in TSR between study groups (47%) was found in a quasi-experimental study conducted in Saint Petersburg, Russian Federation [23].

Few studies did not show effects of SPS on TB treatment outcomes. In a RCT conducted in Dili, Timor-Leste [30] food incentives did not significantly improve these outcomes. A study [40] that assessed effects of transportation incentives in China did not detect differences in TSR. Pragmatic RCT developed in South Africa [43] showed a small but non-significant improvement in TSR after providing economic support to TB patients.

- **Cure rates (CR)**

CR of TB patients were presented by 13 studies. In RCTs (n = 8) intervention groups achieved higher CR (ranging from 26.7 to 97.7%) than in controls (ranging from 10 to 81.4%). In quasi-experimental studies (n = 4) intervention groups also achieved higher CR (ranging from 11.8 to 82.4%) than in controls (ranging from 0 to 74.8%). Among observational studies, only one presented CR (equals to 82.1% in exposed and 76.9% in non-exposed individuals).

- **Treatment default rates**

Twenty studies presented default rates for TB treatment. Quasi-experimental studies (n = 10) showed proportions of default in intervention groups ranging from 0.2-21.8% and in controls from 0.1-68.9%. In RCTs (n = 7) proportions of default in individuals exposed to social protection ranged from

Table 1

Summary of all reviewed studies.

Study/ Country	Income/TB-burden	n	Study location	Study design (score) *	Population and study period	Intervention	Main outcome
Baral et al. [22]/ Nepal	Low-income	I_1: 33 I_2: 42 C: 81	7 DOTS-plus centers	Mixed-method (intervention and qualitative)	MDR-TB patients (Jan-Dec 2008)	I_1: counselling. I_2: counselling and financial support	Cure (I_1: 85%; I_2: 76%; C: 67%)
Cantalice Filho [37]/Brazil	Upper middle-income High TB-burden	142 (I: 74, C: 68)	Primary care clinics in Duque de Caxias, Rio de Janeiro State	Retrospective comparative study (7 points)	≥ 15 years old with confirmed TB diagnosis (Jan 2004-Jul 2006)	Monthly food baskets delivered in the healthcare clinic	Cure (I: 87.1%; C: 69.7%)
Ciobanu et al. [27]/Republic of Moldova	Lower middle-income	4,870 (I: 2378, C: 2492)	National data, before (2008) and after (2011) incentives	Retrospective cohort study (14 points)	≥ 18 years old, TB patients treated in 2008 and in 2011	Cash, non-cash or both incentives. (I: groups that received cash)	TSR (I: 88%; C: 79%; p < 0.001)
Clarke et al. [31]/South Africa	Upper middle-income High TB-burden	89 (I: 47, C: 42)	211 farms (I: 106; C: 105)	Cluster randomized controlled trial	Permanent farm dwellers ≥ 15 years old treated (from Nov 1, 2000 to Oct 31, 2001)	Adult farm dwellers trained as lay health workers	TSR (I: 83%; C: 64.3%; p = 0.042)
Datiko & Lindtjørn [19]/ Ethiopia	Low-income High TB-burden	318 (I: 230, C: 88)	51 kebeles in two rural districts of Southern Ethiopia	Community-randomized trial	All new smear-positive pulmonary TB cases	Trained community health workers	TSR (I: 89.3%; C: 81.3%; p = 0.012)
Demissie et al. [20]/Ethiopia	Low-income High TB-burden	128 (I: 64, C: 64)	2 rural districts of Northern Ethiopia	Mixed-method – cohort and qualitative (12 points)	Smear-positive TB patients (from July 1 to Oct 15, 1998)	TB patients in rural kebeles organized in "TB clubs"	TCR (I: 68.7%; C: 46.8%; p = 0.02)
Gärden et al. [23]/Russia	High-income High TB-burden	518 (I: 142, C: 376)	St. Petersburg's TB dispensary	Historical controlled intervention study (11 points)	Homeless patients referred to TB dispensary (from Dec 2001 to Jan 2004)	Food packages delivered once a day 5 days a week and support from a social worker	TSR (I: 78.2%; C: 31.0%)
Jakubowiak et al. [24]/Russia	High-income High TB-burden	1,389 (I: 382, C: 1,007)	4 regions with TB services	Cross-sectional study (5 points)	New pulmonary TB patients ≥ 15 years old treated (from Jan 1, 2004 to Mar 31, 2005)	Social support during TB treatment (food packs, hygiene kits, transportation incentives, etc.)	28.1% of adherents and 18.4% of non-adherents with incentives
Kliner et al. [29]/ Swaziland	Lower middle-income	1,077 (I: 161, C: 916)	Hospital in a rural district	Pragmatic controlled interventional study (12 points)	TB patients (Jan 2010-Sep 2011)	Treatment support from community workers	TSR (I: 73% vs. C: 60%; p = 0.003)

