PREVENTING TUBERCULOSIS IN PEOPLE AT HIGH RISK

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Declaration of Originality

The research described in this thesis is all my own work with support from an excellent multidisciplinary team in Peru. Chapters 1, 2, and 3 describe research in which I was not involved in study design nor initial data collection but was involved in final follow-up, data collection, data analysis, write-up, and dissemination of findings. This level of involvement is specified in the forewords to Chapters 1, 2, and 3. Chapters 4, 5, and 6 describe research that, along with the team in Peru, I conceived, designed, led, implemented, analysed, and wrote-up. Any other research adopted or adapted from other sources is acknowledged and referenced appropriately.

Copyright Declaration

Abstract

Background

Poverty drives TB rates but the current TB control approach is disproportionately biomedical. In 2015, the World Health Organisation's End TB Strategy explicitly identified the need to address the social determinants of TB through socioeconomic interventions. However, evidence concerning poverty-reduction and costs-mitigation strategies is limited. My PhD research aimed to address this knowledge gap.

Methods

During this PhD, I aimed to develop as an independent researcher while addressing the social determinants of TB in impoverished shantytown communities of Callao, Peru, through integrated projects. The research was divided into two phases:

1) Final follow-up, data collection, analysis, and write-up of: a case-control study defining the TB-poverty association; an ecological study assessing poverty-related risk factors for TB infection and disease; and a cohort study identifying TB-related costs of TB-affected families and creating a clinically-relevant catastrophic costs threshold.
2) Conception, design, implementation, data collection, analysis, and write-up of a household-randomized controlled study of a socioeconomic intervention to improve TB cure and prevention.

Results

The first phase showed that TB remains a disease of people living in poverty, that "free" TB care was expensive for impoverished TB-affected families to afford, and that incurring catastrophic costs explained as many adverse outcomes as multi-drug resistant (MDR) TB.

The second phase showed that, in households receiving the TB-specific socioeconomic intervention, TB-affected households were less likely to incur catastrophic costs, household contacts were more likely to start and adhere to TB preventive therapy, and TB patients were more likely to be cured.

Conclusion

In impoverished Peruvian shantytowns, poverty remains associated with TB and incurring catastrophic TB-related costs predicted adverse TB outcome. A novel TB-specific socioeconomic intervention reduced catastrophic costs and improved TB preventive therapy uptake and TB cure. The impact of the intervention on TB control will now be evaluated during the Community Randomized Evaluation of a Socioeconomic Intervention to Prevent TB (CRESIPT) study.

To Thea,

with all my love.

Contents

General Introduction

150 years ago, Virchow recognised that TB was a social disease.[1] Since then, Koch's discovery of the bacillus and the discovery of streptomycin and other antimicrobials provided humankind with a means to both diagnose and treat TB disease. Yet TB rates in Europe were falling during the industrial revolution, prior to either the discovery of the TB bacillus or TB anti-microbial therapy. This decrease was predominantly mediated through social determinants with improvements in socioeconomic position leading to, among other factors, better living conditions[2,3] and nutrition.[4,5]

In the modern era, global rates of TB are declining slowly and remain unacceptably high: a third of the world's population is estimated to be infected with TB and 1.5 million people died of TB in 2014, the majority of whom were impoverished people living in resource-constrained settings.[6] However, the global TB control strategy and TB-related research continued to be disproportionately focused on a biomedical rather than socioeconomic response to the epidemic. It is clear that despite helping to cure millions of people of TB disease,[7] the current global response to TB alone will not be enough to eradicate TB within this century.

Thus, 150 years on from Virchow's astute observation, TB remains a social disease inextricably linked in a vicious cycle with poverty. Specifically, being poor increases the risk of acquiring TB infection and disease;[7–9] and having TB disease worsens poverty in TB-affected households.[10–12] Therefore, a more holistic approach is required to eliminate TB globally, which addresses not only biomedical responses but also the broader socioeconomic determinants of this disease of poverty.[11,13–16]

Addressing the social determinants of TB is not a new concept: almost 100 years ago the Papworth study (a socio-medical experiment performed at the Papworth Village Settlement in England) showed that stable employment and adequate housing and nutrition for households of parents with active TB disease decreased the incidence of TB infection and disease in their children.[2]

Nevertheless, since the advent of the antibiotic era, such social and economic support interventions received less attention and the response to TB became focused almost solely on the biomedical.

In the post-2015 End TB Strategy, the World Health Organisation - for the first time in the modern era of TB control – cited mitigation of TB-related costs and provision of socioeconomic support to TB-affected households as key pillars in the global response to TB.[16] However, rigorous evidence with which to guide TB civil society, policy-makers, and national TB programs on the implementation of costs mitigation and TB-specific socioeconomic interventions (e.g. focused only on TB-affected people) remains extremely limited.[9,17,18] In addition, the intricacies of the social determinants mediating the causal pathway from poverty to TB disease continue to be poorly understood and require further evaluation if socioeconomic interventions are to provide a targeted response to TB with optimal impact on TB control.

This thesis builds on a decade of research by the Innovation For Health and Development (IFHAD, www.ifhad.org) research group, including the Innovative Socioeconomic Interventions Against TB (ISIAT) project.[15] Generally, this PhD research aimed to identify and address poverty-related risk factors for TB infection, disease and adverse TB treatment outcome. Specifically, this PhD research aimed to: assess the association of TB and poverty; measure catastrophic costs of TB care and their impact on treatment outcomes; and implement a TB-specific socioeconomic intervention to improve TB prevention and cure in TB-affected households of shantytown communities of Callao, Peru.

In addition to the goals above, this research aimed to provide the candidate with comprehensive, structured, training in epidemiological field research principles and practices, in order that he could develop as an independent investigator. Therefore, the scope of the training was necessarily broad to enhance the depth of experience for the candidate. Over the three years of this PhD research, a planned, progressive series of six research projects was undertaken to address the existing knowledge gaps in global TB control strategy identified above. Each project is described in detail in its own chapter, and each chapter includes a specific, comprehensive literature review.

Chapter 1: This initial project trained the candidate in data analysis and assessed the association of TB and poverty in study site communities using data from a case-control study nested within a previous cohort study. The project also evaluated the application of a novel composite poverty score of stable variables of socioeconomic position, including household assets and education level.

Chapter 2: Having established that poverty was more common in TB patients than controls, this second study went on to explore this relationship further by examining the social determinants mediating the causal pathway from poverty to TB in the study site. To do this, an ecological analysis of the relationship between proxy variables of poverty (including household crowding and vitamin D deficiency), TB infection, and incident TB disease was performed using data from a cohort study.

Chapter 3: The projects detailed in Chapters 1 and 2 demonstrated the effect of poverty on developing TB disease. We then took this further by examining the effect of poverty on outcomes of TB treatment. To do this, final cohort follow-up was completed and - using the data collected to measure TB-related costs of TB-affected families - an innovative, clinically-relevant catastrophic costs threshold was created that has since been endorsed by WHO as part of global TB policy.

Chapter 4: Having identified risk factors for incident TB disease and adverse TB treatment outcomes, the candidate worked with the multi-disciplinary IFHAD team in Peru to conceive, design, and subsequently lead the implementation of a household-randomized controlled evaluation of a socioeconomic intervention including conditional cash transfers to improve access to TB prevention and cure. This chapter describes: a systematic review of the existing evidence concerning socioeconomic and conditional cash transfers interventions to control TB; and - in order to inform policy makers, implementers, and national TB programs – provides a practical description of the design, implementation, and refinement of the novel socioeconomic intervention.

Chapter 5: evaluated the extent to which TB-related and catastrophic costs were mitigated by the intervention. In addition to exploring the limitations of the intervention, this chapter also suggests refinements to the intervention, with which to improve its impact on TB control during the larger-scale Community Randomized Evaluation of a Socioeconomic Intervention to Prevent TB (CRESIPT).

Chapter 6: assessed the impact of the intervention on TB prevention and cure. The primary outcome was TB preventive therapy uptake by eligible household contacts of recruited TB patients. The secondary outcome was cure of TB patients confirmed by the Peruvian National TB Program.

In summary, this PhD research: addressed knowledge gaps concerning the association between poverty and TB including TB-related costs of “free” TB treatment; and designed a TB-specific

socioeconomic intervention that improved access to TB preventive therapy and TB treatment, mitigated the catastrophic costs of TB, and thereby improved TB cure and prevention measures.

Chapter 1: Poverty and TB

This chapter is adapted from a section of the peer-reviewed, published paper Wingfield *et al* "Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru." PLOS Medicine. 2014 Jul 15;11(7):e1001675. doi: 10.1371/journal.pmed.1001675.[19] The paper is bound in PDF format in Appendix 2 of this thesis. The candidate's contribution to this study was final data collection, data management, data analysis and analysis strategy, study write-up and dissemination of findings. The candidate was not involved in study design nor initial data collection, which took place as part of a cohort study of TB-affected households in Ventanilla/Callao, Peru, that has been ongoing for the past 15 years.

Introduction

Tuberculosis (TB) disease kills 1.5 million per year and remains a major global health problem.[6] Many low and middle income countries are unlikely to meet the Millennium Development Goals for reduction of TB disease prevalence and mortality.[6] This is due in part to poorer people experiencing inequitable healthcare provision and access[20] and suffering a disproportionate burden of morbidity and mortality from TB disease.[9,21] Poverty increases TB risk[22] and TB exacerbates poverty, affecting the most economically productive age group.[23–25] We aimed to measure poverty in TB patients versus healthy controls. The study hypothesis was that TB patients would be poorer than healthy controls, thus confirming the recognised association of socioeconomic position and TB disease.

Methods

Ethical approval

The internationally accredited ethical committees of the Universidad Peruana Cayetano Heredia, Peru, and Imperial College London, UK, approved the project. All interviewed participants gave written informed consent.

Study design and participants

We conducted a case-control study comparing TB patients with healthy controls. From October 2002 to November 2009, in collaboration with the Peruvian TB program, all consecutive patients with laboratory-proven pulmonary TB were invited to participate in the study. This included those patients starting TB treatment by the Peruvian TB Program without confirmed culture or with confirmed smear positivity or culture; patients who were diagnosed and treated in military or non-governmental facilities in the study site were not invited to participate as outcome data was not available for such patients. All interactions between the research team and the participants occurred during household visits. From December 2006 to December 2007, healthy control households were also recruited. This was achieved using an up to date satellite map which identified houses/residences in the study site which were all numbered sequentially by a research nurse. Buildings known to be commercial enterprises, hospitals, offices, or government buildings were not numbered. All identified houses were then numbered sequentially across each district map, selected using random number tables, and a household visit made in order to invite the household members to participate in the study as a healthy control household. If all control participants were unavailable or declined then the nearest neighbouring household was instead invited to participate. Inclusion criteria in both cases and healthy controls included age more than 15 years. Exclusion criteria included declining or being unable to give informed written consent. The sample size was opportunistic and consequently no power calculations were performed.

Study setting

The study was conducted in Ventanilla, 16-periurban contiguous shantytowns in northern Lima/Callao, Peru, with an estimated population of 277,895 people, and frequent poverty (32% of inhabitants live on ≤1 US dollar per day). During the study period, the annual TB notification rate in Ventanilla was 162 new cases per 100,000 people, higher than the rest of the country which was estimated to be 106 per 100,000 people annually.[26]

Data source and measurement

A questionnaire was developed locally, piloted, refined, and then used to interview patients and collect socio-demographic data concerning household income and expenses throughout TB illness. Interviews were conducted with both TB patients and healthy controls. Questions characterized earnings, income, expenses, employment (paid or unpaid), days unable to work due to illness, additional household food expenditure due to TB illness, and crowding. For all participants, height and weight were measured and body mass index (BMI) was calculated. Poverty was measured using a composite household poverty index in arbitrary units derived by principal component analysis from 13 variables, as described in our research group's previous work.[15]

Data analysis

Means were compared with the Student's t-test. Categorical data were summarised as proportions with 95% CI and were compared with the z-test of proportions. Univariable regression analyses examining differences between patients with MDR and non-MDR TB and controls were adjusted for sex because of under-recruitment of male healthy controls due to their availability.

Results

Participants

During the study period, the Peruvian TB program within the study site of Ventanilla registered 1,014 patients. We located 99% of these registered TB patients of whom 95% (n=966) met inclusion criteria. Of these eligible patients, 1% (n=10) declined, 8% (n=80) were excluded because they completed fewer than half of our planned research interviews. Data are presented for the remaining 91% (n=876) participants. 11% (n=93) of patients recruited had MDR TB. 487 healthy controls were also recruited and had only a baseline interview. The characteristics of the study population are summarized in Table 1 (Page 20).

Descriptive data

TB patients were more likely than healthy controls to be younger (31 versus 34 years old, 3 years difference [95% CI 2-4], p=0.001), to be male (59% versus 37% male, 22% difference [95% CI 21-23], p<0.001), to have a lower body mass index (21 versus 26 units of individuals, 5 units difference [95% CI 4-6], p<0.001), to have lower earnings (510 versus 651 Peruvian soles, 141 Peruvian soles difference [95% CI 114- 168], p<0.001), to not be in paid work at recruitment (81% versus 63%, 18% difference [95% CI 15-23], p<0.001), and to have had a previous TB episode (18% versus 5.4% of individuals, 13% difference [95% CI 12-13], p<0.001). Patients with MDR TB were more likely than patients with non-MDR TB to have had a previous TB episode (40% versus 15% of individuals, 25% difference [95% CI 17-32], p<0.001), to have longer pre-treatment symptom duration (83 versus 52 days, 31 days difference [95% CI 0-73], p<0.001), to not be in paid work (90% versus 80% of individuals, 10% difference [95% CI 7-13], p<0.03), and to have had more days not working pre-treatment due to TB-related illness (29 versus 18 days, 11 days difference [95% CI 0-34], p=0.004).

Discussion

Social determinants are important in the causal pathway of TB disease.[27] Indeed, reduction of poverty, advocating improved equity of access and universal health care, and eliminating catastrophic costs in TB-affected households are key components of the World Health Organisation's post-2015 Global TB strategy.[14,28–30] Our results demonstrate that TB predominantly affects poorer people.[8,9,21,31] In this study we did not find any strong evidence that non-MDR and MDR TB differed in their association with poverty. Our poverty score used time-stable variables such as household assets, education level, and housing;[32] thus poverty can be assumed to have preceded TB disease.

The study was limited by the healthy control selection process. Using satellite maps and identifying households to randomly select to participate may have meant that there was selection bias against the poorest members of the communities, who may: have established residences after the satellite map images were taken (i.e. the maps are out of date as soon as they are published with the ever-expanding population of the Callao shantytowns); be living in buildings not identified as residences/houses (e.g. in a room at the back of a commercial enterprise); or live in smaller, peripheral accommodation not identified by the satellite map. In addition, the extent and effect of poverty may be underestimated in our study given that geographical and socioeconomic barriers and stigma may particularly preclude the poorest people from seeking healthcare.[33]

Conclusions

In impoverished shantytowns of Callao, Peru, having TB disease was associated with being poor. This research confirms that TB remains a social disease. Thus, in order to control TB, the global response may benefit from socioeconomic as well as biomedical approaches.

Table 1: Study population baseline data. Note 'CI' indicates confidence intervals, 'SD' is standard deviation, and IQR is interquartile range. All data are at individual level and pre-treatment except where indicated. 'NA' indicates not applicable. The column "Controls" refers to "Healthy Controls".

	Controls	TB patients	P value*	Non-MDR TB	MDR TB	P value*
Participants	487	876	.	783	93	.
Demographics						
Age; mean years	34	31	0.001	31	31	0.8
[SD]	[20 - 48]	[18 - 44]		[30 - 32]	[17 - 45]	
Sex; % males	37	59	<0.001	59	59	0.9
[95% CI]	[33 - 41]	[55 - 62]		[55 - 62]	[49 - 69]	
Health and finances						
Secondary complete;%	46	44	0.3	45	36	0.1
[95% CI]	[41 - 50]	[41 - 47]		[42 - 49]	[26 - 46]	
Household crowding						
Above mean; %	66	57	0.07	57	61	0.5
[95% CI]	[59 - 72]	[54 - 61]		[53 - 60]	[51 - 71]	
People per house	5.1	4.9	0.8	4.9	4.9	0.9
[IQR]	[4.6 - 5.6]	[4.8 - 5.0]		[4.7 - 5.0]	[4.5 - 5.4]	
Body mass index; (kg/m^2)	26	21	<0.001	21	21	0.3
[95% CI]	[25 - 26]	[21 - 22]		[21 - 22]	[20 - 21]	
Previous TB; %	5.4	18	<0.001	15	40	<0.001
[95% CI]	[3.3 - 7.4]	[15 - 20]		[13 - 18]	[30 - 50]	
Monthly earnings**						
Pre-treatment	651 (1.40)	510 (1.09)	<0.001	511 (1.09)	497 (1.07)	0.8
[95% CI]	[595 - 707]	[481 - 539]		[482-540]	[381-613]	
During treatment	.	434 (0.93)	.	436 (0.94)	418 (0.90)	0.6
[95% CI]	.	[415 - 453]		[416-456]	[341-495]	
Intensive phase	.	379 (0.81)	.	379 (0.81)	376 (0.81)	0.9
[95% CI]	.	[358 - 400]		[357-401]	[295-457]	
Continuation phase	.	454 (0.97)	.	457 (0.98)	424 (0.91)	0.4
[95% CI]	.	[431 - 477]		[434-480]	[339-509]	
Debt***	812 (1.7)	383 (0.82)	0.004	377 (0.81)	435 (0.93)	0.7
[95% CI]	[507 - 1117]	[292 – 474]		[283 – 471]	[87 – 872]	
Not in paid work; %	63	81	<0.001	80	90	<0.03
[95% CI]	[56 - 69]	[79 - 84]		[77 - 83]	[84 - 96]	
Poverty score						
Above control mean;%	51	58	<0.02	58	60	0.8
[95% CI]	[47 - 56]	[55 - 61]		[54 - 61]	[50 - 70]	
Current tuberculosis						
Symptom duration						
Mean days	.	55	.	52	83	<0.001
[SD]		[0 - 127]		[0 - 118]	[0 - 192]	
Too unwell to work						
Mean days	.	19	.	18	29	0.004
[SD]		[0 - 51]		[0 - 47]	[0 - 81]	
Time to health centre						
Mean minutes	.	13	.	13	13	0.9
[SD]		[0 - 30]		[0 - 30]	[0 - 33]	
MDR tuberculosis; %	.	11	.	.	.	.
[95% CI]		[9 - 13]		.	.	

*univariable regression adjusted for sex. The central p value corresponds to comparison of controls (n=487) with all TB patients regardless of MDR status (n=876). The right-hand column p value corresponds to comparison of non-MDR TB patients (n=783) with MDR TB patients (n=93).

**Household earnings per month during different treatment stages represented as mean Peruvian Soles and, in parenthesis, as a proportion of TB patients' mean monthly household earnings throughout entire illness. Confidence intervals are those of mean monthly earnings in Peruvian Soles.

***Debt at recruitment represented as mean Peruvian Soles and, in parenthesis, as a proportion of TB patients' mean monthly household earnings. Debt at recruitment was used in the final multivariable regression model rather than total debt (sum of debt at recruitment plus debt at 24 weeks of treatment) as only 461 patients had 24-week debt data available

Chapter 2: Examining poverty-related TB risk factors: The seasonality of tuberculosis, sunlight, vitamin D, and household crowding

This chapter is adapted from the peer-reviewed, published paper Wingfield et al "The seasonality of tuberculosis, sunlight, vitamin D, and household crowding." J Infect Dis. 2014 Sep 1;210(5):774-83. doi: 10.1093/infdis/jiu121. Epub 2014 Mar 4.[5] The paper is bound in PDF format in Appendix 3 of this thesis. The candidate's contribution to this study was design of the ecological study analysis, data collection concerning hours of sunlight, final follow-up and data collection, data management, data analysis and analysis strategy, study write-up and dissemination of findings. Apart from the data concerning hours of sunlight, which were gathered by the candidate, all other data used for this analysis was collated from a randomized placebo-controlled trial examining the effect of micronutrient supplementation (vitamins A, D, and zinc) on the incidence of secondary TB disease. The candidate was not involved in the conception, design, or data collection of this micronutrient supplementation trial, which was nested in the ongoing cohort study mentioned in Chapter 1.

Following evaluation of the association between TB and poverty, this PhD research next aimed to assess specific poverty-related risk factors for TB infection and disease through an ecological study examining seasonality.

Introduction

Although the incidence of certain infectious diseases is seasonal,[34] the seasonality of tuberculosis (TB) is incompletely understood. TB infects approximately a third of the world's population, causing symptomatic disease in 8.7 million people annually.[6] Prior to antibiotics, spring peaks were noted in TB illness.[35] Later studies in the antibiotic era from Cameroon,[36] India,[37] Britain,[38] Kuwait,[39] Spain,[40] America,[41] Japan,[42] and South Africa[43,44] also revealed TB seasonality. contrary to recognized patterns of acute respiratory illnesses,[45] most studies report a nadir of new TB cases during winter and a peak in spring and summer. This seasonal variation is presumed to relate more to recent transmission than

TB reactivation.[44,46] However, interpretation of seasonality studies is complicated by heterogeneity in definition of season and seasonal variables studied (i.e. temperature, rainfall).[36,39,43]

Vitamin D is an important determinant of adaptive and innate immunity. The principal active metabolite of vitamin D, 25-hydroxy-vitamin D (hereafter referred to as "vitamin D"), has immunosuppressive effects on T-helper and dendritic cells but, conversely, an immuno-stimulatory effect on monocytes and macrophages.[47,48] Low vitamin D concentrations contribute to an increased risk of TB contacts' tuberculin skin test (TST) converting to positive[49] and a higher likelihood of active TB disease in people with specific vitamin D receptor polymorphisms.[50] Apart from diet, humans derive a proportion of their vitamin D through synthesis from 7-dehydrocholesterol on exposure of skin to sunlight.[51] Historically, both ultraviolet light and vitamin D supplementation were used in the treatment of pulmonary and cutaneous TB.[52] More recently vitamin D supplementation during TB treatment was investigated but did not improve treatment outcomes.[53,54] This TB and vitamin D interaction has stimulated interest in seasonal variation in vitamin D concentrations as a potential risk factor for TB susceptibility.[43,46,53–56]

Poverty and social determinants are associated with TB infection and disease.[9,15,57] In diverse settings, household crowding (hereafter referred to as "crowding") is associated with poverty, TB infection, and TB disease in household contacts.[58–61]

Understanding TB seasonality and its potential associations with both endogenous and exogenous factors, including vitamin D and crowding, may inform the health effects of climate change and influence TB prevention through interventions to reduce crowding and vitamin D deficiency. We therefore studied the seasonal relationship between putative TB risk factors (crowding, hours without sunlight, and vitamin D concentrations), TB infection (measured by TST and interferon-gamma release assays, "IGRA"), and subsequent TB illness (symptom onset and disease) within impoverished communities of Callao, Peru.

Methods

Design overview

This was an ecological analysis of seasonality conducted during a cohort study investigating risk factors for incident TB amongst household contacts of TB patients.[15]

For the current research, the TB patients had their date of symptom onset and diagnosis recorded and their TB-exposed cohabitants were tested for TB infection and vitamin D deficiency whilst sunlight levels were recorded. An ongoing nested trial of micronutrient supplementation also assessed whether micronutrient supplementation prevents TB but all data reported here involved participants who declared they had not taken micronutrient supplements.

Setting and climate data

The study took place over four years from 1st January 2003 until December 31st 2006 in Ventanilla, a periurban shantytown with high rates of poverty and TB disease (162/100,000/year) but low rates of HIV-TB co-infection (<2%). The study time period was chosen because it was the same as the time period over which the nested micronutrient supplementation trial and follow-up took place.

Hours without direct sunlight were studied because we hypothesised that these would be associated with vitamin D deficiency. The Peruvian Ministry for Environment provided data defining the presence or absence of direct sunlight in the area over the 32,640 consecutive hours of the study period. Direct sunlight was present during daylight hours when cloud cover was minimal or absent. Conversely, direct sunlight was absent during hours of darkness or when cloud cover prevented the measuring apparatus from directly receiving sunlight. Northern Lima/Callao has two main seasons: we defined winter as the six consecutive months with fewest hours of direct sunlight. Summer was defined as the rest of the year.

Participants

Inclusion criteria were adult TB patients with laboratory-proven (sputum smear or culture positive) pulmonary TB and, with respect to latent TB infection and vitamin D levels, their adult TB-exposed household cohabitants. Adults in this setting were defined as aged 16 years or older. TB-exposed cohabitants were individuals who reported being in the same house as these TB patients for over two hours per day at least three times per week. Exclusion criteria were declining or inability to give informed written consent (Figure 1, Page 38).

The national TB program registered 1,058 patients with pulmonary TB during the study period. We located 99%, and 93% (n=852) of those who met our inclusion criteria (n=912) consented to participate. We concurrently aimed to recruit all TB-exposed cohabitants of these patients and 73% (n=2,004) of those who met our inclusion criteria (n=2737) consented to participate. Thus 3,589 members of TB-affected households were recruited. The internationally accredited ethics committees of the Universidad Peruana Cayetano Heredia, Peru, and Imperial College London, UK, approved the project.

Procedures

At enrolment, a questionnaire was completed with all participants to record baseline data. For TB patients this questionnaire included information defining the date of symptom onset (see Table 2, Page 35) and the date of diagnosis.

For all participants, height and weight were measured and body mass index (BMI) was calculated. Socioeconomic position was measured using a composite household poverty index incorporating 13 variables including education, housing, services and assets.[15] A household unit was defined as a house (a building or connected buildings of the same property with walls and a roof, constructed purposefully to accommodate people) and its occupants or members (the people who sleep at the house for the majority of nights of the week).

Crowding was measured by number of people per room at the initial visit within two weeks of the patient of the household initiating treatment. This was calculated as the number of people sleeping in the house (including household members of any age) divided by the total number of rooms in the house. This method was felt to be appropriate as it followed existing World Health Organisation guidance and, following research team focus groups, was felt to be the most locally-appropriate and accurate reflection of the number of people in the household, as opposed to number of people eating which can vary widely in the study setting.

At enrolment, all TB-exposed cohabitants were asked to undergo testing for latent tuberculosis with TST as described.[62] From 7th March 2005 to 9th November 2006, additional resources became available that allowed all consecutive recruited TB-exposed cohabitants who agreed to provide a blood sample to also undergo IGRA using the QuantiFERON TB-Gold® assay (Cellestis). From this date, 68% (n=576) of cohabitants agreed to provide a blood sample and had interpretable IGRA results. As recommended by the manufacturer, IGRA results were reported qualitatively as positive, negative or indeterminate, not quantitatively.

Vitamin D concentrations

Of the TB-exposed cohabitants enrolled in the micronutrient supplementation trial who had TST and IGRA results, a subset (n=102) selected using random-number tables provided blood samples at recruitment. These TB-exposed cohabitants stated that they were not taking micronutrient supplements. Those TB-exposed cohabitants who did not receive micronutrient supplements also provided blood samples one (n=48) and six months (n=45) post-recruitment. Therefore, a total of 195 (102 + 48 + 45) blood samples were taken. Vitamin D concentrations were measured by radio-immunoassay using inductively-coupled mass spectrometry. Plasma concentrations of <50 nmol/L vitamin D were considered to be deficient and ≥50 nmol/L replete.[53]

Statistical analysis

Raw data and 6-month moving averages (a series of averages of time-series data subsets used to highlight longer-term trends/cycles) were analysed to examine seasonal variation and divided into "peak" season (3-months prior to and after the peak value for that variable) and "the rest of the year" (the remaining 6-months). Power calculations for sample size were not performed. Continuous data with a Gaussian distribution were summarised as means with their 95% confidence intervals (CI) and compared by Student's t-test. Continuous data with a non-Gaussian distribution were converted to categorical data above or below the median value (for crowding 2 people/room and for poverty arbitrary units were used), summarised as proportions with their 95% CI and compared with the z-test of proportions. For multiple regression analyses, non-contributory variables were removed in a backwards-stepwise manner according to the likelihood-ratio test. Relative risks (RR) were calculated using generalized linear model and binomial analysis. The regression model was repeated using season as both a categorical variable (summer versus winter) and as a continuous variable (days from lowest "trough" number of hours of direct sunlight). TB incidence was calculated using the population of Ventanilla of 307,623 people estimated by national census during the study period. All p-values were two-sided and analyses, including calculation of population attributable fractions (PAF), used the Stata program (version 12).

Results

Study population

The study population is summarised in Table 2 (Page 35). Amongst participants, TB-exposed cohabitants were older, had lower education level, were more often female and were more likely to be overweight than TB patients (all $p<0.05$). There was a median household average of 2.0 (IQR 1.5-3.0) people per room.

Vitamin D

Figure 2 (Page 39) shows the average vitamin D concentrations and figure 3 (Page 40) the proportion of vitamin D replete samples, both analysed by season and sex. The mean vitamin D concentration was 48.6 nmol/L [95% CI 46.9–50.3].

The proportion of samples that were vitamin D replete (≥50 nmol/L) was 43.1% [95% CI 36.1–50.1]. During summer the average vitamin D concentration was 51.0 nmol/L and significantly higher than during the winter (45.8 nmol/L, $p<0.003$, Figure 2, Page 39). Male sex and summer were significantly associated with greater likelihood of being vitamin D replete (Figure 3, Page 40).

The randomly-selected subgroup of TB-exposed cohabitants who had vitamin D assays were more likely to be poor ($p=0.0006$) and have more crowding ($p<0.003$) than the entire cohort of TB-exposed cohabitants. However, neither poverty nor crowding were associated with vitamin D concentrations or being vitamin D replete (all $p>0.1$, Table 3, Page 36). There were no other differences between this subgroup and the other TB-exposed cohabitants.

Seasonal association of crowding, sunlight, vitamin D deficiency, and TB

Figure 4 (Page 41) demonstrates the seasonality of TB risk factors, infection and illness: the mid-winter peak in putative TB risk factors (crowding, hours without direct sunlight, and vitamin D deficiency), the sequential late-winter (TST) and early-spring (IGRA) peak in TB infection and finally the mid-summer peak in TB symptom onset followed after three weeks by subsequent TB diagnosis. Table 4 (Page 37) shows the analysis by season of crowding, hours without direct sunlight, vitamin D deficiency, TB infection and illness.

TB risk factors

Crowding: The peak in proportion of households with crowding occurred in mid-winter in July prior to both the peak in hours without direct sunlight and vitamin D deficiency (Figure 4, Page 41). During the six months with most crowding, the proportion of crowded households was 13% points higher than the rest of the year ($p<0.001$, Table 4, Page 37).

Hours without direct sunlight: The peak in proportion of hours without direct sunlight occurred in August, mid-winter, as can be seen in Figure 4 (Page 41). The proportion of hours without direct sunlight was 19% points higher in winter than summer ($p<0.0001$, Table 4, Page 37).

Vitamin D deficiency: Vitamin D deficiency was detected in 56.9% (111/195) of samples (Table 4, Page 37). Figure 4 (Page 41) demonstrates that the peak proportion of samples with vitamin D deficiency occurred in midwinter in the week following the peak in hours without direct sunlight. During the six months around this peak the proportion of samples that were vitamin D deficient was 17% points higher than the rest of the year ($p=0.01$, Table 4, Page 37).

TB infection in TB-exposed cohabitants

TST: Six weeks following the peak in vitamin D deficiency, the peak in the proportion of positive TST results occurred in late winter (Figure 4, Page 41). During the six months around this peak the proportion of positive TST results was 8% points higher than the rest of the year ($p=0.003$, Table 4, Page 37).

IGRA: The peak in the proportion of positive IGRA tests occurred in early summer, 12 weeks following the peak in proportion of positive TST results. During the six months around the IGRA peak the proportion of positive IGRA tests was 9% points higher than the rest of the year ($p<0.04$, Table 4, Page 37).

TB disease in laboratory-proven TB patients

TB symptom onset: Five months after the peak in TB infections as indicated by TST, the peak in TB symptom onset occurred in midsummer (Figure 4, Page 41). During the six months around this date 14% more patients had TB symptom onset than the rest of the year ($p<0.05$, Table 4, Page 37).

TB diagnosis: The peak in TB diagnosis occurred in late summer, three weeks following the peak in TB symptom onset (Figure 4, Page 41). During the six months around this date 13% more patients were diagnosed with TB than the rest of the year ($p<0.01$, Table 4, Page 37).

Regression analyses

Table 2 (Page 35) shows the multiple regression analysis of the association between vitamin D concentrations (and the likelihood of being vitamin D replete) and the characteristics of the study population. Male sex (RR 2.0, PAF 24%, $p<0.001$) and summer (RR 1.4, PAF 19%, $p<0.05$) were associated with greater likelihood of being vitamin D replete (i.e. lower likelihood of deficiency). To assess the robustness of these findings, additional analyses of vitamin D concentrations (instead of being vitamin D replete) were performed and showed the same pattern of significance (Table 3, Page 36; Figure 2, Page 39 and Figure 3, Page 40).

Discussion

Vitamin D deficiency was common in this high-risk group of TB-exposed people, more common in females, and peaked in midwinter, shortly after peak crowding and hours without direct sunlight. This was followed by a peak in TB infections in late winter and, after the known 5-month median TB incubation period,[63] by a peak in TB symptoms in midsummer. Finally, after the three week interval required for TB case finding in this setting,[64] TB diagnoses subsequently peaked in late summer. These findings suggest that seasonal vitamin D deficiency and crowding may explain the previously

enigmatic interval from the mid-winter peak in TB risk factors until the late-summer peak in TB diagnoses.

Vitamin D deficiency was found in over half of this Peruvian cohort of TB-exposed cohabitants. Deficiency associated closely with hours without direct sunlight as reported in temperate climates in Europe[65] and North America.[66] Defining vitamin D deficiency is controversial.[51] We selected the threshold of vitamin D concentrations <50 nmol/L as recently suggested in international guidance and relevant studies.[53,67] While such a threshold may be suitable at a population level to predict diseases like osteomalacia, it may fail to detect significant linear associations between vitamin D concentrations and non-skeletal disease risk (such as type-2 diabetes, ischaemic heart disease or cancer).[68] Therefore, we examined vitamin D as both a categorical *and* linear dependent variable and found the results to be concordant.

Female sex was associated with greater likelihood of vitamin D deficiency, independent of season. This is important because international vitamin D supplementation guidelines do not generally differentiate between gender, apart from pregnancy or lactation. The predominance of vitamin D deficiency in females in our study may relate to genetic predisposition or diet. However, the most likely explanation may be difference in behaviour because in this setting men spend more time outside working.[69]

Vitamin D deficiency is a biologically plausible risk factor for TB infection and disease because it suppresses immune responses specific to TB infection.[48] and has been epidemiologically associated with TB disease.[43,55] The active metabolite of vitamin D (1,25-dihydroxyvitamin D) up-regulates the cellular vitamin D receptor to inhibit mycobacterial growth[70] and increases cathelicidin expression by macrophages which promotes mycobacterial cell death.[47,48] Therefore, increasing vitamin D concentrations in spring may potentially lead to a “seasonal immune reconstitution” with increased granuloma formation, tissue inflammation and corresponding symptoms in people subsequently diagnosed with TB in summer. Moreover, although current in-vivo evidence suggests no effect,[53,54] there is some in-vitro evidence that vitamin D supplements could theoretically improve the

treatment response of patients with TB disease through immunostimulatory responses including increased cathelicidin production.[55] Work in a similar Peruvian population has demonstrated that vitamin D receptor polymorphisms were associated with TB patients' time to sputum culture conversion.[71] Thus, vitamin D deficiency, immunology and genetic factors imply a role in TB susceptibility.

The temporal association we observed between peak crowding and vitamin D deficiency followed by TB infection as indicated by the peak in TST positivity extends previous TST conversion findings in TB-exposed cohabitants in Spain.[49] The 12-week interval we observed from peak TST positivity until the peak IGRA positivity may be explained by differences in time to conversion between these tests: the optimum timing of IGRA testing remains to be defined[72] and in TB outbreaks IGRA conversion occurred three[73] to six months[74] after exposure, often later than TST conversion.[75] Moreover, serial IGRA analysis has shown high rates of both initial conversion and subsequent reversion in healthcare workers without known TB exposure, complicating interpretation.[76] However, our study did not measure TST or IGRA conversion but the proportion of positive tests at different cross-sectional time-points. A final possible explanation for the difference between IGRA and TST is that their accuracy for TB infection may be influenced by vitamin D concentrations: work in the study setting has shown that other micronutrients affect TST sensitivity.[4] Thus, the temporal discrepancy we found between seasonal proportion of positive IGRA and TST tests is novel and the mechanisms behind such a discrepancy require further exploratory research.

The seasonality of winter vitamin D deficiency and summer TB diagnoses that we characterised in TB-exposed cohabitants extends findings in TB patients in Europe[50] and South Africa.[43] Low vitamin D concentrations and more vitamin D deficiency in midwinter may have led to increased host-susceptibility to TB infection seen in late winter and to the subsequent progression to TB disease, after a five-month incubation period. This five-month incubation period is the same as that found in a study that used DNA fingerprinting to accurately identify progression from household TB exposure to TB infection and disease.[63] Although our findings are relevant to both, we were unable to determine which episodes of TB disease were a result of recent TB infection versus reactivation of

latent TB. However, other recent studies showed that TB seasonal variation was more pronounced in children and clustered cases suggesting recent infection as the more likely explanation.[46]

The interaction of social determinants along the causal pathway from TB exposure to infection and disease is complex and likely relates to increased transmission (greater exposure through crowding, increased time spent indoors and poorer ventilation[58]), susceptibility (poorer nutrition, lower immunity) and marginalisation (health-seeking behaviour, education). Our study measured crowding - potential TB exposure that in winter may contribute to the seasonality we observed. Crowding is a known marker of poverty and both crowding and poverty are independently associated with TB.[58,59] However, crowding is complex, poorly defined and specific to geographical settings.[60] Research in high-resource countries has defined crowding as >1 person/room and severe crowding as >1.5 people/room,[61] which would have classified virtually all of our households as crowded, preventing meaningful analysis. The World Health Organisation suggests that measuring floor space[60] can be problematic and that it may be more appropriate to consider crowding as above the mid-point number of persons/room. We used this a priori definition as a locally-appropriate crowding definition in this current research and also in ventilation research that is being published separately. Our finding of more crowding in winter than summer is novel. The reasons behind this crowding seasonality require further investigation and may include economic migration (seasonal employment), schooling, public holidays, and selling food produce after harvests. As noted in another recent study,[77] it is unlikely that crowding and increased transmission in winter alone is the factor responsible for TB seasonality. Our findings suggest that both crowding and vitamin D deficiency are independently associated with TB seasonality.

Temporal associations cannot prove causation and other confounding factors may have contributed to TB seasonality. For example, diet was not examined in our study. However, there is little variation in foodstuff availability and consumption in Ventanilla and BMI was used as a proxy nutrition indicator. Climate-related confounding factors could include temperature,[45] humidity, rain, and climate change. Despite high humidity all-year round, annual rainfall in northern Lima/Callao is very low (10-30mm) and there is minimal variation in temperature (average 14^{o}C in winter and 20^{o}C in

summer). An important confounder not measured in the present study was seasonal variation in healthcare seeking and access. Healthcare-seeking behaviour may vary with work-market, harvest or school season as may provision of medical care at health posts and hospitals. Such variations may extend to the number of people tested for TB. Other confounding factors include: concomitant respiratory tract infections, smoke inhalation, and air quality. With regards to vitamin D concentrations, the inductively coupled mass spectrometry assay we used is now recognised to be prone to inter-laboratory variations and isotope-dilution liquid chromatography tandem mass spectrometry may be preferable[78] but was not widely available during our study. In addition to this ecological analysis, it would be valuable to perform larger future studies to test for associations between baseline vitamin D concentrations in TB-exposed household contacts and subsequent progression to TB disease although such a study would be confounded by the seasonality of vitamin D concentrations that we report here. Vitamin D concentrations were measured in a random subset of TB-exposed cohabitants who happened to be poorer and live in more crowded households than all TB-exposed cohabitants. This chance occurrence does not appear to have been important because multiple regression demonstrated that neither crowding nor poverty were independently associated with vitamin D concentrations or being vitamin D replete.

Conclusions

The sequential peaks in midwinter crowding, vitamin D deficiency, TB infection, TB symptom onset and finally late summer TB diagnoses potentially explain the previously enigmatic seasonality of TB. These findings suggest that climate change and recommendations to reduce the risk of skin cancer by avoiding sun exposure may influence TB susceptibility. The associations that we have identified between season, crowding, vitamin D and TB emphasise the potential for correcting vitamin D deficiency and mitigating poverty to contribute to TB prevention.

Table 2: Study population baseline data.

	TB-exposed cohabitants		TB patients
	All	Randomly selected individuals for plasma vitamin D measurement	All
Number of participants	1389	102	852
Number of blood vitamin D analyses	N/A	195	N/A
Demographics			
Sex; % males [95% CI]	37 [34 - 39]	31 [25 - 38]	60 [56 - 63]
Age; mean years [95% CI]	34 [33 - 34]	34 [32 - 36]	31 [30 - 32]
Socioeconomic factors			
Any post-primary education; % [95% CI]	75 [73 - 78]	72 [65 - 78]	81 [78 - 84]
Household crowding; % [95% CI] above median people (>2) per room[a]	57 [55 - 60]	69 [64 - 74]	NA NA
Household poverty score; % [95% CI] above median score[b]	50 [47 – 53]	63 [57 – 68]	NA NA
Anthropometry			
Overweight; % [95% CI] above median body mass index (>25 kg/m^2)[c]	48 [45 - 50]	46 [40 - 52]	12 [10 - 14]

Note 'CI' indicates confidence intervals; 'NA' indicates not applicable, because these variables were assessed at the household rather than individual level.

[a]A continuous measure of crowding was calculated by people sleeping in the house divided by number of rooms in the house. The median of this continuous crowding variable was exactly 2 people per room. The variable 'household crowding' shown below refers to the percentage of household's containing more people per room than the cohort median (2). When splitting into above and below this median, "2" cannot be split and therefore those houses with exactly 2 people per room were apportioned to the "crowded" (i.e. above the median) households. This results in 57% of cohort households being above the cohort median people per room and thus crowded.

[b]The variable household poverty score refers to the percentage of households with a poverty score above the household median.

[c]The variable 'overweight' refers to the percentage of individuals whose body mass index was above the median body mass index of the entire cohort of TB-exposed cohabitants and patients and is the same as that defined by the World Health Organisation (>25kg/m^2).

Table 3: Regression analysis of associations with vitamin D levels. This table shows the results of linear regression of vitamin D plasma concentrations in nmol/L as the outcome variable and binomial regression with odds of being vitamin D replete (≥50 nmol/L) as the outcome variable.

	Vitamin D 25OHD plasma concentrations (nmol/L), linear regression				Vitamin D replete (≥50 nmol/L), binomial regression				
	Univariate regression		Multiple regression		Univariate regression		Multiple regression		
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Relative risk (95% CI)	P value	Adjusted PAF	Relative risk (95% CI)	P value
Sex (male)	9.3 (4.4 - 14)	<0.001	9.3 (5.8 - 13)	<0.001	2.00 (1.4 - 2.9)	<0.001	24 (9 - 36)	2.0 (1.4 - 2.8)	<0.001
Season (summer) [a]	5.2 (2.2 – 8.3)	0.001	5.3 (2.0 - 8.5)	<0.001	1.4 (1.0 - 2.0)	0.03	19 (1 - 33)	1.4 (1.0 – 1.9)	<0.05
Age; years	0.11 (-0.088 - 0.30)	0.2			1.0 (0.99 - 1.0)	0.3			
Any post-primary education	2.0 (-2.8 - 6.8)	0.4			1.3 (0.83 – 2.2)	0.2			
Household crowding; above median people per room	-1.2 (-6.2 - 3.9)	0.6			1.0 (0.68 - 1.6)	0.9			
Household poverty score; above median score	-1.006 (-5.7 - 3.7)	0.6			0.78 (0.53 - 1.2)	0.2			
Overweight; above median BMI (>25 kg/m^2) [b]	3.1 (-1.9 – 8.1)	0.2			1.1 (0.73 – 1.6)	0.7			

Note 'Adjusted PAF' indicates population attributable fraction derived from multiple logistic regression using the "aflogit" function of STATA. All analyses presented above were clustered by individual because some individuals had more than one blood sample taken. Specifically, 102 TB exposed cohabitants provided blood samples at recruitment, and 48 and 45 of these individuals provided blood samples again at 1 and 6 months following recruitment, respectively. Therefore, a total of 195 blood samples were taken. Blank cells indicate variables that did not meet the criteria for inclusion in the multiple regression analysis.

[a]In addition to the analysis of season shown, when univariate and multiple linear regression analyses were repeated using "days from trough in hours of direct sunlight" as a continuous variable in place of "season", male sex and days from trough in hours of direct sunlight remained associated with greater likelihood of being vitamin D replete or having higher vitamin D concentrations.

[b]BMI indicates body mass index (weight in kilograms divided by height in metres squared).

Table 4: Seasonality of TB risk factors, TB infection and TB disease. The peak seasons for the TB risk factors, TB infection and TB disease and the proportion occurring during the peak season versus the rest of the year is shown.[a]

	Peak season and dates			6 month proportions		
	Season start date	**Peak date**	**Season end date**	**Peak season**	**Rest of year**	**P value**
TB risk factors						
Household crowding; % (n/N) [95% CI]	April 8th	July 8th (midwinter)	October 7th	58.9% (206 / 350) [53.7 - 64.0]	46.2% (171 / 370) [41.1 - 51.3]	<0.001
Hours without direct sunlight; % (n/N) [95% CI]	May 20th	August 18th (midwinter)	November 18th	92.7% (15622 / 16848) [92.3 - 93.2]	74.4% (11746 / 15792) [73.7 - 75.1]	<0.0001
Vitamin D deficient (<50 nmol/L); % (n/N) [95% CI]	May 24th	August 23rd (midwinter)	November 22nd	66.7% (58 / 87) [56.8 - 76.6]	49.1% (53 / 108) [39.6 - 58.5]	0.01
TB infection						
TST positivity; % (n/N) [95% CI]	July 8th	October 7th (late winter)	January 6th	62.5% (388 / 621) [58.7 - 66.3]	54.7% (420 / 768) [51.2 - 58.2]	0.003
IGRA positivity; % (n/N) [95% CI]	October 4th	January 3rd (early summer)	April 4th	59.1% (166 / 281) [53.3 - 64.8]	50.5% (149 / 295) [44.8 - 56.2]	<0.04
TB disease						
TB symptom onset incidence; % (n/N) [95% CI] [b]	December 1st	March 2nd (midsummer)	June 1st	0.14% (416 / 307623) [0.12 - 0.15]	0.12% (361 / 307623) [0.11 - 0.13]	<0.05
TB diagnosis incidence; % (n/N) [95% CI][c]	December 24th	March 24th (late summer)	June 23rd	0.15% (466 / 307623) [0.14 - 0.17]	0.13% (390 / 307623) [0.11 - 0.14]	<0.01

Note 'CI' indicates confidence intervals. [a]These observed 6-monthly actual count data differ slightly from the 6-month moving average data shown in Figure 4 (Page 41) because of differences in the way these data are calculated. [b]TB symptom onset was calculated using longest duration of symptoms including cough (with or without phlegm or blood), weight loss, fever and night sweats. More general symptoms (e.g. headache and nausea) were not included in symptom onset calculations. Incidence is shown as the total number of people with onset of symptoms that were subsequently diagnosed to be caused by laboratory-proven pulmonary TB over four 6-month periods as a percentage of the total population of the study site estimated in a national census during the study period. [c]Incidence is shown as the total number of people diagnosed with laboratory-proven pulmonary TB over four 6-month periods as a percentage of the total population of the study site estimated in a national census during the study period.

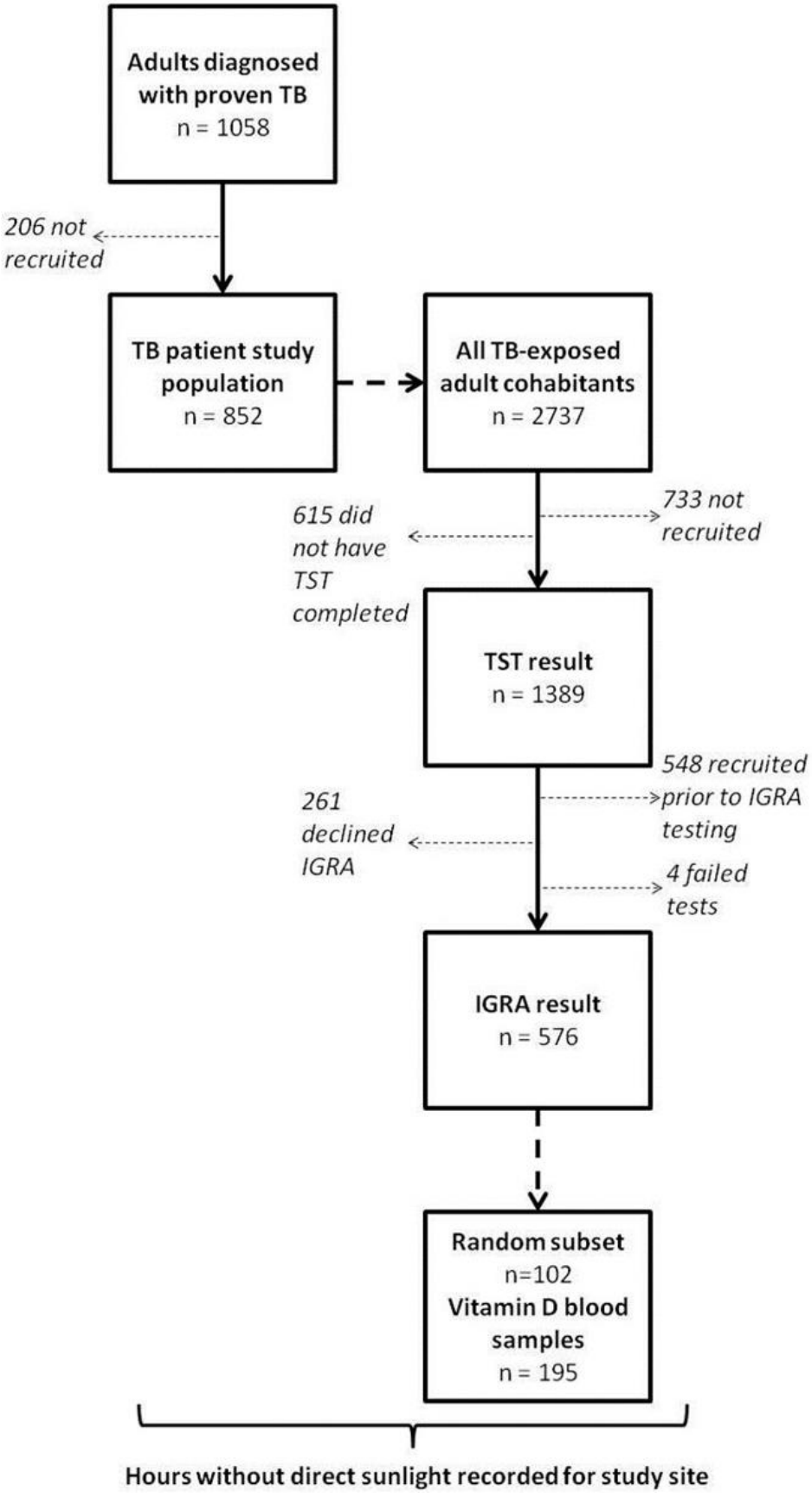


Figure 1: Study design. Abbreviations: TST = tuberculin skin test; IGRA = Interferon gamma release assay; TB = tuberculosis

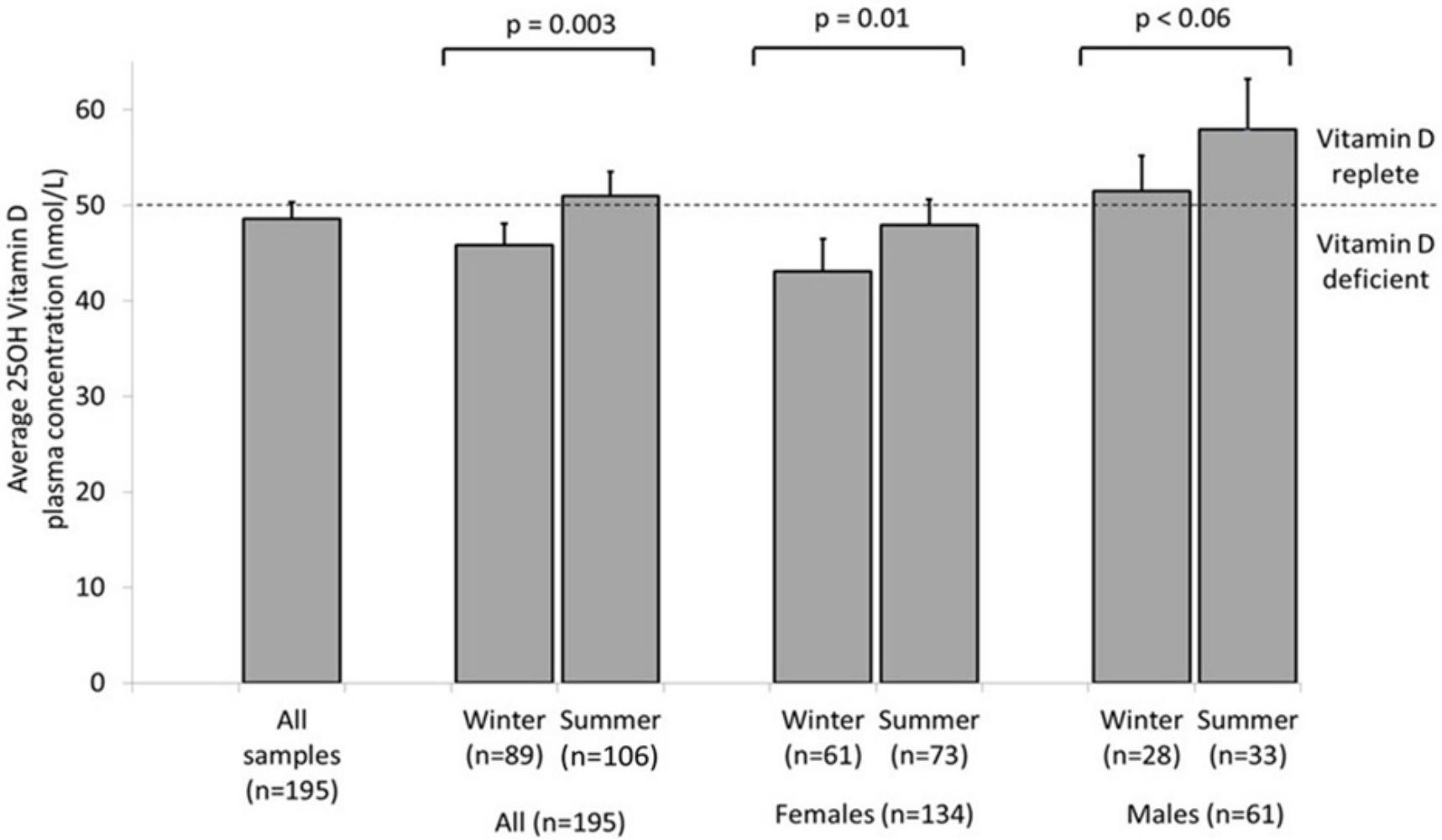


Figure 2: Vitamin D plasma concentration; for the entire study population (n=195) by sex and season. Bars represent 95% confidence intervals.

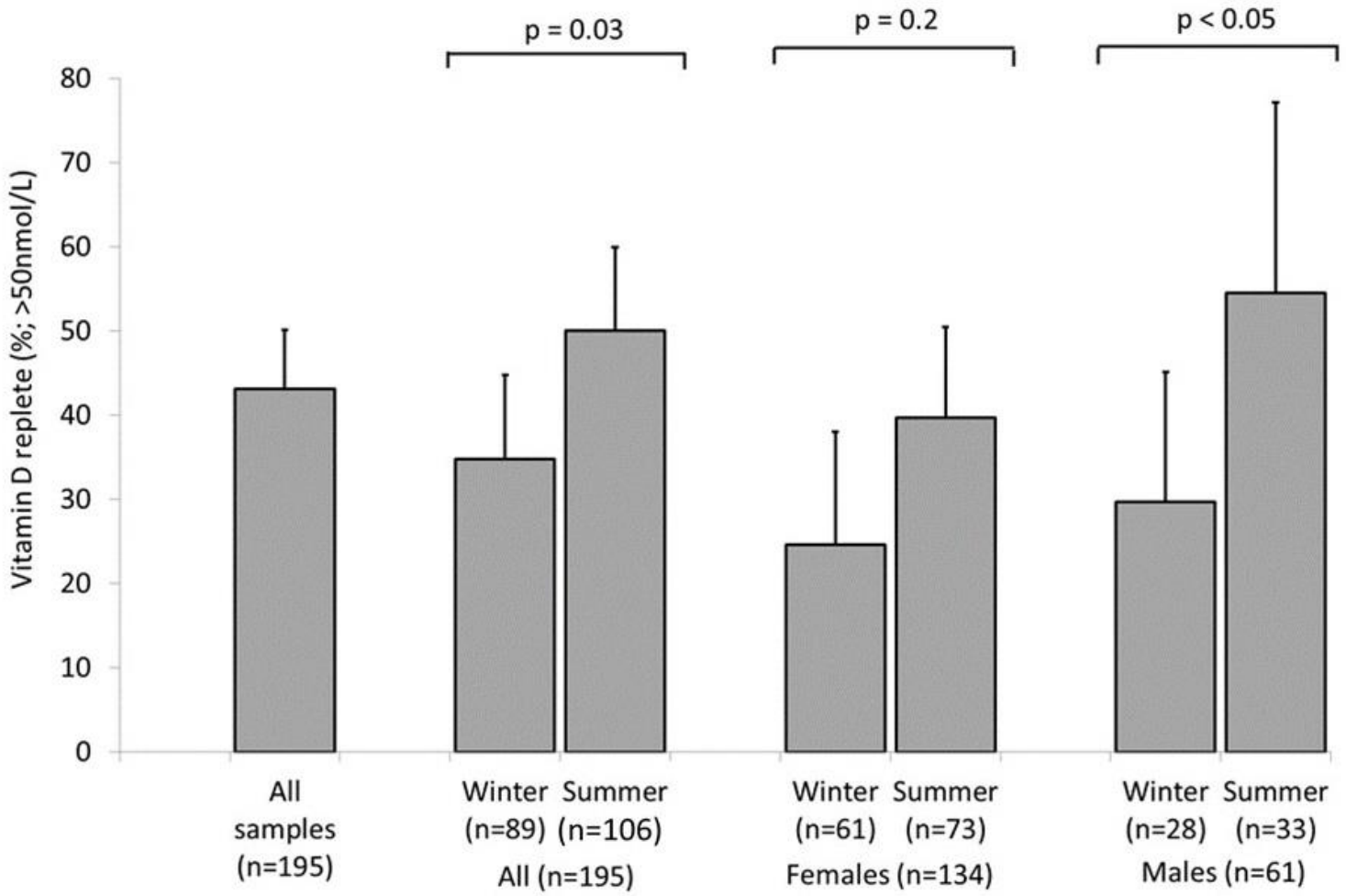


Figure 3: Vitamin D replete (25OHD concentrations ≥50 nmol/l) **for the entire study population (n=195) by sex and season.** Bars represent 95% confidence intervals.

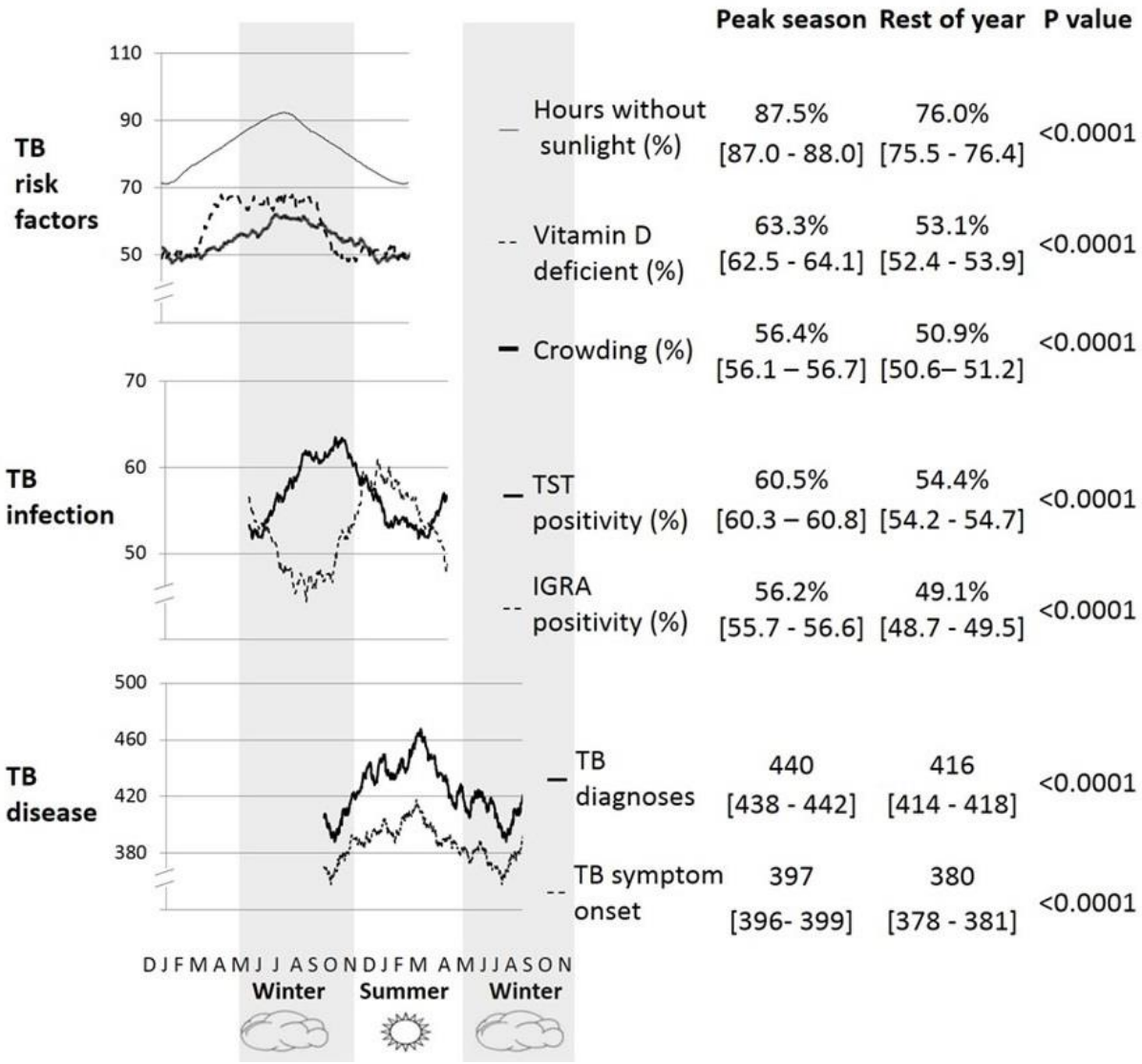


Figure 4: Schematic demonstrating the seasonality of TB risk factors in midwinter, infection in late winter and early summer, and disease in midsummer**.** Letters represent months of the year. Trendlines represent 6-month moving averages of raw data that differ slightly from the 6-monthly actual counts shown in Table 4 (Page 37) owing to the latter being raw data. In the "TB risk factors" section, hours without sunlight is represented by the thin continuous black trendline, vitamin D deficiency by the dashed black line, and crowding by the thick continuous black trendline. The numbers stated for the incidence of TB symptom onset and TB diagnoses are the 6-month moving average data corresponding to those in Table 4 (Page 37).

Chapter 3: Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru

This chapter is adapted from the peer-reviewed, published paper Wingfield et al "Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru." PLOS Medicine. 2014 Jul 15;11(7):e1001675. doi: 10.1371/journal.pmed.1001675.[19] The paper is bound in PDF format in Appendix 2 of this thesis. The candidate's contribution to this study was final data collection, data management, data analysis and analysis strategy, study write-up and dissemination of findings. The candidate was not involved in study design or original data collection.

Following evaluation of the association between TB and poverty including assessment of seasonal poverty-related risk factors such as vitamin D deficiency and household crowding, this PhD research went on to describe hidden costs of TB illness and create a clinically-relevant catastrophic TB-related costs threshold. The threshold was subsequently endorsed by the World Health Organisation for use in measurement of catastrophic costs during its roll-out of a TB Costs Measurement Tool in sentinel country sites in 2015.[79]

Introduction

Whilst many countries aim to offer "free" TB treatment to their patients, this may only cover some diagnostic tests and anti-mycobacterial medications. Patients and their households may incur hidden costs, be they direct "out-of-pocket" expenses such as transport, symptom-relieving medicines, additional food or indirect expenses associated with lost income.[24,25,80,81]

In its "Global TB strategy for tuberculosis prevention, care and control" at the 67th World Health Assembly in May 2014, the World Health Organization adopted a target of eradicating catastrophic

costs for TB-affected families by 2035.[14] However, hidden TB-related costs remain understudied and, at the time of writing, consensus about defining catastrophic costs is awaited.[14,22,28,82,83] Some catastrophic costs definitions have incorporated symptoms of financial shock and coping mechanisms.[84,85] Others have used operational thresholds of total costs of 10-25% of that household's annual income [83,86,87] or 40% or more of that household's "capacity to pay".[88,89] Recently, concerns have been raised that the current approach of measuring catastrophic costs using "out-of-pocket" payments is too narrow because it overlooks lost income and consequently risks misinforming policy makers.[23,24] Thus, there is an urgent need to improve indicators of financial risk to better inform health policy guidance.[13,90,91] However, although there is broad agreement that some vulnerable TB-affected households will require social protection (such as socioeconomic support) to avoid catastrophic costs, more evidence is needed to define such costs and characterise their importance.[13,25,28,29,88–93]

We prospectively quantified changes in income and hidden costs prior to and throughout treatment of patients with non-MDR and MDR TB in impoverished shantytowns surrounding northern Lima/Callao, Peru. The aims of the study were to better characterise TB-related costs, their association with adverse TB outcome, and contribute to an evidence-based definition of catastrophic costs that is both clinically and financially relevant. The study hypothesis was that catastrophic costs of TB-affected households are independently associated with adverse TB outcomes in TB patients.

Methods

Ethical approval

The internationally accredited ethical committee of the Universidad Peruana Cayetano Heredia, Peru, and Imperial College London, UK, approved the project. All interviewed participants gave written informed consent.

Study design and participants

We conducted a prospective cohort study of TB patients and a baseline case-control study comparing them with healthy controls. From October 2002 to November 2009, in collaboration with the Peruvian TB program, all consecutive patients with laboratory-proven pulmonary TB were invited to participate in the study. All interactions between the research team and the participants occurred during household visits. Until November 2012, patients were followed-up for recurrent TB by monitoring TB treatment records and re-visiting each household approximately every 3 years to enquire about TB diagnoses. From December 2006 to December 2007, control households were selected using random number tables from an up to date satellite map and were invited to participate during a household visit. In the case that all control participants were unavailable or declined then the nearest neighbouring household was instead invited to participate. Controls were not matched to cases because the study aimed to characterise the effect of relevant exposures including sex, age and socioeconomic position on the outcome variables of catastrophic costs and adverse TB outcome. Inclusion criteria in both cases and controls included age more than 15 years. Exclusion criteria included declining or being unable to give informed written consent. Both for the cohort and the baseline case control study, the sample size was opportunistic and consequently no power calculations were performed.

Study setting

The study was conducted in Ventanilla, 16-periurban contiguous shantytowns in northern Lima/Callao, Peru, with an estimated population of 277,895 people, and frequent poverty (32% of inhabitants live on ≤1 US dollar per day). During the study period. the annual TB notification rate in Ventanilla was 162 new cases per 100,000 people, higher than the rest of the country which was estimated to be 106 per 100,000 people annually.[26]

TB was treated by the National TB Program in community health posts where sputum smear was offered free of charge to all patients and chest radiographs to selected patients. TB patients received their anti-TB directly observed therapy (DOT) free of charge at their local health post, administered by the National TB program.

Variables

Operational definitions of the key study variables (TB disease, TB treatment phases, TB adverse outcome, and TB costs) are summarised in Box 1.

Patients were defined as having MDR TB if they were initially prescribed an MDR treatment regimen or sputum testing was positive for MDR TB by the Microscopic-Observation Drug-Susceptibility (MODS) assay or the proportions assay. All other patients recruited to the study were defined as having non-MDR TB.

For both patients with MDR and non-MDR TB, stages of treatment were operationally defined as follows: “pre-treatment” was from self-reported onset of TB-related symptoms until treatment initiation; “intensive treatment phase” was the first two months of TB treatment; “continuation treatment phase” was the four months immediately following the “intensive treatment phase”; “during treatment” was the period of time from the start of “intensive treatment phase” to the end of the “continuation treatment phase”; and “entire illness” was from TB-related symptom onset to the end of the “continuation treatment phase”.

Early TB treatment outcome for each patient was assessed by the TB program at the time of treatment cessation and was not influenced by this research. These early TB treatment outcome assessments were based on sputum microscopy results that are insensitive to treatment failure.[94,95] Therefore, we also collaborated with the TB program in continuous surveillance of TB program treatment records and re-visited each patient in their home to check for TB recurrence that we defined as TB re-treatment within 30 months from the date that treatment started (in most cases 2 years from treatment cessation). We defined good TB outcome as cure without recurrence. We

defined adverse TB outcome as death during treatment, treatment abandonment, treatment failure or recurrence. Patients who were transferred away or were lost to follow-up were considered to have undefined outcome.

Data source and measurement

A questionnaire was developed locally, piloted, refined, and then used to interview patients and collect socio-demographic data concerning household income and expenses throughout TB illness. Interviews were conducted at baseline with both TB patients and controls. For patients this baseline interview occurred prior to or at the time that treatment commenced. The baseline (but not subsequent) interview included detailed assessment of: household assets ownership; access to basic services; and education level. Patients were subsequently interviewed after 2, 4, 6, 8, 12, 16, 20 and 24 weeks of treatment. At all baseline and subsequent interviews, questions characterized earnings, income, expenses, employment (paid or unpaid), days unable to work due to illness, additional household food expenditure due to TB illness, and crowding. Household debts were assessed at recruitment and subsequently at 24 weeks of treatment.

As in previous research, TB-related costs were categorized as "direct expenses" [25,79,96,97] and "lost income" [79,96,98] incurred since the previous interview. All costs and incomes were quantified in cash amounts in Peruvian Soles (average 1 US dollar equivalent to 2.9 Peruvian Soles during the study period). Inflation and especially exchange rates varied considerably during the study period, so actual costs were reported without adjustments in order to be more informative to users including policy makers. Table 5 (Page 60) shows the table of annual inflation in Peru and average annual exchange rates 2002-2009. To further facilitate interpretation internationally, costs were also expressed as the proportion of the average monthly income of all patient households. Also, to assess impact on the patient households, costs were calculated as a proportion of the same household's annual income.

"Direct ("out-of-pocket") expenses" included direct medical expenses (medical examinations and prescribed medicines) and direct non-medical expenses (natural non-prescribed remedies, TB-care

related transport, extra food, and other miscellaneous expenses). “Lost income” (indirect expenses) was the income the patient estimated that the household lost due to TB illness or tuberculosis-related time off work (such as attending clinics) since the previous interview, measured in Peruvian Soles. Days of work lost due to TB illness could not be used to directly calculate lost income because salaried employment with fixed rates of remuneration were uncommon in this setting. “Total expenses” were direct expenses plus lost income. “Earnings” were defined as the monthly money actually received by the household and “income” was defined as the monthly money earned by the household *plus* lost income. Household debts at recruitment and total household debts (sum of debts at recruitment plus debts at 24 weeks of recruitment) included both formal debts (e.g. bank loans) and informal debts (e.g. money borrowed from friends and family).

For all participants, height and weight were measured and body mass index (BMI) was calculated. Poverty was measured using a composite household poverty index in arbitrary units derived by principal component analysis from 13 variables, as described.[15]

A threshold for catastrophic costs was calculated by plotting the sensitivity, specificity and population attributable fraction for adverse TB outcome against total household expenses as a proportion of annual income. In order to assess the strength of this new definition of catastrophic costs and in accordance with relevant recent studies,[83,87] a sensitivity analysis was also performed comparing the association of other existing catastrophic costs thresholds (including total expenses equal to or greater than 10%, 15% or 25% of annual income) with adverse TB outcome.

Data analysis

Continuous data were summarized by their arithmetic means and their 95% confidence intervals (CI) whether the data was Gaussian or non-Gaussian because this approach is considered to be robust for health economics data analysis.[23,99,100] Furthermore, because of the skewed nature of some expenditure data, most median values were 0 or close to 0 limiting the descriptive usefulness of presenting median values. Any direct expenses, lost income, or annual income recorded as “zero” or

missing was replaced with 0.5 soles per day (i.e. the midpoint of zero and the lowest unit of measurement, 1 Peruvian Sol). Means were compared with the Student's t-test. Categorical data were summarised as proportions with 95% CI and were compared with the z-test of proportions. Univariable regression analyses examining differences between patients with MDR and non-MDR TB and controls were adjusted for sex because of under-recruitment of male controls due to their availability.

The association between catastrophic costs and adverse TB outcome was explored through both univariable and multivariable analysis to determine odds ratios (OR). The likelihood ratio test was used to test for trend and interaction between variables. Non-Gaussian continuous variables such as total costs as a proportion of annual income were transformed to their base-10 logarithm for regression analysis. All the variables associated ($p<0.15$) with adverse TB outcomes in univariable analysis and all predetermined presumed confounding variables (age, poverty score, previous TB episode, symptom duration, and current MDR TB) were concurrently included in a multivariable model.[101]

Population attributable fractions were calculated using the Stata program "aflogit" function, which computes population attributable fraction estimates while adjusting for the reciprocal confounding effect of covariates on the association of interest. The population attributable fraction of an exposure was interpreted as the proportion of adverse TB outcomes that would be averted by eliminating that exposure, both unadjusted and adjusted for known confounding factors. All p-values were two-sided and statistical analyses were performed using the Stata program (StataCorp, version 10).

Results

Participants

During the study period, the Peruvian TB program within the study site of Ventanilla registered 1,014 patients. We located 99% of these registered TB patients of whom 95% (n=966) met inclusion criteria. Of these eligible patients, 1% (n=10) declined, 8% (n=80) were excluded because they completed fewer than half of our planned research interviews and data are presented for the remaining 91% (n=876). 11% (n=93) of patients recruited had MDR TB. 487 controls were also recruited and had only a baseline interview. The characteristics of the study population were summarized in Table 1, Page 20, Chapter 1.

Earnings and debt

Patients earned more per month pre-treatment than during treatment (510 [95% CI 481-539] versus 434 [95% CI 415-453] Peruvian Soles, p<0.001, Table 6, Page 61) or the continuation treatment phase (454 [95% CI 431-477] Peruvian Soles, p<0.001) and earned least during the intensive treatment phase (379 Peruvian soles [95% CI 358-400], p<0.001). During all treatment phases, patients with MDR TB tended to earn less than TB patients with non-MDR TB (Table 6, Page 61). Household debts at recruitment were greater in controls than patients with TB (812 [95% CI 507-1117] versus 383 [95% CI 292-474] Peruvian Soles, p=0.004) but there was no difference between household debts of patient with MDR and non-MDR TB (497 [95% CI 381-613] versus 511 [95% CI 482-540] Peruvian soles, p=0.8). Household debts decreased from 383 Peruvian soles [95% CI 292-474] at recruitment to 296 Peruvian soles [95% CI 176-414] at 24 weeks of treatment. Households with above cohort median total debt were more likely to incur catastrophic costs (OR 1.58 [95% CI 1.17-2.14] p=0.003). Households with above cohort median increase in debt from recruitment to 24 weeks were also more likely to incur catastrophic costs (OR 1.74 [95% CI 1.10-2.77] p=0.003).

Outcome data

725 (83%) of patients had a defined TB outcome at follow-up. Of these patients, 166 (23%) had adverse TB outcome, 40% (n=67) due to treatment abandonment, 22% (n=36) due to treatment failure, 12% (n=15) due to death during treatment, and 26% (n=48) due to TB recurrence.

Costs data

Constituent direct expenses and lost income: Constituent direct expenses and lost income are summarized in Figure 5 (Page 70). Throughout the entire illness, medical and non-medical expenses were similar (49% [95% CI 43-55] versus 51% [95% CI 47-54] of total direct costs, p=0.7). Medical expenses were greatest pre-treatment, were higher than non-medical costs and constituted almost two-thirds of overall direct expenses (0.20 [95% CI 0.18-0.22] versus 0.13 [95% CI 0.11-0.15] monthly incomes, p<0.001). Conversely, during treatment non-medical expenses were higher than medical expenses and constituted approximately two-thirds of overall direct expenses (0.22 [95% CI 0.20-0.24] versus 0.14 [95% CI 0.12-0.16] monthly incomes, p<0.001). Direct expenses were higher pre-treatment than during treatment (0.52 [95% CI 0.46-0.59] versus 0.41 [95% CI 0.37-0.44] monthly incomes, p<0.001) whereas lost household income was lower pre-treatment than during treatment (0.60 [95% CI 0.50-0.69] versus 0.75 [95% CI 0.68-0.82] monthly incomes, p<0.005). Lost household income was higher than direct expenses throughout all treatment phases with the greatest difference during the intensive treatment phase (69% lost income [95% CI 61–77], Figure 5, Page 70).

Total expenses: In addition to direct expenses and lost income, total expenses are summarized in Figure 5, Page 70. Total expenses were similar pre-treatment versus during treatment (1.1 [95% CI 1.0-1.2] versus 1.2 [95% CI 1.1-1.2] monthly incomes, p=0.6). Total expenses (1.12 [95% CI 0.99-1.25] versus 0.62 [95% CI 0.56-0.68] monthly incomes, p<0.001), direct expenses (0.52 [95% CI 0.46-0.59] versus 0.19 [95% CI 0.16-0.22] monthly incomes, p<0.001) and lost income (0.6 [95% CI 0.50-0.69] versus 0.43 [95% CI 0.38-0.48], p=0.001) were significantly higher pre-treatment than during

intensive treatment phase. Total expenses (0.62 [95% CI 0.56-0.68] versus 0.54 [95% CI 0.49-0.59] monthly incomes, p=0.01) and lost income (0.43 [95% CI 0.38-0.48 versus 0.32 [95% CI 0.28-0.36], p<0.001) were higher in intensive than continuation treatment phase but there was no difference in direct expenses between these treatment phases (0.19 [95% CI 0.16-0.22] versus 0.22 [95% CI 0.20-0.23], p=0.07). When total expenses were examined per month, monthly intensive treatment phase total expenses were approximately double those of continuation treatment phase.

Poverty and expenses: TB patients were poorer than controls (58% [95% CI 55-61] versus 51% [95% CI 47-56] above control mean, p<0.02, Table 1, Chapter 1, Page 20). In poorer households, direct expenses were lower (mean direct expenses of poorest households 330 [95% CI 287-373], poor households 418 [95% CI 351-485], and least poor households 435 Peruvian soles [95% CI 380-490], p<0.001, Figure 6, Page 72) but total expenses made up a greater proportion of that household's annual income (poorest households 48% [95% CI 35-50], poor households 47% [95% CI 24-70], and least poor households 27% [95% CI 20-34], p<0.001, Figure 6, Page 72).

Main findings

Catastrophic costs: A threshold of 20% of total expenses as a proportion of annual household income was defined as catastrophic because this threshold had the highest sensitivity, specificity and population attributable fraction for association with adverse outcome (Figure 7, Page 73). Catastrophic costs were incurred by 345 households (39%). Incurring catastrophic costs was independently associated with MDR TB (OR 1.61 [95% CI 0.98-2.64], p<0.06), more days not working pre-treatment (OR 1.00 [95% CI 1.00-1.01], p=0.03), greater debts at recruitment (OR 1.00 [95% CI 1.00-1.00], p=0.02), being male (OR 2.16 [95% CI 1.57-2.96], p<0.001), older (OR 1.01 [95% CI 1.00-1.03], p=0.02), poorer (OR 1.25 [95% CI 1.15-1.36], p<0.001) and not in paid employment (OR 1.86 [95% CI 1.23-2.79], p=0.003, Table 7, Page 62). Households of patients who had MDR TB were more likely to incur catastrophic costs (54% MDR [95% CI 43-64] versus 38% non-MDR [95% CI 34-41],

p<0.003, Figure 8, Page 74). When the catastrophic costs multivariable regression analyses were repeated with total costs as a proportion of annual income analysed as a continuous outcome variable (instead of a dichotomous variable above versus below a threshold indicating catastrophic costs), the results and patterns of significance were similar (Table 8, Page 63).

Catastrophic costs and adverse TB outcome: Of the 725 patients with both TB outcome and catastrophic costs data, 166 (23%) had an adverse TB outcome. In multivariable regression analysis, having MDR TB was most strongly associated with adverse TB outcome (OR 8.4 [95% CI 4.7–15], p<0.001). Having had previous TB (OR 2.1 [95% CI 1.3-3.5], p=0.005), having more days off work prior to TB diagnosis (OR 1.01 [95% CI 1.00-1.01], p=0.02) and incurring catastrophic costs (OR 1.7 [95% CI 1.1–2.6], p=0.01, Table 9, Page 64, and Figure 9, Page 75) were also independently associated with adverse TB outcome. When the adverse TB outcome multivariable regression analyses were repeated with total costs as a proportion of annual income analysed as a continuous outcome variable (instead of a dichotomous variable above versus below a threshold indicating catastrophic costs), the results and patterns of significance were similar (Table 10, Page 65). The likelihood ratio test did not reveal any interaction between having MDR TB and incurring catastrophic costs (whether analysed using quantiles of costs as a continuous variable or using our catastrophic costs threshold).

Population attributable fraction. The unadjusted population attributable fraction of adverse TB outcomes explained by catastrophic costs was 26% [95% CI 14–36], similar to MDR TB 23% [95% CI 17–28]. When catastrophic costs, MDR TB and previous TB episode were included in the multivariable regression model, the adjusted population attributable fraction of adverse TB outcomes explained by catastrophic costs and MDR TB was similar; 18% [95% CI 6.9–28] for catastrophic costs and 20% [95% CI 14–25] for MDR TB.

Sensitivity analysis of other catastrophic costs thresholds. Using a threshold of total costs of 10% or more of annual income, 578 patients (66%) incurred catastrophic costs. When this threshold was increased to total costs of 15% or more of annual income, 457 patients (52%) incurred catastrophic

costs. Finally, at a threshold of total costs of 25% or more of annual income, 281 patients (32%) incurred catastrophic costs. When these thresholds were included in the multivariable regression models, it was found that catastrophic costs at a threshold of 10% or more, or 15% or more, of annual income were not independently associated with adverse TB outcome (Table 11, Page 66, and Table 12, Page 67). Conversely, catastrophic costs at a threshold of 25% of annual income were independently associated with adverse TB outcome (Table 13, Page 68).

Discussion

In this prospective cohort study of impoverished TB patients in Peruvian shantytowns, accessing free TB care was expensive for poor TB patients, especially those with MDR TB. Our novel findings also define the evidence-based threshold of total costs greater than 20% of annual income as catastrophic for TB-affected households. Moreover, an additional sensitivity analysis revealed that other recognised catastrophic costs thresholds (such as expenses equal to or greater than 10% and 15% of annual income) did not identify any association between catastrophic costs and adverse TB outcome in this setting. Our new definition is innovative in demonstrating the strong association between this 20% catastrophic costs threshold and the increased chances of adverse TB outcome, independent of MDR TB status. Our population attributable fraction analysis supports this observation by implying that a similar proportion of adverse TB outcomes may be averted by eliminating catastrophic costs or MDR TB from the study population. Overall, our findings suggest that the costs imposed on TB-affected households are not only financially but also clinically relevant and highlight the importance of financial circumstances on TB epidemiology, outcome and control.

As in previous studies,[24,25,80] poorer people incurred the most catastrophic costs which they were less able to afford, probably causing further impoverishment.[23,33] In agreement with other findings, our results indicate that costs as a proportion of that household's income indicate economic challenge better than actual monetary expenditures: this highlights the "medical poverty trap" that as incomes

decrease, proportional costs increase.[79,102] In addition to exemplifying this medical poverty trap, our results also show that being poorer was independently associated with incurring catastrophic costs. Catastrophic costs in poor households can lead to financial shock: reducing consumption below minimum needs; selling assets; and taking children out of education. These actions may in turn increase stigmatization.[84,85,103,104] Moreover, TB principally affects the most economically productive age group and patient and household income decreases post-diagnosis [79] and may not return to pre-diagnosis levels. Our study adds a new dimension to the social protection TB literature by showing how catastrophic costs can also have significant clinical implications: loss of income and increasing hidden costs have previously been associated with poor treatment adherence and high dropout rates in TB patients [25,33,105] but their independent effect on long term TB outcome has not been previously characterized. We hypothesize that the relationship we found between catastrophic costs and adverse TB outcome may relate to a number of factors along the causal pathway from TB susceptibility to illness to recurrence including: inadequate nutrition due to lower food spending, more severe disease (both MDR and non-MDR TB), and barriers to cure due to the disproportionate hidden costs associated with adherence to and completion of treatment. These adverse TB outcomes associated with catastrophic costs may increase TB and MDR-TB transmission, especially in poorer households. Thus catastrophic costs may worsen TB control.

Regardless of the mechanisms mediating the association between catastrophic costs and adverse TB outcome, the policy implications of our findings are clear: future TB prevention strategies should incorporate social protection to mitigate decreased economic production, loss of employment, TB-associated poverty, and reduce the clinical vulnerability of TB patients. This highlights the potential role of social protection not just as a poverty-reduction strategy, but also as a tool to improve disease control and, ultimately, health.[90,91]

Our previous social protection intervention project “ISIAT” provided evidence that in Peru multidisciplinary social protection intervention can improve adherence and completion of TB

treatment and prophylaxis.[15] Social protection interventions targeting disadvantaged and vulnerable populations have shown much promise in Latin America [106] with conditional cash transfer projects such as "Progresa" in Mexico.[107] In order for these programs to be adopted on a larger scale and reduce the social health gradient, they require a rigorous evidence base that is currently lacking. Our present study suggests that by reducing catastrophic costs, social protection has the potential to protect families from TB illness and deepening poverty.[84,108]

Despite TB treatment being free of direct charges in Peru, overall TB-affected households' costs were high and similar pre-treatment versus during treatment. Regardless of MDR status, higher total expenses were incurred in those who had longer symptom duration, consistent with the known association of increased expenses and diagnostic delay.[30] A strength of our study is that it analysed patients with both MDR and non-MDR TB and found that expenses as a proportion of household annual income were significantly higher in MDR patients as has been noted in other Latin American countries.[109,110]

Medical expenses made up the largest proportion of pre-treatment direct expenses, probably because TB care was only provided free of charge when TB was being tested for or after TB was diagnosed. Consequently, formal medical care for the presenting illness was often expensive for the patient prior to TB being suspected and/or diagnosed.[32,111] We found no evidence of healthcare providers requesting the "informal" or "under the table" costs that have been reported in other countries.[32]

Extending findings from previous studies,[25,79,80] lost income formed the majority of the economic burden of total expenses and TB patients, especially those with MDR TB, were more likely than controls to have a lower income, to be without paid work or to be missing work due to TB-related illness. In addition, having more days off work due to TB illness was independently associated with having an adverse TB outcome. These results suggest that the socioeconomic and employment situation of TB patients is often precarious and this may negatively impact their health, as has been

found in another study.[112] Indeed, our finding that having more days off work due to TB illness was independently associated with both incurring catastrophic costs and having an adverse TB outcome suggests that TB illness in such patients may be more severe or advanced and financial shock more likely.

Some definitions of catastrophic costs incorporate signs of financial shock when a household is forced to employ coping mechanisms such as: sacrifice of basic needs; selling assets; selling household items; removing children from education; and incurring formal or informal debt.[84,85,103,104,113,114] Others have defined costs as catastrophic when they exceed 10-40% of annual household or individual income [82,84,113,115] or 40% or more of a household's "capacity to pay" (the effective income remaining for non-food spending [88,89,103,116–118] but this approach may be too narrow and potentially misleading to policy makers because it overlooks lost income.[90,91] A strength of the threshold of catastrophic costs that our results defined is that it includes not only "out-of-pocket" direct expenses but also lost income and that it is proven to be clinically relevant. Specifically, our definition was calculated from serial, prospective data [82,85] of household expenses, actual household income [23,115] and long-term TB outcomes of a cohort of impoverished TB patients in Peruvian shantytowns. It has been estimated that 4% of households in Peru incur catastrophic health expenditure when aiming to meet overall health needs.[116] Rates of catastrophic health expenditure in our cohort were much higher than the general population. This may be due to TB-affected households being poorer, the TB treatment model in Peru having greater hidden costs for TB patients or that we included lost income to calculate catastrophic costs whereas only direct expenses were used in some other studies.[119]

The sensitivity analysis we performed showed that the proportion of patient households incurring catastrophic costs was similar to other studies that used varying thresholds: at a threshold of total costs of 10% or more of annual income, 65% of our cohort incurred catastrophic costs compared to 66-75% in related studies from Africa;[83,87] at a threshold of total costs of 15% and 25% or more of

annual income, 52% and 32% of our cohort had catastrophic costs compared to 68% and 48% respectively in a cohort from Africa.[87] More importantly, the sensitivity analysis also showed that thresholds of total costs of 10% and 15% or more of annual income were not independently associated with adverse TB outcome in this setting. Our results demonstrate that these previously published arbitrary thresholds for catastrophic costs that were defined without patient follow-up were not associated with adverse tuberculosis outcomes of TB patients in our setting. Thus our findings provide the first evidence-based threshold for clinically-relevant catastrophic costs and demonstrate a methodology to assess the generalizability of this threshold in other settings.

This study has several limitations. Firstly, cases and controls were not matched in this study because controls were specifically included to provide an estimate of typical income and expenditure in this community to be compared with TB patients at baseline. Matching would have impaired this comparison. A baseline difference was noted in debts at recruitment, a proxy for "dissaving". Poorer households have diminished access to establishments that offer formal loans (e.g. banks) because of their uncertain repayment capacity and/or lack of requisites such as a national identity card.[15] However, even if controls had been matched to cases, controls may still have had higher debt than patients because households were not eligible for some loans due to serious ill health or if they were extremely poor.[15] Apart from debt, no other data was collected on specific "dissaving" coping mechanisms (including using savings, taking loans, taking children out of education, and selling assets). In the CRESIPT study (see Chapters 5 and 6), we overcame this deficiency and collected comprehensive dissaving data for analysis complementary to the direct and indirect costs data. In addition, despite costs being calculated at a household level (i.e. transport costs included both patients' and/or carers' transport costs), data was not collected on the indirect costs of lost work/labour for patients' guardians/carers for whom the loss may not be monetary (e.g. pastoralists or houseworkers). Secondly, the data available did not allow assessment of an existing WHO definition of catastrophic costs (40% or more of a household's capacity to pay)[120] against which other studies have compared.[12] Moreover, while the catastrophic costs threshold of ≥20% established by

this research was appropriate because adjusted population attributable fraction showed it to be associated with the greatest number of adverse TB treatment outcomes (hence eliminating catastrophic costs at this threshold would have the greatest impact on reducing adverse TB treatment outcomes), the sensitivity and specificity of the threshold were both low. However, the threshold was never intended to be equivalent to a "rule-in" or "rule-out" prognostic marker of the possibility of adverse TB outcome. Thirdly, we may have underestimated the financial effects of MDR TB because our questionnaires quantifying costs continued for only 6-months whereas patients with MDR TB are usually treated for 18 months or more. We decided a priori to analyse the catastrophic costs of both MDR and non-MDR patients together given their equal follow-up and small numbers of MDR TB patients. Fourthly, the study did not collect qualitative data on how the patients and their household members viewed the financial strain placed upon the household and what they perceived as "catastrophic"; this omission was corrected in the initial phase of the CRESIPT study as described in Chapters 5 and 6. Finally, our research demonstrates a new methodology that should be repeated in other settings to assess the external validity of our findings.