(continues)

Table 1 (continued)

Study/ Country	Income/TB-burden	n	Study location	Study design (score) *	Population and study period	Intervention	Main outcome
Lönnroth et al. [38]/ Myanmar	Lower middle-income High TB-burden	253 (non-controlled)	National case notification data and survey in clinics in Yangon	Cross-sectional study (10 points)	All patients treated in Sun Quality Health (SQH) clinics in Yangon (from Sep 1 to Oct 30 2004)	Sun Quality Health (SQH), a social franchise that licensed practitioners with clinics serving low-income people	TSR for new smear-positive cases was 84%
Lutge et al. [43]/ South Africa	Upper middle-income High TB-burden	4,091 (I: 2,107, C: 1,984)	20 public sector clinics in Kwazulu-Natal	Cluster-randomized controlled trial	TB patients within (July 1, 2009 to Mar 31, 2010)	Monthly vouchers (US$ 15) redeemable at specific general stores	TSR (I: 76.2% vs. C: 70.7%; p = 0.107)
Martins et al. [30]/Timor-Leste	Lower-middle income	265 (I: 136, C: 129)	3 primary clinics in Dili: government, private and church operated)	Randomized controlled trial	TB patients aged ≥ 18 and that agree to treatment at diagnostic clinic for eight months	Daily meal in attendance to the clinic and unprepared food to take home, in continuation phase	TSR (I: 76% vs. C: 78%; p = 0.7)
Ngamvithaya-pong-Yanai et al. [35]/Thailand	Upper middle-income High TB-burden	759 (I: 192, C: 567)	Chiang Rai, Thailand's northern province	Intervention study – before and after (7 points)	Extremely poor TB patients, living alone, with elderly caregivers or isolated from community	Engagement of Chiang Rai women's organization to support them financially and socially	TSR (I: 69.3% vs. C: 51.6%; p < 0.00)
Ritchie et al. [21]/Malawi	Low-income	110 (I: 30, C: 80)	28 health centers in Zomba district	Cluster randomized controlled trial	All lay health workers involved in providing care to TB patients	Two knowledge translation interventions: educational outreach and reminders	TSR (I: 70% vs. C: 58%; p = 0.578)
Rocha et al. [28]/Peru	Upper middle-income	1,861 (I: 307, C: 1,554)	Eight contiguous slums in Northern Lima	Intervention study (4 points)	Subsequently diagnosed TB patients and their household contacts (Dec 2007-Oct 2010)	Household visits, counselling, food and cash transfers, microenterprise, microcredits and training	TSR (91% before vs. 97% after intervention)
Singh et al. [32]/India	Lower middle-income High TB-burden	617 (I:1 41, C: 476)	One tuberculosis unit covering a population of 600,000 in Haryana State	Intervention study (10 points)	New sputum smear-positive patients registered in the tuberculosis unit for treatment	Directly Observed Treatment (DOT) from community volunteers vs. government health workers	TSR (I: 78% vs. C: 77%)

(continues)

Table 1 (continued)

Study/ Country	Income/TB-burden	n	Study location	Study design (score) *	Population and study period	Intervention	Main outcome
Soares et al. [33]/Brazil	Upper middle-income High TB-burden	2,623 (I: 1,771, C: 852)	Rocinha Favela, the largest urban slum in South America	Intervention study (before and after) (13 points)	All patients with pulmonary or extra-pulmonary TB who started treatment between 2001 and 2008	DOT implementation and training 40 lay persons as community health workers	TSR (83.2% vs. 67.6%; $p < 0.001$) pre- and post-intervention
Sripad et al. [25]/ Ecuador	Upper middle-income	191 (I: 105, C: 86)	Ecuador's NTP	Non-randomized trial with historical controls (8 points)	Drug-resistant (DR-TB) patients (from Aug 2011 to Jan 2012 – intervention and from Jan to Aug 2010 – pre-program)	Ecuador's NTP enacted a monetary incentive program giving adherent DR-TB patients a USD 240 bonus each month	1-year default rate (9.5% vs. 26.7%; $p < 0.05$), in program and pre-program
Sudarsanam et al. [36]/India	Lower middle-income High TB-burden	97 (I: 48, C: 49)	One of four clinics in Vellore town, southern Indian state of Tamil Nadu	Randomized controlled trial	Patients aged > 12 years diagnosed with TB (recruited between Jan and Nov 2005)	Macronutrient supplement (cereal and lentil mixture) and micronutrients (one-a-day multivitamin table)	Higher poor outcomes in the non-supplemented HIV-TB co-infected group
Torrens et al. [42]/Brazil	Upper middle-income High TB-burden	7,255 (I: 5,788, C: 1,467)	Brazilian national databases (SINAN and CadÚnico)	Retrospective cohort (14 points)	All new TB cases diagnosed in 2010, recorded in SINAN database and registered in CadÚnico	Brazilian national conditional cash transfer (Brazilian Income Transfer Program)	Cure rates (I: 82.1% vs. C: 76.9%; $p < 0.001$)
Wei et al. [39]/ China	Upper middle-income High TB-burden	183 (I: 90, C: 93)	2 districts of Shanghai (1 intervention/1 control)	Controlled intervention study – before and after (8 points)	Poor migrants TB patients	Financial incentives to poor migrant TB patients (transportation and living subsidies)	TCR (I: from 78% to 89%; and C: from 73% to 76%; $p = 0.03$)
Yao et al. [40]/ China	Upper middle-income High TB-burden	9,194 (I: 5,449, C: 3,745)	Fifty poor counties of Shanxi (Fidelis project) and 51 control counties	Pilot evaluation study (8 points)	New TB cases in baseline (Jan-Sep 2004) and during the intervention (Jan-Sep 2005) using routine TB reporting data	Financial incentives for doctors. Incentives to village leaders for community health education	TSR baseline (I: 95.3 vs. C: 93.9%; $p < 0.01$); project (I: 96.9 vs. C: 96.9%; $p > 0.05$)

(continues)

Table 1 (continued)

Study/ Country	Income/TB-burden	n	Study location	Study design (score) *	Population and study period	Intervention	Main outcome
Zou et al. [41]/ China	Upper middle-income High TB-burden	356 (I: 263, C: 93)	Three districts located in Shanghai: (i) Communi cable Disease Research Consortium (COMDIS), (ii) The Global Fund Project, (iii) control	Intervention study (case study) – before and after (8 points)	Poor migrants TB patients living in Shanghai, China, targeted by two projects involving financial incentives (introduced in Oct 2007)	COMDIS: single living and transportation subsidies Global Fund Project: living and, transportation incentives, plus incentives to clinic staff for each extended working hour	TCR District I (78 vs. 89%); District II (73 vs. 88%); Control (73 vs. 76%).
Zwarenstein et al. [34]/South Africa	Upper middle-income High TB-burden	98 (I: 54, C: 44)	Four clinics in Elsies River, suburb (20km from Cape Town)	Randomized controlled trial	Adult (aged > 15 years) pulmonary TB patients, who started TB treatment (new and retreatment)	Supervision by volunteers lay health workers in a poor community/ Supervision by clinic nurse/Self-supervision	% of success: lay health workers (74%), clinic DOT (57%) and self-supervision (59%)
Álvarez Gordillo et al. [26]/Mexico	Upper middle-income	87 (I: 44, C: 43)	Health centers in Chiapas	Controlled intervention study	> 15 years old with sputum smear-positive pulmonary TB (Feb 2001-Jan 2002)	Training program for health professionals and self-help groups for TB patients	TSR (I: 97.7%; C: 81.4%)

C: control group; CadÚnico: Unified Registry for Social Programmes; I: intervention group; NTP: National Tuberculosis Programme; SINAN: Notifiable Diseases Information System; TCR: treatment completion rates; TSR: treatment success rates.

* Quality scores with Downs & Black [15] tool, except for randomized controlled trials – RCTs (in this review, we arbitrarily established that scores < 9 indicates bad quality evidences and ≥ 9 indicates good quality evidences).

2.3-14.8% and from 4.6-26.2% in controls. Observational studies (n = 3) showed lower default rates in exposed (4.2-12.5%) than in non-exposed to SPS (7.0-40.6%).