Conclusions

Despite free TB care, having TB disease was expensive for impoverished TB patients in Peru to afford. Higher relative costs were associated with greater likelihood of adverse TB outcome. Having MDR TB and incurring catastrophic costs were independently associated with a similar adjusted population attributable fraction for adverse TB outcome. Thus, catastrophic costs were an indicator of both financial and clinical vulnerability. Mitigating catastrophic costs through social protection interventions as well as diagnosing and treating MDR TB deserve attention in TB control programs. In conclusion, control interventions must consider TB as an infectious and socioeconomic problem and address both the clinical and financial aspects of this public health challenge.

Table 5: Annual inflation rate of the Peruvian Sol and exchange rate of the Peruvian Sol to the United States (US) Dollar, 2002-2009

Year	Inflation rate (%)	Exchange rate Peruvian Soles to US Dollar
2002	0.192	0.284
2003	2.261	0.287
2004	3.662	0.432
2005	1.618	0.484
2006	2.001	0.305
2007	1.779	0.319
2008	5.788	0.342
2009	2.935	0.334

Source: International Monetary Fund –World economic outlook 2011: a survey by the staff of the International Monetary Fund. Washington, DC: International Monetary Fund, 1980-2011; ISBN 978-1-61635-119-9
http://www.imf.org/external/pubs/ft/weo/2011/02/pdf/text.pdf

Table 6: Comparison of mean monthly earnings of patient households by treatment stage. Mean monthly earnings are shown in Peruvian Soles and in brackets as a proportion of mean monthly average cohort earnings. Confidence intervals below earnings are those of mean monthly earnings in Peruvian Soles. P values represent the difference in earnings between treatment stages by Student's t test. From left to right, data and p values correspond to all patients, non-MDR patients and MDR patients. In addition to the p values shown in the table, there was also a significant difference between intensive and continuation treatment phases in all (p<0.001) and non-MDR (p<0.001) patients but not in MDR (p=0.1) patients.

	Earnings as mean monthly Peruvian Soles and proportion of mean monthly average cohort earnings [95% CI]					
	All patients (n=876)	**p value**	**Non-MDR patients** (n=783)	**p value**	**MDR patients** (n=93)	**p value**
Pre-treatment (n=876)	510 (1.09) [481 - 539]	.	511 (1.09) [482 - 540]	.	497 (1.07) [381 - 613]	.
During treatment (n=876)	434 (0.93) [415 - 453]	<0.001	436 (0.94) [416 - 456]	<0.001	418 (0.90) [341 - 495]	0.09
Intensive treatment phase (n=876)	379 (0.81) [358 - 400]	<0.001	379 (0.81) [357 - 401]	<0.001	376 (0.81) [295 - 457]	0.1
Continuation treatment phase (n=876)	454 (0.97) [431 - 477]	0.001	457 (0.98) [434 - 480]	0.0003	424 (0.91) [339 - 509]	0.1

Table 7: Factors associated with incurring catastrophic costs**.** Factors associated (p<0.15) with catastrophic costs in univariable regression were included in the multivariable regression analysis (those not included are marked with a dot). 95% confidence intervals (95% CI) are shown in parenthesis. All patients (n=876) had data available and entered the univariable and multivariable logistic regression analyses. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease

	Univariable		Multivariable logistic regression	
	OR	P	OR	p
Demographics				
Age; mean years [95% CI]	1.02 [1.01-1.03]	0.001	1.01 [1.00-1.03]	0.02
Sex; males [95% CI]	1.86 [1.40-2.47]	<0.001	2.16 [1.57-2.96]	<0.001
Socioeconomic and health factors				
Completed secondary school; [95% CI]	0.73 [0.55-0.96]	<0.03	1.06 [0.77-1.46]	0.7
BMI; [95% CI]	0.97 [0.92-1.01]	0.2	. .	.
Previous TB episode; [95% CI]	1.48 [1.04-2.10]	0.03	1.16 [0.79-1.71]	0.5
Earnings at recruitment; [95% CI]	0.99 [0.99-1.00]	<0.001	NA NA	NA
Patient without paid employment; [95% CI]	1.42 [0.99-2.05]	<0.06	1.86 [1.23-2.79]	0.003
Debts at recruitment;* [95% CI]	1.00 [0.99– 1.00]	0.1	1.00 [1.00 - 1.00]	0.02
Poverty; [95% CI] household poverty score	1.26 [1.17-1.35]	<0.001	1.25 [1.15-1.36]	<0.001
Current tuberculosis episode				
Symptom duration; % [95% CI]	1.003 [1-1.005]	0.002	1.00 [1.00-1.00]	0.06
MDR; % [95% CI]	1.92 [1.25-2.96]	0.003	1.61 [0.98-2.64]	<0.06 .
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.02]	<0.001	1.00 [1.00-1.01]	0.03 .

* Debt at recruitment was used in the final multivariable regression model rather than total debt (debt at recruitment plus debt at 24 weeks of treatment) as only 461 patients had 24-week debt data available

Table 8: Factors associated with total costs as a proportion of annual income. Total costs as a proportion of annual income data had a non-Gaussian distribution so this variable was transformed to its base-10 logarithm for regression analysis. Factors associated (p<0.15) with increasing costs in univariable linear regression were included in the multivariable analysis (those variables not included are marked with a dot). 95% confidence intervals are shown in parentheses. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. All patients (n=876) had data available and were included in the univariable and multivariable linear regression analyses.

	Univariable		Multivariable logistic regression	
	Coefficient	P	Coefficient	P
Demographics				
Age; mean years [95% CI]	0.0053 [0.0028-0.077]	<0.001	0.0038 [0.0014-0.0061]	0.002
Sex; males [95% CI]	0.12 [0.056-0.19]	<0.001	0.12 [0.060-0.19]	<0.001
Socioeconomic and health factors				
Completed secondary school; [95% CI]	-0.19 [-0.18 - -0.054]	<0.001	-0.012 [-0.078-0.055]	0.7
BMI; [95% CI]	-0.0056 [-0.016 - 0.047]	0.3	. .	.
Previous TB episode; [95% CI]	0.12 [0.039-0.21]	0.004	0.074 [-0.0077-0.16]	0.08
Earnings at recruitment; [95% CI]	-0.00029 [-0.00036 - -0.00021]	<0.001	NA NA	NA
Patient without paid employment; [95% CI]	0.094 [0.010-0.18]	<0.03	0.13 [0.031-0.065]	0.001
Debts at recruitment; [95% CI]	0.000014 [0.000006 – 0.000038]	0.2	. .	.
Poverty; [95% CI] household poverty score	0.060 [0.044-0.076]	<0.001	0.048 [0.034-0.067]	<0.001
Current tuberculosis episode				
Symptom duration; % [95% CI]	0.0011 [0.00070-0.0016]	<0.001	0.00080 [0.00037-0.0012]	<0.001
MDR; % [95% CI]	0.17 [0.068-0.29]	0.001	0.075 [-0.028-0.18]	0.2
Days too unwell to work prior to treatment; [95% CI]	0.0024 [0.0014-0.0034]	<0.001	0.0010 [0.000059-0.0020]	<0.05 .

Table 9: Univariable and multivariable logistic regression of factors associated with adverse TB outcome**.** Adverse TB outcome was defined as death during treatment, treatment failure or abandonment, and recurrence of TB within 30 months of starting treatment. Factors associated (p<0.15) with adverse TB outcome in univariable regression were included in the multivariable regression analysis. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. 725/876 (83%) of patients had TB outcome data available and entered the univariable and multivariable logistic regression analyses.

	Univariable		Multivariable logistic regression	
	OR	p	OR	P
Demographics				
Age; mean years [95% CI]	1.01 [1.0-1.02]	0.06	1.00 [0.99-1.02]	0.6
Sex; males [95% CI]	1.53 [1.07-2.20]	0.02	1.25 [0.80-1.95]	0.3
Socioeconomic/health factors				
Completed secondary school; [95% CI]	0.66 [0.46-0.95]	<0.03	0.71 [0.45-1.11]	0.1
BMI; [95% CI]	0.93 [0.87-0.98]	0.01	0.95 [0.89-1.03]	0.2
Previous TB episode; [95% CI]	2.95 [1.92-4.52]	<0.001	2.11 [1.26-3.54]	0.005
Income at recruitment; per month in Peruvian soles; [95% CI]	1.00 [0.99 - 1.00]	0.2	NA	NA
Patient without paid employment at treatment; [95% CI]	1.47 [0.79-1.02]	0.1	1.25 [0.70-2.24]	0.5
Debt at recruitment;* [95% CI]	1.00 [0.99-1.00]	0.1	1.00 [0.89-1.12]	0.7
Poverty; [95% CI] household poverty score	1.10 [1.00-1.20]	<0.05	1.00 [1.00-1.01]	1.0
Current tuberculosis illness				
MDR; [95% CI]	8.38 [5.04-13.93]	<0.001	8.37 [4.67-15.0]	<0.001
Symptom duration; [95% CI]	1.00 [1.00-1.01]	<0.05	1.00 [1.00-1.01]	0.7
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.01]	<0.001	1.01 [1.00-1.01]	0.02
Catastrophic TB costs (20% or more of annual income); [95% CI]	2.36 [1.62-3.43]	<0.001	1.72 [1.11-2.64]	0.01

* Debt at recruitment was used in the final multivariable regression model rather than total debt (the sum of debt at recruitment plus debt at 24 weeks of treatment) as only 461 patients had 24-week debt data available

Table 10: Univariable and multivariable logistic regression of factors (including costs as a continuous variable) associated with adverse outcome**.** Adverse outcome is defined as death during treatment, treatment failure or abandonment, and recurrence of TB within 30 months of starting treatment. Total costs as a proportion of annual income data had a non-Gaussian distribution so this variable was transformed to its base-10 logarithm for regression analysis. Factors associated (p<0.15) with adverse outcome in univariable logistic regression were included in the multivariable logistic regression analysis. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. 725/876 (83%) of patients had outcome data available.

	Univariable		Multivariable logistic regression	
	OR	P	OR	P
Demographics				
Age; mean years [95% CI]	1.01 [1.0-1.02]	0.06	1.00 [0.99-1.02]	0.7
Sex; males [95% CI]	1.53 [1.07-2.20]	0.02	1.26 [0.81-1.95]	0.3
Socioeconomic and health factors				
Completed secondary school; [95% CI]	0.66 [0.46-0.95]	<0.03	0.72 [0.46-1.13]	0.2
BMI; [95% CI]	0.93 [0.96-1.00]	0.01	0.95 [0.89-1.02]	0.2
Previous TB episode; [95% CI]	2.95 [1.92-4.52]	<0.001	2.07 [1.24-3.48]	0.006
Income at recruitment; per month in Peruvian soles; [95% CI]	1.00 [0.99 - 1.00]	0.2	NA	NA
Patient without paid employment at treatment; [95% CI]	1.47 [0.79-1.02]	0.1	1.24 [0.69-2.22]	0.5
Debts; [95% CI]	1.00 [0.99-1.00]	0.1	1.00 [1.00-1.00]	0.8
Poverty; [95% CI] household poverty score	1.10 [1.00-1.20]	<0.05	1.00 [1.00-1.00]	1.0
Current tuberculosis illness				
MDR; [95% CI]	8.38 [5.04-13.93]	<0.001	8.38 [4.68-15.0]	<0.001
Symptom duration; [95% CI]	1.00 [1.00-1.01]	<0.05	1.0 [1.00-1.00]	0.7
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.01]	<0.001	1.00 [1.00-1.01]	0.2
Total costs as a proportion of annual income (log transformed)*; [95% CI]	2.53 [1.77-3.61]	<0.001	1.84 [1.18-2.88]	0.007

*if the non-Gaussian original total costs as a proportion of annual income is used instead of the transformation to base-10 logarithm the association is similar: Univariable logistic regression OR 1.69 [95% CI 1.33-2.15] p<0.001, multivariable logistic regression (same pattern of significance as shown) OR 1.56 [95% CI 1.22-1.98], p<0.001

Table 11: Univariable and multivariable logistic regression of factors (including 10% threshold for catastrophic costs) associated with adverse outcome. Adverse outcome is defined as death during treatment, treatment failure or abandonment, and recurrence of TB within 30 months of starting treatment. Factors associated (p<0.15) with adverse outcome in univariable logistic regression were included in the multivariable logistic regression analysis. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. 725/876 (83%) of patients had outcome data available and entered the univariable and multivariable logistic regression analyses. In contrast to Table 9 (Page 64), in this table total costs ≥10% of annual income were used as the threshold for catastrophic costs

	Univariable		Multivariable logistic regression	
	OR	p	OR	P
Demographics				
Age; mean years [95% CI]	1.01 [1.0-1.02]	0.06	1.01 [0.99-1.02]	0.5
Sex; males [95% CI]	1.53 [1.07-2.20]	0.02	1.37 [0.89-2.12]	0.2
Socioeconomic and health factors				
Completed secondary school; [95% CI]	0.66 [0.46-0.95]	<0.03	0.72 [0.46-1.12]	0.1
BMI; [95% CI]	0.93 [0.96-1.00]	0.01	0.95 [0.89-1.03]	0.2
Previous TB episode; [95% CI]	2.95 [1.92-4.52]	<0.001	2.13 [1.28-3.57]	0.004
Income at recruitment; per month in Peruvian soles; [95% CI]	1.00 [0.99 - 1.00]	0.2	NA	NA
Patient without paid employment at treatment; [95% CI]	1.47 [0.79-1.02]	0.1	1.34 [0.75-2.39]	0.3
Debts; [95% CI]	1.00 [0.99-1.00]	0.1	1.00 [1.00-1.00]	0.9
Poverty; [95% CI] household poverty score	1.10 [1.00-1.20]	<0.05	1.03 [0.92-1.16]	0.6
Current tuberculosis illness				
MDR; [95% CI]	8.38 [5.04-13.93]	<0.001	8.76 [4.90-15.7]	<0.001
Symptom duration; [95% CI]	1.00 [1.00-1.01]	<0.05	1.0 [1.00-1.01]	0.9
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.01]	<0.001	1.00 [1.00-1.01]	0.2
Catastrophic costs threshold ≥10% of annual income; [95% CI]	1.47 [1.01-2.14]	<0.05	1.03 [0.65-1.63]	0.9

Table 12: Univariable and multivariable logistic regression of factors (including 15% threshold catastrophic costs) associated with adverse outcome**.** Adverse outcome is defined as death during treatment, treatment failure or abandonment, and recurrence of TB within 30 months of starting treatment. Factors associated (p<0.15) with adverse outcome in Univariable logistic regression were included in the multivariable logistic regression analysis. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. 725/876 (83%) of patients had outcome data available and entered the Univariable and Multivariable logistic regression analyses. In contrast to Table 9 (Page 64), in this table total costs ≥15% of annual income were used as the threshold for catastrophic costs

	Univariable		Multivariable logistic regression	
	OR	P	OR	p
Demographics				
Age; mean years [95% CI]	1.01 [1.0-1.02]	0.06	1.00 [0.99-1.02]	0.5
Sex; males [95% CI]	1.53 [1.07-2.20]	0.02	1.3 [0.84-2.02]	0.2
Socioeconomic and health factors				
Completed secondary school; [95% CI]	0.66 [0.46-0.95]	<0.03	0.72 [0.46-1.12]	0.1
BMI; [95% CI]	0.93 [0.96-1.00]	0.01	0.95 [0.89-1.03]	0.2
Previous TB episode; [95% CI]	2.95 [1.92-4.52]	<0.001	2.14 [1.28-3.58]	0.004
Income at recruitment; per month in Peruvian soles; [95% CI]	1.00 [0.99 - 1.00]	0.2	NA	NA
Patient without paid employment at treatment; [95% CI]	1.47 [0.79-1.02]	0.1	1.30 [0.73-2.32]	0.4
Debts; [95% CI]	1.00 [0.99-1.00]	0.1	1.0 [1.0-1.0]	0.8
Poverty; [95% CI] household poverty score	1.10 [1.00-1.20]	<0.05	1.01 [0.90-1.14]	0.8
Current tuberculosis illness				
MDR; [95% CI]	8.38 [5.04-13.93]	<0.001	8.61 [4.82-15.4]	<0.001
Symptom duration; [95% CI]	1.00 [1.00-1.01]	<0.05	1.0 [1.00-1.00]	0.8
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.01]	<0.001	1.00 [1.00-1.01]	0.2
Catastrophic costs threshold ≥15% of annual income; [95% CI]	1.78 [1.25-2.53]	0.002	1.35 [0.88-2.09]	0.2

Table 13: Univariable and multivariable logistic regression of factors (including 25% threshold catastrophic costs) associated with adverse outcome**.** Adverse outcome is defined as death during treatment, treatment failure or abandonment, and recurrence of TB within 30 months of starting treatment. Factors associated (p<0.15) with adverse outcome in univariable logistic regression were included in the multivariable logistic regression analysis. NA indicates that earnings at recruitment was not entered into multiple regression analysis because it is strongly and acutely affected by having TB disease. 725/876 (83%) of patients had outcome data available and were included in the univariable and multivariable logistic regression analyses. In contrast to Table 9 (Page 64) in this table total costs ≥25% of annual income were used as the threshold for catastrophic costs

	Univariable		Multivariable logistic regression	
	OR	p	OR	P
Demographics				
Age; mean years [95% CI]	1.01 [1.0-1.02]	0.06	1.00 [0.99-1.02]	0.8
Sex; males [95% CI]	1.53 [1.07-2.20]	0.02	1.23 [0.79-1.92]	0.4
Socioeconomic and health factors				
Completed secondary school; [95% CI]	0.66 [0.46-0.95]	<0.03	0.70 [0.45-1.10]	0.1
BMI; [95% CI]	0.93 [0.96-1.00]	0.01	0.95 [0.89-1.03]	0.2
Previous TB episode; [95% CI]	2.95 [1.92-4.52]	<0.001	2.18 [1.30-3.65]	0.003
Income at recruitment; per month in Peruvian soles; [95% CI]	1.00 [0.99 - 1.00]	0.2	NA	NA
Patient without paid employment at treatment; [95% CI]	1.47 [0.79-1.02]	0.1	1.23 [0.69-2.20]	0.5
Debts; [95% CI]	1.00 [0.99-1.00]	0.1	1.00 [1.00-1.00]	0.8
Poverty; [95% CI] household poverty score	1.10 [1.00-1.20]	<0.05	1.00 [0.89-1.13]	0.9
Current tuberculosis illness				
MDR; [95% CI]	8.38 [5.04-13.93]	<0.001	8.30 [4.63-14.9]	<0.001
Symptom duration; [95% CI]	1.00 [1.00-1.01]	<0.05	1.00 [1.00-1.00]	0.8
Days too unwell to work prior to treatment; [95% CI]	1.01 [1.00-1.01]	<0.001	1.00 [1.00-1.01]	0.2
Catastrophic costs threshold ≥25% of annual income; [95% CI]	2.59 [1.81-3.71]	<0.001	1.98 [1.28-3.07]	0.002

Box 1: Glossary of operational definitions of TB disease, treatment, outcome, and costs

TB Disease

MDR: Those patients initially prescribed an MDR treatment regimen or who had a sputum test positive for MDR TB by the Microscopic-Observation Drug-Susceptibility (MODS) assay or the proportions assay

Non-MDR TB: All patients recruited to the study not meeting the definition for MDR TB

TB Treatment Phases*

Pre-treatment: the period of time from self-reported onset of TB-related symptoms until treatment initiation

Intensive treatment phase: the first two consecutive months of TB treatment

Continuation treatment phase: the four consecutive months immediately following intensive treatment phase

During treatment: the period of time spanning from the beginning of the intensive phase to the end of continuation treatment phases

Entire illness: the period of time from the onset of TB-related symptoms to the end of the continuation treatment phase

TB Treatment Outcome

Adverse tuberculosis outcome: patients who died during treatment (irrespective of cause), abandoned treatment, had treatment failure or had recurrent TB disease within 30 months of starting TB treatment

No adverse tuberculosis outcome: patients who were declared cured by the TB program and had no recurrence of TB disease within 30 months of starting treatment were defined as having good treatment outcome. Patients who were transferred away or were lost to follow-up were considered to have undefined outcome

TB Costs

Direct ("out of pocket") expenses: the sum of the direct medical expenses and direct non-medical expenses

Direct medical expenses: costs of medical examinations and medicines

Direct non-medical expenses: costs of natural remedies, TB-care related transport, extra food, and other miscellaneous expenses

Lost income (indirect expenses): the income the patient estimated that the household lost due to TB illness or tuberculosis-related time off work (such as attending clinics) since a) symptom onset until the recruitment interview and since b) the previous interview date until subsequent interviews

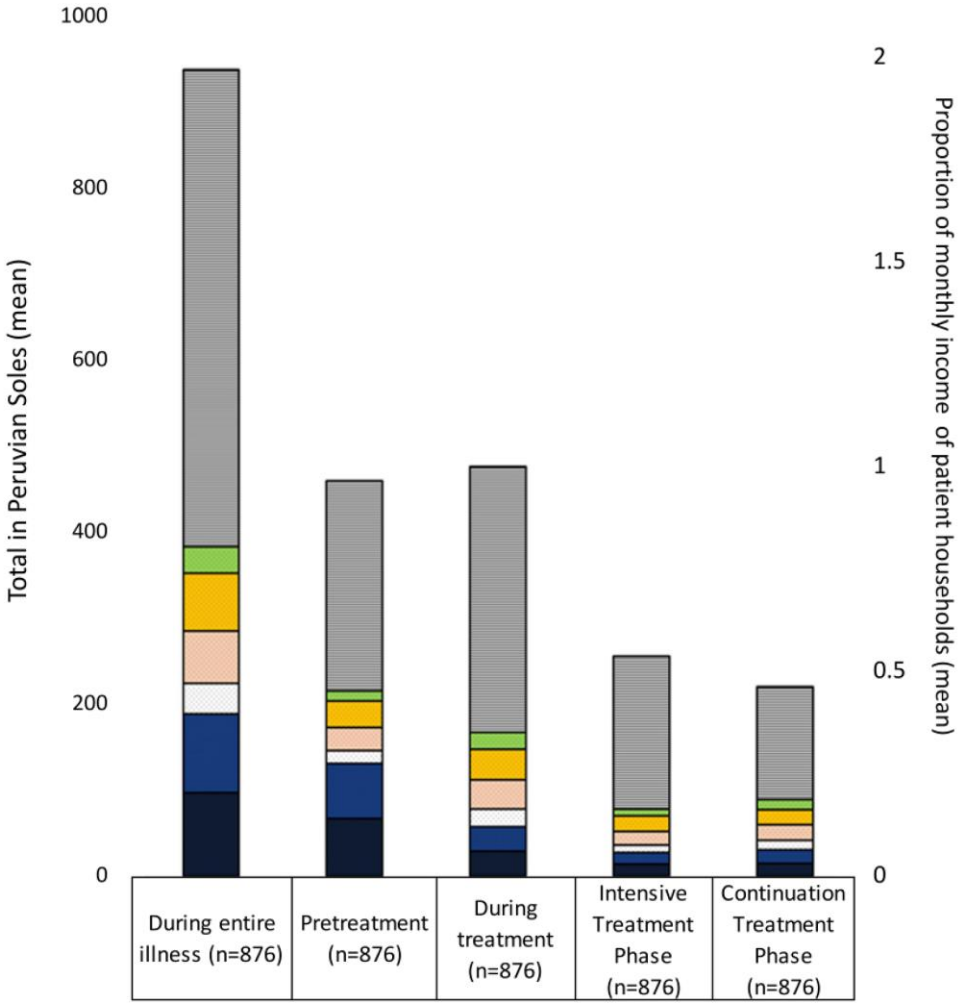
Total expenses: direct expenses plus lost income

Earnings: the monthly money actually received by the household

Income: the monthly money that would have been earned by the household if it were not TB-affected (earnings *plus* lost income)

Catastrophic costs: the threshold at which total household expenses as a proportion of annual income were most strongly associated with adverse tuberculosis outcome. The strength of the association was assessed by the highest sensitivity, specificity and population attributable fraction for adverse outcome

*These treatment definitions apply to all TB patients, irrespective of whether they had MDR or non-MDR TB



Lost income	569 (59)	251 (54)	317 (65)	182 (69)	135 (60)
Direct expenses: Other expenses	31 (8)	12 (5)	20 (12)	8 (10)	12 (13)
Direct expenses: Extra food	69 (18)	32 (15)	37 (21)	18 (24)	18 (20)
Direct expenses: Transport	62 (16)	27 (12)	35 (20)	17 (21)	19 (20)
Direct expenses: Natural remedies	36 (9)	15 (7)	21 (12)	9 (11)	12 (13)
Direct expenses: Clinical examinations	95 (24)	66 (30)	29 (17)	13 (16)	16 (17)
Direct expenses: Medicines	99 (25)	69 (31)	30 (18)	15 (18)	15 (17)
Direct expenses: Total direct expenses	392 (41)	221 (46)	172 (35)	80 (31)	92 (40)
Total expenses	961 (100)	472 (100)	489 (100)	262 (100)	227 (100)

Non-medical

Medical

Figure 5: Lost income, constituent direct expenses, and total expenses by treatment stage in mean soles and as a proportion of mean monthly household income. The top row shows lost income in mean Peruvian Soles and, in parenthesis, as a percentage of total expenses. The next 6 rows show constituent direct expenses in mean Peruvian Soles and, in parenthesis, as a percentage of total direct expenses. "Medical" expenses are defined as the sum of direct expenses for medicines (blue bar) and clinical exams (dark blue bar); "non-medical" expenses are defined as the sum of direct expenses for natural remedies, TB-care related transport, extra food, and other TB-related expenses. The lowermost two rows show total direct expenses (i.e. sum of medicines, clinical exams, natural remedies, transport, extra food, and other expenses) and total expenses in mean Peruvian soles and, in parenthesis, as a percentage of total expenses. P values represent the difference between treatment stages by Student's t test. 23/876 (2.6%) of the TB patient cohort had direct expenses of "0" Peruvian soles and 14/876 (1.6%) had total expenses of "0" Peruvian soles and thus these zero values were replaced with 0.5 Peruvian soles per day

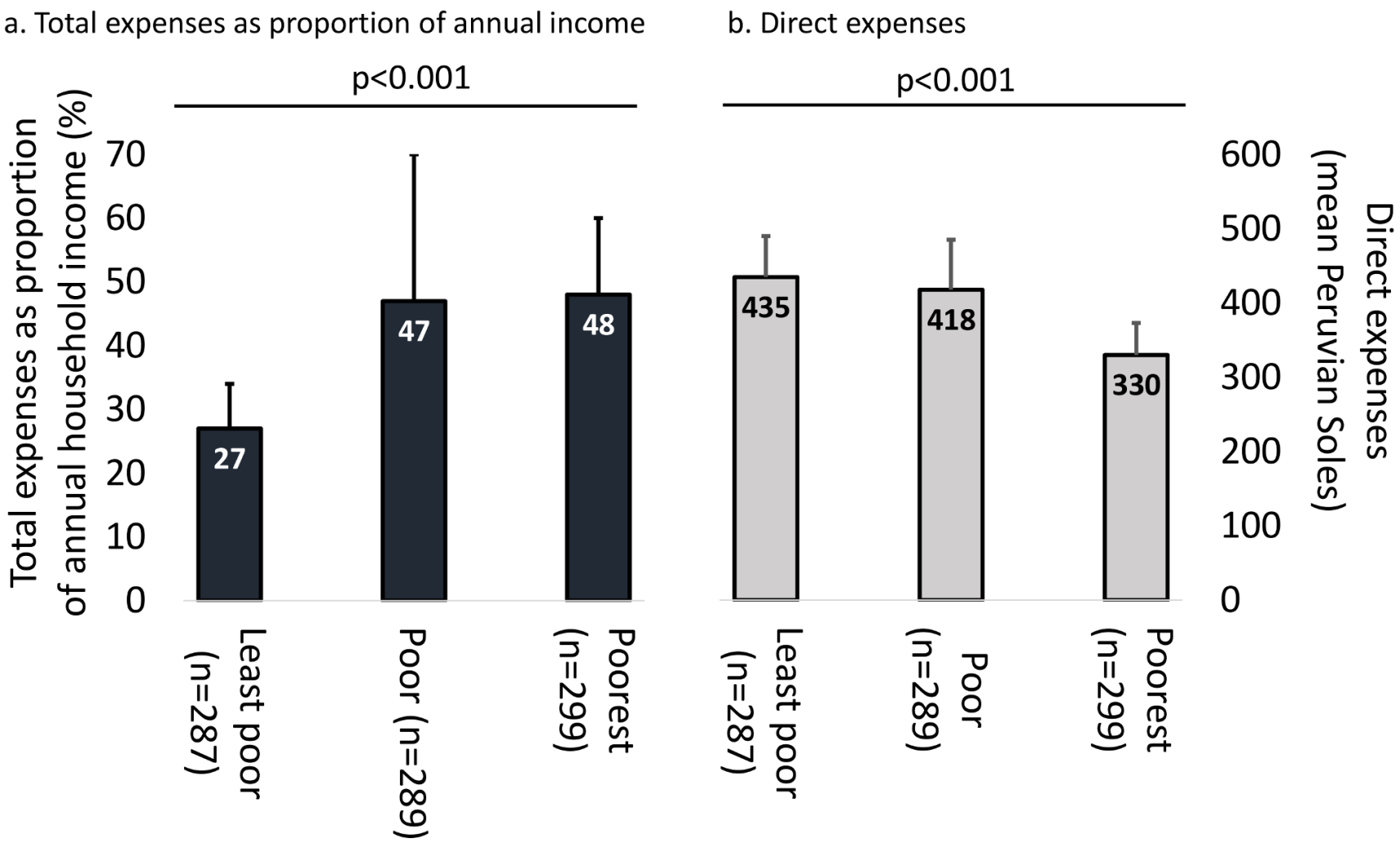


Figure 6: Expenses and economic burden of TB illness across poverty terciles. a. Total expenses as proportion of annual income (left sided graph) b. Direct expenses (right-sided graph). P values represent Pearson's coefficient of trend. Bars represent confidence intervals. The numbers in the three left-sided dark grey bars of part a. refer to the left hand y-axis of total expenses as a proportion of annual household income. The numbers in the three right-sided light grey bars of part b. refer to the right hand y-axis of direct expenses in mean Peruvian soles.

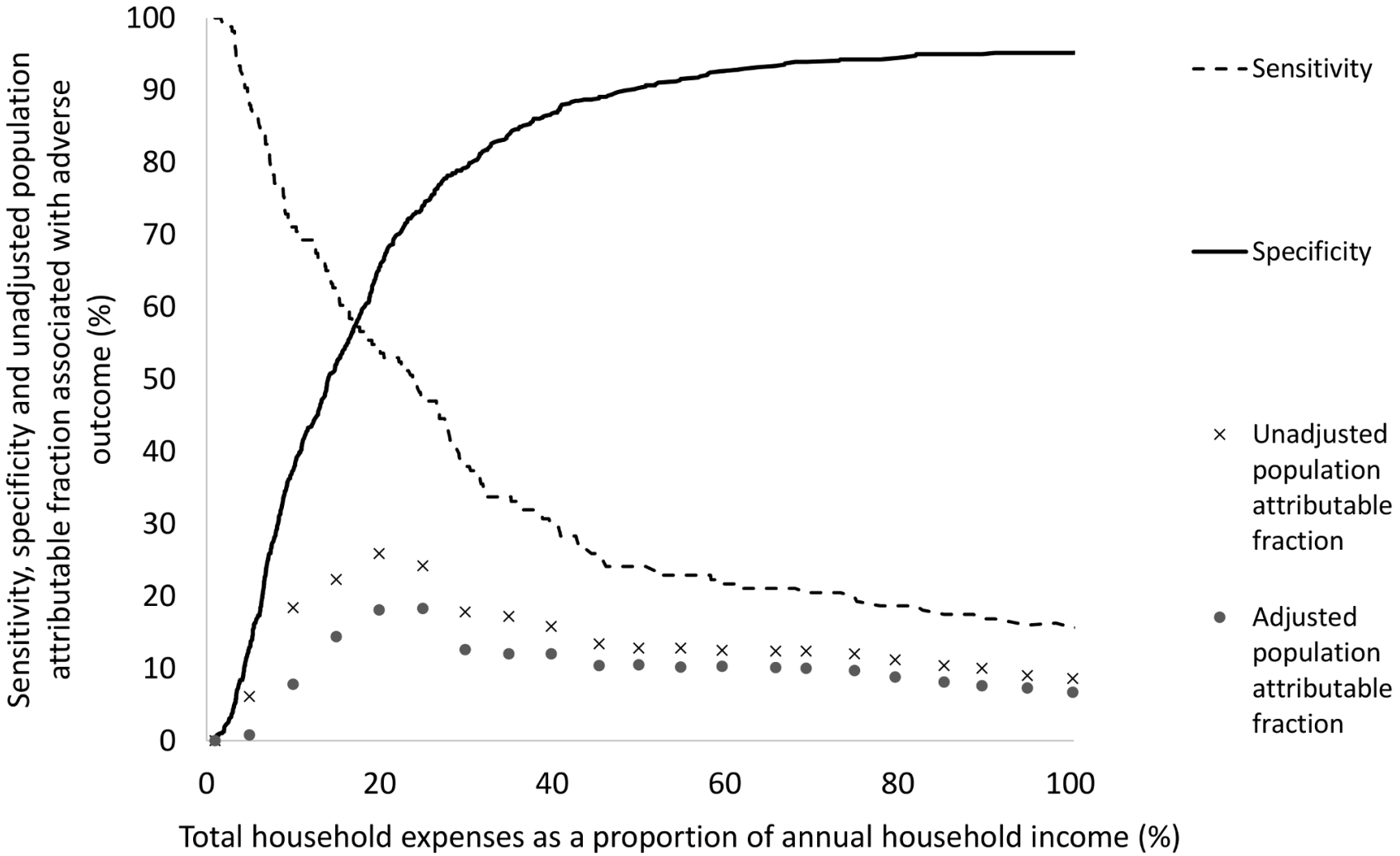


Figure 7: Sensitivity, specificity and univariable population attributable fraction of the association of total expenses as a proportion of annual income with adverse TB outcome. Total household TB-associated costs were defined as catastrophic when they exceeded 20% of household annual income because this threshold had the highest sensitivity, specificity and population attributable fraction for association with adverse outcome.

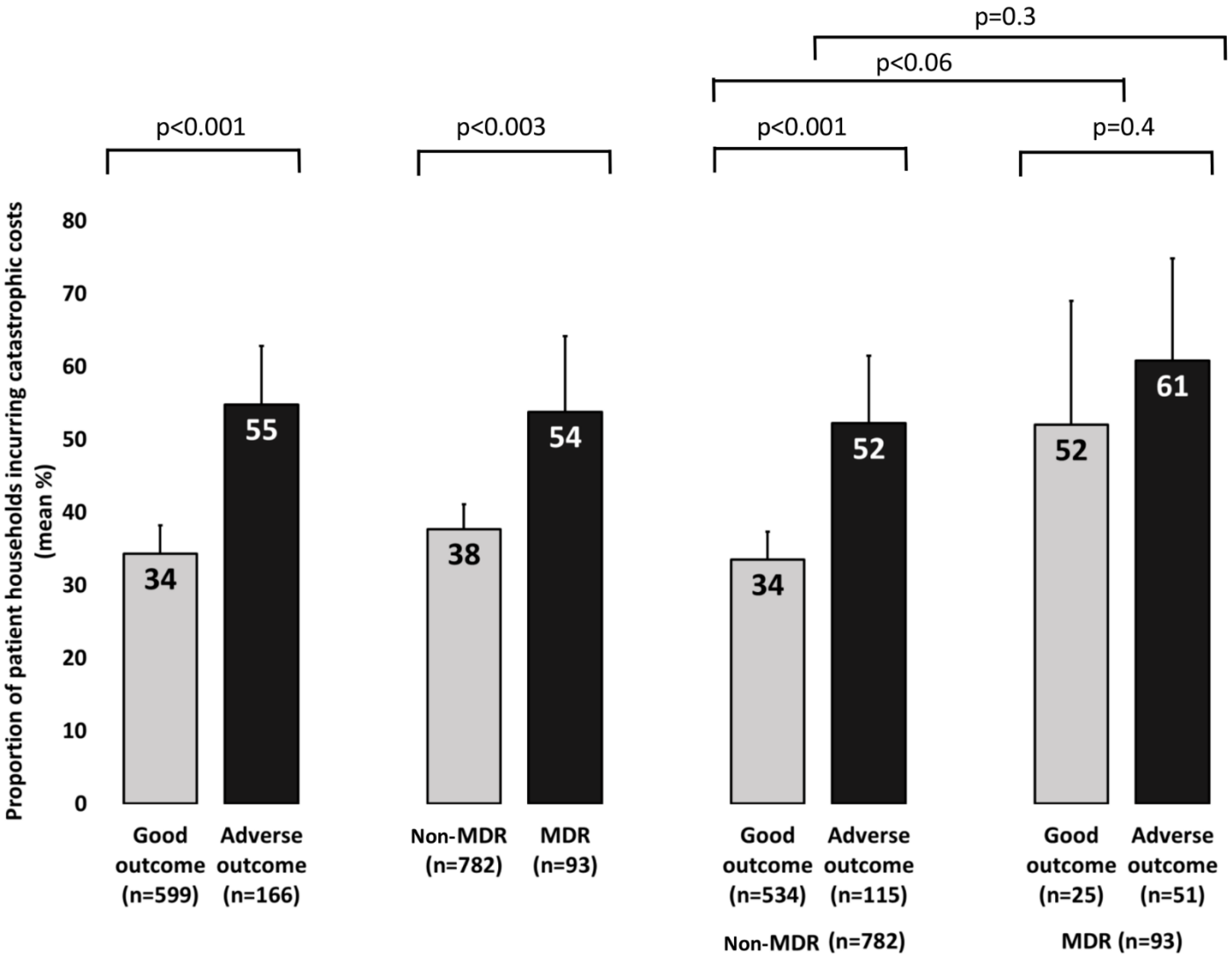


Figure 8: Patient households incurring catastrophic costs by TB resistance profile and adverse TB outcome. Error bars represent 95% confidence intervals. P values represent association in univariable logistic regression.

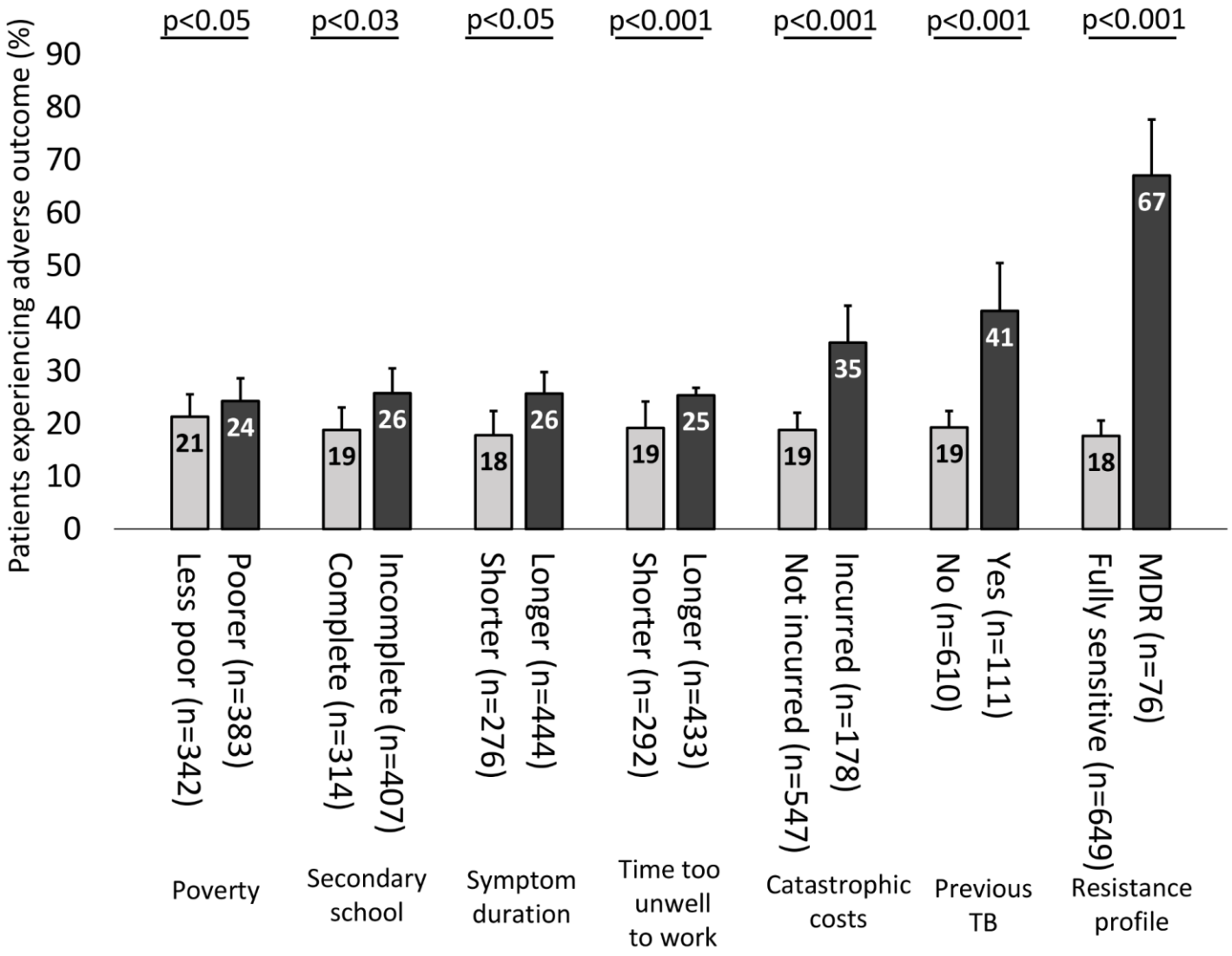


Figure 9: Percentage of patients experiencing an adverse TB outcome analysed by poverty, education level, symptom duration, previous TB, catastrophic costs, and resistance profile. Error bars represent 95% confidence intervals. P values correspond to the association of each variable with adverse TB outcome in univariable logistic regression except for poverty and symptom duration that were analysed as continuous variables. In multivariable regression analysis, the following variables remained independently associated with adverse TB outcome: time too unwell to work (p=0.02); catastrophic costs (p=0.003); having had a previous episode of TB (p=0.004); and currently having MDR TB (p<0.0001).

Chapter 4: Designing and implementing a socioeconomic intervention to enhance TB control: operational evidence from the CRESIPT project in Peru

This chapter is adapted from the peer-reviewed, published paper Wingfield et al "Designing and implementing a socioeconomic intervention to enhance TB control: operational evidence from the CRESIPT project in Peru." BMC Public Health. 2015 Aug 21;15(1):810. doi: 10.1186/s12889-015-2128-0.[121] The paper is bound in PDF format in Appendix 4 of this thesis. With the support of the multi-disciplinary Innovation For Health And Development team and the team leader and PhD supervisor, Dr Carlton Evans, the candidate led this project from conception, design, implementation, and refinement of the intervention. In addition, the candidate led the data analysis, manuscript write-up, and dissemination of results, including as part of the World Health Organisation's Task Forces on Catastrophic Costs and Social Protection.

Having identified poverty-related TB risk factors and TB-related catastrophic costs, the next part of this PhD research focused on addressing these findings by designing and implementing one of the world's first TB-specific socioeconomic interventions including cash transfers. The new knowledge generated by this paper aimed to provide preliminary evidence with which to guide policy-makers in implementing the socioeconomic interventions mandated in the World Health Organisation's End TB Strategy.

This chapter describes the design and implementation of the intervention with particular focus on the evolution of the elements of social and economic support provided to TB-affected households. Given its descriptive contents, the chapter does not follow the standard scientific structure of Introduction, Methods, Discussion, Results, and Conclusion and is instead divided into the headings: Introduction; Conceiving the intervention; Designing and implementing the intervention; Lessons learnt and persisting knowledge gaps; and Conclusions. Details concerning outcome measures, sample size calculation, adjustment for clustering, randomisation, and recruitment are explored in more detail in Chapters 5 and 6.