- **Treatment failure rates**

Twelve studies showed treatment failure rates. In RCTs (n = 6), they ranged from 0-8.5% in intervention groups and 0-9.5% in controls. In quasi-experimental studies (n = 4), rates ranged from 0-5.6% in intervention groups and 0.1-1% in controls. Observational studies (n = 2) showed failure rates ranging from 0-2.1% in intervention groups and 0-9.5% in controls.

- **Death rates**

Twenty studies showed death rates of TB patients. Among them, quasi-experimental (n = 10), with values ranging from 0.2-21.8% in intervention groups and 0.1-68.9% in controls; RCTs (n = 7) with values ranging from 2.3-14.8% in intervention groups and 4.6-26.2% in controls. Finally, observational studies (n = 3) showed death rates ranging from 4.2-12.5% in intervention groups and 7-40.6% in controls.

- **Quality assessment results**

The quality assessment with Downs & Black checklist [15] showed a median score equal to 9 (with interquartile range from 7-12). The lowest score was four and the highest was 14. Studies with the best quality evidences (n = 8) obtained scores greater than 9 (Table 1). The most important limitations of these studies were: lack of blinding of participants and study team, lack of information about follow-up lengths, and regarding the participants' compliance with study interventions. Lack of sample representativeness was also a common limitation in the studies.

- **Risk of bias assessment for RCTs**

Regarding randomization approach, all RCTs presented low risk of bias for random sequence generation and most of them (five studies) described an adequate allocation concealment. However, all RCTs were associated with high or unclear risk of bias due to lack of blinding of participants and study team. Outcome assessors were blinded in only one study. Incomplete outcome data and selective reporting did not account for relevant bias. Other sources of bias were associated with baseline imbalances, possibility of contamination across groups, low protocol fidelity and inadequate sample sizes (Figure 2).

According to GRADE approach [17], evidences from most TB treatment outcomes presented serious limitations because of study design and execution (risk of bias). Only the outcome cure was downgraded once by inconsistency, which was classified as "serious" because of a high unexplained heterogeneity observation across studies (Table 2). Indirectness of evidences was observed for all outcomes. We downgraded evidences in one level by indirectness for both primary and secondary outcomes because of the diversity of interventions comprehended in the field of social protection and specific characteristics of participants in some studies (restricted to individuals with multidrug-resistant TB, participants with TB and HIV-TB coinfection, and homeless patients). Finally, imprecision did not account for serious limitations in the reviewed RCTs (Table 2).

Risk of bias assessment and visual inspection of funnel plots did not suggest the presence of selective reporting (publication bias). In addition, under the GRADE approach [17], the overall quality of evidences for effects of SPS on TB treatment outcomes was rated as low, except the evidences for cure (rated as very low quality).

Meta-analysis

The total number of participants in the RCTs included in meta-analysis (n = 9) was 1,687. These studies were conducted in seven countries, among them: South Africa [29,30,31], Ethiopia, India, Malawi, Mexico, Nepal and Timor-Leste. We separately performed meta-analyses according to each TB treatment outcome.

- **Primary outcome**

Pooled results of nine RCTs showed a significant association between SPS and TB treatment success (RR = 1.09; 95%CI: 1.03-1.14). Heterogeneity was not important among these studies (I^2 = 0%; p = 0.48) (Figure 3a).

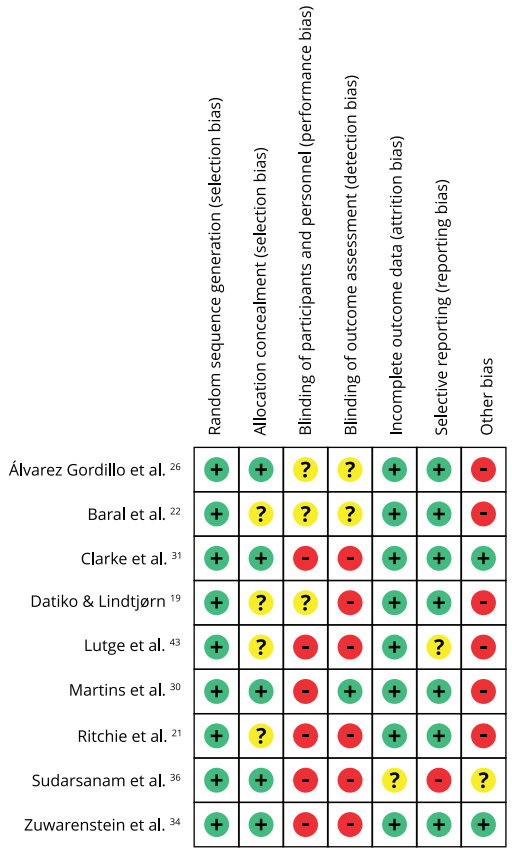
- **Secondary outcomes**

In total, eight RCTs provided evidences for the cure of TB patients. A significant association between SPS and cure was found (RR = 1.11; 95%CI: 1.01-1.22). Additionally, substantial heterogeneity studies were not important (I^2 = 23%; p = 0.25) as observed in Figure 3b.