Introduction

Tuberculosis kills 5000 people per day,[6] mostly in resource-constrained settings. TB has long been recognised as an illness inextricably linked with social deprivation and marginalisation.[122,123] Poverty predisposes individuals to TB[5,22] and hidden costs associated with even free TB treatment can be catastrophic: exacerbating poverty,[24] leading to adverse TB treatment outcome, increasing TB transmission, and potentially worsening TB control.[19] Nevertheless, the global model for TB prevention, management and research has been principally focused on biomedical rather than social approaches.[124,125] There is a pressing need to expand the traditional TB control paradigm based on case finding and treatment, in order to embrace more holistic approaches that encompass the wellbeing of people and households living with TB and communities affected by TB.[9,126–130] This vision has been formally acknowledged in the World Health Organisation's post-2015 global TB strategy[14] which, for the first time in the modern era of TB control, explicitly identifies poverty reduction strategies, including universal health coverage and socioeconomic interventions, as key pillars of the future global response to TB.[14,80]

Social protection and socioeconomic interventions consist of policies and programs designed to reduce poverty and vulnerability by improving people's capacity to manage social and/or economic risks,[131] and includes health insurance, food assistance, travel vouchers, and cash transfers.[132] Cash transfers generally provide economic support to impoverished people with the aim of moving them out of extreme poverty and vulnerability whilst improving human capital.[133–138] Cash transfers are already used to modulate behaviour in HIV/AIDS[139,140] and improve maternal health.[141] Mitigating poverty-related TB risk factors of TB-affected households using cash transfers may be a cost-effective investment from a societal perspective[142] because it may support TB treatment, improve TB prevention and cure, and potentially enhance TB control.[143] However, there is little operational evidence to guide implementation or evaluate the impact of TB-related socioeconomic support including cash transfer interventions.[9,15,17,18,132–134,144–150]

For over a decade, our research group (www.ifhad.org) has worked with TB-affected households in the shantytowns of Callao, Peru. From 2007 to 2011, we conducted an assessment of Innovative

Socioeconomic Interventions Against TB (ISIAT).[15] The interventions had two dimensions: i) education, community mobilization, and psychosocial support to increase uptake of TB care; and ii) food transfers, microcredit, microenterprise and vocational training to reduce poverty. This intervention increased preventive chemotherapy in household contacts and HIV testing and TB treatment completion in TB patients.[15]

Building on the lessons learnt during the ISIAT project, we designed a larger 6-year research project called CRESIPT: a "Community Randomized Evaluation of a Socioeconomic Intervention to Prevent TB" to test for impact on TB control. This paper aims to describe the challenges of implementation, lessons learnt, and refinement of this complex social protection intervention to control TB, focusing on set up of a TB-specific cash transfer scheme, and thus provide research groups, non-governmental organisations (NGOs), civil-society representatives, policy-makers, stake-holders and the wider TB community with an interim guidance document concerning the operational logistics of TB-adapted social protection interventions involving cash transfers in resource-constrained settings.

Conceiving the intervention

Intervention objectives

The CRESIPT project aims to evaluate a socioeconomic intervention to support prevention and cure of TB in TB-affected households and, ultimately, improve community TB control. The CRESIPT socioeconomic intervention was developed over seven months in two contiguous suburbs in north of Peru's capital, Lima: Ventanilla, 15 peri-urban shantytown communities in which our research group has been recruiting patients to an on-going cohort study for over a decade;[15] and Callao, an area including 17 impoverished urban communities.

The CRESIPT project was informed by our previous research,[15] extensive expert consultation,[132] and a systematic review[133] of cash transfer interventions published in 2011.

We built upon an *a priori* conceptual framework reflecting the postulated pathways through which the intervention could lead to improved TB control in the study site (Figure 10, Page 95). The intervention outputs related to shared CRESIPT project and Peruvian National TB program goals: i. screening for TB in household contacts and MDR-TB in TB patients; ii. adhering to TB treatment and preventive therapy; and iii. engaging with CRESIPT social activities. Thus, our intervention targeted defined outcomes along the TB causal pathway. In TB patients, we aimed to improve early diagnosis and treatment, provide support to increase adherence to and completion of treatment, and achieve sustained cured. Amongst household contacts living with these TB patients, we aimed to prevent TB.

The previous systematic review of cash transfer interventions was updated in 2014: Medline, Embase, Global Health and HMIC databases were searched from 1st January 2011 onwards using the term **"Tuberculosis/economics"[Mesh] OR "Tuberculosis, pulmonary/economics"[Mesh] OR "Tuberculosis/prevention and control"[Mesh] AND "Economic support" OR "Cash transfers"**. This search found only one randomized controlled trial of economic support to improve tuberculosis treatment outcomes.[18] Other necessary and informative literature on economic interventions did not meet inclusion criteria for this systematic review because it either related specifically to HIV/AIDS (such as the IMAGE study)[151] or was limited by having no control group or impact assessment.[80,152]

A consultation process was undertaken to inform the project and its scope: a total of 135 formative activities were conducted including multi-sectorial meetings, focus group discussion (FGDs), semi-structured interviews, evidence reviews, and other expert consultations (Table 14, Page 92, and Figure 11, Page 96). Specifically, with regards to qualitative work with intervention patients and household contacts, an exit interview was conducted at 24 months that involved the patient and invited household members during a household visit. The interview detailed their evaluation of the socioeconomic intervention both qualitatively in free text comments and quantitatively through ranking the importance of the different elements of the intervention (e.g. cash transfers, household visits, TB Club, educational workshop, and interactions in the health post) for preventing and curing TB. In addition, at the end of each participatory

community meeting, feedback forms were completed by all participants about their favourite elements of the meetings and what could be improved (see Appendix 1). In addition to the TB-affected households, a civil-society of ex-TB patients was formed and registered as an independent body ("LUPORFAT" – Lucha Por Familias Afectadas por TBC / Advocates of families affected by TB). Members of the civil society were trained to assist in the running of day-to-day project activities and given responsibility for patients within their community. Civil society members also led the participatory community meetings. We conducted monthly meetings concerning the project and the intervention's uptake and acceptance with round table discussions, brainstorming, and problem solving about how to refine and improve the intervention to be both more accessible and acceptable to TB-affected families in the locality.

Table 15 (Page 93) summarises the critical review of the available evidence that occurred during the planning process, and the manner in which this review subsequently informed the main operational design and implementation decisions relating to some of the main aspects of the cash transfer intervention, including: existing cash transfer schemes, conditionality, and transfer size.

Thus the planning process involving previous research, extensive expert consultation, and systematic reviews of cash transfer interventions led to the design of a novel social protection intervention that aimed to be locally-appropriate, feasible and sustainable, and consisted of:

- economic support: conditional cash transfers to reduce TB vulnerability, incentivise and enable care; and
- social support: household visits and participatory community meetings for information, mutual support, stigma reduction, and empowerment.

The participatory community meetings, which are reported separately, consisted of an interactive educational workshop concerning issues surrounding TB and household finances, and a "TB Club" in which participants shared TB-related and other experiences in a support group format specifically adapted to the local setting.

Acceptability

To characterise operational challenges and the participants' perspectives, we performed an acceptability assessment using a mixed-methods approach. This involved the collection of quantitative and qualitative data from participants, a civil society group of ex-patient community representatives, CRESIPT project staff, and local and regional Peruvian TB Program staff and co-ordinators.

Ethical Approval

Approval was granted by the ethics committees of the Callao Ministry of Health, Peru; Asociación Benéfica PRISMA, Peru; and Imperial College London, UK. All interviewed participants gave written informed consent to participate in the study and for subsequent publication of anonymised data.

Sample Size

The main outcome of this preliminary work of the CRESIPT study (reported elsewhere) was completion of TB preventive therapy in household contacts of TB patients. TB patients had an average of five contacts and 25% of those eligible for TB preventive therapy completed it.[15] Therefore, *a priori*, we calculated that 312 patients would give 80% statistical power to detect a 33% increase in the primary outcome comparing intervention versus control households with two-sided 5% significance. The 312 patients recruited were randomly assigned in a 1:1 ratio to the intervention arm (normal standard of care from the National TB Program plus socioeconomic intervention) and control arm (normal standard of care from the National TB Program).

Designing and implementing the intervention

Designing the conditional cash transfers

Targeting: to provide evidence to assist national TB programs considering implementing TB-related socioeconomic interventions, our intervention exclusively targeted TB-affected households (i.e. was "TB-specific") rather than targeting all households living below the poverty line. The reasons for this decision were: encouraging results from the TB-specific ISIAT project;[15] the urgent need for impact assessment and

operational evidence for TB-specific socioeconomic interventions; the lack of existing TB-specific or TB-sensitive socioeconomic initiatives with which to feasibly collaborate in Peru; and the achievability of focusing on relatively small numbers of TB patients versus much larger, operationally unmanageable numbers of people at risk of TB in the wider community. In addition, it was expected that by working exclusively with TB-affected families we would generate evidence concerning those sections of the community most at risk of TB.

Cash delivery strategy: Cash transfers directly into bank accounts were selected as the most locally-appropriate way to deliver economic support because in the impoverished shantytown communities of the study site there were many: local bank agencies; food or material vouchers had poor accessibility and acceptability; direct cash transfers posed a security risk; and transfers using mobile-phone technology potentially overlooked the most vulnerable patients[153] and were prone to handset loss/theft, damage, or faults.

Cash transfer size: Deciding on the size and duration of cash transfers was difficult because this has varied considerably in past projects.[154,155] Learning from similar regional projects,[154] our local catastrophic costs findings,[19] and ongoing liaison and site visits from key policy-makers from WHO, Pan-American Health Organisation, and the World Bank, we aimed to completely mitigate TB-related direct out-of-pocket expenses, which was expected to be equivalent to 10% of median TB-affected household annual income in the study site.[19] This amount was: empirically believed to be too small to act as a perverse incentive;[147,156] affordable for a TB program in a resource-constrained country (expert opinion suggests that a socioeconomic intervention that adds less than 50% to the cost of biomedical treatment but reduces TB risk by 30-40% would be likely to justify policy change and widespread implementation);[92,157] large enough so that poverty-related TB risk factors in TB-affected households may be reduced; and that incentivized and enabled TB-affected households to achieve the shared goals of the Peruvian National TB Program and CRESIPT project.

Cash transfer timing: We designed the intervention so that cash transfers would be provided throughout treatment but weighted towards the first two months, when TB-affected households incur the majority of hidden costs (Figure 13a, Page 98, and Figure 13b, Page 99).[11,30,87]

Cash transfer conditions, levels, and responsiveness: We stratified cash transfer incentives into "double" and "simple" incentives. Double incentives were made for meeting the condition with "optimally" (i.e. monthly adherence missing less than two daily tablets). Simple incentives were made for meeting a condition "acceptably" (i.e. monthly adherence in which two or more tablets had been missed but the patient had not abandoned treatment). Figure 12 (Page 97) summarizes seven different potential scenarios of TB patients and the total amount of cash transfer incentives they would receive. Were a participant to receive all the double incentives available throughout treatment, they would receive a total of 230 US Dollars; for all simple incentives, they would receive a total of 115 US dollars (Figure 14a, Page 100, and Figure 14b, Page 101). In situations in which TB treatment routinely extended beyond 6 months, such as HIV-TB co-infection (9 months) or multi-drug resistant (MDR) TB (18 to 24 months), cash transfers continued throughout the duration of treatment. The decision to stratify simple and double incentives was taken in order to encourage a positive feedback loop of behaviour change through graded incentives whilst increasing the opportunity for vulnerable patient groups to receive cash transfers even when they could not achieve optimal behaviour.

Implementation of the conditional cash transfers

Banks: Of 10 banks visited, formal meetings were organised with four that aimed to: create a relationship with the bank to achieve sustainable cash transfers throughout the study; identify charge-free appropriate accounts; create a "virtual" way of opening accounts to minimize paperwork, time spent "in branch", and travel-related patient costs; establish a mutually suitable day on which to accompany patients to open accounts; and to clarify the bank's accessibility in our study sites (i.e. branches and agencies).

Logistical concerns of the banks: The banks we consulted raised similar concerns about the proposed intervention, including: infection risk; cash transfer flow; and difficulties opening accounts with patients who

have no national identification, fixed abode, or are illiterate. We initially chose one bank that appeared to be more likely to overcome these issues because it had a social inclusion department with previous involvement in successful microfinance initiatives.

Opening bank accounts: Recruited patients with a negative sputum smear microscopy test (indicating low infectiousness) were accompanied by our project staff to open a bank account. The account holder's details were then relayed to our project office with a copy of the bank's original documents. In the case that the patient was a minor, did not have legal capacity, wished for another household member to be the named bank account holder, or had prolonged sputum smear positivity, then a household member was selected by the patient or household to be the named bank account holder. Patient transport and time costs were reimbursed by our project.

Cash transfer administration: The patient's incentive card (Figure 13a, Page 98, and Figure 13b, Page 99) was updated by the field nurses when each condition was achieved. Confirmation of completion was made through liaison with the patient, review of CRESIPT project records (e.g. participatory community meeting attendance) and Peruvian National TB Program records and treatment cards (e.g. medication adherence verification). Signed incentives cards were returned to a project administrator who double digitized the data. Thus, a weekly list of patients, their bank account details, and required transfers was generated. The same day, this list was submitted electronically to a member of the social inclusion department of the bank, and the virtual transfers made. The transaction codes and receipts generated were double digitized in the CRESIPT project database and delivered to the patients in the health post by the CRESIPT field nurses.

Recruitment

From February to August 2014, we expanded project activities from 2 to 32 communities. As per the *a priori* sample size calculations and study protocol, 312 consecutive TB patients from the study site were invited to participate of whom 149 were randomized to receive the socioeconomic intervention. 12/149 (8%) patients declined to participate, 2/149 (1%) died prior to recruitment, and 2/149 (1%) were recruited and subsequently did not complete follow up. Thus, 133/149 (89%) were recruited and participated throughout the study period.

The number of patients declining to participate was higher in urban than in peri-urban communities (15% [95% CI 6-23] versus 5% [95% CI 1-10%] respectively, p=0.04). Of the 133 participants, 9/133 (7%) had MDR TB, 5/133 (4%) were HIV positive, and 7/133 (5%) were diabetic.

Cash transfers achieved up to 1st July 2015: Of 1299 potential cash transfers, 964 (74%) were achieved (of these, 885/964 [92%] were achieved optimally and 79/964 [8%] sub-optimally), 259 (19%) were not achieved, and 76 (7%) were yet to be achieved. Thus, 964 conditional cash transfers totalling 61,120 Peruvian Soles (20,373 US dollars) were made to TB-affected households for meeting the conditional goals of the Peruvian National TB Program and CRESIPT project (Figure 14a, Page 100, and Figure 14b, Page 101). The average cash transfer amount received by each TB-affected household over the course of the intervention was $173 USD.

Lessons learnt and persisting knowledge gaps

The implementation and acceptability assessment identified strengths and limitations of our theoretical approach during the design of CRESIPT. The lessons that emerged are grouped into successes, challenges and refinements in Table 16 (Page 94) and, ultimately, allowed us to identify persisting knowledge gaps in this field (Box 2, Page 102).

Successes

This project generated evidence that conditional cash transfers to TB patients were logistically achievable in impoverished shantytown communities of northern Lima/Callao, Peru. The intervention considerably supplemented small monthly food baskets given unconditionally to TB patients by the Peruvian National TB Program.

Through regular steering meetings, focus group discussions, and contact in the health posts, strong collaboration was achieved between our team, banks and the Peruvian National TB Program:

> *"The CRESIPT project and Peruvian National TB Program are complementary and should continue to support each other in a common goal."* [Peruvian National TB Program Regional Chief].

Such ongoing collaboration and adaptation to stakeholder and participant feedback helped the project to be more locally-appropriate, responsive, and patient-centred.

The conditional cash transfers were facilitated by multi-sectorial collaboration including with the bank's social inclusion department. Multiple, regular, simultaneous, virtual cash transfers were achieved through online banking with a digital record reduced the likelihood of fraud. Because field team staff were not directly carrying or giving cash or cash-equivalents (such as cash vouchers or cheques), cash transfers were a secure method of providing incentives. The majority of participants did not have bank accounts[158] and some patients described the act of opening a bank account as empowering:

> *"…especially for female patients, who are not normally the financial decision-makers of the households in these communities"* [CRESIPT Project Nurse Technician]

The social protection intervention was holistic and household-centred with the economic dimension of cash transfers being complemented by social activities including household visits and participatory community meetings.[159] In addition to TB prevention and control messages, an educational component was an important element of the participatory community meetings, in which participants were involved in educational activities concerning: managing a household budget; spending and saving responsibly; and how to meet the conditions for cash transfers. This financial education was highly rated by participants and perceived as an ethically sound accompaniment to cash transfers by CRESIPT project staff and TB-affected households:

> "*I understood and learnt more, and saw that I was not alone"* [TB-Affected Household Member]

> "*The meetings generated good solidarity and camaraderie*" [TB-Affected Household Member]

Our experience is consistent with reports that financial incentives should be complemented by education or "social marketing" if health objectives are to be achieved.[124] Further research is needed to investigate the relative importance of health and financial education on the impact of cash transfer interventions aiming to improve health.

Challenges and refinements

The lack of published evidence of similar studies was particularly challenging for the implementation of TB-specific cash transfer incentives in resource-constrained communities.

Cash transfer targeting: The significantly higher number of patients declining to participate seen in the urban rather than peri-urban communities may have been due to the fact that CRESIPT project activities were new in this area or reflect distinctions between these communities:

> *"We don't fully understand the demographic differences and challenges between the urban and peri-urban communities"* [CRESIPT Project Investigator]

The field staff reported that some patients were not willing to participate because: i) they thought that CRESIPT project staff were part of a governmental body; ii) they did not want to register their true address with either the TB program, a bank, or the CRESIPT project in order to keep *"under the radar"* [CRESIPT Project Nurse] especially those formerly-incarcerated or involved with "*pandillas*" (drugs gangs); iii) they did not wish our team to visit their home because their household was unaware of their diagnosis or they frequently moved location; or iv) the incentives were insufficient to match the money they lost for participating in project activities and, perhaps more importantly, for continuing on their treatment. In addition, patients with recognised "high-risk" factors for treatment default such as prolonged treatment courses (e.g. MDR-TB and/or HIV), mental illness, drug use, homelessness, or being formerly-incarcerated were difficult to recruit and retain. Because these patients did not consent to participate we could not formally characterise their reasons for declining. This lack of engagement and formal feedback is concerning given that such groups may have benefited most from the intervention.

> *"Conditions are appropriate but you need to provide additional support to those people who find it harder to meet those conditions."* [Ex-TB Patient Civil Society Representative]

> *"Some patients would never open a bank account because they don't want to register their name."* [CRESIPT Project Nurse]

"[A negative aspect of the CRESIPT project intervention is] giving an economic incentive to a patient with drug-dependency and for that matter any other benefit/incentive such as food baskets (which some of these patients sell to buy drugs)." [Peruvian National TB Program Nurse]

To combat some of these issues, extra care was taken during consent to reassure potential participants that the CRESIPT project team is a non-governmental research organisation with no connections to the justice system and that no project activity, especially household visits, was mandatory. In an attempt to address the needs of participants with HIV and/or MDR-TB, we explicitly specified that cash transfers for adherence were provided throughout treatment, regardless of treatment duration. This longevity meant that TB-affected household support, staff-household relationship, and financial benefits of the cash transfers were refined to be more equitable and responsive to the ongoing needs of patients with HIV and MDR-TB.

Hard-to-reach populations and/or difficult urban settings, such as those in which our intervention was implemented, may be characterised by violence, drug use and severe marginalisation that are also associated with TB. Future studies may further investigate the barriers, feasibility and impact of delivering TB-specific social protection interventions to challenging, vulnerable groups in such settings.

Cash transfer delivery strategy: We changed bank-provider because the initial bank-provider: had limited geographical accessibility; provided inconsistent information "in branch" (resulting in some patients opening accounts with maintenance fees); was reported during feedback sessions to have been stigmatizing towards patients, not due to TB (the branch staff were unaware of patients' diagnoses) but possibly due to other sociocultural factors such as poverty or appearance; and introduced account maintenance charges to previously charge-free accounts.

"Some patients lost faith in the project due to the hidden bank charges" [CRESIPT Project Nurse]

The new bank-provider, while not having a specific social inclusion department, provided improved coverage and accessibility because of a greater density of agency micro-branches in local shops that facilitated participant transactions. While the new bank-provider overcame the challenges described above, these

experiences have led us to question whether banks are the most appropriate delivery strategy. Indeed, conditional cash transfer programs in Sub-Saharan Africa have predominantly used specified pay points to pay participants in cash rather than banks which may be less accessible to the poor and may have user fees.[160] However, banks have been the favoured partner agent in existing conditional cash transfer programs in Peru (JUNTOS), Brasil (Bolsa Familia), and Mexico (Progresa) with the co-ordination of national cash transfer programs being centralised through national banks in these countries.[160] This level of coordination may only be suitable in countries with comparatively developed financial infrastructure, information and communications technologies, and accessibility to bank branches or micro-agencies.[155] We have reviewed other modalities of conditional cash transfers in greater detail elsewhere.[133] Future research into implementation of socioeconomic interventions may compare the effectiveness and cost-effectiveness of cash delivery mechanisms including mobile phone vouchers, mobile banking, automated or other pay points, or innovative strategies,[155,161] for which rigorous evidence is currently lacking. To achieve optimal impact, implementers of conditional cash transfer programs may work more closely with the local communities and civil societies to establish how a program can be adapted to be appropriate and acceptable in that specific setting.

Cash transfer size: During focus group discussions, the internal research committee debated what the most important objective of cash transfers is: mitigating TB-related costs; avoiding catastrophic costs; or reducing poverty-related TB risk factors. This confounded deciding the cash transfer amounts. To address this challenge, we analysed TB patients' costs, which demonstrated that direct out-of-pocket expenditure was 10% of that household's annual income.[11] These results, together with additional data characterising annual household income for TB-affected households in the study site, informed the cash transfer amount necessary to match direct out-of-pocket expenditure and subsequently avoid catastrophic costs. The optimal cash transfer size is likely to depend on the intervention setting and proposed outcomes of the intervention. This will require baseline evaluation of local TB-related costs prior to planning for and implementing cash transfers of suitable amounts. Further research is required to evaluate how cash transfer size affects intervention impact and cost-effectiveness.[162] It is noteworthy that the strategy we adopted in this research was a "costs-mitigation" rather than a "poverty-reduction" strategy and involved a cash transfers amount that was appropriate and feasible

for the local setting. While long-term poverty reduction would be an appealing additional goal, this would likely require greater socioeconomic support than national TB programs could afford.

Cash transfer timing: During focus group discussions, the delay from incentivized behaviour to cash transfer was noted as a barrier to achieving project conditions due to the lack of a tangible "reward" and accompanying positive reinforcement loop. For example, when a household attended a participatory community meeting, it could be one to two weeks before they received the corresponding cash transfer.

> *"Patients want immediate and tangible gratification on the same day as they complete their condition"* [Ex-TB Patient Civil Society Representative]

Cash transfers were initially delayed due to the flow of information from the field, to the research office, to the bank-provider. While cash transfer flow improved during the project, patients and households stated that such delays made household budgeting difficult:

> *"Due to the initial cash transfer delays, some patients didn't get the money when they most needed it"* [CRESIPT Project Nurse]

Consequently, we increased the speed of the cash transfers and plan to instigate a system in which on the *same* day that a household attends a community meeting, they received a small high-protein food basket and a high-quality certificate-like voucher detailing the amount and date by which the cash transfer will be made.

Participants reported that they would prefer to receive cash transfers at the beginning of the month for their adherence in the subsequent month rather than wait until the end of the month. As has been reported in other settings,[163] the waiting was perceived as financially stressful and, on occasion, demoralising. Learning from this setting-specific qualitative feedback, in the planned CRESIPT study in these same communities, we will combine unconditional monthly cash transfer provided to all TB patients taking treatment with supplementary conditional cash transfers for meeting project and National TB Program conditions. Furthermore, we have self-imposed penalties on our project if incentives do not reach the patient's bank

account within one week of confirmation that the condition has been met. Specifically, if a delay occurs, their cash transfer is doubled.

Cash transfer conditions, levels, and responsiveness: Project conditions requiring involvement of "100%" of the TB-affected household in order to receive the cash transfer (e.g. attendance at participatory community meetings) were hard to achieve. In addition, the amount of these cash transfers was fixed and independent of household size (see Figure 12, Page 97) and thus felt to be inequitable because larger households received a lower cash transfer amount per household member. There was, therefore, a perceived challenge in balancing operational simplicity (e.g. fixed-amount incentives) while responding to patient household needs (e.g. variable incentive depending on household size). Consequently, on the basis of this qualitative evaluation of the implementation process, we suggest designing relevant incentives to be more equitable and responsive to household size: a fixed amount added to the patient's cash transfer for *each member* of their household completing the condition. In this way, larger households will receive the same amount per household member as smaller households.

Conclusions

A novel TB-specific socioeconomic intervention was: designed through multi-sectoral collaboration coupled with evidence from a systematic review; refined during implementation through community participation, engagement and acceptability feedback to meet patient and household needs; and proved to be feasible in an impoverished, challenging environment. The intervention is now ready for impact assessment, including by the CRESIPT project. Further lessons from CRESIPT will aim to assist TB control programs to effectively implement the recent global policy change of including socioeconomic support as part of TB control activities.

Table 14: CRESIPT consultation process

Formative Activities	Attendees	Events (n)	Partici-pants (n)	Notes / details
A. Analysis of evidence	CRESIPT project research team and international collaborators from Imperial College London, London School of Hygiene & Tropical Medicine, and John Hopkins School of Public Health	3	28	Analysis and publication of ISIAT project results in 2011[15] WHO-commissioned systematic review of conditional cash transfer schemes' impact on TB control in 2011[133] plus updated review in 2014
B. Expert consultation	Peruvian National TB program chiefs	10	8	Steering meetings with regional and national TB Program coordinators
	JUNTOS (www.juntos.gob.pe) (Peruvian conditional cash transfer program)**	1	5	Discussed logistics and minimal impact evaluation of conditional cash transfers for health/education to female heads of rural households[164]
	WHO Stop-TB partnership	3	5	Ongoing meetings and site visits
	World Bank	2	3	Ongoing meetings with senior World Bank economists especially relating to cost-effectiveness considerations
C. Symposia and conferences	International multi-sectoral researchers (including World and Pan-American Health Organisation members)	3	30	"Social protection interventions for TB control", UK, 2012[132] WHO led policy consultation on social protection for TB,Brazil, 2013[14] TB Union World Lung Health conference in France, 2013
D. Focus group discussions (FGDs)	CRESIPT multidisciplinary team	9	10	www.ifhad.org FGDs with the CRESIPT field team research personnel
	Ex-TB patient civil society "LUPORFAT"	4	13	Registered "Junta Directiva" (board of directors) of ex-TB patient community representatives "Lucha Por Familias Afectadas Por TBC"
	Key NGO Stakeholders	4	5	www.prisma.org Structured interviews and FGDs
	CRESIPT project participants	19	20	Including participatory community meetings and training of facilitators
	Peruvian National TB program health post staff	18	12	Multi-disciplinary teams: co-ordinators, doctors, nurses, and technicians
	Banks	6	5	Account executives and social inclusion department representatives
E. Field team Meetings	CRESIPT multidisciplinary team	34	11	Covered operational field logistics and acceptance of the intervention
F. Steering committee	CRESIPT multidisciplinary team & international Collaborators	19	6	Twice monthly committee review of published literature (including systematic review) and discussion of financial, methodological and statistical design issues and potential intervention improvements
TOTAL	NA	135	NA	NA

*mean average **We were unable to integrate our urban TB-specific intervention with JUNTOS' existing rural cash transfer scheme. While JUNTOS may be TB-inclusive (i.e. some TB patients will receive incentives as they are below this poverty threshold), it is neither TB-sensitive nor TB-specific.[133] Abbreviation: FGD = focus group discussion

Table 15: Available evidence and CRESIPT project operational decisions relating to cash transfers

	The available evidence - what do we know?	**Operational decisions for implementation of the CRESIPT project intervention**
Cash transfer schemes	• Cash transfer schemes were implemented in Latin America in the 1990s to tackle the socioeconomic consequences of financial crises.[134] Schemes include: Bolsa Familia (Brasil, 1995); Oportunidades (Mexico, 1997); Red de Protección Social (Nicaragua, 2000-2005); Bono de Desarrollo Humano (BDH Ecuador, 2004); Red Solidaria (El Salvador, 2005); and JUNTOS (Peru, 2005). • Our systematic review revealed only one controlled trial of TB-specific cash transfers from South Africa that showed no significant increase in successful TB treatment outcome.[18] During treatment, vouchers (15 US Dollars) that could be exchanged for foodstuffs were given to patients by local health post nursing staff. The authors opted for vouchers over cash due to: posing a lower security risk; not being able to be spent on unhealthy items such as alcohol or cigarettes; being easy to monitor; and "public health sector clinics would not have bank accounts, making electronic transfers difficult".[18]	• We investigated the use of food or other vouchers/cards but found very few existing systems in the study site. Those that were in place could only be redeemed in supermarkets (felt in FGDs to be inappropriate for the study population due to infrequent use, limited access, and higher costs of goods). • Based on our experiences and the limited published evidence, we opted for a bank cash transfer scheme. Bank transfers reduce the likelihood of fraud, robbery or security risk (a concern in impoverished shantytowns in Callao, Peru)[18,148] and are reliable for maintaining accurate transfer records for cost-effectiveness analysis. We also felt opening a bank account and having freedom of choice to decide how transfers were spent was empowering[165] • We decided not to impose conditions on how the cash transfers were spent. Successfully funded social protection interventions related to TB (especially MDR TB) have mainly focused on mitigating non-medical direct costs associated with having TB such as food or travel.[80,165] There is some evidence that even when money rather than food vouchers is given as a form of social protection, it is commonly spent on food and travel costs anyway.[163]
Condition-ality of cash transfers	• Cash transfers can be unconditional, conditional (requiring specific behavioural, education or health actions) or combined.[155,166] • *Unconditional* cash transfer schemes include: Ecuador's BDH targeting those below poverty threshold or by location;[154,167] and village bankloans for TB-affected households in Cambodia.[168] • Conditions can be "hard" (if the condition is not met, the transfer is not made) or "soft" (less stringent conditions where transfers are made even when a condition is unmet). Soft conditionality may be preferable in settings with poor health infrastructure.[134,166,169]	• Perú has an exemplary, well-established and organised National TB program. Learning from ongoing collaboration with regional heads of the TB program, we decided that our cash transfers conditions would relate to National TB Program treatment and prevention goals and selected project activities. • We chose to use conditional cash transfers that mixed both hard and soft conditions to be more inclusive: "hard" in that if participants met the condition with "perfect behaviour" then a double cash transfer was provided and "soft" in that if participants met the condition with adequate behaviour, then a simple cash transfer incentive was provided (Figures 13a and 13b).
How much cash to give	• Minimal evidence exists on the size of cash transfers. In Latin America, total amounts have varied widely in previous projects: 6-10% of annual income in Ecuador;[154] 21.8% in Mexico; and 29.3% in Nicaragua.[155]	• We aimed to establish a cash transfer amount that was too small to act as a perverse incentive,[147] but large enough so that poverty-related TB risk factors in TB-affected households were reduced and the households were both incentivized and enabled to achieve National TB program and project goals.
When to give cash	• Most initiatives deal more with poverty than a finite illness such as TB, so evidence of duration and frequency of TB-specific cash transfers is scarce. Longer duration and more frequent cash transfers may have greater impact in TB-affected households.[17] • Our previous work in the study setting showed that hidden TB costs were mainly incurred pre-diagnosis or early in treatment.[11]	• We decided to provide the majority of the cash transfer incentives in the intensive treatment phase (the first two months of treatment) and to continue monthly cash transfers specific for treatment adherence throughout treatment. This meant the intervention was designed to increase equity for people with TB-HIV co-infection and MDR TB whose treatment lasted longer than six months.

Table 16: Successes, challenges, and refinements of the cash transfer incentive dimension of the socioeconomic intervention.

	Successes	***Challenges***	***Refinements***
New evidence	New experience and evidence was generated that TB-specific cash transfers for TB-patients were feasible in this study setting	There was a lack of available evidence and thus clarity when prioritising the output of the cash transfers in these TB-affected households. Thus, deciding on the cash transfer amounts and timing was difficult	Following previous and updated analysis of hidden costs and income of TB-affected households,[11] cash transfer amounts were increased with the aim of reducing their poverty-related TB risk factors
Collabo-ration	There was strong multi-sectorial collaboration with Peruvian National TB Program and bank staff, allowing multiple, virtual cash transfers to be made and recorded, reducing fraud and security risks	Account maintenance charges were introduced by the bank during implementation of the intervention and delays in cash transfers eroded participants' trust in the project	We changed our bank service provider: the new bank had better accessibility and no charges. We self-imposed penalties on our project for late cash transfers (participants gained additional transfers)
Cash Transfers	Cash transfers lasted throughout treatment, increasing equity for people with TB and HIV co-infection or MDR TB, whose treatment duration extended beyond six months Opening a bank account was a first-time experience for many of the participants and qualitative participant feedback suggested that this was perceived as an empowering action, especially for female members of the household who have previously been shown to be a vulnerable subpopulation in the study setting.[5]	As a research team, we had limited experience of cash transfer interventions or working with new urban study communities Feedback suggested that patients would prefer immediate gratification for completion of conditions rather than delayed cash transfer bank payments Project conditions requiring all members of the TB-affected household to participate were poorly achieved and not equitable due to different household sizes	Achieving a balance between operational simplicity and complex TB-affected household needs was challenging Immediate incentives were provided for attending participatory community meetings (including food baskets and high-quality vouchers documenting the date and amount owed to the participant) We combined conditional and unconditional cash transfers. Conditions requiring household participation were altered to be responsive to household size: incentives given were refined to be given per household member involved
Inclusive-ness and high risk groups	The intervention was holistic and household-centred because, in addition to cash transfers, it provided community meetings consisting of educational workshops (covering themes such as TB treatment, transmission, prevention and also financial themes such as responsible household budgeting in an interactive manner) and TB Clubs (mutual support to reduce stigma and increase empowerment, reported separately)	"High risk" patients in more urban communities were difficult to engage with (especially the formerly-incarcerated, drug- or alcohol-dependent, and gang members)	Participatory community meetings for patients with MDR TB were established and increasing social support was provided to other high risk patients (including the homeless, drug or alcohol dependent, those with poor adherence and/or lack of engagement with our project)

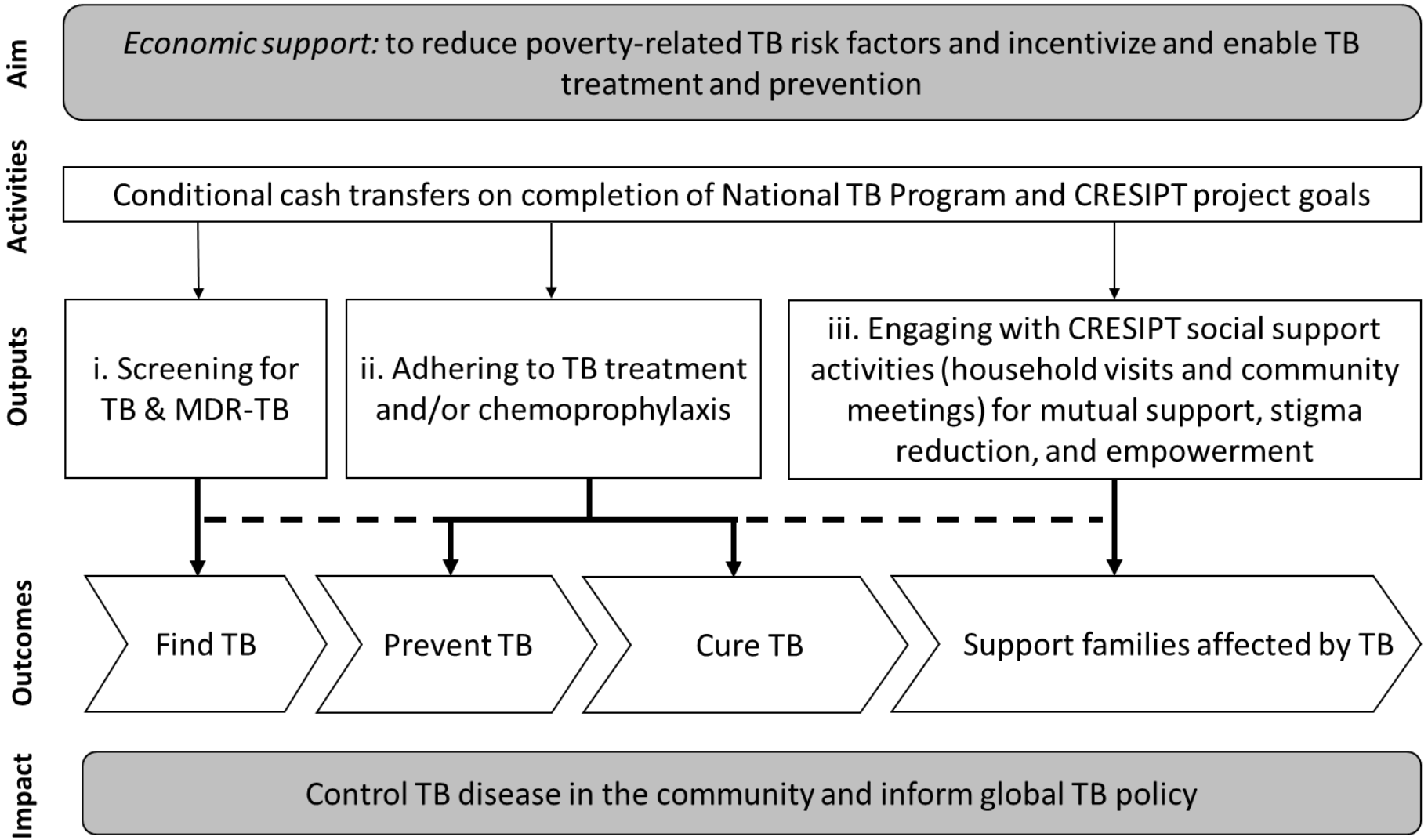


Figure 10: Conceptual framework of the conditional cash transfer scheme within the CRESIPT project

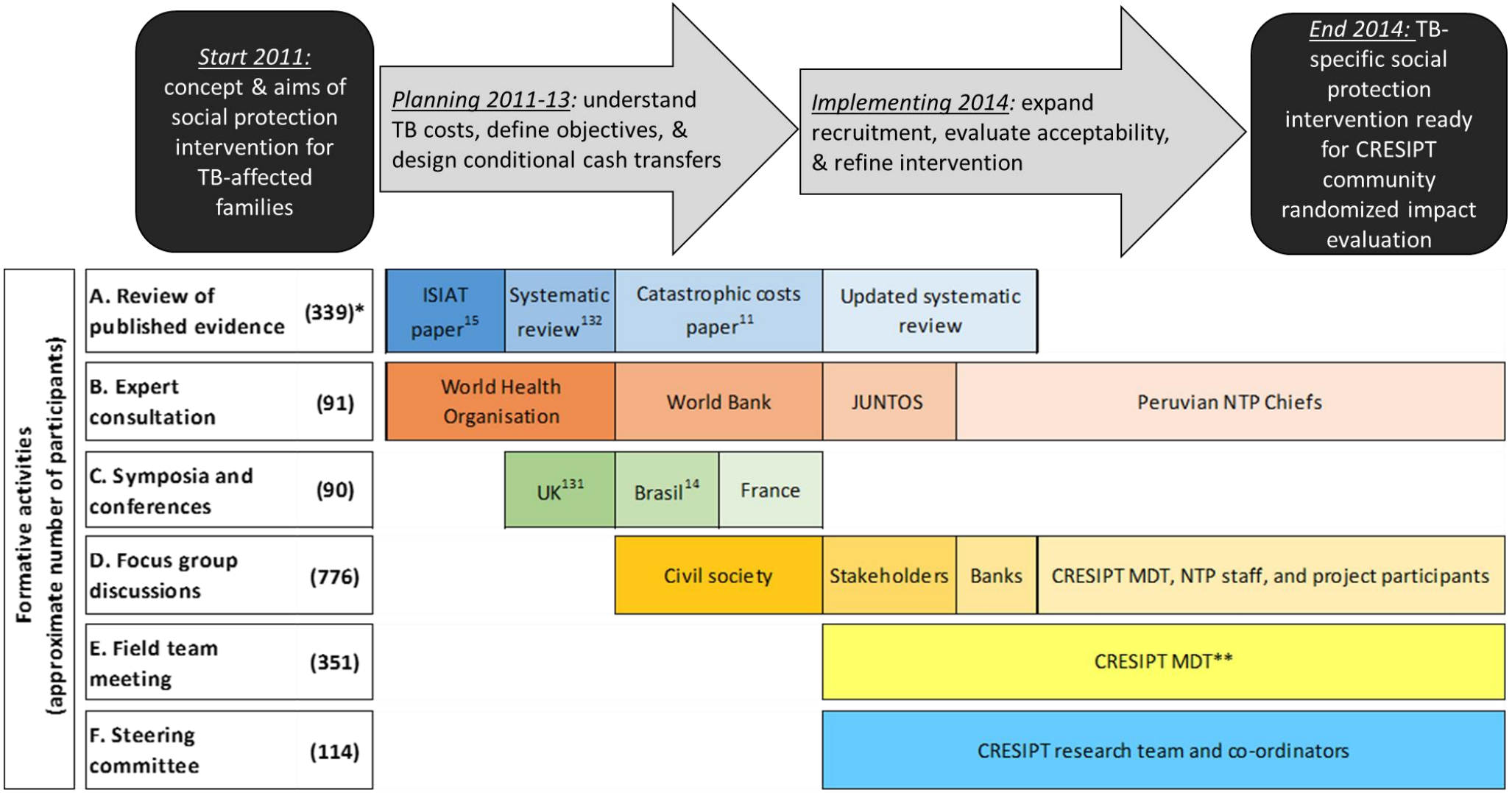


Figure 11: Flow diagram of CRESIPT project activities during planning, implementation, and refinement of the social protection intervention.
Abbreviations: MDT = multi-disciplinary team; NTP = National TB Program. *Includes documents of potential interest reviewed or used as references. **These weekly meetings have been an ongoing part of team activities for the past decade and are included here to illustrate when they focused solely on the CRESIPT project

Participant	i. Screening for TB & MDR-TB		ii. Adhering to treatment or chemoprophylaxis		iii. Engaging with CRESIPT social activities	
	Patient	Contacts	Patient	Patient & Contacts	Household visit	Community meeting
Patient who declines to participate	X	X	X	X	X	X
Patient who defaults immediately	✔	X	X	X	X	X
Patient who adheres, completes and is cured but does not engage with social activities	✔	✔	✔	✔	X	X
Patient who lives alone and optimally achieves all conditions	✔	✔	✔	✔	✔	✔
Patient who lives with partner and 7 children and optimally completes all conditions	✔	✔	✔	✔	✔	✔
Patient with HIV who optimally completes all conditions	✔	✔	✔	✔	✔	✔
Patient with MDR TB who optimally completes all conditions	✔	✔	✔	✔	✔	✔

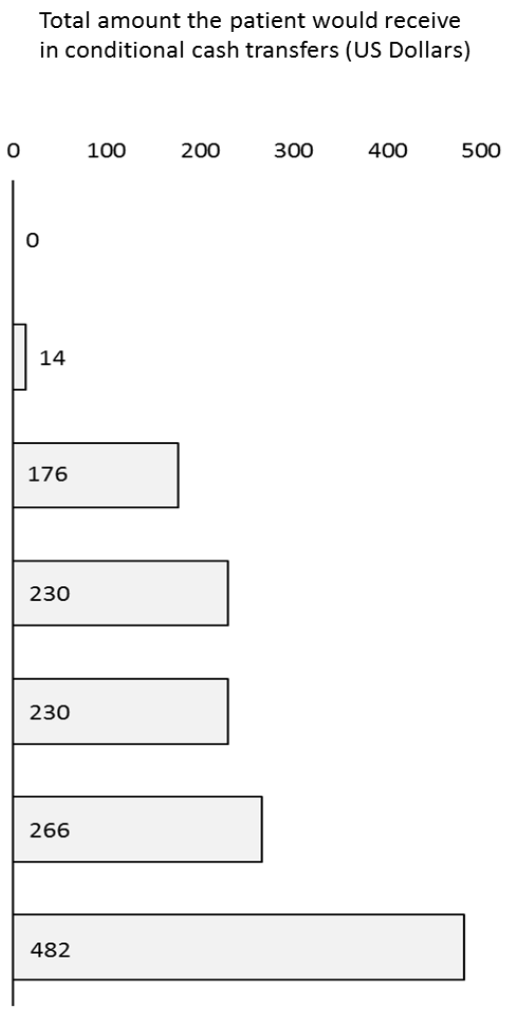


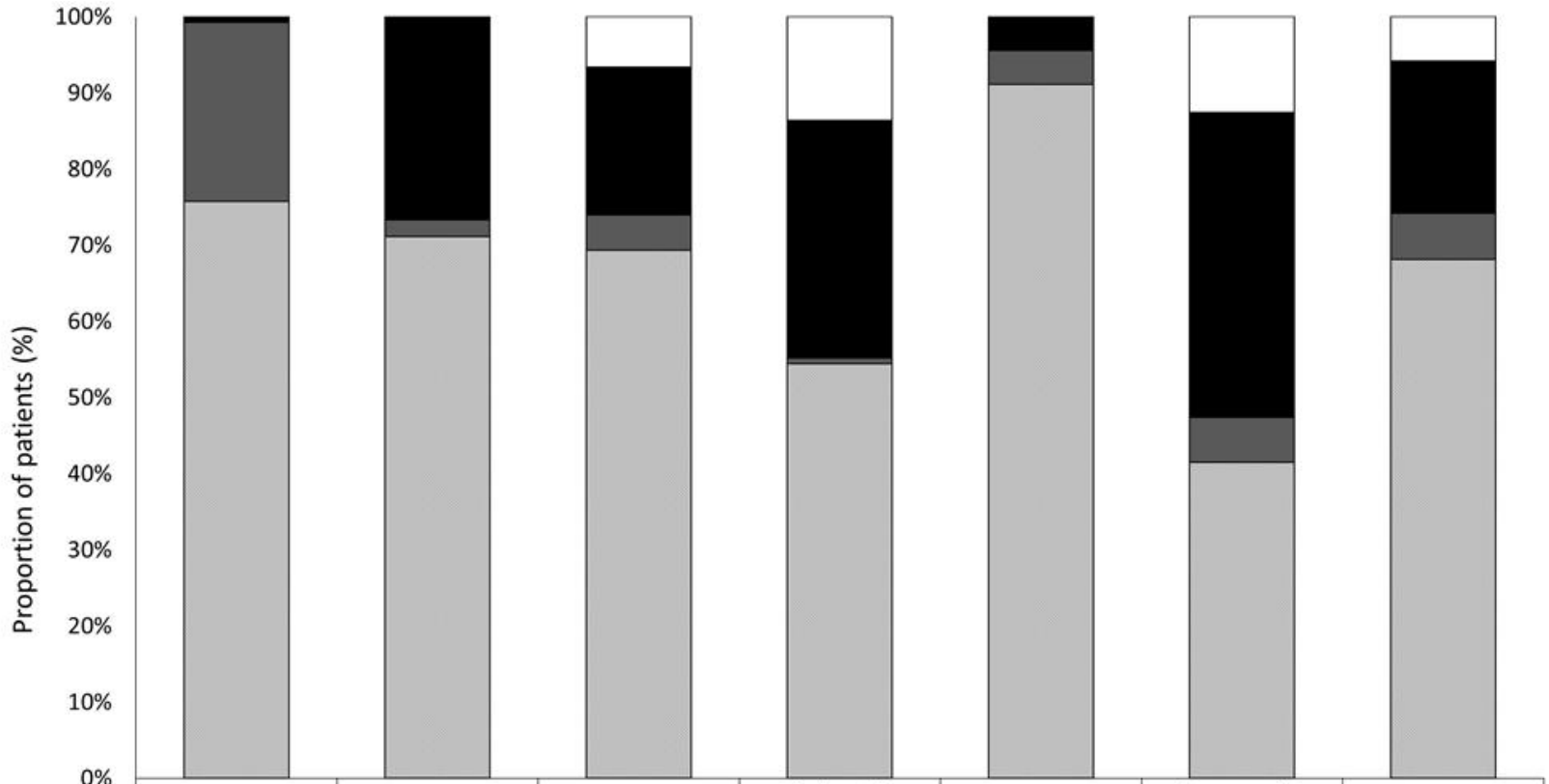
Figure 12: Cash transfer received by participants in seven different potential scenarios during intervention implementation**.** Note: Typically in Peru, treatment of TB in people with non-MDR TB has a duration of 6 months, in people with HIV-TB co-infection treatment lasts 9 months, and in people with MDR TB treatment lasts 24 months. Key: ✔ = condition optimally achieved and double incentive cash transfer provided; **X** = condition not achieved thus no incentive cash transfer given/paid