Seven RCTs provided data regarding treatment default. A significant reduction in default was associated with SPS (RR = 0.63; 95%CI: 0.45-0.89), without evidences of important heterogeneity among studies (I^2 = 0%, p = 0.67) (Figure 3c). Pooled RCTs also did not show an overall protective

Figure 2

Risk of bias in randomized controlled trials summary.



effect between SPS and treatment failure (RR = 0.78; 95%CI: 0.44-1.40), without evidences of heterogeneity (I^2 = 0%, p = 0.52) (Figure 3d).

Finally, overall risk ratio obtained from six RCTs showed that SPS was also not associated with TB death rates (RR = 0.98; 95%CI: 0.61-1.57). Heterogeneity was also not detected among these studies (I^2 = 0%, p = 0.87) (Figure 3e).

Discussion

This is the first systematic review focused on studies conducted in low and middle-income countries and/or with high TB-burden. We found an association between SPS and TB treatment success and a reduction in the risks of treatment default and therapeutic failure in patients under SPS. These evidences support the implementation of the social support along with a universal health coverage, especially in high-endemic TB or poor populations [1,8]. However, our findings should be interpreted with caution, considering the low quality of evidences provided by current studies.

Among the reviewed studies, only one RCT developed in South Africa [43], showed that social protection did not improve the cure of TB patients. However, low fidelity to the trial protocol (leading to a third of eligible patients without intervention) and omission of data about HIV status of participants were important limitations to this study.

Table 2

Summary of findings table.

Outcomes	Number of participants (studies) – follow-up	Quality of the evidence (GRADE)	RR (95%CI)	Anticipated absolute effects	
				Risk with TB usual care	Risk difference with social protection interventions
Treatment success	1,687 (9 RCTs)	⨁⨁◯◯ LOW [a,b]	1.09 (1.03-1.14)	723 per 1,000	65 more per 1,000 (22 more to 101 more)
Cure	1,590 (8 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	1.11 (1.01-1.22)	493 per 1,000	54 more per 1,000 (5 more to 109 more)
Treatment default	1,325 (7 RCTs)	⨁⨁◯◯ LOW [a,b]	0.63 (0.45-0.89)	126 per 1,000	46 fewer per 1,000 (69 fewer to 14 fewer)
Treatment failure	1,245 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	0.78 (0.44-1.40)	50 per 1,000	11 fewer per 1,000 (28 fewer to 20 more)
Death	1,238 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	0.98 (0.61-1.57)	68 per 1,000	1 fewer per 1,000 (27 fewer to 39 more)

95%CI: 95% confidence interval; RCTs: randomized controlled trials; RR: risk ratio.

Note: a. most of information was provided by studies with some limitations (no information about allocation concealment, blinding, and with biases from other sources); b. differences in study populations and interventions might influence directness of evidences; c. high unexplained heterogeneity observation.

Figure 3

Forest plots for comparison of social protection interventions versus tuberculosis usual care.

3a) Outcome: treatment success

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random (95%CI)
Baral et al. [22]	32	42	54	81	5.0	1.14 (0.91; 1.44)
Clarke et al. [31]	39	47	27	42	3.8	1.29 (1.00; 1.44)
Datiko & Lindtjørn [19]	205	230	74	88	25.1	1.06 (0.96; 1.17)
Lutge et al. [43]	208	273	182	257	24.5	1.08 (0.97; 1.19)
Martins et al. [30]	103	136	100	129	14.6	0.98 (0.86; 1.12)
Ritchie et al. [21]	15	22	33	58	2.0	1.20 (0.83; 1.72)
Sudarsanam et al. [36]	43	48	41	49	10.5	1.07 (0.92; 1.25)
Zuwarenstein et al. [34]	40	54	26	44	3.0	1.25 (0.94; 1.68)
Álvarez Gordillo et al. [26]	43	44	35	43	11.5	1.20 (1.03; 1.39)
Total		**896**		**791**	**100.0**	**1.09 (1.03; 1.14)**
Total events	728		572			