Figure 13a: Details of the operational conditions to be met in order to receive double incentives

		DOUBLE INCENTIVES	
Output	Condition	What the person with TB and their household members are required to do to receive a DOUBLE incentive	What each TB-affected family will receive in Soles (Dollars)
i. SCREENING FOR TB AND MDR-TB	Patient: sputum sample	Give a sputum sample prior to starting treatment and complete the questionnaire with the research nurse. The national TB program must have registered the person with TB in their health post's TB patient register	40 (14)
	Contact: TB screening	All (100%) of the people registered as living in the same house as the person with TB attend their medical appointment or give a sputum sample (that has a result) to rule out TB. Those people who need to take medicine to prevent TB (chemoprophylaxis) or TB treatment, must have started it. Contacts who do not need to take such treatment must be confirmed in the medical treatment cards	150 (54)
ii. ADHERENCE TO TB TREATMENT OR CHEMOPROPHYLAXIS	Patient: adherence to treatment	SENSITIVE/NON-MDR PATIENTS (INCLUDING THOSE WITH HIV), DURING THE FIRST 50 DOSES OF TREATMENT: each 25 doses (approximately each month) of TB treatment taken missing no more than 2 doses	50 (18)
		MDR PATIENTS, DURING THE FIRST 150 DOSES OF TREATMENT (APPROXIMATELY 6 MONTHS): each 25 doses (approximately each month) of TB treatment taken missing no more than 2 doses	50 (18)
		SENSITIVE/NON-MDR PATIENTS (INCLUDING THOSE WITH HIV), AFTER THE FIRST 50 DOSES OF TREATMENT TO THE END OF TREATMENT: each 24 doses (approximately two months) of TB treatment taken missing no more than 1 dose	50 (18)
		MDR PATIENTS, AFTER THE FIRST 150 DOSES OF TREATMENT UNTIL THE END OF TREATMENT: each 50 doses (approximately two month) of TB treatment taken missing no more than 2 doses	50 (18)
	Patient and contacts: completion of TB treatment and chemoprophylaxis	The person with TB completes their TB treatment and all (100%) of the people who live with them who started chemoprophylaxis to prevent TB, finish their chemoprophylaxis	100 (36)
iii. ENGAGE WITH CRESIPT SOCIAL ACTIVITIES	Patient and contacts: home visit	In the first week following recruitment to our project, allow the CRESIPT team to visit the person with TB's house, complete the questionnaire (if necessary), and list all the people who live in the same house as them	50 (18)
	Patient and contacts: community meetings	By 3 months following recruitment, the person with TB and all (100%) of the people that the CRESIPT team listed as living in the same house as them attend at least 1 CRESIPT community meeting	100 (36)
COMPLETE ALL CONDITIONS		The person with TB and all of their contacts complete all the above project conditions including adhering to treatment for the duration of treatment	640 (230)

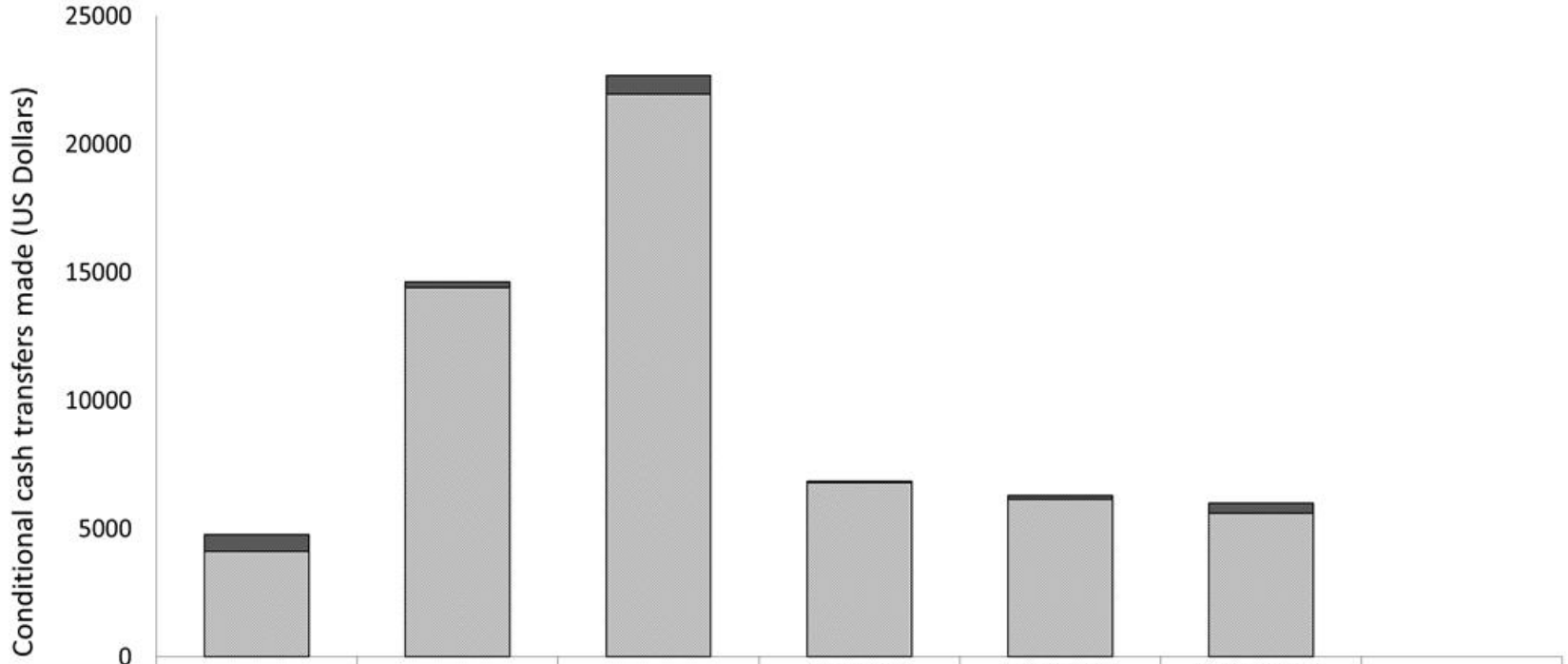
Figure 13b: Details of the operational conditions to meet in order to receive simple incentives

		SIMPLE INCENTIVES	
Output	Condition	What the person with TB and their household members are required to do to receive a SIMPLE incentive	What each TB-affected family will receive in Soles (Dollars)
i. SCREENING FOR TB AND MDR-TB	Patient: sputum sample	Give a sputum sample as soon as possible after starting treatment and complete the questionnaire with the research nurse. The national TB program must have registered the person with TB in their health posts TB patient register	20 (7)
	Contact: TB screening	>80% of the people registered to live in the same house as the person with TB attend their medical appointment or give a sputum sample (which has a result) to rule out TB. Those people who need to take medicine to prevent TB (chemoprophylaxis) or TB treatment, must have started it. Contacts who do not need to take such treatment must be confirmed in the medical treatment cards	75 (27)
ii. ADHERENCE TO TB TREATMENT OR CHEMOPROPHYLAXIS	Patient: adherence to treatment	SENSITIVE/NON-MDR PATIENTS (INCLUDING PEOPLE WITH HIV), DURING THE FIRST 50 DOSES OF TREATMENT: each 25 doses (approximately each month) of TB treatment taken missing equal to or more than 3 doses	25 (9)
		MDR PATIENTS, DURING THE FIRST 150 DOSES OF TREATMENT (APPROXIMATELY 6 MONTHS): each 25 doses (approximately each month) of TB treatment taken missing equal to or more than 3 doses	25 (9)
		SENSITIVE/NON-MDR PATIENTS (INCLUDING PEOPLE WITH HIV), AFTER THE FIRST 50 DOSES OF TREATMENT TO END OF TREATMENT: each 24 doses (approximately two months) of TB treatment taken missing equal to or more than 2 doses	25 (9)
		MDR PATIENTS, AFTER THE FIRST 150 DOSES OF TREATMENT UNTIL THE END OF TREATMENT: each 50 doses (approximately two month) of TB treatment taken missing equal to or more than 3 doses	25 (9)
	Patient and contacts: completion of TB treatment and chemoprophylaxis	The person with TB completes their TB treatment and 80% or more of the people who live with them who started chemoprophylaxis to prevent TB, finish their chemoprophylaxis	50 (18)
iii. ENGAGE WITH CRESIPT SOCIAL ACTIVITIES	Patient and contacts: home visit	In the first month following recruitment to our project, allow the CRESIPT team to visit the person with TB's house, complete the questionnaire (if necessary), and list all the people who live in the same house as them	25 (9)
	Patient and contacts: community meetings	By 5 months following recruitment, the person with TB and all (100%) of the people that the CRESIPT team listed as living in the same house as them attend at least 1 CRESIPT community meeting	50 (18)
COMPLETE ALL CONDITIONS		The person with TB and most of the people who live with them complete all the above project conditions including adhering to treatment for the duration of treatment	320 (115)



	Patient	Contact	Patient	Patient & contact*	Household visit	Community meeting	Total
	i. Screening for TB & MDR-TB		ii. Adhering to treatment or chemoprophylaxis		iii. Engaging with CRESIPT social activities		
□ Not yet achieved	0	0	42	17	0	17	76
■ Failed to achieve	1	36	123	39	6	54	259
■ Achieved adequately (simple incentive)	32	3	29	1	6	8	79
■ Achieved optimally (double incentive)	103	96	439	68	123	56	885

Figure 14a: Proportion of patients optimally achieving (double incentive), adequately achieving (simple incentive), and not yet achieving project conditions. *This condition was achieved when the patient finished their treatment and 100% (double incentive) or ≥80% of the household contacts who were eligible for and started preventive therapy then finished preventive therapy. At the time of writing (July 2015), there remain some patients with prolonged treatment courses (predominantly those with HIV-TB co-infection or MDR TB) are still ongoing on treatment.



Achieved adequately (simple incentive)	640	225	725	50	150	400	2190
Achieved optimally (double incentive)	4120	14400	21950	6800	6150	5600	59020

Figure 14b: Total amount provided to patients by conditional cash transfers in total and for each condition achieved. *This condition was achieved when the patient finished their treatment and 100% (double incentive) or ≥80% of the household contacts who were eligible for and started preventive therapy then finished preventive therapy. At the time of writing (July 2015), there remain some patients with prolonged treatment courses (predominantly those with HIV-TB co-infection or MDR TB) are still ongoing on treatment.

Box 2: Lessons learnt and persisting research gaps

Lessons learnt	**Research gaps**
Social protection interventions for TB control require inter-sectorial collaborations	• What are the most effective and cost-effective partnership models for welfare and TB control bodies? • What are the best ways to integrate poverty reduction strategies and biomedical activities for TB control?
TB-specific conditional cash transfers are feasible and safe, but logistically complex	• What is the role of conditions in achieving the intervention objectives? • Are conditional, unconditional or combined cash transfers preferable and how does this depend on the settings in which the cash transfer program is implemented?[161] • What conditions are too hard to achieve for TB patients despite being well rewarded? • What is the best way to balance the conditions for the cash transfers in order that they reflect both the priorities of patients and their households, and the priorities of researchers and policy makers?[162] • What is the role of the size and timing of cash transfers on the impact of the intervention? • What is the effectiveness and cost-effectiveness of different delivery mechanisms?
TB-specific conditional cash transfers can be challenging to deliver to difficult-to-reach populations	• What are the optimal ways to adapt conditional cash transfer settings targeted at hard-to-reach populations in challenging urban environments characterised by violence, drug-addiction and marginalisation? • Should social protection interventions only be offered to high-risk patients or is it more cost-efficient to offer them to all patients plus an enhanced intervention to high-risk patients? • Is cash without social support sufficient to reach high-risk-patients or is social support necessary?
Health and financial management education are necessary and ethically appropriate	• Would cash transfers have the same impact even without an educational component? • What is the empowering factor of the cash transfers to TB patients: 1) receiving cash; or 2) being acknowledged and seen as individuals with rights and needs? • What is the aspect of the social protection intervention most likely to impact on TB prevention and cure: a) the economic dimension of cash transfers; b) the social dimension of home visits and community meetings; or c) both?

Chapter 5: The economic effects of a socioeconomic intervention for TB-affected households: the CRESIPT pilot study, Peru

At the time of writing (February 2016), this chapter is under review as a manuscript for publication with the European Respiratory Journal. As described in Chapter 4, with the support of the multi-disciplinary Innovation For Health And Development team and the team leader and PhD supervisor, Dr Carlton Evans, the candidate led this project's conception, design, implementation, and refinement of the intervention. In addition, the candidate led the data analysis, manuscript write-up, and dissemination of results.

Following the implementation and refinement of the socioeconomic intervention, the next step was to analyse the effect of the intervention on mitigation of TB-related and catastrophic costs (using the innovative, clinically-relevant catastrophic costs threshold created in Chapter 3).

Introduction

In order to enhance TB control, the World Health Organisation's (WHO) End TB Strategy mandates complementing the existing biomedical response with approaches that combat the financial burden of TB. Specifically, the strategy recommends providing social protection for TB-affected households and includes a target of zero TB-affected households incurring catastrophic costs by 2035.

Previously, catastrophic costs were defined financially as TB-related out-of-pocket expenses that led to worsening impoverishment of TB-affected households. In recent research, we defined a *clinically-relevant* catastrophic costs threshold, demonstrating that TB patients from households that incurred total TB-related household costs of ≥20% of their household annual income were more likely to die, abandon, or not be cured by TB treatment.[19] Additionally, this research suggested that such catastrophic costs led to as many adverse outcomes as MDR TB.[19] This catastrophic costs' threshold has been included by the WHO within a tool to estimate country-specific TB-related and catastrophic costs of TB patients and their TB-affected households. The tool, which builds on the published "Tool to estimate patients' costs"[79] and includes measurement of lost income in addition to direct out-of-pocket expenses, is being piloted and rolled-out in sentinel countries in 2015-6.

However, collecting such costs data is complex, labour-intensive, and thus may be logistically difficult for national TB programs to perform. A potential solution may be to collect data on other

indicators of financial weakening or shock, called “dissaving”, as part of catastrophic costs surveillance. Examples of dissaving include households using savings, taking out a loan, taking a child out of education, and/or selling household items or assets. Evidence is needed concerning the accuracy of dissaving as a proxy measure for catastrophic costs and its validity in the WHO costs tool.

Social protection, such as cash transfer interventions, aim to reduce or prevent further poverty and vulnerability by improving people’s capacity to manage social and/or economic risks.[131–138] Socioeconomic interventions include social protection and may additionally aim to defray TB-related costs, incentivise and enable care and reduce TB vulnerability. Social risks of having TB disease include TB-related stigma whereas economic risks include incurring TB-related costs. TB-related costs may be considered in terms of national economic costs, health-system costs, and human costs. In the setting of Peruvian shantytowns, the human costs associated with TB are generally experienced and shared by all the members of the household in which someone receives TB treatment.[15] In this manuscript we focus on costs experienced by TB-affected households that are henceforth referred to as TB-related costs.[132–134,142] There is minimal operational research assessing the impact of socioeconomic interventions on mitigation of the effects of TB-related costs. Such interventions may be a cost-effective investment from a societal perspective[170] through their potential ability to enhance TB control as part of the post-2015 End TB Strategy.

Building on the findings of the Innovative Socioeconomic Interventions Against TB “ISIAT” study,[15] we designed a new more focused, clearly defined socioeconomic intervention aiming to support TB-affected households (i.e. be “TB-specific”) in order to better achieve TB prevention and cure.[121] During a household-randomized controlled study, we piloted this intervention in order to optimise its impact for the larger Community Randomized Evaluation of a Socioeconomic Intervention to Prevent TB (CRESIPT). Here we report the economic effects of this new intervention during the CRESIPT pilot study, including an evaluation of dissaving as a possible proxy marker for catastrophic costs and an assessment of the intervention’s impact on defraying TB-related costs and catastrophic costs.

Methods

Participants, study setting, and description of the socioeconomic intervention are provided in greater detail in Box 3.

Box 3: The CRESIPT Pilot study: Socioeconomic intervention methods, participant recruitment, and impact of the intervention

Study methods[15]

Study setting

The study took place in 32 shantytown communities in Callao, Peru, with an estimated population of one million people.[33] The annual TB notification rate across these communities was 206 new cases per 100,000 people between 2011 and 2013,[33,34] greater than the national rate of 95 per 100,000 people.[27,35,36]

Intervention

The intervention aimed to increase: i. screening for TB in household contacts and MDR-TB testing in TB patients; ii. adherence to TB treatment and preventive therapy; and iii. engagement with socioeconomic support activities.

This integrated intervention consisted of:

- Economic support component: conditional cash transfers throughout treatment to mitigate TB-related costs and thereby reduce TB vulnerability, incentivise, empower, and enable equitable access to care; and
- Social support component: household visits and participatory community meetings for information, mutual support, stigma reduction and empowerment.

The cash transfers of the economic component of the intervention were designed so that if a patient achieved all possible conditions and thereby received all possible cash transfers throughout treatment, this would largely defray their direct out-of-pocket expenses for their entire illness that were previously found to be 10% of annual household income in this study site.[19,121]

Participants

Inclusion criteria: any patient initiating treatment with the Peruvian national TB program for TB disease in health posts in the study setting was invited to participate between 10th February and 14th August 2014.

Exclusion criteria: inability or unwillingness to give informed, written consent. For patients who were minors, a parent or guardian was asked to give informed, written consent and patients who were old enough were also invited to provide their assent to participate.

After informed written consent, patient households were randomised to the intervention or control arm:

- *Control TB-affected households*: TB-affected households in which a TB patient received the Peruvian national TB program standard of care only; and
- *Intervention TB-affected households:* TB-affected households in which a TB patient received the Peruvian national TB program standard of care plus the socioeconomic intervention.

*Healthy control households***:** were randomly-recruited households not known to have TB-affected household members and recruited concurrently with TB patients. Potential healthy control households were randomly selected from maps of the 32 study site communities. Either this household or the nearest inhabited household to this location was invited to participate during a household visit. All available household members, regardless of age, were invited to participate in the study. Healthy controls were not matched to patients because the study aimed to characterise risk factors for TB outcomes including sex, age, and poverty.

General analysis of costs. Continuous data were summarized by their arithmetic means and their 95% confidence intervals (CI) and compared with the Student's t-test whether the data was Gaussian or non-Gaussian because this approach is considered to be robust for health economics data analysis (and facilitates comparison with previous studies).[11] Furthermore, because of the skewed nature of some expenditure data, most median values were zero or close to zero limiting the descriptive usefulness of presenting median values. As described previously,[19] any direct expenses, lost income, or annual income recorded as "zero" or missing was replaced with 0.5 Peruvian Soles per day i.e. the midpoint of zero and the lowest unit of measurement, 1 Peruvian Sol. Categorical data were summarised as proportions with 95% CI and were compared with the z-test of proportions. We Operational definitions of the key study variables (TB disease, TB treatment phases, TB costs, and dissaving) were used from our group's published research[19] as reported in Chapter 3. However, in addition to the existing study definitions, new definitions of novel study variables such as "dissaving" were also created (Box 4).

Box 4: Operational definitions

TB Treatment Phases*

Pre-treatment: the time from self-reported onset of TB-related symptoms until treatment initiation

Intensive treatment phase: the initial phase of daily (or 6 days per week) TB therapy, usually the first two consecutive months of TB treatment

Continuation treatment phase: the months following intensive treatment phase in which treatment is given three times per week, usually for four consecutive months

During treatment: the intensive treatment phase plus the continuation treatment phase

Entire illness: the time from TB-related symptom onset to the end of the continuation treatment phase

TB Costs‡

Direct medical expenses: costs of medical examinations and medicines

Direct non-medical expenses: costs of natural non-prescribed remedies, TB-care related transport, extra food, and other miscellaneous expenses caused by the TB illness

Direct ("out of pocket") expenses: the sum of direct medical and non-medical expenses [25,79,96]

Lost income (indirect expenses): the income the patient estimated that the household lost due to TB illness or tuberculosis-related time off work since symptom onset and during treatment [25,79,96]

Total costs: direct expenses plus lost income

TB-related costs: refers collectively to direct expenses, lost income, and total costs

Income: the money earned by the household, stated monthly or annually

Catastrophic costs: a threshold of total costs of the entire TB illness ≥20% of that household's annual income, which were associated with a higher likelihood of TB patient death, abandonment, or TB recurrence in a cohort of TB-affected households from impoverished Peruvian shantytowns.[19]

TB-related costs cohort impact: To estimate the impact of TB-related costs at a cohort level, TB-related costs are expressed as a proportion of average annual income of the entire study cohort of TB-affected households

TB-related costs impact: To estimate the impact of TB-related costs at an individual household level, TB-related household costs are expressed as a proportion of the same household's annual income

Poverty and Dissaving

Socioeconomic variables: relatively stable proxy poverty markers including: home ownership, highest patient education level, material that walls were composed of, material that floors were composed of, toilet services, electricity use, water facilities, phone ownership (landline and/or cell), fuel used to cook at home, TV ownership, radio ownership, cooker/stove ownership, and refrigerator ownership.

Poverty score: a composite score using arbitrary units derived by principal component analysis (PCA) of all the socioeconomic variables[15]

Dissaving variables: proxy markers of household financial weakening and shock that included household members having: taken loans (informal and formal); left education (e.g. to care for or accompany patient); sold or pawned household items; used savings; started a new or second job; been asked to eat elsewhere; been asked to move out or find other lodgings; and performed fund-raising events (e.g. buying and cooking food to sell to friends, family, colleagues, and others for a small profit)

Dissaving score: a composite score using arbitrary units derived by PCA of all the dissaving variables

*These treatment definitions apply to all TB patients, irrespective of whether they had MDR TB or non-MDR TB. Peruvian National TB Program guidance recommends at least 18 months of treatment for MDR TB patients. Treatment is tailored to patients with MDR TB by a multi-disciplinary team according to their resistance profile and may not correspond to a specific “intensive” and “continuation” treatment phase.

ǂ Income, expenses, and costs are all measured in Peruvian Soles (average 1 US dollar equivalent to 2.9 Peruvian Soles during the study period) at the household level unless otherwise stated.

Costs and poverty. A locally-validated questionnaire [15,19] was updated and used to interview patients and collect socio-demographic data concerning household income and expenses throughout TB illness. Interviews were conducted at baseline with TB patients in intervention and control arms, as well as healthy controls. For all patients, this baseline interview occurred prior to or at the time at which treatment commenced. All patients (but not healthy controls) were subsequently interviewed after 2, 4, 8, 12, 16, and 20 weeks. At all baseline and subsequent interviews, data was collected characterizing earnings, income, expenses, employment (paid or unpaid), days unable to work due to illness, additional household food expenditure due to TB illness (e.g. over and above normal food expenditure), and crowding since the previous interview. As per previous research,[11] crowding was defined as both a continuous variable (number of people per room) and a dichotomous variable (percentage of households with greater than cohort median people per room). A final "exit" interview took place at 24 weeks or, in those who continued TB treatment beyond 24 weeks, at 28 weeks of treatment. The baseline and exit interviews (but no other interview) included anthropometric measurement of height and weight, calculation of body mass index (BMI), and a detailed assessment of 13 key stable variables associated with socioeconomic position (Box 2). These variables were used to create a composite household poverty index score in arbitrary units using principal component analysis (PCA), as described previously.[19] The Eigenvector loading values derived by PCA analysis were analysed in order to assess which of the socioeconomic variables contributed the most to - and thus had the highest discriminatory power to explain - the poverty score in this setting. The proportion of intervention patient households' TB-related costs that were defrayed by the conditional cash transfers was calculated. Additionally, changes in poverty score and body mass index (BMI) from recruitment to the exit interview was analysed in order to evaluate the impact of the intervention on nutritional and other poverty-related TB risk factors.

Dissaving. Elements of "dissaving" specifically related to the patient's TB illness were also recorded at each interview (Box 4, Page 107), cumulative dissaving episodes (i.e. each separate occasion on which an element of dissaving occurred) were measured, and a composite dissaving score was derived by PCA from all of the dissaving variables.[19] The dissaving score was measured as a continuous variable in arbitrary units with the mean dissaving score of the patient cohort being 0 units. A higher score implied greater dissaving and thus implied that the TB illness was causing a greater financial challenge. The Eigenvector loading values derived by PCA analysis were analysed in order to assess which of the dissaving variables had the highest discriminatory power to explain the dissaving score in the setting (variables with higher Eigenvector loading values being more discriminatory). Univariate and multiple logistic regression analyses with stepwise exclusion of non-contributory variables were used to assess the association between dissaving and socioeconomic variables including catastrophic costs. For these analyses the dissaving score was considered as a binary variable of higher than versus lower than average dissaving. This dissaving analysis tested

whether dissaving may be a possible proxy indicator of catastrophic costs (see Introduction to this chapter).[29]

Data shown: Data concerning TB-related costs, catastrophic costs, and dissaving is shown for both intervention TB-affected households and control TB-affected households. Data concerning the effect of the socioeconomic intervention on defraying costs are only shown for the intervention TB-affected households. This is because control TB-affected households did not receive the socioeconomic intervention and thus their TB-related costs were not defrayed.

Ethical approval: The project had ethical committee approval and all participants gave informed written consent prior to participation.

Results

Participants. The recruitment period was from 10th February 2014 to 14th August 2014 when the *a priori* study sample size was reached and data collection on TB-affected household costs continued until 1st June 2015. Figure 15 (Page 121) shows TB-affected household recruitment and participation: 312 TB patients from separate households were invited to participate, of whom 90% (282/312) were recruited. Of these, 147 were randomized to the control arm and received normal standard of care only ("control TB-affected households") and 135 were randomized to the intervention arm and additionally received the socioeconomic intervention ("intervention TB-affected households"). Of the intervention TB-affected households, 98% (132/135) completed final follow-up. Nevertheless, all 135 intervention TB-affected households had TB-related costs data available for analysis. Healthy control households were randomly recruited from the same 32 study site communities concurrently with the TB-affected households. 98% (262/266) of healthy control household members gave informed consent and participated.

Descriptive data. Baseline demographic data are summarised in Table 17 (Page 118), which compares all patients with healthy controls, and their households. There were no significant demographic differences between intervention and control patients or their households. TB patients' household income in Peruvian Soles was lower during the intensive phase (1109 [95% CI 1011-1206], p<0.0001) and maintenance phase (1155 [95% CI 1050-1261], p=0.004) than pre-treatment (1316 [95% CI 1210-1421], Table 17, Page 118). Multiple logistic regression analysis revealed that being a TB patient versus healthy control was independently associated with being poorer (OR 1.7 [95% CI 1.2-2.4], p=0.002, Table 18, Page 119).

Costs: direct expenses and lost income. Constituent direct expenses and lost income are summarized in Figure 16 (Page 122). Throughout the entire illness, non-medical expenses were greater than medical (67% [95% CI 65-68] versus 33% [95% CI 32-35] of total direct costs, p<0.0001), predominantly due to additional food and transport expenses during treatment. Direct expenses and lost income were higher during treatment than pre-treatment (direct expenses 7.1% [95% CI 6.2-8.1] versus 2.3% [95% CI 1.9-2.8] of average TB-affected household annual income, p<0.0001; and lost income 8.0% [95% CI 6.5-9.2] versus 2.2% [95% CI 1.8-2.6], p<0.0001). As a proportion of total costs during the entire illness, lost income was similar to direct expenses (48% [95% CI 48–52% versus 52% [95% CI 50-54], p=0.3, Figure 16, Page 122).

Total costs are summarized in Figure 16 (Page 122). Total costs were significantly lower pre-treatment (4.5% [95% CI 3.8-5.3] of average TB-affected household annual income) than during treatment (15% [95% CI 13-18], p<0.0001), intensive phase (6.3% [95% CI 5.6-7.1], p<0.02), or maintenance phase (9.2% [95% CI 6.8-10.8], p<0.0001). While total costs were higher during maintenance phase than

intensive phase (9.2% [95% CI 6.8-10.8] versus 6.3% [95% CI 5.6-7.1], p=0.0005). This was because maintenance phase was twice as long as intensive phase. In fact, costs per month during intensive phase costs were approximately one and a half times greater than costs per month during maintenance phase (p=0.001).

Poverty and TB-related costs: In poorer versus less poor households, direct expenses in Peruvian Soles throughout the entire illness were lower (mean direct expenses 1267 [95% CI 1070-1464] versus 1470 [95% CI 1001-1938], Figure 17, Page 123). However, total costs made up a greater proportion of poorer household's annual income (poorest households 29% [95% CI 23-34] versus least poor households 19% [95% CI 14-23], p<0.001, Figure 17, Page 123). The socioeconomic variables with the highest discriminatory power to explain the poverty score in this setting were: not having a refrigerator; quality of wall material (e.g. a wall made of mud/straw rather than bricks); quality of floor material (e.g. a floor made of mud/rubble rather than concrete); type of toilet (e.g. no toilet facility or rudimentary outdoor latrine rather than a flushing toilet in a specific separate bathroom of the house; and not having a television (Figure 18, Page 124).

Dissaving and the association of dissaving with catastrophic costs: Patient households experienced an average of 1.3 episodes (95% CI 1.1-1.5) of dissaving pre-treatment, 3.4 episodes (95% CI 3.0-3.8) in the intensive phase of treatment, and 3.7 episodes (95% CI 3.2-4.2) in the maintenance phase of treatment. Thus, cumulatively, patient households experienced an average of 8.4 (95% CI 7.5-9.2) episodes of dissaving during the entire TB illness. Multiple regression analysis of the dissaving score demonstrated that patients who belonged to households with more than average dissaving were independently more likely to: incur catastrophic costs (OR 1.8 [95% CI 1.1-3.1], p=0.02), be poorer (OR 1.8 [95% CI 1.1-3.0], p<0.03), and have more food insecurity (OR 2.2 [95% CI 1.2-3.8], p=0.008, Table 19, Page 120). The variables with the highest discriminatory power to explain the dissaving score in this setting were: missing scheduled payments; starting a new job; selling or pawning household items; undertaking small scale fundraising activities; and being asked to eat elsewhere to conserve household food (Figure 18, Page 124).

Conditional cash transfers and mitigation of direct costs, total costs, and catastrophic costs: 122/135 (90%) of intervention TB-affected households received at least one conditional cash transfer. These 122 intervention TB-affected households received a total of 890 conditional cash transfers (80% of potential conditional cash transfers), receiving on average a total of 520 Peruvian Soles (173 US Dollars), which is equivalent to 3.5% of average TB-affected household annual income or 42% of average TB-affected household monthly income).[121,159] The conditional cash transfers defrayed 20% (95% CI 15-25) of total costs, 39% (95% CI 37-43) of direct costs (Figure 19, Page 125), and hence 19% of lost income. Overall, 36% of patient households incurred catastrophic costs. Compared to control households, intervention households were less likely to incur catastrophic

costs (30% [22-38] of intervention households versus 42% [34-50] of control households, p=0.002, Figure 19, Page 125).

Equity: The data in three pairs of columns at the left of Figure 20 (Page 126) suggest that the conditional cash transfers were equitable in their TB-related costs mitigation in terms of poverty, gender, and food insecurity. Conditional cash transfers defrayed total costs to a greater extent in poorer households (22% [95% CI 19-25] versus 18% [95% CI 14-22], p=0.08) and female patients (23% [95% CI 19-27] versus 18% [95% CI 15-21], p=0.06, Figure 20, Page 126).

Conditional cash transfers and poverty-related TB risk factor reduction: Figure 21a (Page 127) shows the change in poverty score from baseline to final follow-up for control versus intervention patients. There was no significant difference in poverty score or change in poverty score in control patients, intervention patients, or control versus intervention patients. BMI increased significantly from baseline to final follow-up in the intervention patients (2.2 kg/m^2 increase from 22 kg/m^2 [95% CI 21-23] to 24.2 kg/m^2 [95% CI 23-25], p=0.0003) and also the control patients (1.6 kg/m^2 increase from 21.6 kg/m^2 [95% CI 21-22] to 23.2 kg/m^2 [95% CI 22-24], p<0.004, Figure 21b, Page 128). There was a non-significant trend towards intervention patients' BMI increasing to a greater extent than control patients (Figure 21c, Page 129). Post hoc subgroup analyses of the poorest third of patients or on the subset of patients who experienced catastrophic costs also showed no statistically significant effect of the intervention on BMI, savings, income, or poverty score (data not shown).

Discussion

We evaluated the effect of a TB-specific socioeconomic intervention[121] including cash transfers on mitigation of the effects of TB-related costs in impoverished Peruvian shantytowns. The financial burden of TB was high, especially amongst poorer TB-affected households. Over one-third of the TB-affected households experienced catastrophic costs and thus were at increased risk of adverse treatment outcome.[19] Households with greater dissaving were nearly two-times as likely to incur catastrophic costs, suggesting that dissaving may be a useful and simple proxy indicator of catastrophic costs risk. The intervention defrayed only a fifth of patient households' TB-related costs but, despite this, households that were randomized to receive the intervention were less likely to incur catastrophic costs. The intervention was equitable to vulnerable groups within the cohort including poorer households and patients who were female. This evidence suggests a socioeconomic intervention including a social protection component can contribute to defraying TB-related costs, reduce the likelihood of incurring catastrophic costs, and will inform future implementation of such interventions in line with the End TB Strategy.

Impact of the socioeconomic intervention on defraying TB-related costs and mitigating catastrophic costs

The findings of this current research are important because they indicate that a socioeconomic intervention reduced the likelihood of incurring catastrophic costs – an encouraging finding that contributes to WHO's goal of eliminating catastrophic costs by 2035. However, despite reducing the likelihood of incurring catastrophic costs, the impact of the socioeconomic intervention may have been limited by the fact that the conditional cash transfers defrayed only 20% of patient households' total costs. During planning of the intervention, it had been estimated that if implemented nationally this conditional cash transfer program would increase the Peruvian TB program budget by between 5 and 26% per patient.[22] Focus group discussions with key stakeholders including local staff of the Peruvian TB program and a civil society of TB-affected people suggested that such an increase in program expenditure was locally appropriate, affordable, and potentially sustainable.[13,15] Therefore, to enhance the impact of the intervention, it will likely be necessary to increase the proportion of costs defrayed by conditional cash transfers in order to further incentivize TB-affected households, eliminate catastrophic costs, reduce TB vulnerability, and enable improved access to TB treatment and care. This could be achieved by a combination of: reducing system costs (e.g. through rapid diagnosis, improved access to treatment and preventive therapy); increasing the value of the cash transfers; and increasing access to and uptake of the conditional cash transfers (e.g. stratifying the intervention so that high-risk groups receive greater and more frequent socioeconomic support).

Equity of the socioeconomic intervention on TB-related costs mitigation

There was evidence that the intervention was equitable because the proportion of direct expenses, lost income, and total costs defrayed by conditional cash transfers was higher in poorer households and female patients. These findings are encouraging because such vulnerable and marginalised patient groups have previously been found to have reduced access to TB care and prevention in the study setting, and thus are more likely to experience adverse TB treatment outcome.[11,69,171] In order to reach these underserved groups in the future, national TB-specific socioeconomic interventions may benefit from a broader approach than simply money and education, including cross-sector provision of improved access to health insurance, social housing, housing improvements (e.g. optimizing ventilation), employment services (nearly half of total TB-related costs were due to lost income), and multi-disciplinary drug and alcohol addiction clinics (services not widely available during the study period in the study setting. In addition, alternative forms of DOT may be beneficial to reduce TB-related financial burden and allow an early return to work, such as VOT (video-observed therapy) or peer-observation of therapy.

The association of poverty and TB

Patients were poorer than healthy controls whether assessed by factors acutely affected by having TB disease (such as employment status and income) or stable, long-term measures of socioeconomic position that constituted the poverty score (including household ownership, household assets, and education level). These findings reinforce Virchow's 150 year-old assertion that TB is a social disease[1,9,11] and imply that poverty scores may be useful tools with which to assess TB risk, especially in vulnerable groups. The relationship between poverty and TB is complex and requires further descriptive and particularly interventional research, especially in the light of the End TB Strategy's renewed call to combat the social determinants of TB.[16]

Dissaving and the association of dissaving with catastrophic costs

Dissaving is a simple, proxy measure of financial shock.[172] A key research question to be answered by the current research is how well the prevalence of certain dissaving measures correlates with likelihood of incurring catastrophic costs. In the current study setting, dissaving was associated with being a vulnerable, underserved individual or household. Patients from households with more than average dissaving were: poorer; more likely to incur catastrophic costs; and have greater food insecurity. In addition to a recently published study demonstrating the correlation of dissaving with TB-related costs in different settings,[173] our current results provide evidence to inform the potential role of dissaving and provide provisional support for dissaving as a proxy marker of catastrophic costs.[172] This is important because our previous work showed that catastrophic costs were associated with adverse TB treatment outcome and may be assumed to have a negative effect on

TB control. Thus, the same may be the case for dissaving. Were dissaving to be adopted as a proxy indicator of catastrophic costs, it is probable that local adaptation of dissaving measures will be necessary: in specific settings, certain dissaving variables may be more relevant to, and correspond more closely with, likelihood of incurring catastrophic costs. For example, in rural sub-Saharan Africa where formal loans or payments may be less frequent, other dissaving variables such as selling livestock may be more important contributors to dissaving.[10] Piloting of the WHO TB costs tool including dissaving measures may soon shed new light on this under-researched area.

Limitations. Firstly, the study sample size was determined by TB outcomes (see linked BMC Medicine article on the impact of the intervention on TB prevention and cure) so no *a priori* power calculations were made to evaluate the impact of the intervention on financial outcomes. Secondly, despite the encouraging findings concerning equity of the intervention, research nurses reported their subjective impression that patients who declined to participate in the study were much more commonly from groups associated with high-risk of adverse treatment outcome (including the formerly incarcerated, homeless, and/or those with drug addictions). However, this qualitative observation cannot be quantitatively verified because these patients chose not to give informed consent and so we were unable to formally collect data on their specific risk factors. Thirdly, costs of accessing treatment for concurrent comorbidities (including HIV and diabetes) throughout TB illness were not specifically examined during this study. However, only 6% of the cohort had diabetes and 5% HIV respectively and these comorbidities were equally distributed in the intervention TB-affected households and control TB-affected households, so it is unlikely that this would have influenced our results. Fourthly, we only studied the financial effects of MDR TB for six to seven months, whereas patients with MDR TB are usually treated for 18 months or more. We decided *a priori* to analyse the catastrophic costs of both MDR and non-MDR patients together for six to seven months, given the small number of MDR TB patients, and in order to be consistent with our previous published research into catastrophic costs of TB-affected households.[19] Finally, there is currently no standardized, accepted method by which to measure mitigation of the effects of catastrophic costs and defraying TB-related costs.

Conclusions

Accessing even free TB care was associated with higher dissaving, high TB-related costs, and frequent catastrophic costs in Peruvian shantytowns, especially for poorer households. This research provides evidence supporting the use of dissaving as a proxy indicator of catastrophic costs. A novel, complex, socioeconomic intervention was feasible, equitable, defrayed a substantial proportion of TB-related costs, and reduced the likelihood of incurring catastrophic costs. Informed by these findings, the socioeconomic intervention has been increased in value and its impact on TB health outcomes is ready to be evaluated during the Community-Randomized Evaluation of a Socioeconomic Intervention to Prevent TB (CRESIPT) study.

Table 17: Baseline demographic characteristics of patient and healthy-control study populations. P values are the difference between all healthy-controls and all patients by univariate logistic regression adjusted for age and sex.

	Patients (n=282)		Healthy control (n=262)	P value
	Intervention (n=135)	All (n=282)	All (n=262)	
GENERAL				
Age (median; IQR)	30 (21-45)	28 (21-44)	25 (11-44)	0.02
Sex (% male; 95% CI)	64 (55-72)	62 (56-67)	50 (44-56)	0.006
SOCIOECONOMIC				
Education level (%; 95% CI)				
Preschool minor	3 (0-6)	2 (0-4)	5 (2-8)	0.1
Illiterate	3 (0-6)	2 (0-4)	1 (0-3)	0.5
Primary school incomplete	12 (6-17)	9 (6-12)	12 (8-17)	0.2
Primary school complete	10 (5-15)	7 (4-10)	11 (7-15)	0.1
Secondary school incomplete	29 (22-37)	27 (22-33)	21 (16-26)	0.1
Secondary school complete	27 (20-35)	32 (27-38)	32 (26-38)	0.8
Higher education	16 (10-22)	20 (16-25)	11 (7-15)	0.01
Employment (%; 95% CI)				
Paid Employment	28 (20-36)	29 (24-35)	39 (33-45)	0.019
Unpaid Employment	25 (17-32)	23 (18-28)	16 (12-21)	0.05
Student	6 (2-10)	8 (5-12)	30 (24-36)	<0.0001
Minor	3 (0-6)	2 (0-4)	5 (2-8)	0.1
Unemployed	36 (28-44)	36 (30-41)	6 (3-9)	<0.0001
Monthly household income (mean monthly Peruvian Soles; 95% CI)				
Throughout entire illness	1190 (1071-1309)	1231 (1138-1325)	2204 (2002-2407)	<0.0001
Pretreatment	1358 (1206-1510)	1316 (1210-1421)	NA	NA
Intensive phase	1091 (976-1207)	1109 (1011-1206)	NA	<0.0001*
Maintenance phase	1082 (958-1207)	1155 (1050-1261)	NA	0.004**
Crowding (mean people/room; 95% CI)	1.9 (1.7-2.1)	2 (1.8-2.1)	2.1 (2.0-2.2)	0.082
Proportion poor (%; 95% CI)				
Poorer tercile	41 (32-49)	39 (34-45)	27 (22-32)	0.002
Poor tercile	30 (23-38)	33 (27-38)	36 (30-42)	0.4
Less poor tercile	29 (21-37)	28 (23-33)	37 (31-43)	0.027
Food insecurity (mean days went to bed hungry in the past month; 95% CI)	1.7 (1.0-2.4)	1.5 (1.0-2.0)	0.5 (0.1-0.9)	0.003
TB AND HEALTH				
Sputum smear positive (%; 95%CI)	40 (32-48)	40 (34-45)	0	NA
MDR (%; 95%CI)	7 (2-11)	9 (5-12)	0	NA
Previous TB episode (%; 95%CI)	18 (11-25)	23 (18-28)	5 (0-15)	0.05
BMI (mean; 95% CI)	22 (21-23)	22 (21-22)	24 (23-25)	<0.001

*Pre-treatment versus intensive phase **Pre-treatment versus maintenance phase. Note: there was no significant difference between household incomes during intensive versus maintenance phase

Table 18: Univariate and multiple logistic regression of specific poverty indicators associated with TB disease (comparing patient versus healthy-control study populations). After univariate logistic regression adjusting for age and sex, contributory variables (p≤0.1) were entered into a multiple logistic regression analysis. The variables that have blank data cell rows in the multiple logistic regression column were those non-contributory variables excluded from the final model. The variables "Not in paid employment" and "Lower monthly household income" were not included in the multiple regression model because these variables were strongly collinear with the variable "Poor". "NA" refers to these variables. Body mass index was not included in the analysis because this variable is strongly and acutely influenced by having TB disease.