Heterogeneyty: Tau²: 0.00; χ^2 = 7.54; df = 8 (p = 0.48); I^2 = 0%

Test for overall effect: Z = 3.24 (p = 0.001)

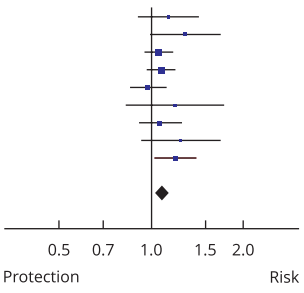


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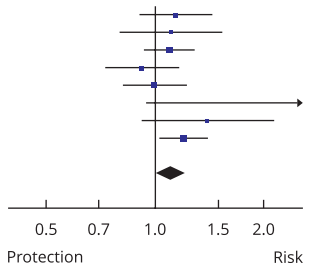
Figure 3 (continued)

3b) Outcome: cure

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random (95%CI)
Baral et al. [22]	32	42	54	81	13.1	1.14 (0.91; 1.44)
Clarke et al. [31]	31	47	25	42	7.5	1.11 (0.80; 1.53)
Datiko & Lindtjørn [19]	172	230	60	88	21.6	1.10 (0.93; 1.29)
Lutge et al. [43]	90	273	92	257	12.7	0.92 (0.73; 1.17)
Martins et al. [30]	80	136	76	129	16.0	1.00 (0.82; 1.22)
Ritchie et al. [21]	6	22	6	58	0.9	2.64 (0.95; 7.31)
Zuwarenstein et al. [34]	31	54	18	44	4.6	1.40 (0.92; 2.14)
Álvarez Gordillo et al. [26]	43	44	35	43	23.6	1.20 (1.03; 1.39)
Total		**848**		**742**	**100.0**	**1.11 (1.01; 1.22)**
Total events	485		366			

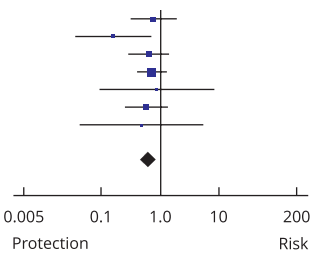
Heterogeneyty: Tau²: 0.00; χ^2 = 9.06; df = 7 (p = 0.25); I^2 = 23%
Test for overall effect: Z = 2.10 (p = 0.04)



3c) Outcome: default

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random (95%CI)
Baral et al. [22]	6	42	15	81	15.5	0.77 (0.32; 1.84)
Clarke et al. [31]	2	47	11	42	5.6	0.16 (0.04; 0.69)
Datiko & Lindtjørn [19]	15	230	9	88	18.9	0.64 (0.29; 1.40)
Lutge et al. [43]	20	273	26	257	38.0	0.72 (0.41; 1.26)
Ritchie et al. [21]	1	22	3	58	2.4	0.88 (0.10; 8.01)
Zuwarenstein et al. [34]	8	54	11	44	17.5	0.59 (0.26; 1.34)
Álvarez Gordillo et al. [26]	1	44	2	43	2.1	0.49 (0.05; 5.19)
Total		**712**		**613**	**100.0**	**0.63 (0.45; 0.89)**
Total events	53		77			

Heterogeneyty: Tau²: 0.00; χ^2 = 4.01; df = 6 (p = 0.67); I^2 = 0%
Test for overall effect: Z = 2.63 (p = 0.009)



3d) Outcome: failure

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random (95%CI)
Baral et al. [22]	2	42	4	81	12.4	0.96 (0.18; 5.05)
Clarke et al. [31]	4	47	2	42	12.6	1.79 (0.34; 9.26)
Datiko & Lindtjørn [19]	2	230	0	88	3.7	1.93 (0.09; 39.73)
Lutge et al. [43]	10	273	15	257	55.9	0.63 (0.29; 1.37)
Zuwarenstein et al. [34]	3	54	2	44	11.2	1.22 (0.21; 6.99)
Álvarez Gordillo et al. [26]	0	44	5	43	4.2	0.09 (0.01; 1.56)
Total		**690**		**555**	**100.0**	**0.78 (0.44; 1.40)**
Total events	21		28			

Heterogeneyty: Tau²: 0.00; χ^2 = 4.22; df = 5 (p = 0.52); I^2 = 0%
Test for overall effect: Z = 0.82 (p = 0.41)