			Univariate logistic regression		Multiple logistic regression	
	Patients (n=282) % (95% CI)	Controls (n=262) % (95% CI)	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Poor (% poorer than median poverty score)	50 (44-56)	38 (32-43)	1.7 (1.2-2.4)	0.002	1.7 (1.2-2.4)	0.002
Crowding (% above median number of people per room)	46 (41-52)	53 (47-59)	0.81 (0.57-1.1)	0.2		
Head of household did not complete secondary school (%)	47 (40-53)	52 (46-58)	0.82 (0.57-1.2)	0.3		
Food insecurity (% above median days of going to bed hungry in past month)	29 (23-34)	21 (16-26)	1.5 (1.0-2.3)	0.03		
Not in paid employment (%)	62 (56-68)	31 (25-36)	4.7 (3.2-6.9)	<0.001	NA	NA
Lower monthly household income (% below median income)	58 (52-64)	27 (21-32)	3.7 (2.6-5.4)	<0.001	NA	NA

Table 19: Patient household (n=282) dissaving score associations with health and socioeconomic variables. The patient cohort had a median average dissaving score of 0. Higher (more positive) scores indicate greater dissaving and hence greater financial shock. Lower (more negative) scores indicate lower dissaving and hence less financial shock. Health and socioeconomic variables were analysed for association with dissaving score by univariate logistic regression. Multiple logistic regression was then performed with stepwise exclusion of non-contributory (p>0.1) variables. The variables that have blank data cell rows in the multiple logistic regression column were those non-contributory variables excluded from the final model.

Variable		Dissaving score	Univariate logistic regression		Multiple logistic regression	
		(mean)	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Catastrophic costs	*Incurred*	0.58	2.4 (1.5-3.9)	0.001	1.8 (1.1-3.1)	0.02
	Not incurred	-0.43				
Poverty	*Poorer*	0.37	2.3 (1.4-3.7)	0.001	1.8 (1.1-3.0)	0.026
	Less poor	-0.35				
Food insecurity	*High*	0.3	2.6 (1.5-4.5)	0.001	2.2 (1.2-3.8)	0.008
	Low	-0.26				
Secondary education	*Incomplete*	0.36	1.7 (1.0-2.7)	0.03	___	___
	Complete	-0.165				
Employment	*Unpaid/no work*	0.16	1.1 (0.68-1.8)	0.6		
	Paid work	-0.23				
Symptom duration	*Longer*	0.09	1.4 (0.84-2.2)	0.2		
	Shorter	-0.068				
Type of TB	*Non-MDR*	0.008	1.1 (0.49-2.6)	0.8		
	MDR	-0.09				
Gender	*Female*	0.07	1.1 (0.66-1.7)	0.8		
	Male	-0.04				

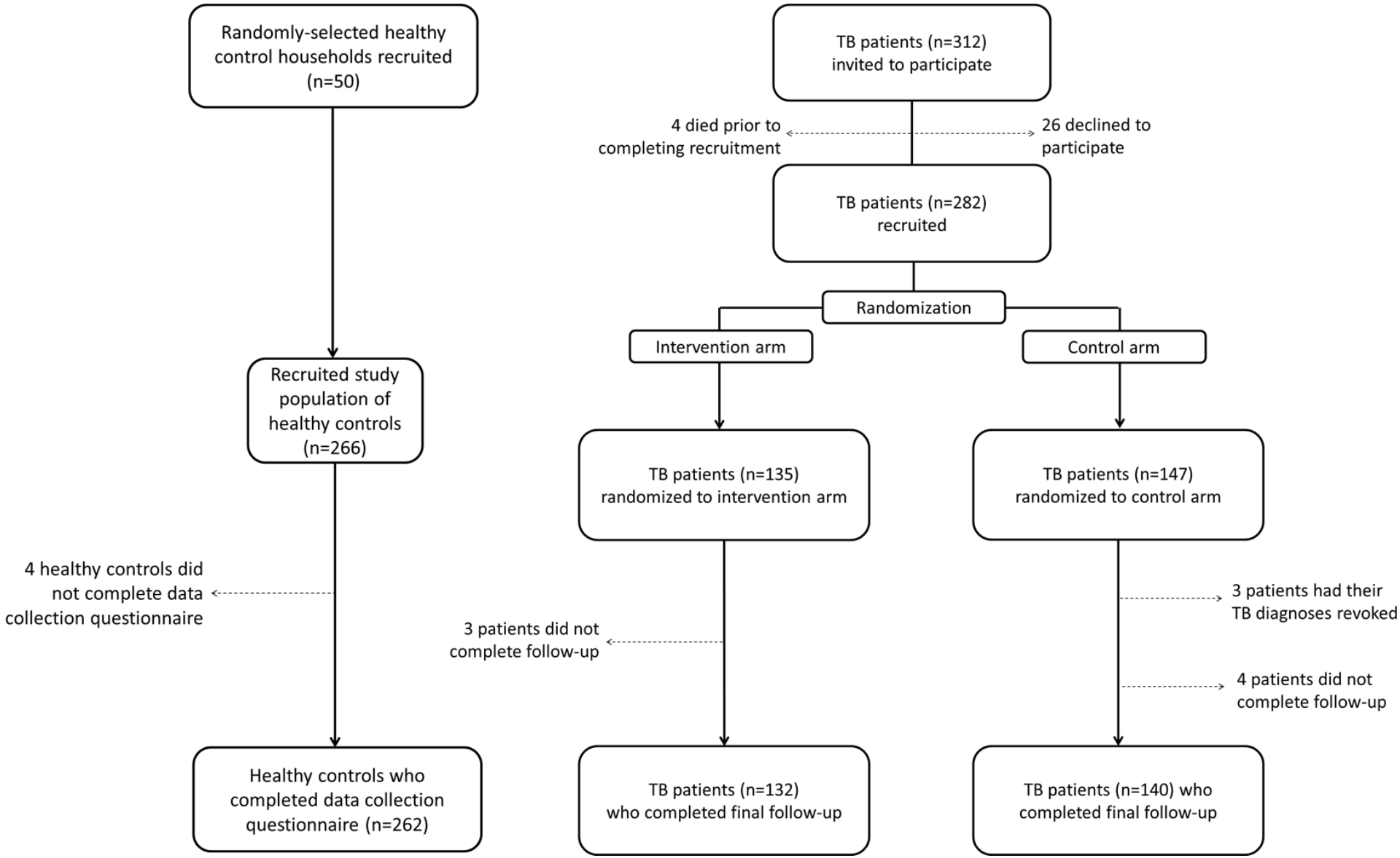
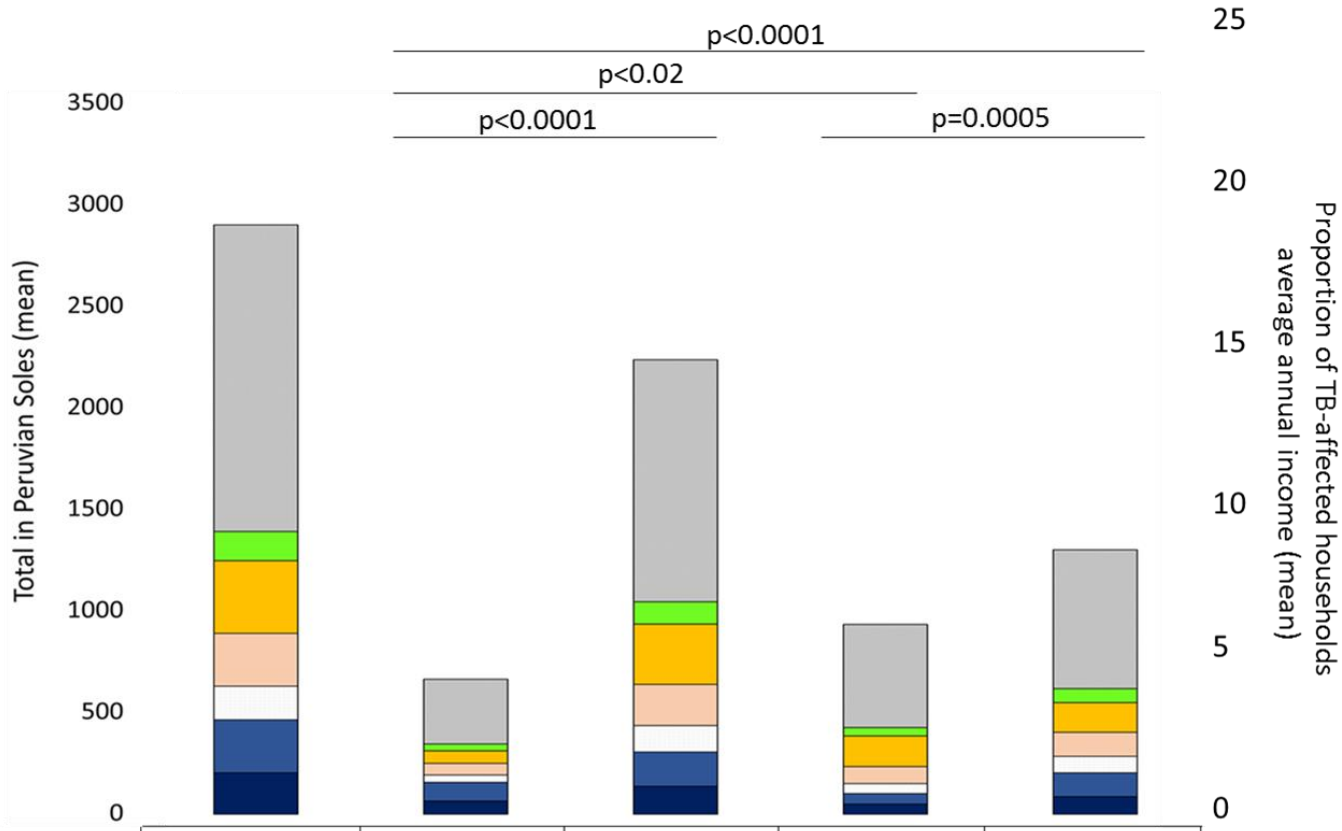


Figure 15: Participant recruitment and randomisation. Recruitment constituted completing informed consent and a recruitment questionnaire. Dashed arrows refer to participants who were not included in the final analysis.



		During entire illness (n=282)	Pretreatment (n=282)	During treatment (n=282)	Intensive phase (n=282)	Maintenance phase (n=282)
	Lost income	1510 (52)	319 (48)	1192 (53)	508 (54)	684 (52)
Type of Direct expense	Other expenses	166 (12)	36 (10)	130 (12)	49 (11)	81 (13)
	Extra food	358 (26)	61 (18)	297 (28)	151 (35)	146 (24)
	Transport	260 (19)	58 (17)	203 (19)	84 (20)	119 (19)
	Natural remedies	144 (10)	34 (10)	110 (10)	41 (10)	69 (11)
	Clinical exams	261 (19)	92 (27)	169 (16)	52 (12)	117 (19)
	Medicines	205 (15)	66 (19)	139 (13)	51 (12)	88 (14)
	Total direct expenses	1394 (48)	347 (52)	1048 (47)	428 (46)	620 (48)
	Total costs	2904 (100)	666 (100)	2240 (100)	936 (100)	1304 (100)

Figure 16: TB-affected household direct expenses, lost income, and total costs by treatment phase**.** P values are differences of total costs between treatment phases by T-test

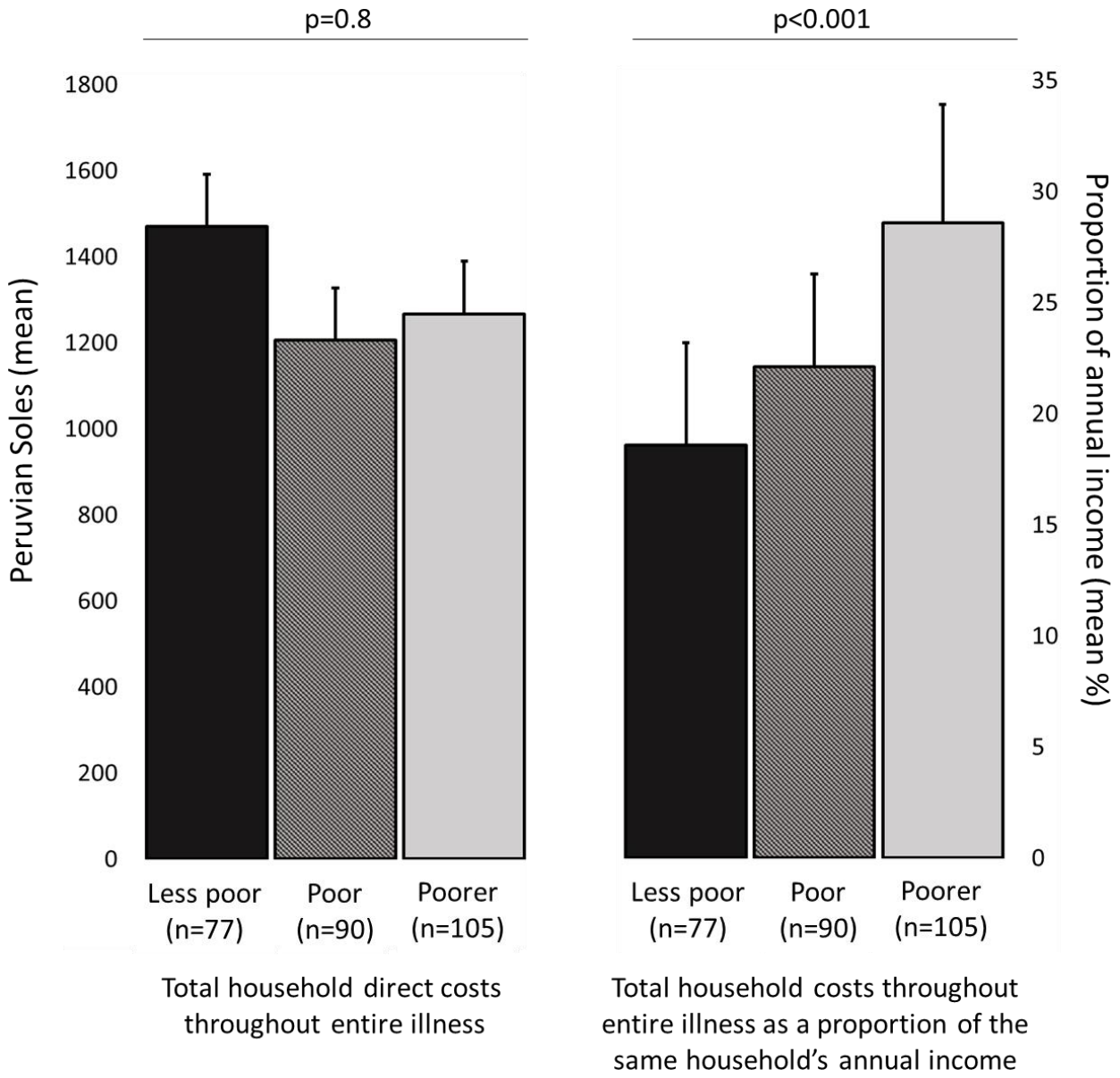


Figure 17: Total direct household expenses during the entire illness and total costs during the entire illness as a proportion of annual income by poverty tercile (n=282). This analysis is comparable with previous research.[19]

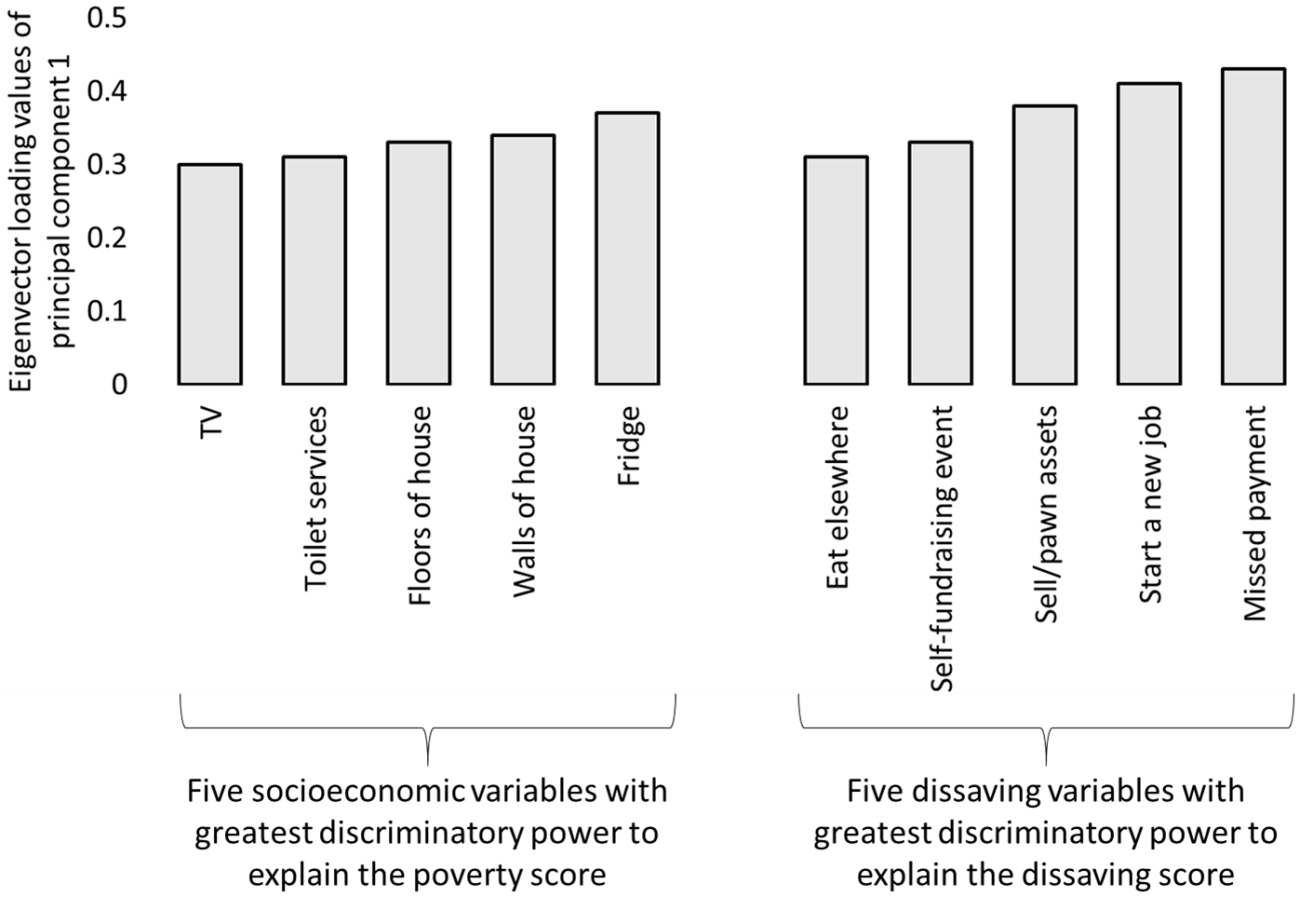


Figure 18: Variables with the highest Eigenvector loading values derived by principal component analysis. Higher eigenvector values represent a higher discriminatory power of that specific variable to explain the poverty score and dissaving scores (see Box 2).

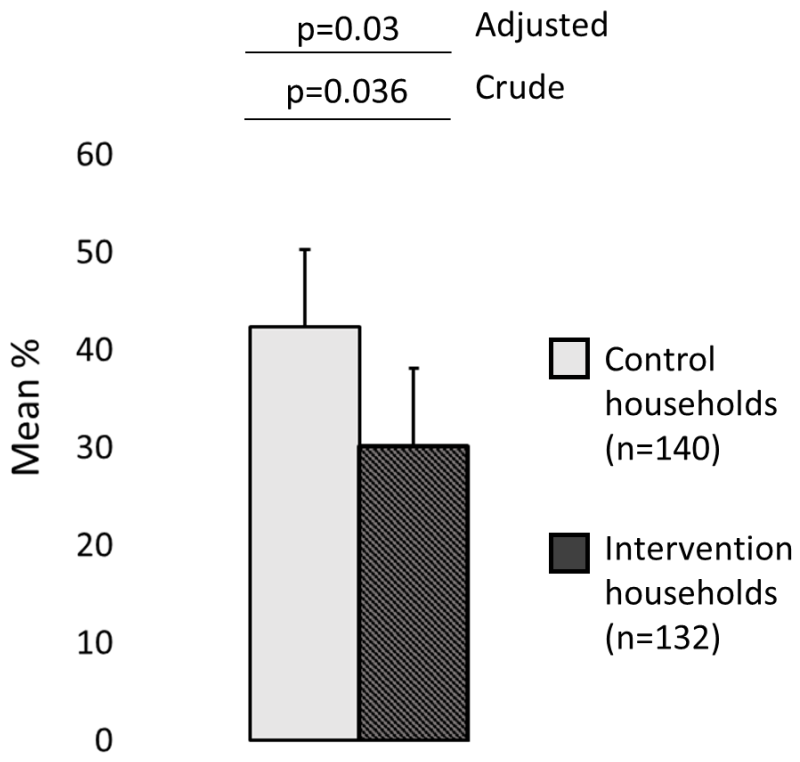


Figure 19: Catastrophic costs incurred by intervention (n=132) and control (n=140) households. The top p value is regression analysis adjusted for confounders including food insecurity, poverty level, household crowding, highest level of education of head of household, resistance profile of patient, and employment of patient.

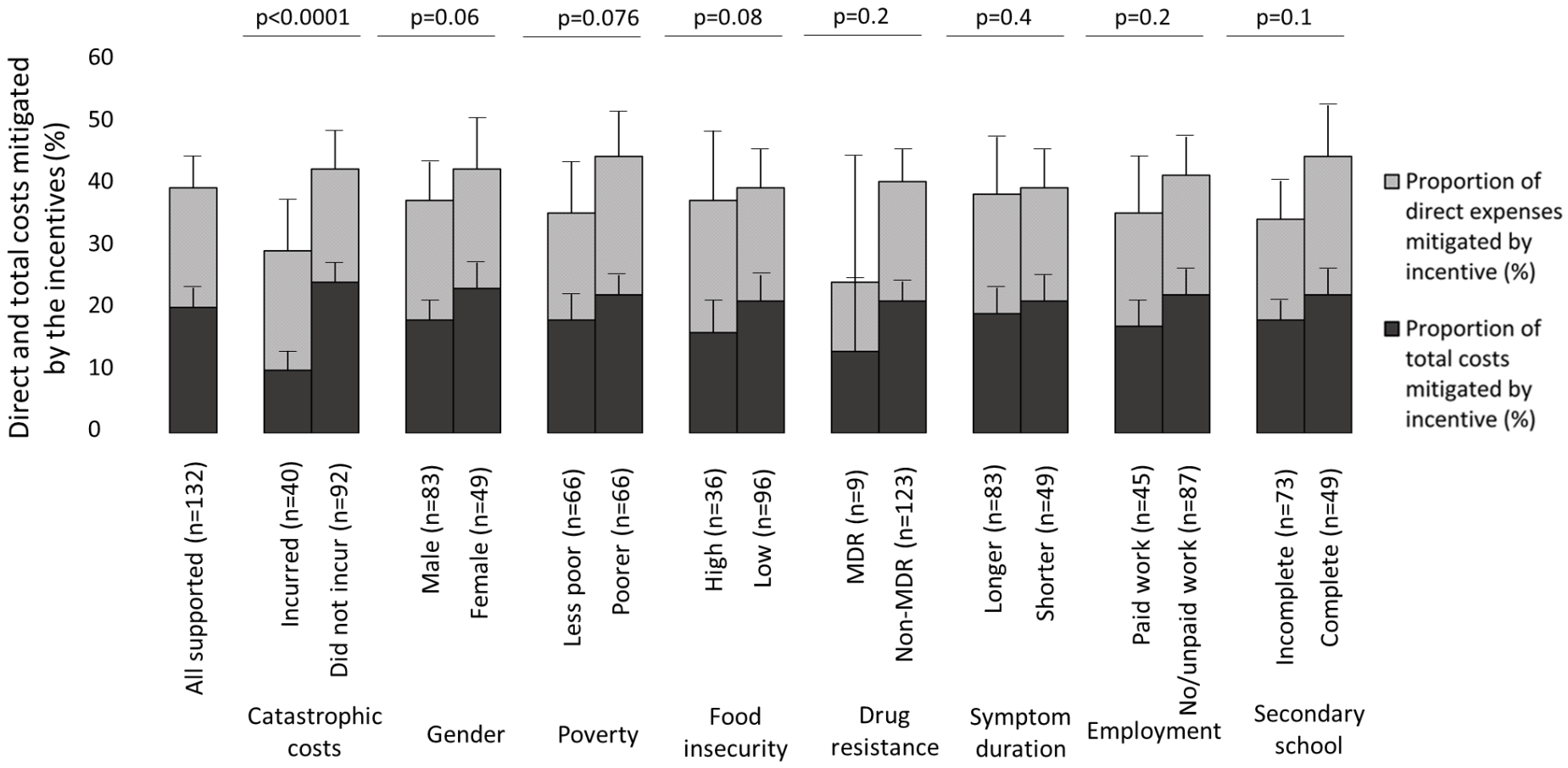


Figure 20: Intervention incentives as a proportion of direct expenses and total costs of that household**.** Incentives refer to conditional cash transfers received by the intervention patient households. P values are univariate logistic regression of each binary variable against total costs mitigated by the incentives.

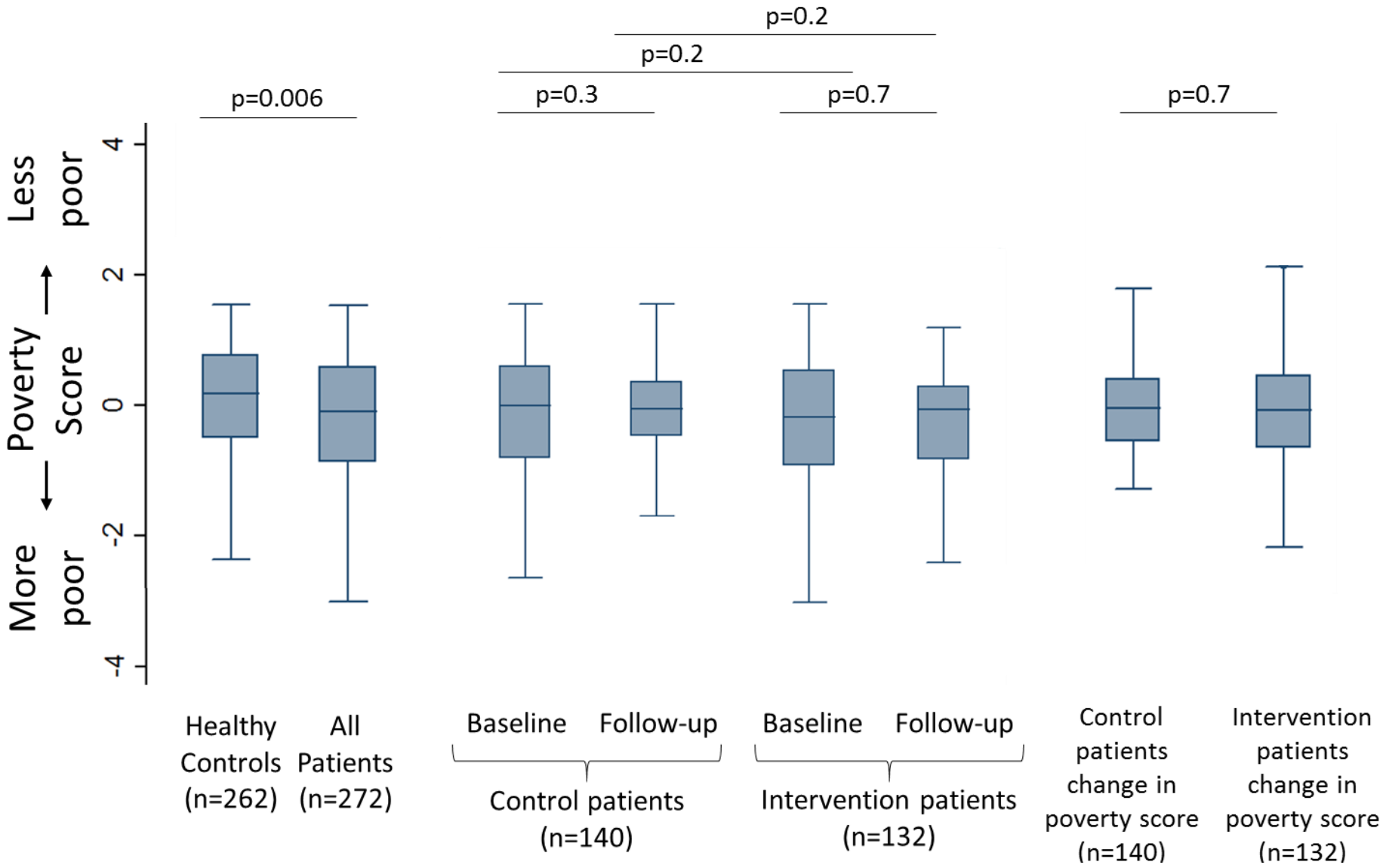


Figure 21a: Relative poverty score and changes in relative poverty score between all patients and healthy-controls at baseline, and intervention patients and control patients at baseline and follow-up. P values are the difference of poverty score between all patients and healthy-controls, and the change in poverty score from baseline to follow-up in and between intervention and control patients.

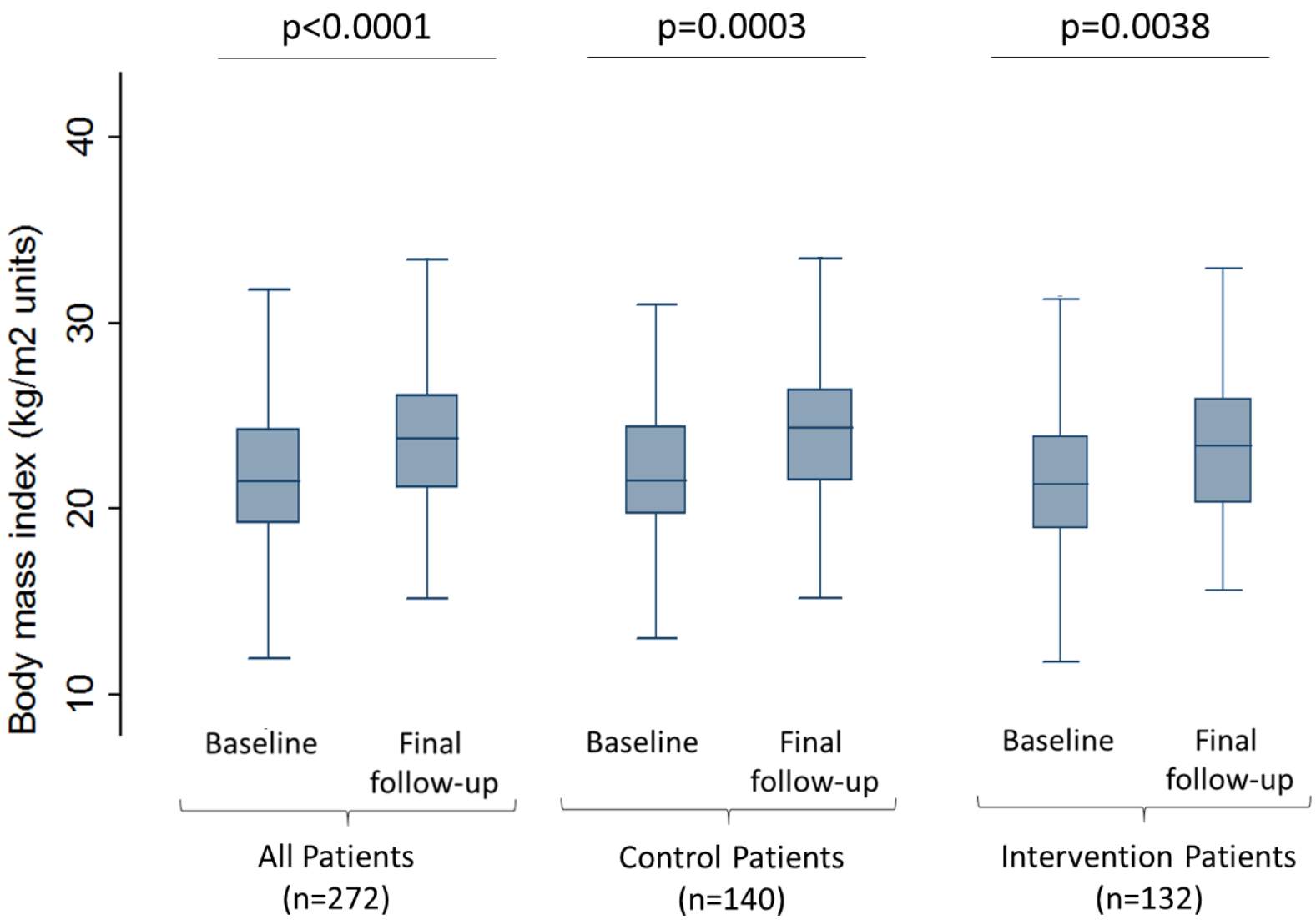


Figure 21b: BMI at baseline and final follow-up in all patients, supported arm patients, and control arm patients. P values represent the difference in BMI between baseline and follow-up on univariate logistic regression.

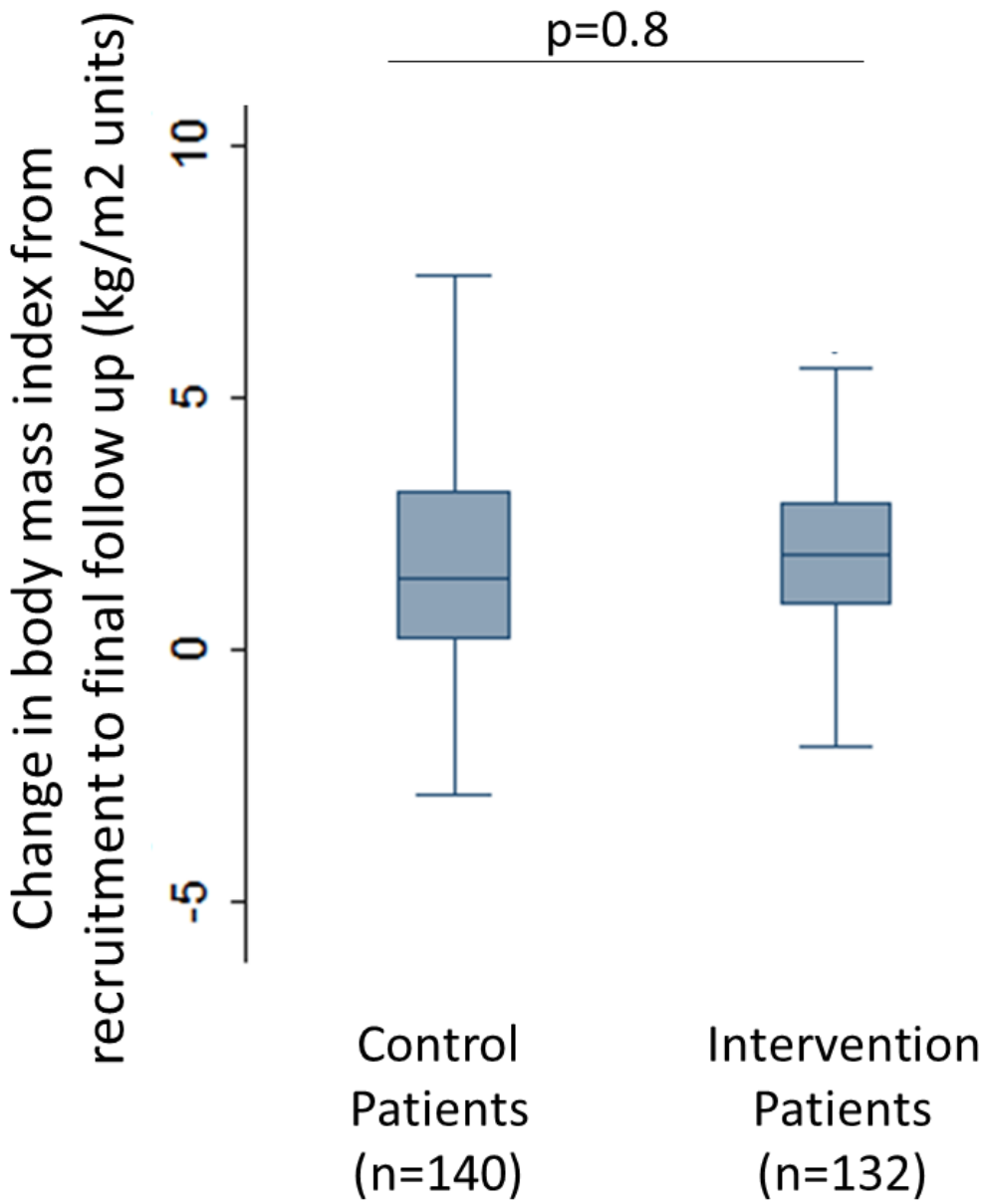


Figure 21c: Change in BMI from baseline to follow-up in supported arm patients and control arm patients**.** P values represent the difference in change in BMI from baseline to final follow-up between patient and control arms on univariate logistic regression.

Chapter 6: A randomized controlled evaluation of a socioeconomic intervention to improve tuberculosis prevention and cure in impoverished shantytowns of Callao, Peru

At the time of writing (February 2016), this chapter is under review as a manuscript for publication with the Bulletin of the World Health Organisation. The findings reported in this chapter form the crux of this PhD thesis: the impact of the socioeconomic intervention on TB preventive therapy uptake in household contacts and TB cure in patients from impoverished Peruvian shantytowns.

Introduction

One third of the world's population is estimated to have latent tuberculosis (TB) infection, mostly in resource-constrained settings.[174] Those at highest risk of progressing from latent TB infection to TB disease include: household contacts of TB patients and people living in poverty.[175] It has previously been shown that HIV-negative people with latent TB infection who took TB preventive therapy had a 60%[175] decreased risk of progressing to active TB disease. Despite this proven benefit, the global utilisation and impact of preventive therapy on TB control are severely limited because latent TB infection is infrequently tested[6] and people with latent TB infection are infrequently prescribed, start, adhere to, or complete TB preventive therapy.[15,176–178] Such people are more likely to develop TB disease, hampering global TB control.[179–181]

Difficulty adhering to medicines including TB preventive therapy is common and reduces the intended benefits.[176,177,179,182] However, it is not only TB contacts who are at increased risk due to non-adherence: TB patients who do not start, adhere to, or finish TB treatment are more likely to have adverse treatment outcomes (including death, treatment failure, and TB recurrence)[183] and transmit TB to other people including households contacts.[184] In addition, such patients are more likely to develop multi-drug resistant TB (MDR-TB);[185] an increasingly prevalent, global public health threat.[6]

Enhancing access to TB preventive therapy and treatment is likely to improve TB prevention and cure. The current slow decline in TB incidence is associated with a predominantly biomedical approach, which is proving insufficient to meet the reductions recommended in the End TB Strategy. To meet these goals, complementary strategies including socioeconomic support are required.[156,186–202]

Social protection interventions include conditional cash transfers and aim to reduce poverty and vulnerability by improving people's capacity to manage social and/or economic risks.[131–138] Although these and other socioeconomic interventions are already relatively common tools in the response to HIV/AIDS and maternal health,[139,140] there is extremely limited evidence on the impact of these interventions on access to TB preventive therapy in household contacts or cure in TB patients.[132–134,142]

Our research group (www.ifhad.org) was funded to undertake the Community Randomized Evaluation of a Socioeconomic Intervention to Prevent TB (CRESIPT) project. Prior to initiating CRESIPT, we report here the household-randomized controlled pilot evaluation of the complex TB-specific socioeconomic intervention that is proposed for the CRESIPT study [159,171]. The aims of the current pilot project were to evaluate the impact of this intervention on TB prevention and TB cure, and refine the intervention for the CRESIPT study.

Methods

Setting. 32 contiguous shantytown communities in Callao, Peru, with a population of approximately one million people[203] and an annual TB notification rate of 109 new cases/100,000 people/year in 2014,[203,204] higher than nationally.[26,158]

Design. This household-randomized controlled study evaluated the impact of a socioeconomic intervention on TB preventive therapy uptake by household contacts (henceforth termed "contacts") and TB cure in patients.

Intervention. The intervention is detailed in Chapters 4 and 5 and Box 5.

Box 5: Description of the socioeconomic intervention

Background: The project was informed by the findings of our group's Innovative Socioeconomic Interventions Against TB (ISIAT) study,[15] two systematic reviews of cash transfer interventions,[133,159,171] expert consultations,[132] and feedback from civil society and local and regional heads of the Peruvian TB Program.[171]

Outputs: The intervention targeted defined outcomes along the TB causal pathway and promoted equitable access to TB program activities[205] including:

i. screening for TB in contacts and MDR-TB in TB patients;

ii. adherence to TB treatment and preventive therapy; and

iii. engagement with social support activities.

The socioeconomic intervention has previously been described in Chapters 4 and 5.[171] Briefly, it constituted economic and social support:

- Economic support consisted of conditional cash transfers throughout treatment to defray average household TB-related costs thereby reducing TB risk factors whilst also incentivizing, and enabling care. Economic support was designed so that direct out-of-pocket expenses (previously found to be 10% of annual household income in the study setting)[171] would be mitigated in patients who achieved all conditional cash transfers. During planning of the intervention, it had been estimated that if implemented nationally this conditional cash transfer program would increase the Peruvian TB Program budget by approximately 15% per patient.[206] Focus group discussions with key stakeholders including local and regional staff of the Peruvian TB Program suggested that such an increase in program expenditure was locally appropriate, affordable, and potentially sustainable.[19,79,171].

- Social support consisted of household visits and participatory community meetings that aimed to provide information, mutual support and empowerment, and stigma reduction. The household visits were made shortly after patients were started on treatment and focused on education concerning TB transmission, treatment, preventive therapy, and domestic finances. The community meetings took place monthly in each study site community.[171] The meetings re-emphasized the educational themes of the household visit, and developed an event entitled "TB Club" in which participants shared TB-related and other life experiences within a mutually supportive group setting (to be reported elsewhere).[207] All household members were invited and encouraged to participate in both the household visits and community meetings.

Participants. *Inclusion criteria* were patients commencing treatment for TB disease administered by the Peruvian TB Program in the study communities. These patients were invited to participate with a consent form that explained the randomization process. For patients who were minors, a parent or guardian was invited to give informed written consent and the patient to assent to participate. *Contacts* were defined as individuals who reported being in the same house as the recruited TB patient for over 6 hours/week. *Exclusion criteria* were inability or unwillingness to consent.

Randomization was performed by TW and DH using random number tables to generate an individual household randomization sequence for each health post that was restricted to blocks of 30. The randomization assigned a patient household at a ratio of 1:1 to either the control arm, in which households received Peruvian TB Program standard of care, or the intervention arm in which households additionally received the socioeconomic intervention. The mechanism for allocation concealment consisted of cards placed in pre-numbered sealed envelopes detailing allocation to the intervention or control arm. Once patients gave informed consent to participate, a project nurse opened the envelope in front of the patient and informed them of their allocation.

Data collection. A locally-validated questionnaire [11,15] was used to collect health, wellbeing, and socio-demographic data, at baseline as treatment commenced and 24 weeks later (28 weeks if treatment was prolonged, usually because of MDR-TB and/or HIV-TB co-infection). Both interviews included measurement of height and weight to calculate body mass index (BMI), and assessment of 13 stable socioeconomic position indicators including assets, access to services, and education level.[159,171] The final interview also included a mixed-methods qualitative and quantitative questionnaire concerning feedback, in which participants were asked to rank the importance of each activity constituting the intervention (time spent with our project's research nurses and technicians in the health post, home visits, educational workshops, TB Clubs, and the conditional cash transfers).

Preventive therapy. The most recent Peruvian TB Program guidelines that applied throughout this study recommended that preventive therapy be provided to all contacts under 5 years old of a patient with non-MDR pulmonary TB (unless the contact had had previous TB disease), and preventive therapy should also be considered for contacts aged 5 to 19 years of a patient who have a tuberculin positive skin test indicating latent TB infection and were a contact of a patient with non-MDR pulmonary TB.[205] However, tuberculin was generally unavailable throughout this study. Preventive therapy consisted of a six-month course of daily isoniazid that was collected weekly from health posts by patients and taken unsupervised at their home.[205] Data concerning preventive therapy uptake were collected collaboratively and prospectively from Peruvian TB Program records. Of note, control households did receive information concerning household contacts of the TB

patien being tested and treated for latent TB infection in the form of face-to-face clinic contact (most commonly with Peruvian TB Program nurses) and also Peruvian TB Program educational leaflets, posters, and booklets (all available to download in Spanish from www.tuberculosis.mins.gob.pe). However, the extent to which this information was communicated was highly variable between health posts in the different study site communities.

Treatment. The Peruvian National TB Program offered free TB diagnostic testing to all suspected TB patients who, once diagnosed, received free anti-TB directly observed therapy (DOT) administered at health posts.[205] As an incentive and benefit for participation, all patients, regardless of their randomisation, were offered an additional sputum test with Xpert MTB/rif™ performed by our research laboratory for rapid rifampicin susceptibility testing, which was not otherwise routinely available. TB treatment outcome data were collected collaboratively with the Peruvian TB Program from their treatment cards at the time of final follow-up and were not influenced by this research.

Treatment outcomes. Peruvian TB program outcomes were consistent with those defined by the World Health Organisation.[174] The Peruvian TB Program defined cure of drug-susceptible TB as a patient with bacteriologically confirmed TB at diagnosis who completes treatment and has a negative sputum smear during the final month of treatment.[205] This involved confirmation during clinical assessment by a National TB program physician to evaluate symptoms, examination, weight trend, and, when necessary, investigation such as chest radiographs and blood tests. Patients who completed their TB treatment course but did not complete the required sputum testing and/or physician review were classified as having completed treatment. Other programmatic outcomes were death (all-cause mortality during TB treatment); failure of treatment (as determined by the physician and/or demonstrated by positive sputum microscopy/culture after 4 months of treatment); abandonment of treatment; and unknown outcome (patient relocated to another region or was lost to follow-up with inability to determine outcome). The Peruvian TB Program defined treatment success as patients who completed treatment or were cured, as per WHO guidance. An additional project definition was continuing on treatment after our 28-week follow-up interview. MDR-TB patients, whose treatment duration commonly extends to 24 months, were defined as continuing treatment if still taking TB treatment at this 28-week follow-up interview.