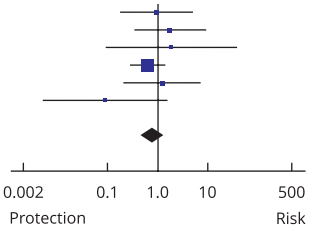


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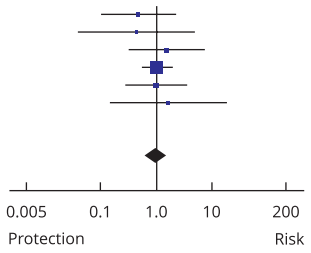
Figure 3 (continued)

3e) Outcome: death

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random (95%CI)
Baral et al. [22]	2	42	8	81	9.7	0.48 (0.11; 2.17)
Clarke et al. [31]	1	47	2	42	4.0	0.45 (0.04; 4.75)
Datiko & Lindtjørn [19]	8	230	2	88	9.4	1.53 (0.33; 7.07)
Lutge et al. [43]	20	273	18	257	58.5	1.05 (0.57; 1.93)
Ritchie et al. [21]	3	22	8	58	14.5	0.99 (0.29; 3.39)
Zuwarenstein et al. [34]	2	54	1	44	4.0	1.63 (0.15; 17.38)
Álvarez Gordillo et al. [26]	0	44	0	43	-	Not estimable
Total		**668**		**570**	**100.0**	**0.98 (0.61; 1.57)**
Total events	36		39			

Heterogeneyty: Tau²: 0.00; χ^2 = 1.83; df = 5 (p = 0.87); I^2 = 0%
Test for overall effect: Z = 0.008 (p = 0.94)



95%CI: 95% confidence interval; M-H: Mantel-Haenszel method.

Despite treatment success being considered a primary outcome, SPS showed a higher effect size against treatment default. This finding can be explained by the capacity that social protection has to increase health care access, leading to better treatment adherence through mechanisms to cope with financial hardship due to TB, alleviate poverty and reduce social vulnerability [1,44].

Because of the disease, individuals and families with TB face direct and indirect costs that can be reduced by SPS. Direct costs include expenses with transport to and from the health facilities, medication, exams or consultations incurred by individuals. Indirect costs are associated with income losses that can account for almost 50% of total family expenses (e.g. illness-related work absences) [44,45].

Social protection covering TB patients can provide means for these individuals to compensate catastrophic expenditures and reduce treatment default, especially for the poorest. They can be implemented in different ways, such as material incentives, cash transfers or food security programs [1]. Evidences from RCTs conducted in the United States show that incentives can contribute to patient attendance in TB health care facilities, improving treatment adherence [46].

We noticed that SPS are not limited to cash transfers. In this meta-analysis, financial and non-financial interventions also were effective in protecting against default, leading to treatment success. The scope of social protection includes economic support, food security and nutrition [23,27,28,30,36,37], psychological support and health education approaches [22,26], social mobilization [35] and training of volunteers to act as patient's supporters [19,28,31,32,33,34].

Despite these relevant results, there were some limitations to our meta-analyses. First, the limited number of available studies on social protection effects on TB treatment outcomes. Second, possible uncontrolled biases in the individual studies. Third, methodological limitations of reviewed studies and diversity of their interventions also might have affected our results. Future research based on well-designed randomized studies covering low and middle-income populations might provide better quality evidences.

In order to reduce study selection bias in our meta-analyses, we followed the eligibility criteria previously established in the review protocol. The main differences between this review and the protocol were: inclusion of observational studies in qualitative synthesis and an updated list of countries with high burden of TB. The first change aimed to strength our body of evidences about SPS and TB treatment outcomes. The second change was made to meet WHO current recommendations. In addition, we used Downs & Black [15] instrument to perform a quality assessment of all reviewed studies, since it can be applied not only to RCTs. Finally, we did not present all planned subgroup analyses, since heterogeneity did not substantially affect our results.

Concerning publication bias, we agree that funnel plots (available in the supplemental material – cf. Appendix 2: https://www.4shared.com/web/preview/pdf/BVpsBkhoca?) do not ensure its absence but suggest its presence. Furthermore, we could not find unpublished studies and relevant materials in grey literature, strengthening the argument of absence of publication bias in the analyzed studies.

Conclusions

Our findings endorse the premises that social protection can contribute to TB treatment success, especially improving its adherence. The reach of goals for TB elimination after 2015 depends on the strengthening of social protection among the National Tuberculosis Programs (NTPs) priorities as a main action.

Evidences from our review suggest that low and middle-income countries should extend health coverage to reach the poorest individuals, associated with effective social support, through income transfer mechanisms and comprehensive interventions that may have beneficial impacts on TB outcomes.

Because of the broad scope of social protection, no conclusions can be drawn on the effect of specific interventions. We highlight the uncertainty in the effect estimates provided by the reviewed studies, given the overall low quality of the data. Further well-conducted randomized studies targeting low- and middle-income populations are needed.

Contributors

K. V. F. Andrade designed the study, searched on databases, selected the articles, performed the statistical analyses and wrote the manuscript. J. S. Nery contributed to quality assessment evidence and to the review of the manuscript. R. A. Souza searched on databases, selected the articles and reviewed the article. S. M. Pereira contributed to all stages of this study, helped in the interpretation of the study findings and reviewed the article.

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Resumo

A tuberculose (TB) é uma doença infecciosa associada à pobreza que afeta milhões de pessoas no mundo. As evidências sugerem que estratégias de proteção social podem melhorar os desfechos do tratamento da TB. O estudo teve como objetivo resumir essas evidências através de uma revisão sistemática da literatura e uma meta-análise. Foram buscados estudos realizados em países de renda baixa e média ou com carga alta de TB, publicados entre 1995 e 2016. A revisão foi realizada através de uma busca em PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect e LILACS. Incluímos apenas os estudos que investigavam os efeitos das estratégias de proteção social sobre os desfechos do tratamento da TB. Foram incluídos 25 estudos na síntese qualitativa. As meta-análises foram realizadas com 9 estudos randomizados e controlados, totalizando 1.687 participantes. Os resultados mostraram que as estratégias de proteção social estavam associadas ao sucesso do tratamento da TB (RR = 1,09; IC95%: 1,03-1,14), à cura dos pacientes de TB (RR = 1,11; IC95%: 1,01-1,22) e à redução do risco de abandono do tratamento (RR = 0,63; IC95%: 0,45-0,89). Não detectamos os efeitos das estratégias de proteção social sobre a falha terapêutica ou mortalidade. Os achados mostram que as estratégias de proteção social podem melhorar os desfechos do tratamento em países com renda baixa e média ou com alta carga da doença. Entretanto, a qualidade das evidências com relação a essas estimativas de efeito é baixa, e são necessários mais estudos randomizados e bem conduzidos.

Tuberculose; Resultado do Tratamento; Seguridade Social; Política Pública

Resumen

La tuberculosis (TB) es una enfermedad infecciosa, característica de la pobreza, que afecta a millones de personas en todo el mundo. Las evidencias sugieren que las estrategias de protección social (EPS) pueden mejorar los resultados del tratamiento de la TB. El objetivo de este estudio ha sido resumir tales evidencias, a través de una revisión sistemática de la literatura y metaanálisis. Buscamos estudios realizados en países de baja renta o ingresos medios y con altas tasas de morbilidad por TB, publicados durante 1995-2016. La revisión la llevamos a cabo realizando búsquedas en PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect y LILACS. Incluimos sólo estudios que investigaron los efectos de las EPS en los resultados de los tratamientos contra la TB. Seleccionamos 25 estudios para realizar su síntesis cualitativa. Realizamos metaanálisis con 9 ensayos controlados aleatorios, incluyendo a un total de 1.687 participantes. Los resultados agrupados mostraron que las EPS estaban asociadas con tratamientos exitosos contra la TB (RR = 1,09; 95%CI: 1,03-1,14), la curación en pacientes de TB (RR = 1,11; 95%CI: 1,01-1,22) y con la reducción en el riesgo de abandono del tratamiento de TB (RR = 0,63; 95%CI: 0,45-0,89). No detectamos efectos de las EPS en los resultados de fracaso del tratamiento y muerte por TB. Estos hallazgos revelaron que las EPS podrían mejorar los resultados de los tratamientos por TB en las economías de países con baja renta o ingresos medios, o países con altas tasas de esta enfermedad. No obstante, la calidad general de las evidencias, en relación con estos resultados, es baja e indica que son necesarios más estudios controlados aleatorios bien realizados.

Tuberculosis; Resultado del Tratamiento; Bienestar Social; Política Pública

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