Primary study outcome. The primary study outcome compared intervention households with control households and was uptake of TB preventive therapy in contacts aged less than 20 years. *A priori* subgroup analysis of uptake, adherence to, and completion of TB preventive therapy for household contacts aged under 5 years old and household contacts aged from 5 to 19 years old was also performed. Completion of TB preventive therapy was operationally defined in line with

Peruvian national guidance: contacts who started and took 6 months (24 weeks) of preventive therapy (as documented in their preventive therapy treatment cards).[205]

The secondary study outcome was National TB Program confirmed TB cure in patients as described above. This analysis evaluated patients with cure versus patients without cure without any exclusions (intention-to-treat). Further sub-analyses were also performed evaluating patients with cure versus patients in whom it was not known whether they had been cured or not, such as patients: with unknown outcome; who were still on treatment; or who completed treatment without assessment. Finally, a sub-analysis of patients who had WHO-defined treatment success versus patients who did not have treatment success was performed.[208]

Sample size. Recent evidence from the study site showed that TB patients had an average of five contacts, three contacts aged <20 years and so potentially eligible for TB preventive therapy, and 25% of them completed it.[15] Therefore, *a priori*, we calculated that 312 patients would give 80% statistical power to detect a 33% increase in the primary outcome comparing intervention versus control households with two-sided 5% significance.

Blinding. It was not feasible for the patients or the research team to be blinded to patient allocation. TB Program staff were not informed of and were generally unaware of patient allocation but were not confirmed to be blinded.

Analysis. Socioeconomic variables were combined into a composite index of household socioeconomic position using principal component analysis, as previously described.[11] Data at the household and individual (patient or contact) level were used for intention to treat and supplementary analyses with adjustments for household clustering using robust standard errors because there was more than one household contact per patient in most households. The primary and secondary outcome were analysed by univariate logistic regression and multiple logistic regression adjusted for household clustering and known confounders measured at baseline (including household-level factors such as poverty, household crowding, head of household's highest education level, monthly income, and food insecurity; and patient-level factors such as age, gender, employment status, and TB resistance profile) that generated adjusted odds ratios (aOR) for relevant, contributory socioeconomic and health factors. Time-to-event analysis was performed in order to generate a crude, unadjusted log-rank value for difference between number of weeks of preventive therapy taken by household contacts from intervention versus supported households.

Approval. The project had ethical committee approval and all participants gave informed written consent prior to participation.

Results

Participants. Recruitment commenced 10th February 2014 and the intended sample size was reached 14th August 2014 and follow-up was completed 1st June 2015. 312 TB patients were invited to participate, 90% (282/312) were recruited and randomized to the intervention (n=135) and control (n=147) arms. Three recruited patients had their TB diagnosis revoked and two died during the study; and seven recruited patients did not complete follow-up. Thus 96% (272/282) recruited patients had complete follow-up (Figure 22, Page 147). 68% of patients had sputum smear-microscopy positive TB. 9% (24/282) of patients had MDR-TB, none of whom had been cured or completed treatment during the study because MDR-TB treatment generally requires at least two years of continuous antibiotic therapy in Peru. No substantive baseline imbalances were found between intervention and control patients in the baseline characteristics shown in Table 20 (Page 141). Patients had an average of five contacts, 97% (1290/1331) of whom were recruited. 40% (518/1290) of recruited contacts were aged under 20 years old of whom 410 completed follow-up (Figure 22, Page 147).

Intervention. 122/135 (90%) of patient households that were randomized to the intervention arm of the intervention received at least one conditional cash transfer. A total of 890 conditional cash transfers were made (80% of potential conditional cash transfers) with an average total of 520 Peruvian Soles (173 US Dollars) per household received a maximum of 640 Peruvian Soles (230 dollars) per household.[159,171]

Primary outcome. Contacts aged less than 20 years old from intervention households were more likely than those from control households to start preventive therapy (44% versus 26%, aOR 2.2 [95% CI 1.1-4.2], p=0.022, Table 21, Page 142 and Figure 23, Page 148). Time-to-event analysis showed that household contacts from intervention households took a greater number of weeks of preventive therapy than those from control households (log-rank test p=0.005, Figure 24, Page 149). Although crude analysis showed that household contacts were more likely to complete three and six months of preventive therapy (Figure 23, Page 148), these increases were not significant after adjusting for household clustering (completion of three months 33% versus 22%, aOR 1.8 [95% CI 0.90-3.7], p=0.095 and completion of six months 20% versus 12%, aOR 1.9 [95% CI 0.79-4.6], p=0.15, Figure 23, Page 148). Subanalysis of contacts aged 5 to 19 years old (Table 22, Page 143 and Figure 25, Page 150) and less than 5 years old (Table 23, Page 144 and Figure 26, Page 151) showed a similar pattern, with those less than 5 years old tending to be more likely to start, adhere to, and complete preventive therapy than 5 to 19 year olds.

Secondary outcome. The intention-to-treat-analysis showed that patients from intervention households were more likely than those from control households to have cure (51% [95% CI 43-60%] versus 37% [95% CI 30-45], aOR 1.8 [95% CI 1.1-2.9], p=0.02, Table 24, Page 145, Table 25, Page 146, and Figure 27, Page 152). This pattern was maintained after excluding patients with unknown outcome, and/or those still on treatment, and/or those who completed treatment (Figure 27, Page 152). However, using the National TB Program definition patients from intervention households only tended to be more likely to have a successful treatment outcome than patients from control households (76% versus 70%, aOR 1.6 [95% CI 0.87-3.0], p=0.13).

Feedback: 74% (100/135) patients from supported households completed a feedback questionnaire. They rated social support (a composite average of home visits, health post project interactions and community meeting educational workshop and TB Club rankings, 3.1 [95% CI 3.0-3.2]) as more important than the economic support (conditional cash transfer ranking 1.9 [95% CI 1.5-4.3], p<0.0001, Figure 28, Page 153). In poorer households, cash transfers tended to be rated more highly (2.2 [95% CI 1.7-2.7] poorest versus 2.0 [95% CI 1.4-2.6] poor versus 1.5 [95% CI 0.8-2.0] least poor, p=0.06) and social support activities less highly (composite social support activities ranking 2.9 [95% CI 2.8-3.1] poorest versus 3.1 [95% CI 2.9-3.3] poor versus 3.2 [95% CI 3.0-3.3], p=0.02).

Discussion

During the CRESIPT pilot study, we designed, implemented, refined,[121] and evaluated a novel TB-specific socioeconomic intervention including cash transfers in a resource-constrained setting. The intervention proved to be feasible[171] and improved rates of TB preventive therapy uptake in contacts and TB cure in patients.

The findings of this paper generate new knowledge suggesting that socioeconomic interventions including conditional cash transfers can modify behaviour and improve TB prevention and cure in a challenging environment. Prior to this study, evidence assessing interventions to improve TB preventive therapy or treatment adherence has been hampered by lack of randomization, limited sample size, and/or being conducted in high-resource countries with restricted patient groups (e.g. HIV-infected people,[209] homeless people,[186,187] migrants,[193] or injecting drug users[156,175,188,198]). Recent systematic reviews concluded that there was currently no evidence that incentives including cash transfers increased TB preventive therapy completion[17] and minimal evidence to guide World Health Organization recommendations concerning implementation and scale-up of TB-specific

socioeconomic interventions in resource-constrained settings.[210] Since the publication of these reviews, there have been very few controlled studies to further knowledge in this area.[15,18] This current research from a resource-constrained setting contributes new knowledge to fill this evidence gap and inform global TB policy.

The finding that this intervention increased TB preventive therapy uptake and number of weeks of preventive therapy taken is important because non-adherence to TB preventive therapy is frequent[156,178–181,196,211–214] and leads to higher rates of secondary TB. Nevertheless, even in the household contacts from intervention households, the uptake of preventive therapy was low with less than half of the household contacts even starting preventive therapy. However, the aim of the study was not to achieve 100% preventive therapy coverage in household contacts because only a subset of household contacts is eligible to receive preventive therapy. Instead, we approximately doubled uptake of TB preventive therapy in household contacts under 20 years old. This increase in preventive therapy uptake was greatest in household contacts under 5 years, the great majority of whom are eligible for TB preventive therapy, at highest risk of death from TB disease, and in whom the impact of preventive therapy will therefore have the greatest health benefits. By contrast, in Peru, household contacts aged 5-19 years are not all eligible for preventive therapy: they generally require a clinical assessment including a tuberculin skin test that confirms TB infection before a decision may be taken to offer TB preventive therapy. Current shortages in the worldwide supply of tuberculin have made such screening difficult to achieve.[215] Despite this logistical challenge, intervention household contacts aged 5-19 years approximately doubled their preventive therapy uptake, highlighting the strength of the effect of the socioeconomic support they received.

While these CRESIPT pilot study findings are encouraging, it must be noted that despite a trend towards increased TB preventive therapy completion in the intervention contacts, there was not statistically significant evidence for this increase and many contacts who were probably eligible for TB preventive therapy did not complete it despite being offered our socioeconomic intervention. A potential reason for this may be that conditional cash transfers for preventive therapy were not given monthly like they were for TB treatment. In addition, the conditional cash transfer for completion of preventive therapy was only made if all (rather than for each of the) eligible contacts in the household completed it. The conditional cash transfer design was informed by our previous analyses of TB-related costs[11] and aimed to temporarily reduce poverty,[11,216] mitigate direct costs,[11] and thereby enable and improve healthcare access.[217] However, results from the economic analysis (see Chapter 5) demonstrate that the transfers did not completely mitigate direct out-of-pocket expenses, suggesting that the financial burden of TB was still high for many of the intervention households. On the basis of the current results of this CRESIPT pilot study, we have since optimised

the design of the economic component of the intervention to completely mitigate direct expenses and to offer monthly conditional cash transfers to individual household contacts to further enhance uptake and completion of preventive therapy and thus prevent incident TB. This new design has been incorporated into the larger, five-year, well-powered community-randomized CRESIPT study, which is currently commencing and will evaluate the cost-effectiveness and impact of the refined socioeconomic intervention on health outcomes, access to TB care, and community TB notification rates.

This research provides preliminary evidence in support of WHO's End TB Strategy, which calls for expansion of the existing biomedical paradigm for TB control by incorporating socioeconomic interventions and Universal Health Coverage initiatives that address poverty and social determinants, the main drivers of the global TB epidemic.[16] This CRESIPT pilot study highlights the potential importance of investing not only in diagnosing and treating TB disease but also in supporting TB-affected people and households. While these findings suggest that conditional cash transfers may contribute to improved patient outcomes (perhaps through diminishing food insecurity during TB treatment as well as improved access to medical care), it must be noted that the intervention went beyond cash transfers by offering education informing and promoting stigma reduction, inclusiveness, and empowerment during household visits and participatory community meetings. This social support focused on risk factors for non-adherence to preventive therapy such as: being female and/or belonging to a marginalized group,[193,218–220] age,[220,221] illegal drug use,[196], homelessness,[197] alcohol misuse,[222] and TB-affected families' and individuals' own knowledge, attitudes and perceptions.[214,223] The design of this CRESIPT pilot study did not allow analysis of the differential impact of the social support component and the economic support component of cash transfers on access to TB cure and access to prevention. Nevertheless, in the field of HIV, conditional cash transfers interventions have often been complemented with health education for beneficiaries, and it has been suggested that, without education or social support, conditional cash transfers are unlikely to have an impact on health outcomes.[140] Thus, optimising social support and addressing specific aspects of poverty such as food insecurity are likely to be key issues on which to focus in order to strengthen the impact of future interventions.

This study had several limitations. Firstly, we used TB cure as an outcome measure rather than TB treatment success, which combines TB cure and TB treatment completion. We took this approach because previous data from the study site demonstrated that patients who complete treatment (rather than being confirmed as cured) are more likely to have early subsequent TB recurrence and so not truly be cured.[5] Thus better characterisation of TB treatment outcomes will be a priority for future research. Secondly, this CRESIPT pilot (as opposed to the forthcoming CRESIPT project) did

not aim to evaluate the impact of the intervention on rates of secondary TB disease in household contacts and thus the intervention's potential influence on TB control.

Conclusions

This CRESIPT pilot study has demonstrated that a novel socioeconomic intervention was feasible, acceptable, enhanced access to TB prevention, and improved TB cure rates in an impoverished setting. These findings support the new global End TB Strategy and highlight the need for larger-scale evaluations, such as CRESIPT, to determine the impact of socioeconomic interventions on TB care and prevention, potentially towards TB elimination.

Table 20: Baseline demographic characteristics of all patients, intervention patients, and control patients

	Intervention arm	Control arm	All
HOUSEHOLD CONTACTS UNDER 20 YEARS OLD CHARACTERISTICS (n=518)			
Age (median; IQR)	8.5 (4.0-15)	9.0 (4.0-14)	9.0 (4.0-14)
Sex (% male; 95% CI)	52 (46-58)	53 (47-60)	53 (49-57)
BMI (mean; 95% CI)	20 (19-21)	20 (20-21)	20 (20-21)
PATIENT CHARACTERISTICS (n=282)			
Age (median; IQR)	30 (21-45)	28 (20-43)	28 (21-44)
Sex (% male; 95% CI)	64 (55-72)	60 (52-68)	62 (56-67)
Secondary school complete (%; 95% CI)	27 (20-35)	37 (29-45)	32 (27-38)
Unemployed (%; 95% CI)	36 (28-44)	35 (27-43)	36 (30-41)
Food insecurity (mean days went to bed hungry in the past month; 95% CI)	1.8 (1.1-2.5)	1.5 (0.9-2.1)	1.6 (1.1-2.1)
Sputum smear positive (mean; 95% CI)	51 (36-66)	63 (47-79)	57 (46-68)
MDR (mean; 95% CI)	7 (2-11)	10 (5-15)	9 (5-12)
Previous TB episode (mean; 95% CI)	18 (11-25)	27 (20-35)	23 (18-28)
BMI (mean; 95% CI)	22 (21-23)	22 (21-22)	22 (21-22)
HOUSEHOLD CHARACTERISTICS (n=282)			
Monthly household income (mean monthly Peruvian Soles; 95% CI)	1190 (1071-1309)	1271 (1127-1415)	1231 (1138-1325)
Crowding (mean people/room; 95% CI)	1.9 (1.7-2.1)	2.0 (1.8-2.2)	2 (1.8-2.1)
Proportion poor (%; 95% CI)			
Poorer	41 (32-49)	38 (30-46)	39 (34-45)
Poor	30 (23-38)	35 (27-42)	33 (27-38)
Less Poor	29 (21-37)	27 (20-34)	28 (23-33)

Table 21: The association of health, socioeconomic position, and receiving the socioeconomic intervention with uptake of TB preventive therapy in household contacts under 20 years old (n=410). Univariate and multiple logistic regression show odds ratios of likelihood of preventive therapy uptake.

	Group	Total number in group	Uptake of preventive therapy in group	Prevalence	Univariate logistic regression		Multiple logistic regression	
					Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Household	Control	204	54	0.26	1		1	
	Intervention	206	90	0.44	2.2 (1.1-4.1)	0.019	2.2 (1.1-4.1)	0.02
Food insecurity (patient of household above or below mean days of going to be hungry in the past month)	More food insecurity	354	127	0.36	1			
	Less food insecurity	56	17	0.31	0.78 (0.32-1.9)	0.6		
Employment status of head of household	Paid employment	253	97	0.38	1			
	Unemployed	157	47	0.3	0.69 (0.36-1.3)	0.3		
Education level of head of household	Completed secondary school	204	71	0.35	1			
	Did not complete secondary school	206	73	0.35	0.97 (0.51-1.8)	0.9		
Poverty (household poorer or less poor than median poverty score)	Less poor	236	81	0.34	1			
	Poorer	174	63	0.36	1.1 (0.57-2.1)	0.8		
Gender	Female	186	68	0.37	1			
	Male	224	76	0.34	0.89 (0.59-1.4)	0.6		
Household income (above or below median monthly household income)	Higher income	168	63	0.38	1			
	Lower income	242	81	0.33	0.84 (0.44-1.6)	0.6		

Table 22: The association of health, socioeconomic position, and being randomized to receive the socioeconomic intervention with uptake of TB preventive therapy in household contacts aged 5 to 19 years old (n=287). Univariate and multiple logistic regression analyses show odds ratios of likelihood of preventive therapy completion.

	Group	Total number in group	Uptake of preventive therapy in group	Prevalence	Univariate logistic regression		Multiple logistic regression	
					Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Household	Control	139	33	0.24	1		1	
	Intervention	148	60	0.41	2.2 (1.1-4.6)	0.036	2.2 (1.1-4.6)	0.04
Food insecurity (patient of household above or below mean days of going to be hungry in the past month)	More food insecurity	43	9	0.21	1			
	Less food insecurity	244	84	0.34	2.0 (0.72-5.5)	0.2		
Employment status of head of household	Paid employment	181	66	0.36	1			
	Unemployed	106	27	0.25	0.60 (0.28-1.3)	0.7		
Education level of head of household	Completed secondary school	146	43	0.29	1			
	Did not complete secondary school	141	50	0.35	1.3 (0.64-2.7)	0.5		
Poverty (household poorer or less poor than median poverty score)	Poorer	159	49	0.31	1			
	Less poor	128	44	0.34	1.2 (0.57-2.4)	0.7		
Gender	Female	135	48	0.36	1			
	Male	152	45	0.3	0.76 (0.48-1.2)	0.3		
Household income (above or below median monthly household income)	Higher income	126	41	0.33	1			
	Lower income	161	52	0.32	0.99 (0.48-2.1)	0.9		

Table 23: The association of health, socioeconomic position, and receiving the socioeconomic intervention with uptake of TB preventive therapy in household contacts aged under 5 years old (n=125). Univariate and multiple logistic regression analyses show odds ratios of likelihood of preventive therapy completion.

	Group	Total number in group	Uptake of preventive therapy in group	Prevalence	Univariate logistic regression		Multiple logistic regression	
					Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Household	Control	65	21	0.32	1		1	
	Intervention	58	30	0.52	2.2 (0.97-5.2)	0.058	2.2 (0.97-5.2)	0.058
Food insecurity (patient of household above or below mean days of going to bed hungry in the past month)	More food insecurity	13	8	0.62	1			
	Less food insecurity	110	43	0.39	0.40 (0.11-1.5)	0.2		
Employment status of head of household	Paid employment	72	31	0.43	1			
	Unemployed	51	20	0.39	0.85 (0.37-2.0)	0.7		
Education level of head of household	Completed secondary school	60	30	0.5	1			
	Did not complete secondary school	63	21	0.33	0.50 (0.22-1.1)	0.1		
Poverty (household poorer or less poor than median poverty score)	Less poor	77	32	0.42	1			
	Poorer	46	19	0.41	0.99 (0.41-2.4)	0.9		
Gender	Female	51	20	0.39	1			
	Male	72	31	0.43	1.2 (0.55-2.5)	0.7		
Household income (above or below median monthly household income)	Higher income	42	22	0.52	1			
	Lower income	81	29	0.36	0.51 (0.21-1.2)	0.6		

Table 24: The association of health, socioeconomic position, and being randomized to receive the socioeconomic intervention with TB cure (n=282). TB cure was defined by the treatment outcome defined by the Peruvian TB Program in their national protocol, consistent with WHO guidance[174] (see Methods).

	Group	Total number of patients in the group	Number of patients cured in the group	Prevalence	Univariate logistic regression		Multiple logistic regression	
					Odds ratio (95%CI)	P value	Adjusted odds ratio (95% CI)	P value
Intervention patient (received socioeconomic intervention)	Control	144	55	0.38	1		1	
	Intervention	135	71	0.53	1.8 (1.1-2.9)	0.016	2.1 (1.3-3.4)	0.004
Less food insecurity (below mean days of going to bed hungry in past month)	More food insecurity	55	17	0.31	1		1	
	Less food insecurity	224	109	0.49	2.1 (1.1-3.9)	0.025	2.1 (1.1-4.1)	0.022
Head of household completed secondary school	Did not complete secondary school	124	49	0.4	1		1	
	Completed secondary school	155	77	0.50	1.5 (0.94-2.4)	0.091	1.6 (0.98-2.7)	0.057
Less poor (above median poverty score)	Less poor	174	70	0.40	1		1	
	Poorer	105	56	0.53	1.7 (1.0-2.8)	0.034	___	___
Higher monthly household income	Lower income	162	71	0.44	1			
	Higher income	117	55	0.47	1.1 (0.71-1.8)	0.60		
Gender	Female	106	53	0.50	1			
	Male	173	73	0.42	0.73 (0.45-1.2)	0.20		
Employment status of patient	Unemployed	171	77	0.45	1			
	Paid employment	103	48	0.47	1.1 (0.65-1.7)	0.80		
Crowding (below median number of people per room)	More crowded	128	57	0.45	1			
	Less crowded	148	69	0.47	1.1 (0.68-1.7)	0.728		

Table 25: Patient (n=282) outcomes according to Peruvian national TB Program definitions.
"Cured" refers to those patients who had confirmed TB cure as defined by the treatment outcome defined by the Peruvian TB Program consistent with WHO guidance[174] (see Methods)

National TB Program and WHO defined outcomes	Intervention patients; % (95%CI) (n=135)	Control patients; % (95%CI) (n=147)
Cured	51 (43-60)	37 (30-45)
Abandoned	15 (9.4-22)	17 (11-23)
Failed	3.0 (0.1-5.8)	2.0 (0.0-4.3)
Died	3.7 (0.1-6.9)	4.1 (0.9-7.3)
On treatment	12 (6.4-17)	18 (12-25)
Completed treatment	11 (5.8-16)	16 (9.8-22)
Unknown	3.7 (0.5-6.9)	5.4 (1.8-9.1)

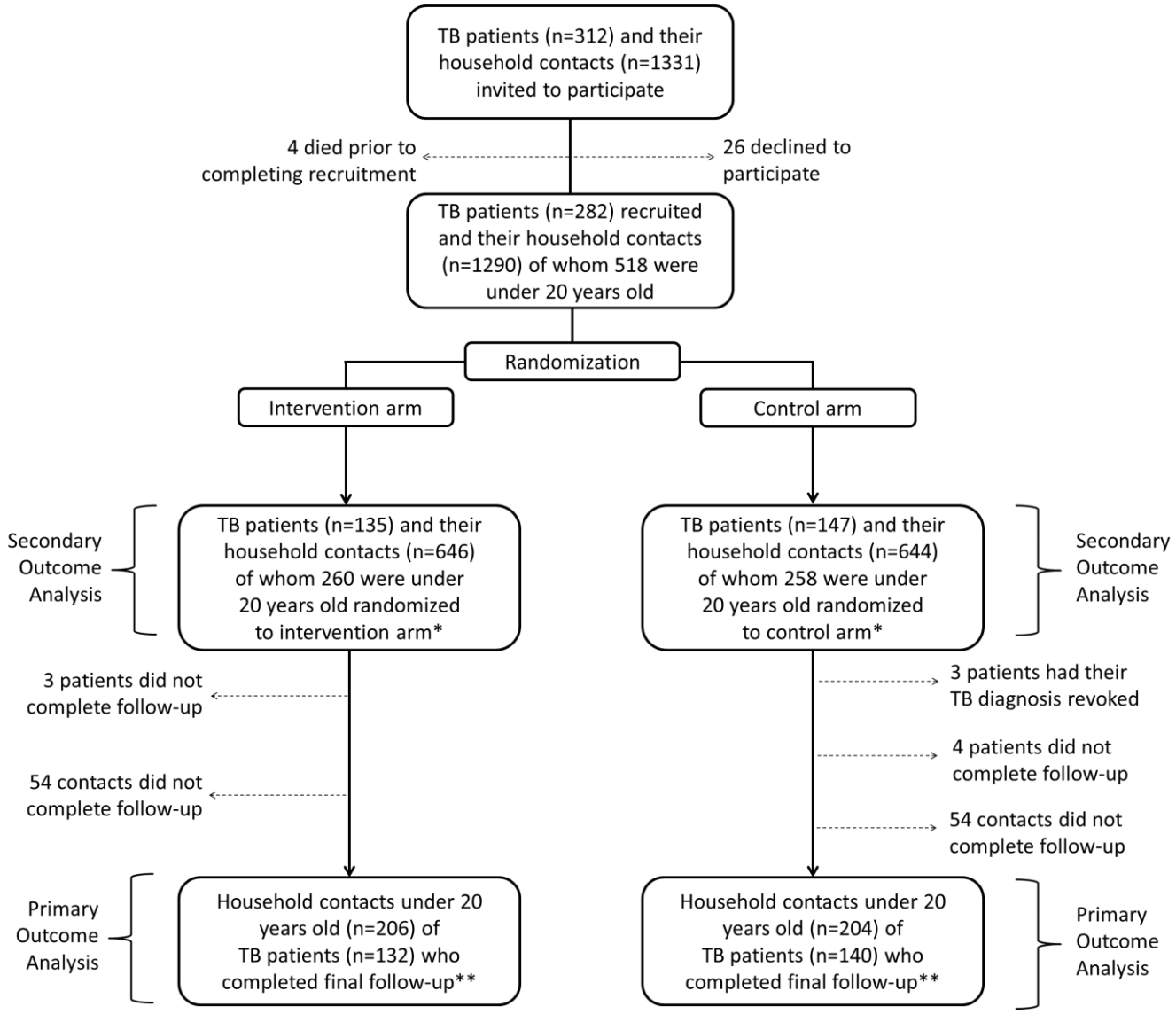


Figure 22: Participant recruitment and randomisation**.** Recruitment constituted completing informed consent and a recruitment questionnaire. Dashed arrows refer to participants who were not included in the final analysis and not to their household contacts

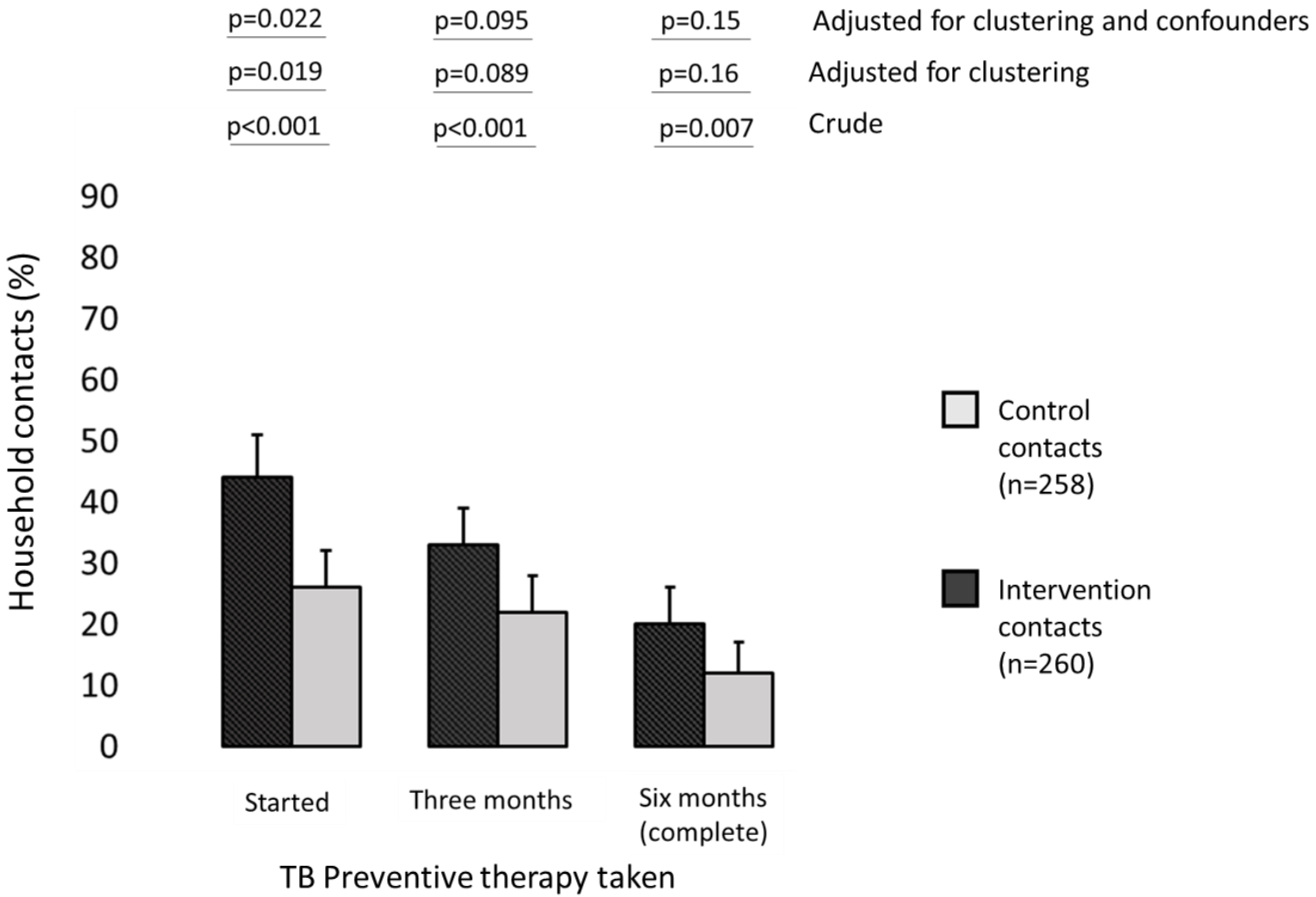


Figure 23: Uptake, completion of three months, and completion of six months of TB preventive therapy in intervention (n=260) and control (n=258) contacts under 20 years old. Error bars are 95% confidence intervals. P values are derived by logistic regression. P values on the lower lines are crude, unadjusted derived by univariate logistic regression. P values on the middle lines are derived by univariate logistic regression adjusting for household clustering. P values on the upper lines are derived by multiple logistic regression adjusting for household clustering and potential confounders (see Methods)

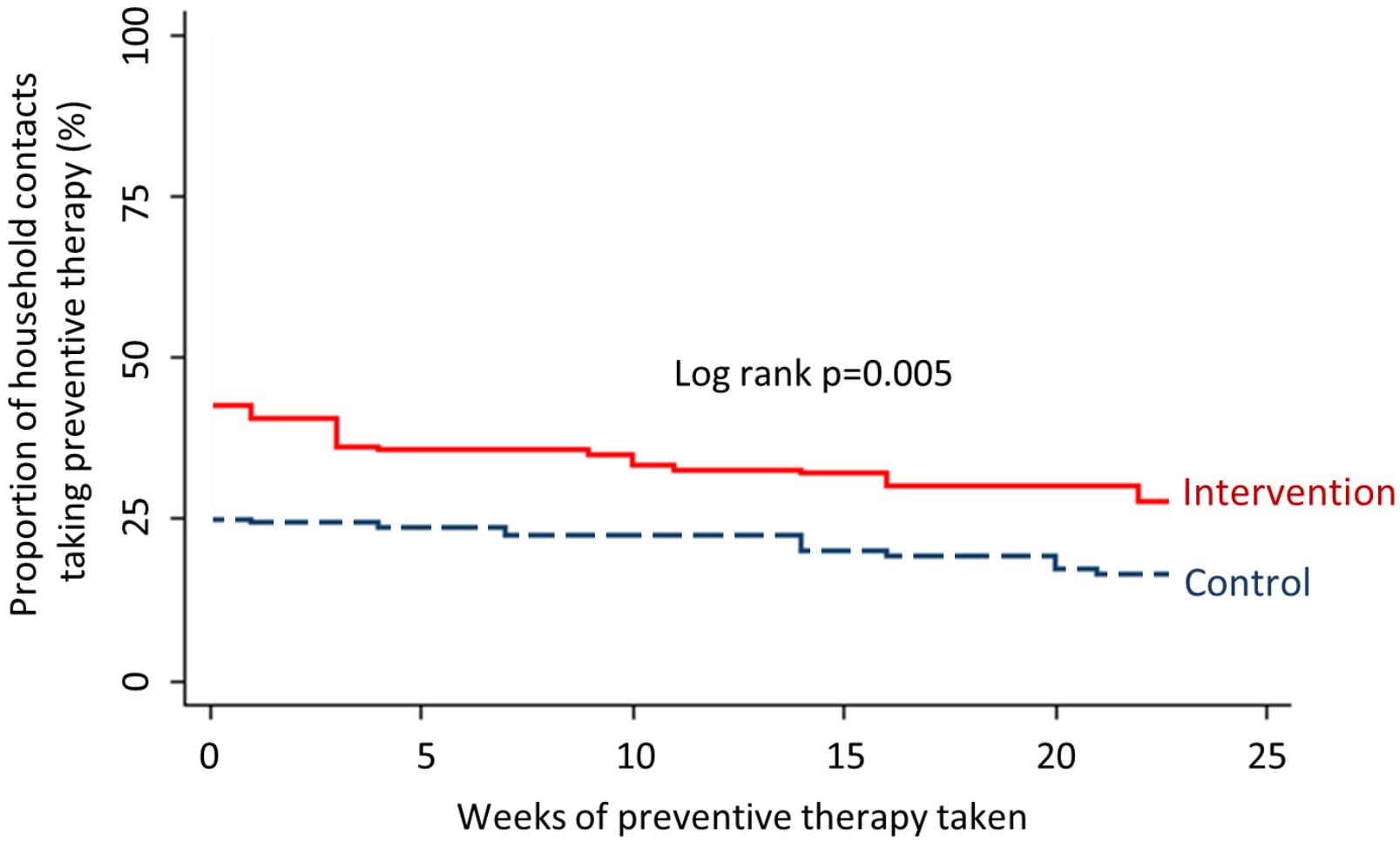


Figure 24: Number of weeks of TB preventive therapy taken by intervention (n=260) and control (n=258) contacts under 20 years old.

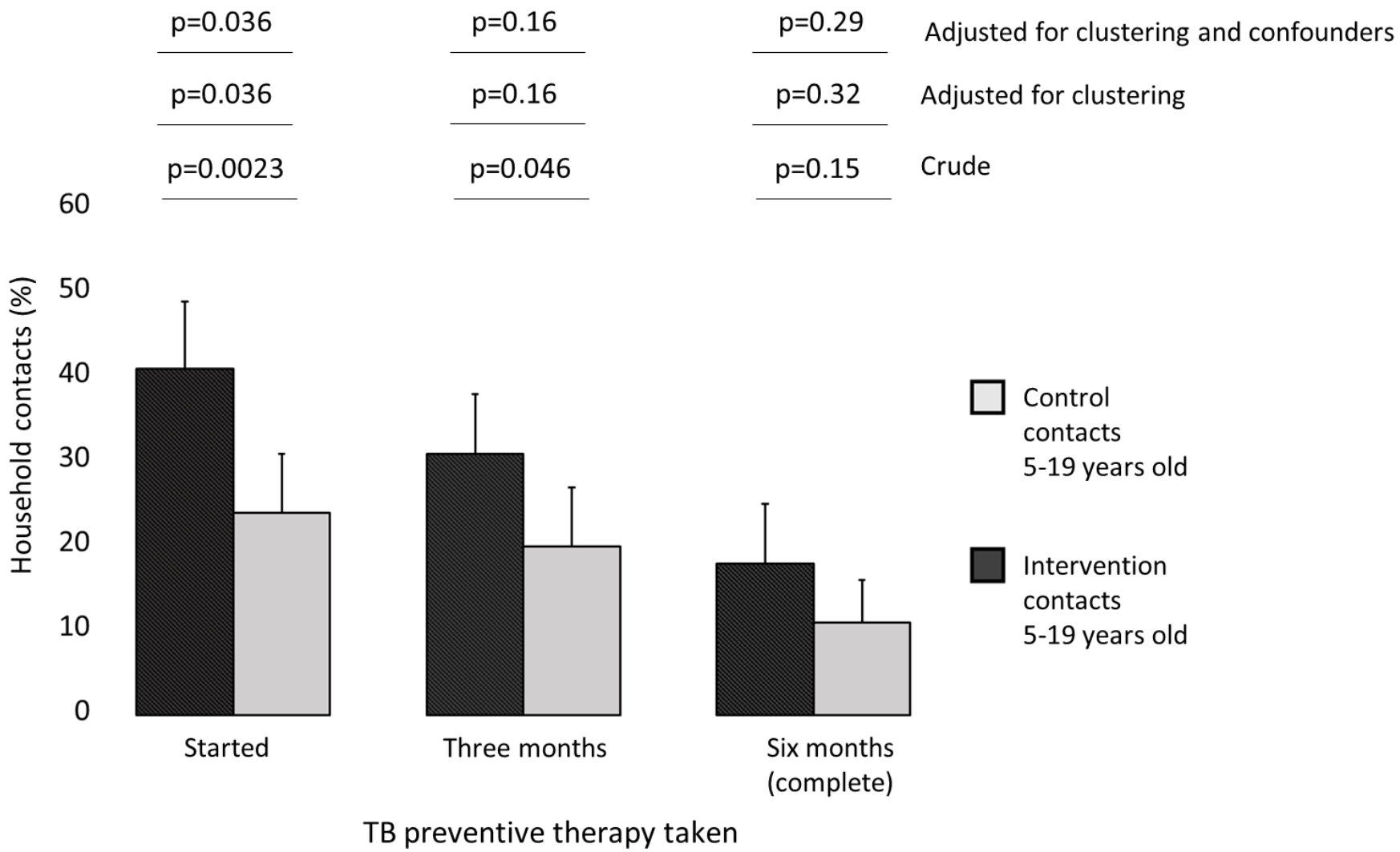


Figure 25: Uptake, completion of three months, and completion of six months of TB preventive therapy in household contacts aged 5 to 19 years old (n=300). Error bars are 95% confidence intervals. P values are derived by logistic regression. P values on the lower lines are crude, unadjusted derived by univariate logistic regression. P values on the middle lines are derived by univariate logistic regression adjusting for household clustering. P values on the upper lines are derived by multiple logistic regression adjusting for household clustering and potential confounders (see Methods)

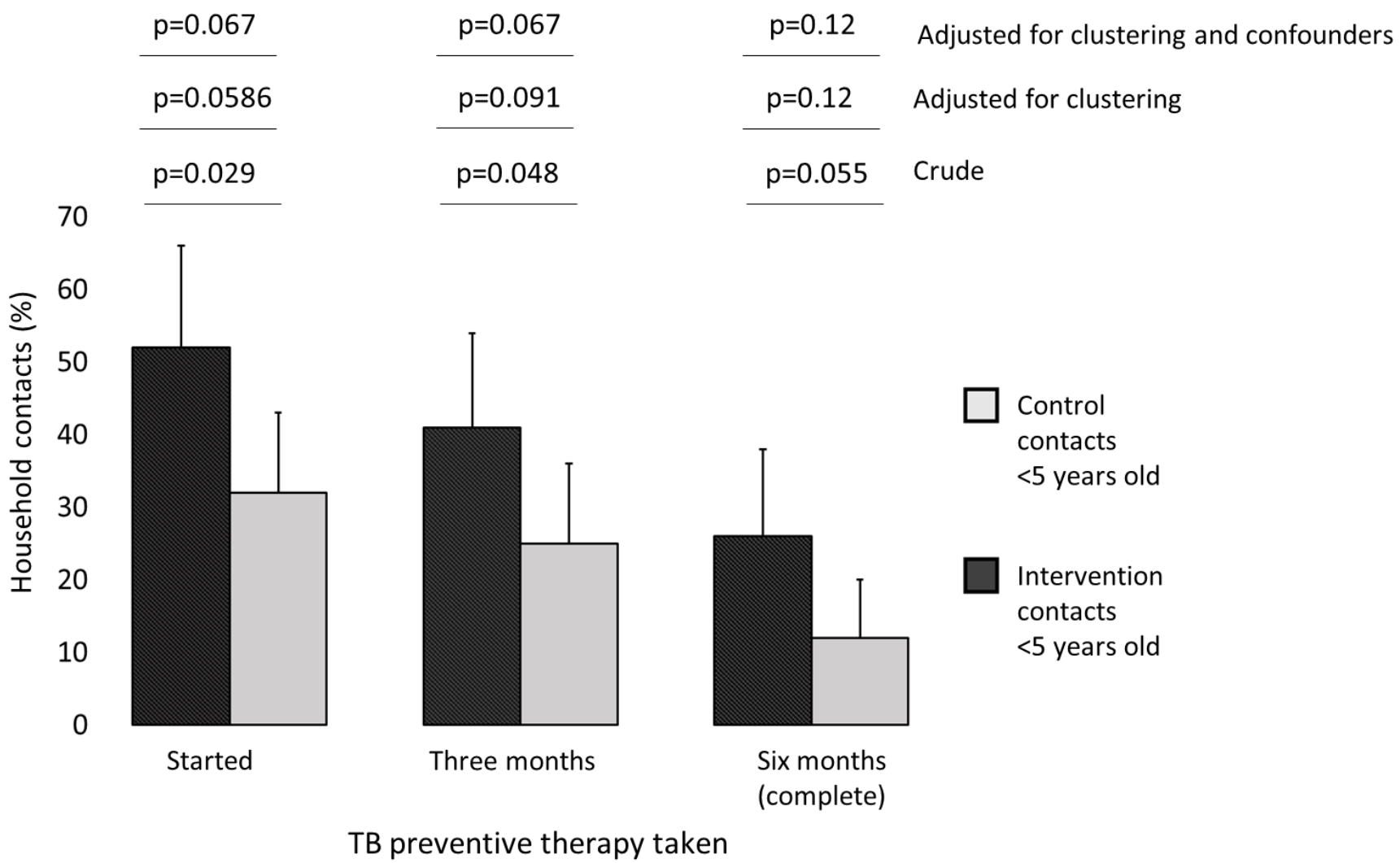


Figure 26: Uptake, adherence to at two and four months, and completion of six months of TB preventive therapy in household contacts aged under 5 years old (n=125). Error bars are 95% confidence intervals. P values are derived by logistic regression. P values on the lower lines are crude, unadjusted derived by univariate logistic regression. P values on the middle lines are derived by univariate logistic regression adjusting for household clustering. P values on the upper lines are derived by multiple logistic regression adjusting for household clustering and potential confounders (see Methods)

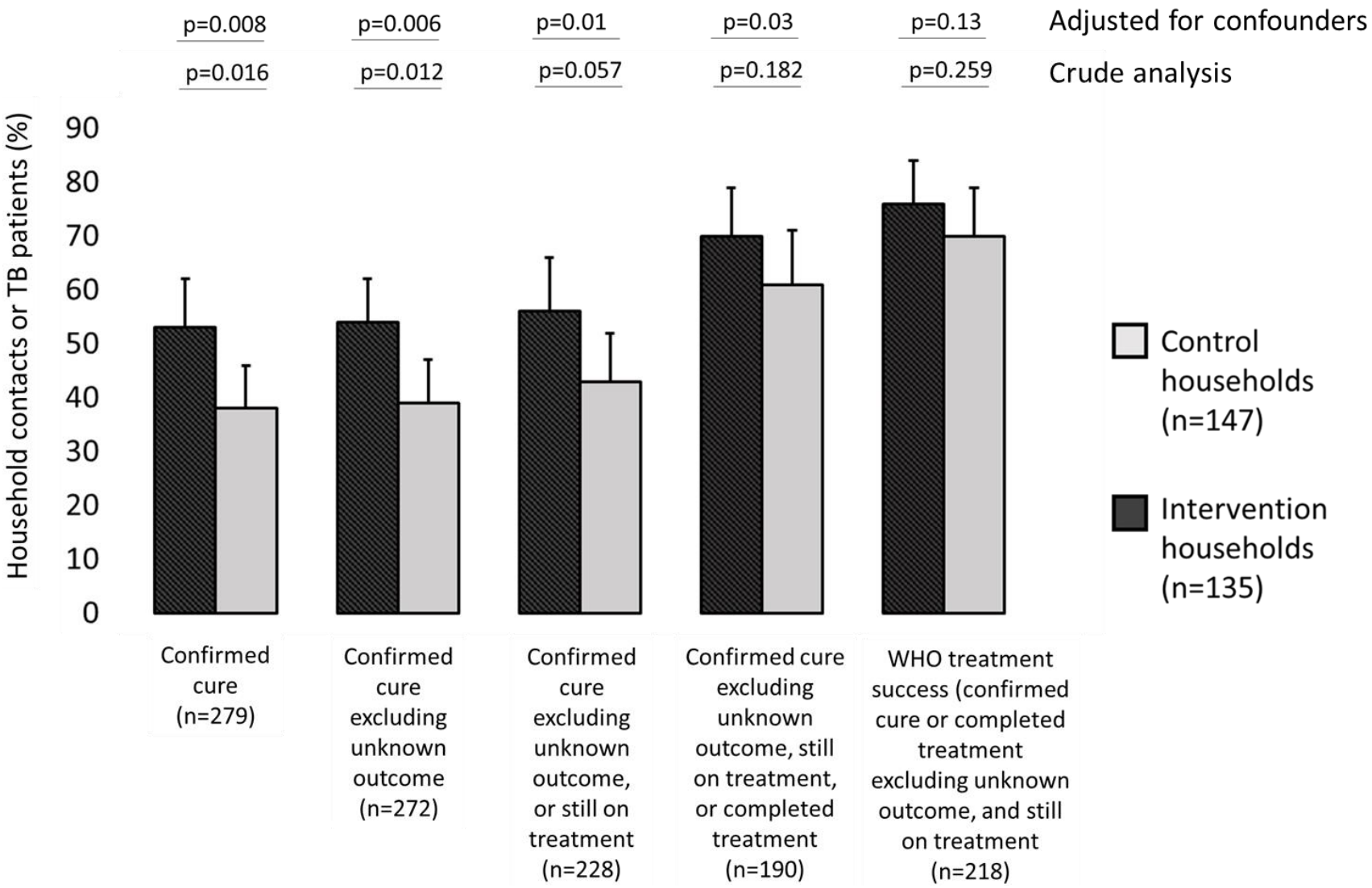


Figure 27: Cure and treatment success in TB patients. Error bars are 95% confidence intervals. P values are derived by logistic regression. P values on the lower lines are derived by univariate logistic regression analysis. P values on the upper lines are derived by multiple logistic regression adjusting for potential confounders (see Methods section of this chapter)

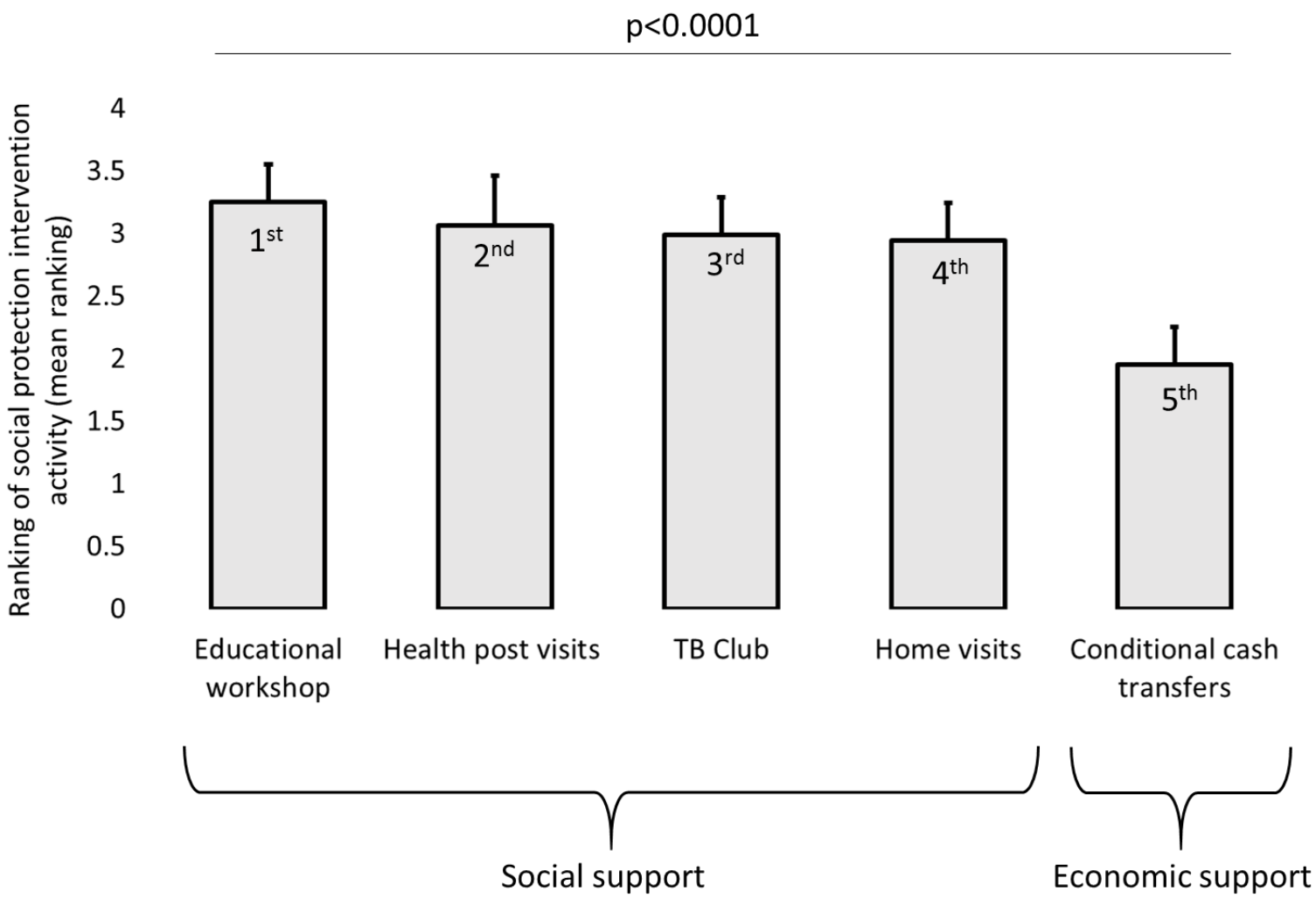


Figure 28: Supported patient feedback ranking of the importance of the social and economic support activities of the social protection intervention. The P value shows the difference between the composite ranking of all the social support activities and the economic support.

Chapter 7: Final Conclusions

In impoverished shantytowns of Callao, Peru, having TB disease was associated with being poor; thus, TB remains a social disease. Quantifying the independent social determinants that constitute poverty and contribute most strongly to acquiring TB infection and progressing to TB disease remains complex. The associations identified between season, crowding, and vitamin D emphasise the potential for improving nutrition, correcting vitamin D deficiency, and reducing poverty to contribute to TB prevention. Thus in order to control TB, the global response may benefit from a socioeconomic as well as biomedical approach.

The association between TB and poverty is bidirectional: despite TB treatment being ostensibly free, having TB disease was expensive for impoverished TB patients in Peru to afford. The new definition of catastrophic costs created by this research demonstrates that such costs are clinically relevant because they are associated with greater likelihood of adverse TB outcome. Indeed, catastrophic costs explained as many adverse outcomes as MDR TB. The novel catastrophic costs threshold defined by this research has since been endorsed by the World Health Organisation and become part of global TB control policy. This research also generated new knowledge concerning the association of dissaving with TB-related costs and catastrophic costs, and the role of dissaving as a practical, logistically-simple, proxy marker of catastrophic costs. These findings have already informed the implementation of the World Health Organisations TB Patient Costs tool, which is being piloted in sentinel sites for potential scale-up from 2015 onwards.

One potential method of broadening the biomedical response to TB disease to be more holistic is by defraying catastrophic costs through targeted socioeconomic interventions. Therefore, through multi-sectoral collaboration and supported by evidence from a systematic review, we designed a novel TB-specific socioeconomic intervention to prevent TB and cure TB disease. The intervention was refined to better meet patient and household needs during implementation through community participation, engagement and acceptability feedback and subsequently proved to be feasible, equitable, acceptable, reduced TB-affected households' catastrophic costs and improved TB care and prevention in a challenging, impoverished setting. This research emphasizes the need for larger-scale integrated socioeconomic interventions to improve TB control and also other health outcomes. In the light of our findings, in conjunction with key stakeholders from the World Health Organisation and World Bank, we have developed the protocol of the larger-scale, adequately-powered, Community Randomized Evaluation of a Social Protection Intervention to Prevent TB study, "CRESIPT", which will evaluate the impact of the intervention on TB prevalence and control in the study setting.

Despite the positive findings of this research, the impact of the socioeconomic intervention may have been limited by the modest defraying of TB-related and catastrophic costs achieved through conditional cash transfers. Such a modest yet significant impact, means that, in its current form, the intervention would be unlikely to show an impact on community rates of incident and prevalent TB during the larger-scale CRESIPT project. Therefore, through liaison with international policy-makers in the World Health Organisation's Task Force on Catastrophic Costs and Task Force on Social Protection, the intervention has been refined for implementation during the CRESIPT study. Refinements include: increased frequency and amounts of conditional cash transfers in order to fully mitigate catastrophic costs; providing conditional cash transfers for individual members of the TB-affected household (including monthly transfers to individual households contacts for adherence to preventive therapy); and strengthening the highly-valued social support provided by the intervention - especially for high-risk patients such as the homeless, those with drug addiction, and those with MDR TB. In this way, the IFHAD team hopes to optimize the CRESIPT project's impact on TB-related costs mitigation, to enhance social support, and hence improve TB control.

This PhD research characterised the social determinants of TB, including TB-related catastrophic costs, in Peruvian shantytowns and subsequently created, implemented, and refined an innovative TB-specific socioeconomic intervention to mitigate catastrophic costs and support TB-affected families. The intervention is now ready for further impact assessment at a community level. The findings of CRESIPT, an extension of this PhD research, will aim to assist TB control programs to effectively implement the recent - yet 150-years overdue - global policy change of providing socioeconomic support to control TB.

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Appendix 1: An operational toolkit detailing how to implement a socioeconomic intervention for households affected by TB (English version)

The Spanish version of this toolkit is available on request.

An operational toolkit detailing how to implement a socioeconomic intervention for households affected by TB

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“Better TB diagnosis for all” from IFHAD: Innovation For Health And Development to evaluate new diagnostic strategies that lead to equitable access to TB and MDR TB diagnosis, and additionally to evaluate the true prevalence of TB in the community.

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Background

TB kills more people each year than any other single infection, so there's an urgent need to evaluate new TB-control interventions. Almost all TB control resources are spent on healthcare, labs and medicines. These save millions of lives, but it is poverty and development not healthcare that principally determine TB rates. For example, despite an acclaimed biomedical TB control program Peru has frequent TB and over the past decade multidrug-resistant TB rates have doubled to the highest levels in the Americas. These problems are concentrated in impoverished "hotspots", such as peri-urban and urban shantytown 'slums' around northern Lima/Callao, where our IFHAD team has been working for more than a decade.

A new approach: fighting poverty to control TB

Poverty increases TB risk through factors such as crowding and malnutrition. Conversely, TB worsens poverty through TB-related expenses and lost income. Poor people are more likely to get TB and less likely to be cured by TB treatment. However, it is the poor who have least access to TB care. This mismatch between need for TB care versus access to TB care undermines TB control. To try to address these issues, we are evaluating supplementing traditional TB healthcare with socioeconomic (social and economic) support for TB-affected households. We aim to improve access to TB care and mitigate TB-related costs in order to improve TB patients cure rates and subsequently prevent TB in those patients' household contacts and the wider community.

Progress so far

Since 2007, our IFHAD team's "Innovative Socio-economic Interventions Against TB (ISIAT)" project evaluated socioeconomic interventions to fight poverty and increase equitable access to TB care. The results of this project showed that socioeconomic support increased: testing for TB and HIV;, successful treatment completion; and also equitable access to TB prevention. Put into context, these exciting results showed that a simple and inexpensive socioeconomic intervention could achieve results even better than some news tests and pills. But can socioeconomic interventions help to control TB?

New project: CRESIPT

Thanks to the encouraging results of ISIAT, the Joint Global Health Trials consortium of the Wellcome Trust, the Medical Research Council and the Department For International Development of the British Government (UK-AID) together with the World Bank have funded our IFHAD research team to undertake a new 6-year project. This project is rigorously assessing the impact of the most effective elements of the socioeconomic support from the previous ISIAT trial. Importantly, not only are we assessing impact on costs-mitigation and access to TB care but also on actual TB control for whole communities. Specifically, in 16 communities, our multi-disciplinary team are offering TB-affected households an integrated program of:

(1) social support for enhancing equitable access to TB-related healthcare and also
(2) economic support to help them to afford TB care and to reduce their vulnerability to TB.

Meanwhile in 16 other 'control' communities, people living with TB receive the standard healthcare provided by Peru's excellent TB control program, without our socioeconomic intervention. Two years later we will compare TB rates in the 16 communities that received our socioeconomic intervention versus the 16 communities that did not, to assess the cost-effectiveness and impact of our intervention and whether this socioeconomic intervention helped to control TB.

Conclusion

A socioeconomic intervention is being assessed for its capacity to reduce poverty-related TB risk factors, improve access to TB care and prevent TB treatment failure, TB recurrence, and TB transmission. The intervention is targeted at those in greatest need in order to transform TB cure and care into TB control.

The goal of this toolkit

The goal of this toolkit is to act as a manual for other groups (including research teams, non-governmental organisations (NGOs), governmental organisations, and others) who aim to implement socio-economic support for individuals, households, or communities affected by TB. Within this manual, we offer simple, practical advice, methods, and document all the tools and materials that we used so that other people may be able to repeat our intervention in other settings.

Preparation

The preparation that is necessary prior to implementation of a socioeconomic support intervention depends on the circumstances in which the intervention is to be undertaken. For example, the requisites of a research team may be different to those of a charity, care provider, or NGO. The following are relevant examples of preparatory exercises that we undertook prior to implementing our socioeconomic support intervention.

Community feedback from the relevant community in which you will be working

- ✓ It is informative to find out the knowledge, attitudes, and practices of different groups within the community itself in order to tailor your socioeconomic support intervention to local circumstances
- ✓ Focus groups can be performed with community leaders, civil society, healthcare personnel, patient groups, and other interested parties

Find out which other related projects already exist in the community in which you will be working

- ✓ It is important to make contact with other organisations, groups or teams working in the same community in order to understand their role
- ✓ Other projects may exist that are performing a similar role or socioeconomic support intervention and it would be preferable not to overlap work
- ✓ Share information with other organisations, groups and teams working in the same community to inform them of the proposed project, get their feedback, and potentially collaborate

Presentations to local healthcare providers

- ✓ When a research team works alongside the local, regional or national health system, or the research project takes place to some extent within health posts and/or hospitals, it is essential to inform the directors of such health directorates and their healthcare staff of the proposed project: who your team members are; what your objectives are; and how those objectives will be achieved. In addition, showing any relevant project approvals obtained is important (see below)
- ✓ Apart from informative presentations, it would also be advisable to invite members of the health post / centre or other relevant staff members to parts of the project or intervention being undertaken

Approval by relevant organisations

- ✓ It is essential to obtain the relevant permissions / approval depending for any intervention in the community within which you are working

- ✓ If you are undertaking a study, accredited local, national, and/or international ethical committee approval will be necessary in accordance with the current revision of the Declaration of Helsinki
- ✓ If you are working as part of a project rather than a study, relevant legal, community or governmental approval will still be required to implement a socioeconomic support intervention

Perform pilots and practice sessions

- ✓ An easy way to involve all the organisations mentioned above is to undertake practice sessions or pilots of the intervention (for example, an educational workshop or interview)

Building an efficient and productive team

Working in a team can have mixed results. Teams that work well together can produce outputs and results far greater than each individual in the team could ever have produced. Conversely, teams that do not work well together may struggle to complete projects successfully. Below are some points to consider when setting up and managing project teams.

Defining goals

- ✓ A team or project without clearly defined goals or objectives will struggle to stay on course
- ✓ Goals can be short-term (e.g. weekly) or long-term (e.g. over the course of the project) and, ideally, should be accessible for any team member to review (i.e. in a project handbook or manual)
- ✓ Goals may be for individual team members (e.g. number of patients recruited per week) or of the project as a whole (e.g. all data double digitized and project recruitment and follow-up completed within a certain time-frame)

Multidisciplinary team work and roles

- ✓ Each team member has their own personal strengths or areas of expertise. A team that is able to recognise and cultivate these personal abilities is likely to have more success in achieving their goals. In addition, members of such a team are likely to feel more highly valued and useful
- ✓ While many roles may overlap, develop and evolve, it is important that each team member understands their own role, the role of other team members, and how the two may affect each other and interact

Communication, communication, communication

- ✓ Regular team meetings attended by as many of the team as possible may be a good way to keep everyone informed of developments and progress

- ✓ Continuous feedback and evaluation of progress is useful to avoid misunderstanding, overlap of work, and to overcome difficulties

Our project field team

Our active IFHAD project field team consists of: 4 principal physician investigators, 1 research nurse co-ordinator, 7 research nurses, 6 research nurse technicians, and 2 data managers. In addition, as will be discussed in further detail, we also provided TB patients and ex-TB patients the opportunity to be trained by our team to become "facilitators" (sometimes known as health promoters or health champions). Such facilitators were not only essential in the design of the socioeconomic support but also its subsequent implementation.

We hope that this toolkit provides useful materials and examples for any team wishing to implement a socioeconomic support intervention, specifically with TB-affected families. Clearly, the size and skills of a team that are required will depend on the scale of the intervention to be implemented and its goals. The essential requirement for the success of a project such as this is motivated people who have sufficient time available and a vocation to work with TB affected families

Project Team Activities

Before starting to implement any activities of a socioeconomic intervention with TB-affected families, you will need to answer certain questions:

- What is the intervention that we are aiming to implement?
- Where are we going to implement the intervention?
- How are we going to implement the intervention?
- Which members of the team will be involved in which activities?

It's possible that a socioeconomic intervention concerning TB patients will be undertaken in health posts and/or hospitals as much as in the community. It may be that team activities not only involve salaried members of the team but also that they rely on the assistance of volunteers from the community itself (for example, ex-patients or patients approaching the end of treatment who may act as facilitators as mentioned above). Therefore, good team communication and coordination concerning project activities and project timescales is essential.

We designed checklists detailing the activities of our team from patient recruitment, throughout each step of patient treatment and screening of contacts for preventive therapy, and until the final follow up of our project two years after treatment initiation. Examples of these checklists can be found in Document 1a-e.

Apart from using the checklist to regulate and document the team activities, we also created a timesheet that each member of the team filled in daily. This timesheet can be found in Document 2. By using this timesheet, we generated a register of not only the different activities performed by each member of the team but also the time invested and money spent on each activity. For any team performing "field work" that involves undertaking a socioeconomic intervention, the timesheet also gives an idea of the project's direct costs (in money and materials) and indirect costs (time invested by members of the team be they voluntary or salaried). These data are essential for analysing the cost-benefit of the project and offer a useful estimation of the true economic project resource costs for other teams that want to implement a similar intervention and need to predict budgetary requirements.

Activities in the healthpost

- **Invitation and explanation** – During the two year recruitment period, we are inviting all patients diagnosed with TB (non-MDR or MDR TB, children or adults, pulmonary or extrapulmonary TB) in the communities in which we work to participate. In order to fully explain our project, its goals, its conditions, its advantages and potential disadvantages to patients (including those who are unable to read), we used a compact, portable flipchart with colourful slides (Document 3). This flipchart details all the steps of the project in a way that is simple and easy to understand for all ages and reading abilities.

- **Informed consent** – Given that our intervention is part of a study and the decision to participate is completely voluntary in nature, we take informed consent from each participant (Document 4) signed by the patient or, in the case that the patient is a minor or person mentally incapable of giving informed consent, their guardian. Patients that do not give informed consent to participate are not included in the project and their treatment by the health post continues as normal. We also reassure all consenting participants that their ongoing participation is completely voluntarily and that they can withdraw from the study at any time they may wish to.
- **Questionnaire** – We complete detailed questionnaires with all consenting participants to collect socioeconomic, health, TB risk factor (social capital, hidden costs, and Beck score), and stigma data. This questionnaire is too long to be included in this document and can be reviewed online at our charity website www.ifhad.org. If you or your team is planning to apply a questionnaire or data-collection tool during your intervention, you should aim to ensure that you can find (or create) a place in the health post which is private, quiet, and has sufficient space in which the patient can feel comfortable, not under pressure, and can respond to the questions posed in the best way possible.

Activities in the community

- **Initial home visit** – We ask all the recruited patients randomized to receive the intervention for permission to visit their home in order to perform a home visit that: reiterates the key educational messages covered in the flipchart; completes any remaining parts of the questionnaire; confirms household contacts (and register their identity cards etc.); performs anthropomorphic measurements of the contacts (height and weight for example); verifies the questionnaire responses concerning the materials from which the house is constructed and number of rooms; and responds to any further questions or concerns that the family may have. These programmed home visits are undertaken by the research nurses or assistants of our team. It is essential to remember that it is of utmost importance to maintain the confidentiality of the patient and their contacts at any time including when conducting household visits. Therefore, bear this in mind with respect to team uniform worn (for example, uniforms that mention "TB") and do not divulge the patient's diagnosis to any person (be it family, a neighbour or other) against the wishes of the patient.
- **Additional home visits** – There are some families amongst those affected by TB, who will require more support than others in order to be able to complete the TB program requirements (such as adhering to treatment, keeping medical clinic appointments etc.). Patients and their families only receive an additional programmed household visit by research nurse or assistant of our team if they are classified by our team as being at "high risk".

This includes patients with MDR TB, patients who have poor early adherence and families in which the contacts fail to attend their screening for TB. The flow chart detailing all the household visits (including initial and additional) and high risk factors can be found in Document 5.

The socioeconomic intervention

Since 2007, ISIAT[1] evaluated socioeconomic support to fight against poverty and increase equitable access to TB care. This socioeconomic support increased testing for HIV and TB, successful completion of treatment, and equitable access to TB prevention measures. These exciting results showed that a simple and inexpensive socioeconomic support package can improve TB care. Our new socioeconomic intervention consists of two integrated elements:

(1) Social support constituted household visits and community meetings (including group-events entitled "TB Clubs") and aimed to inform and empower, reduce stigma, and facilitate mutual support; and

(2) Economic support to mitigate TB-related costs, incentivise and enable more equitable care, and reduce TB vulnerability.

Social support: interactive community meetings

In addition to the home visits described above, which form a valuable part of the social support of the intervention, we also designed interactive community meetings. From the feedback obtained during the ISIAT pilot project[1] workshops and from focus groups with ex-TB patient civil society and regional TB program staff, we analysed various methods of giving socioeconomic support to TB-affected families. In this way, we were able to learn from the community in which we work. Thus, we focused and improved the previous design of the ISIAT workshops to provide the social support necessary within the new CRESIPT project. The new form of social support, "participatory community meetings", consists of two parts: 1) an "Educational Workshop", in which we develop key TB themes (including treatment, preventive therapy, transmission and risk factors); and 2) a "TB Club", in which the patients and their contacts share experiences, reduce stigma, and are empowered.

Economic support: Conditional bank transfers

Learning from a systematic review that our group was commissioned to perform by the WHO,[2] we designed a conditional cash transfer program in which patients who completed national TB program goals (including adherence, contact screening) and our project goals (e.g. attendance at interactive community meetings) received cash incentives in the form of bank transfers. The aim of such bank transfers

[1] Rocha et al. The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. Int J Tuberc Lung Dis. 2011 Jun;15 Suppl 2:S50-7. doi: 10.5588/ijtld.10.0447.

[2] Boccia et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications.Int J Tuberc Lung Dis. 2011 Jun;15 Suppl 2:S37-49. doi: 10.5588/ijtld.10.0438.

is to reduce the potential for TB-affected families to incur catastrophic costs, incurred by 39% of our patients in the communities in which we work[3]

[3] Wingfield et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcomes with multi-drug resistance: A prospective cohort study, Peru. In press PLOS Medicine 2014.

The Interactive Community Meetings

Our interactive community meetings take place each month in each community in which we work. Were the implementing group to have the resources or was only working with a smaller number of communities, it would be recommendable to host the meetings more often. Although the educational workshop and TB Club form two distinct parts of the interactive community meeting, many of the elements that they contain overlap and complement each other.

The aims of an interactive community meeting are to:

1) Educate TB-affected families and patients (and healthcare personnel who attend)
2) Reiterate the CRESIPT conditions (including facilitator selection)
3) Decrease stigma (especially self-stigma)
4) Create community mutual support networks of TB-affected families
5) Learn skills through doing / gain useful knowledge for daily life
6) Mobilize the community of TB-affected families in order to improve active case finding of new TB patients

The above aims will be realised throughout the interactive community meetings. The educational workshop section focus mainly on aims 1 and 2 but aim 3 will also be included when the theme of TB Clubs is introduced. The TB Club itself focuses mainly on aims 3 to 5. Aim 6 is a recurrent theme throughout the interactive community meeting.

Things to consider when organising a community meeting

The key things to be decided prior to the community meeting are:

- Which members of the team will lead the community meeting?
- How many team members are going to participate?
- Where is the community meeting going to take place? Is this place adequate or appropriate (with respect to price, security, lack of interruptions, size and facilities)?
- What materials will be necessary and how much will it cost (making an estimated budget may be valuable)? Will there be travel cost reimbursement or refreshments?
- How are participants going to be invited and registered and will there be a certificate of attendance provided?
- How is feedback from participants going to be collected?

In this manual, we have provided examples of the methodological guide (Document 6), program (Document 7), participant registration form (Document 8), example of list of necessary costs (Document 9) and materials (Document 10), and the certificate of attendance (Document 11).

Specific aims of the educational workshop

1) Educate TB-affected families about:
    a. TB (types, treatment, adherence, risk factors, and importance of active case finding)
    b. Responsible saving and spending
    c. Human rights and the responsibilities of the national TB program

2) Reiterate the conditions of the CRESIPT project:
    a. What are they?
    b. How can they be achieved?
    c. What benefits to you and your family might there be by completing these conditions?
    d. How to become a facilitator?

3) Reduce self-stigma and internalized stigma (introduction to TB Club)
    a. Introduce the themes of stigma and empowerment
    b. Explain the aim behind and the logistics of the TB Club

Exploration of these themes can be found in Document 6. Also in the Document, we include some ideas on how to develop the key learning themes of the educational workshop section of the interactive community meeting (Document 12).

Specific aims of the TB Clubs

1) Decrease anticipated and self-stigma through:
    a. Belonging
    b. Learning
    c. Challenging norms
2) Create networks of mutual support:
    a. Sharing experiences
    b. Getting to know other TB-affected families
    c. Encouraging mutual support outside of the limits of the interactive community meetings
3) Learning through doing – empowerment for everyday life:
    a. Working in a team to resolve problems
    b. Empowerment through reduction of self-stigma
    c. Advocacy, activism and finding a voice

In Document 13, we include a more detailed guide on how to set up and run a TB Club. Within this guide, you will find information on the importance and history of self-help groups, how to divide the TB Club, what materials will be needed, and strategies for using the drawings concerning stigma and empowerment.

Community feedback and observations

The interactive community meetings aim to support families affected by TB. It might be that there are parts of the meetings that are more successful than others but it is important to have a flexible approach that allows the sessions to be adapted to suit the needs and requirements of the individuals, families, and communities in which they are taking place, while keeping in mind the goals listed above. In order to achieve this, it is important to obtain the opinions of the participants throughout the process. This can be difficult to do - especially in an objective manner – if the participants believe that they may lose an incentive from the intervention if they report that part of the meeting was not received well or performed poorly.

It is worth remembering that in the interactive community meetings, we want to involve and affect as many of the participants as possible and both the educational workshop and TB Club sections of the meeting to function well. Well planned feedback sessions or forms can inform:

- If there is a specific subgroup amongst the participants that key messages do not reach (for example women, people who are illiterate, adolescents)
- If there is a part of the meeting not working very well (for example, the educational workshop receives a high feedback score whilst TB Club does not)
- The optimal way to manage and maintain consistency in the quality of the intervention and its concurrence with project goals across all members of the team and communities involved in the intervention

It is recommendable that all the members of the team, including the facilitators sit down together immediately following the meeting to discuss: Which things went well? Why / How? What things can we improve? How can we improve them?

The named member of the team responsible for each interactive community meeting can be in charge of this task and record the team's collective responses. Apart from this feedback between the team, there are other ways of obtaining feedback during the interactive community meetings:

- A team member or facilitator in training participates in the meeting purely as an observer, noting things that went well and things to improve
- At the end of the meeting (for example, when a snack is provided), all of the participants can be asked informally which things they enjoyed and which not (Note: it must be explained clearly to the participants that they can give negative comments and that we only aim to improve the process)
- We also designed an anonymous feedback form (Document 14) to be filled out by participants and deposited in a box or envelope prior to receiving their attendance certificates (Note: additional support will need to be given to those who are illiterate, who have poor sight, and those who have rarely filled out such forms)

Certificates of Attendance

Through community feedback with ex-patients and discussions within the team and project steering committee, we decided to award certificates of attendance to those families participating in the interactive community meetings. This decision was taken in order to formalise the interactive community meeting, to provide another instant gratification apart from the incentive offered, and for the personal (and potentially professional) development of the individual. Attendance at such educational events could be considered a part of continuing education and be provided in a curriculum vitae as evidence of participation in a community activity at a later date.

Certificates were only given to those who attended for the whole duration of the interactive community meeting and had completed their feedback forms. This was explained to participants prior to the meeting. An example of the certificate of attendance that we gave participants can be found in Document 11.

Other ideas relating to the certificates of attendance include:

- Providing different coloured / quality certificates to differentiate people who have attended for example 1/2/3/4/5 interactive community meetings
- Encouraging participants to build a portfolio of these certificates (especially those who wish to become facilitators)
- With each individual and the group's permission, take a photo at the end of the interactive community meeting with all the participants together and give this photo out at the next meeting.

MDR TB and Infection Control

Clearly, while implementing any intervention which involves TB patients, it is vital to maintain infection control measures and to avoid transmission of TB. Specifically, an intervention such as this should aim to:

- Decrease TB transmission in patient households through education concerning how TB is spread;
- Avoid TB transmission or acquisition between TB patients and contacts; and
- Avoid unnecessary exposure to TB for the members of the intervention team or facilitators.

In order to adhere to the above, we made some ground rules for our project:

- Patients with non-MDR TB who had been on uninterrupted appropriate anti-TB treatment for at least 2 weeks and/or had laboratory evidence of sputum smear negativity were allowed to participate in the interactive community meetings
- Patients with MDR or rifampicin resistant TB who had 2 negative cultures were allowed to participate in community meetings as any other patient or contact
- Patients with MDR or rifampicin resistant TB and sputum or culture positive were invited to interactive community meetings specifically for these patients conducted by the team whilst both team and patient wore masks (see below)

Patients with MDR TB are at higher risk of treatment failure and incurring catastrophic costs than patients with non-MDR TB.[2] In addition, patients with MDR TB are more likely to have comorbidities such as HIV and drug addiction. Patients with MDR TB may take some months for their sputum smear to become negative, remaining infectious for longer than those with non-MDR TB. Putting these factors together, for a socioeconomic intervention in patients with MDR to have most effect, it seems likely that it must begin early in the treatment of MDR TB patients whilst they are still sputum smear positive and therefore infective. Due to this we decided for patients with MDR TB:

- We would create a separate interactive community meetings to be performed with only MDR TB patients on a monthly basis with both staff and patients wearing protective N95 masks (for methodological guide see Document 13)
- That once their sputum had become negative, patients with MDR TB could join the interactive community meetings like any other patient and would receive an additional incentive for doing so (see Incentives in Document 15)
- Screened contacts of patients with MDR TB who had no evidence of active TB disease (including symptoms) could attend the interactive community meetings

Economic Support: Conditional Cash Transfers

We detailed the social aspect (interactive community meetings and home visits) of the socioeconomic intervention above. In addition to those activities, economic support is offered to all members of consenting TB-affected households in supported communities. This constitutes (bank account) cash transfers conditional upon completing the TB treatment and prevention activities that are offered free of charge by the national TB control program. A further conditional cash transfer is provided for attendance of all members of the TB-affected household at at least one interactive community meetings.

The bank accounts into which transfers are made have been set up, preferably in the patient's name. Other cash transfer programs such as JUNTOS in Perú elected the female head of the household as the recipient of a bank account and cash transfers. In our intervention, we decided that the patient would be the recipient with the aim to empower them to make their own financial decisions and be incentivized to complete their treatment. In the case that the patient is a minor, the bank account is opened in the name of their guardian. In a few other cases, the patient and family may also decide that another household member would manage the bank account.

The Conditions

Cash transfers were designed to have the same value as the combined food and cash transfers in our previous ISIAT pilot study,[1] equivalent in value to US$230 per household (56% of average TB-affected household monthly income, 10% of TB-affected household median income). Conditions for the cash transfers are the following and can be reviewed in more detail in Document 15:

- *TB prevention in contacts*
    - All relevant household contacts are screened for TB
    - After screening, those that require it, start TB preventive therapy
- *TB treatment in patients*
    - Good adherence to anti-TB therapy, throughout treatment
- *Joint goals for TB-affected households*
    - Allow home visits from our team and attend interactive community meetings
    - The TB patient and all contacts who started preventive therapy, finish their treatment

Soft conditionality

The conditional cash transfers adopted a form of conditionality called "soft" conditionality.[44]Perfect completion of the condition results in a "double incentive" whereas adequate completion of the condition results in a "simple incentive". For example, patients with near perfect adherence (i.e. missed <2 doses in the first month of treatment) will receive a double incentive each month whereas those whose adherence was only adequate (i.e. missed ≥2 doses in the first month of treatment without abandoning treatment) receive a simple incentive (Document 15). Combined with the assessment of "high risk" and additional home visits, this type of soft conditionality has been put in place to ensure that the most vulnerable, unwell, stigmatized and highest-risk TB-affected households can still receive economic support, to reduce costs (e.g. conditionality was associated with 18% of the costs of Mexico's poverty-reducing conditional cash transfer program PROGRESA, between 1997 and 2000).

Previous work in other settings has shown that when cash transfers are provided without supportive education, behavioural changes are not sustained and the intervention can have little impact.[5] For this reason, during initial recruitment, home visits and interactive community meetings, we provide education (both verbal, written and participatory) on responsible domestic economics, spending and saving (Document 6 and Document 7). Also, we give reading material (Document 15a) and accompany all supported TB patients who require assistance to open their bank accounts.

Support from banks and other forms of economic support

We visited many banks to discuss the ways in which we would be able to deliver conditional cash transfers in a timely manner. The main relevant issues and talking points between the bank and our group were:

- What was legally required to open a bank account (i.e. documents, presence of potential account holder in a specific branch)
- The bank's concerns regarding exposure of their clients and staff to TB infection
- Explanations of infection control measures that our group would take to maintain both patient and bank staff safety (including non-MDR TB patients having to have been on treatment for at least 2 weeks prior to opening their account)

4 Adato et al. Social protection to support vulnerable children and families: the potential of cash transfers to protect education, health and nutrition. AIDS Care: Psychological and Socio-medical Aspects of AIDS/HIV. Volume 21, Supplement 1, 2009

5 London et al. for the Ethics Working Group of the HIV Prevention TrialsNetwork (2012) Improving Ethical Review of Research Involving Incentives for Health Promotion. PLoS Med 9(3):e1001193

- The potential for a streamlined or adjusted system for TB patients to open their accounts that would reduce the time spent in the bank
- Establishing if the bank had a social inclusion department that could be involved and/or provide education on responsible spending and saving
- Choosing an appropriate account so that the patient was not charged for withdrawing cash, could not get into debt, and was not open to inappropriate sources of credit, all of which could serve to worsen their socioeconomic position

There are many other methods available to provide economic support (food packages, food vouchers, cards that can be used to buy products in a list of specific establishments, and cash).[36] The method a project decides to use to economically support their participants will depend on the community and area in which they live and existing schemes.

Facilitators and intervention sustainability

TB predominantly affects impoverished people in resource-constrained settings. A project implementing a TB intervention will have a specific duration and will be working within a predefined budget. Therefore, it is essential when planning an intervention with TB-affected families, that sustainability is considered – ideally the positive effects of an intervention will continue within the community after the project itself is finished. In addition, as previously touched upon, in order for an intervention to be both acceptable and relevant to the local population, involving TB patients and their families in the activities of the intervention is necessary.

We decided to invite TB patients and ex-patients to become trained as "facilitators" for our project: people with personal experience of TB who are able to carry out project activities such as home visits, leading interactive community meetings, supporting patients to complete their treatment and receive their cash transfers, and performing active case finding. The role, selection and training of facilitators can be found in more detail in Document 16. We aimed to make the training practical and involving various steps so that quality of training and quality of facilitators completing such training would be high (Document 17).

Criteria to become a facilitator

- No longer an infection risk
- Being a patient or contact who is completing their own conditions for cash transfer (good adherence, all contacts screened, attends community meetings)
- Interested in and available to support other TB-affected families
- Ideally, live in the same community as the patients which they support
- Attend: a half-day training session, two home visits, and two interactive community meetings (initially observing then leading under supervision)

Roles of the facilitator

- Assist the project team: logistics and leading interactive community meetings
- Support TB patients to adhere to and complete treatment
- Support TB-affected families to ensure that all relevant contacts are screened for TB and start, adhere to, and complete preventive therapy
- Undertake additional home visits for high-risk families
- Educate TB-affected families, reduce stigma and increase empowerment

Benefits for the facilitator

- General training in education, leadership, working in a team, and professionalism – broadening of experience for the future (Examples of the facilitator training can be found in Document 17 and the presentations on our website www.ifhad.org)

- Economic benefit of receiving an incentive each time a patient that they support achieves a condition and receives an incentive (Document 15)
- Incentive to complete their own treatment, a positive feedback loop

Feedback and assessment

- Just as is the case for the interactive community meetings, we created a feedback form for the training sessions for facilitators (Document 18). The form is anonymous and it was explained that its sole purpose is to make sure that we are able to respond and improve the training we offer.
- Clearly, it is important that the contents taught during the training day are understandable and that the facilitators are able to use this information to support TB-affected families. We created a pre and post training session "exam" that is a multiple-choice test that covers the key messages of the session (Document 19). The purpose of this test is not so much to test the knowledge of the participants but to review the difference between pre and post session responses and assess the effectiveness of our teaching.

Measuring the impact of the intervention

Prior to initiating the implementation of your intervention (or even prior to planning the design of your intervention), it is important to think about the impact of that the intervention might have. Some useful questions to start exploring the theme could include:

- What are the primary, secondary, and additional objectives of your intervention?
- Which results / outcome measures are you going to use as indicators to measure the impact of your intervention?
- Will you collect and analyse qualitative data (for example, feedback through interviews with the participants or other community members), quantitative data (for example, concrete data such as health or socioeconomic position indicators), or both?
- If the intervention is part of a scientific study: What is the hypothesis? What is the desired measure of effect for your intervention? What is the sample size necessary to give the study sufficient power to detect a difference between intervention and control groups in the outcome measured?

With respect to our specific project, the socioeconomic intervention forms part of a study in which, through randomization, half of the TB-affected families receive the support of the intervention and half do not. With relation to our specific objectives of mitigating TB-related costs, improving TB prevention, and improving TB cure, some of the indicators that we measure include:

- Initiation, adherence to, and completion of preventive therapy
- Direct costs (e.g. medicines and transport), indirect costs (e.g. lost income) and catastrophic costs of having TB
- Proportion of patients with prolonged cure confirmed by a prevalence study two years following treatment initiation (a TB prevalence study involves obtaining a sputum sample from all members of TB-affected households participating in the study and testing it for TB whether the participant is symptomatic for TB or not)
- Rate of secondary TB in household contacts
- Rate of incident TB in the community
-

In addition to the above, it is also advisable to lead focus groups, obtain objective participant testimonies or use a feedback questionnaire in the communities in which the intervention was realised. In this way, you can check the acceptability to the community of the intervention and to listen and take note of their opinions on the intervention and perhaps how it could be improved or locally adapted.

Documents

Document 1a: Checklist of all activities with supported TB patients during the first month of treatment

CHECKLIST OF ALL ACTIVITIES OF IPSYD TEAM WITH SUPPORTED PATIENTS *TW;v15;20140711*

Z Code:_____ **Date of diagnosis:**_____ **Date of recruitment:**_____

Treatment start date:_____ **Healthpost:**_____ **Key:** *Outcome: -9 = impossible; -1 = pending; E = complete; P = in process*
Types of TB: P = pulmonary; EP = extrapulmonary
Resistance profile: S = fully sensitive; M = MDR; R = resistant not MD

Approx Mth	Step	Activity	Outcome	Initials	Date	Notes / Comments
First (as early as possible)	*Recruitment in the healthpost*	1. Confirm diagnosis and type of TB made by national TB program				
		2. Confirm treatment decided by national TB program TB physician				Treatment regimen:
		3. Explanation of study (community meetings, bank transfers, facilitators) and informed consent				
		4. Education: using the pre-printed colour flipchart and inviting any other questions				
		5. Questionnaire (complete if possible)				
		6. Ask for and collect the initial sputum test				
		7. CONDITION FOR SIMPLE CASH/VOUCHER COMPLETED: Give the patient a voucher/cash for giving sputum sample (if already started treatment) and completing questionnaire				NOTE: If the condition is complete, write in the incentives card aswell
		8. CONDITION FOR DOUBLE CASH/VOUCHER COMPLETED: Give the patient double cash/voucher for giving a sputum sample prior to starting treatment and completing questionnaire				NOTE: If the condition is complete, write in the incentives card aswell
		9. If the sputum sample is given after starting treatment and patient registered, give the healthpost the corresponding materials (monthly). Do not give if patient has not been registered in patient registration book				
		10. If the sputum sample is given prior to starting treatment and patient registered, give healthpost double the corresponding materials (monthly). Do not give if patient has not been registered in patient registration book				
		11. Verify randomization of the patient post-interview (by opening pre-sealed envelope)				
		12. Encourage the patient to have/request an HIV test (if had, indicate if reactive or not)				HIV Result:
		13. Verify that the patient has a national ID card (if they do not, advise how to obtain)				
		14. Verify if the patient has health insurance (if not, advise how to obtain)				
		15. Verify that the patient has had glucose test (if not give advice on how to obtain)				Glucose level:_____mg/dL
		16. Verify if the patient has booked / planned other consultations and give relevant education (includes reproductive health, social support, nutrition, and psychology)				

Document 1b: Checklist of all activities with supported TB patients during the first month of treatment (cont.)

CHECKLIST OF ALL ACTIVITIES OF IPSYD TEAM WITH SUPPORTED PATIENTS

TW;v15;20140711

Z Code:_____ **Date of diagnosis:**_____ **Date of recruitment:**_____

Treatment start date:_____ **Healthpost:**_____ **Key:** *Outcome: -9 = impossible; -1 = pending; E = complete; P = in process*
Types of TB: P = pulmonary; EP = extrapulmonary
Resistance profile: S = fully sensitive; M = MDR; R = resistant not MD

Approx Mth	Step	Activity	Outcome	Initials	Date	Notes / Comments
First (before IHV)	*Work in the healthpost*	17. Organise the delivery of the initial sputum test to our laboratory				
		18. Deliver the GeneXpert result to the healthpost as early as possible (within 48 hours)				
		19. (Before IHV) Check adherence				
		20. (Before IHV) Check HIV test (if had, indicate if reactive or not)				HIV Result:
		21. (Before IHV) Check contacts registered in national TB program folder				
First (at the earliest opportunity in the first week following recruitment but if not possible within a month)	*Initial Home Visit ("IHV")*	22. (Repeated during the home visit) Verify adherence				
		23. (Repeated during the visit) Verify HIV test				
		24. (Repeated during the visit) If there exist more household contacts than we have listed in our census, encourage them to have an appointment in the health posts to rule out TB				
		25. Education: including TB in general, risk factors (specifically poverty), TB types (MDR), TB transmission, prevencton, treatment, chemoprophylaxis, the importance of adherence, advice concerning reducing the risk of TB contagion (ventilation, cough hygiene etc)				
		26. Present the family's elected facilitator to the family				
		27. Confirm the patient how has a national ID card (if not, repeat the advice given above				
		28. Confirm that the patient now has health insurance (if not, repeat the above advice)				
		29. Invite the patient to open a bank account, give date for opening (if need assistance)				
		30. Explain the key points about the bank account and the bank card				
		31. Invite patient and their household to attend an interactive community meeting				
		32. Fill in all the details necessary to open their bank account (where necessary)				

Document 1c: Checklist of activities with supported TB patients during first and second months of treatment

CHECKLIST OF ALL ACTIVITIES OF IPSYD TEAM WITH SUPPORTED PATIENTS

TW;v15;20140711

Z Code:_____ **Date of diagnosis:**_____ **Date of recruitment:**_____

Treatment start date:_____ **Healthpost:**_____ **Key:** *Outcome : -9 = impossible; -1 = pending; E = complete; P = in process*
Types of TB: P = pulmonary; EP = extrapulmonary
Resistance profile: S = fully sensitive; M = MDR; R = resistant not MD

Approx Mth	Step	Activity	Outcome	Initials	Date	Notes / Comments
First (after IHV)	*Obtain second sputum sample in the health post*	33. Obtain the second sputum sample (in the healthpost, at 15 days of treatment)				
		34. Deliver the result of the second sputum sample to healthpost (as early as possible)				
First (after IHVI)	*Open bank account (unless already has existing MiBanco acount)*	35. Confirm with the bank the hour and data organised (where necessary)				
		36. Accompany the patient to the bank (or confirm their attendance)				
		37. Verify the patient opened their account successfully and obtain new account number				
		38. Verify that the patient has received their bank card (where necessary)				
First and second	*Work in the health post and using the project registry*	39. CONDITION OF CASH TRANSFER COMPLETED: If we have visited the housed, completed the questionnaire, and listed all households contacts in the first week or first month, sign and deliver the "incentives card" of the patient to the administrator of teh IPSYD team to make the corresponding transfer				NOTE: If the condition is complete, write in the incentives card aswell
		40. Verify patient adherence				
		41. (Before AHV1) Verify adherence of contacts to chemoprophylaxis				
		42. (Before AHV1) Verify that >50% of the family have attended ≥1 interactive community meeting and if not, it is a "high risk" household and will need a AHV1				
		43. (Before AHV1) Speak with a) facilitator b) staff of healthpost to find out if there are any surmountable family problems				
		44. Confirm that the contacts were assessed to rule out TB disease and for prophylaxis				
		45. Confirm that the appopriate contacts have started chemoprophylaxis				
		46. Confirm that the contacts subsequently diagnosed with TB have started their TB treatment				
		47. CONDITION OF CASH TRANSFER COMPLETED: If between 80 and 100% of listed household contacts have had their medical appointment to rule our TB and that those who need to take chemoprophylaxis or be treated for TB have started their treatment, sign and deliver the "incentives card" of the patient to the IPSYD team administrator to make the respective payment				NOTE: If the condition is complete, write in the incentives card aswell
		48. CONDITION OF CASH TRANSFER COMPLETED: In the first month - confirm that the patient has completed 25 doses, sign and deliver the incentives card to the IPSYD team administrator to make the corresponding payment				25 doses in total (NOTE: If the condition is complete, write in the incentives card aswell)
		49. In the first month: if the patient has not completed 25 doses coordinate with their facilitator				
		50. CONDITION OF CASH TRANSFER COMPLETED: In the second month - confirm that the patient has completed 25 doses, sign and deliver the incentives card to the IPSYD team administrator to make the corresponding payment				50 doses in total (NOTE: If the condition is complete, write in the incentives card aswell)
		51. In the second month: if the patient has not completed 25 doses coordinate with their facilitator				
		52. Ask about the relationship of the family with the facilitator (good/normal/bad)				

Document 1d: Checklist of activities with supported TB patients during third to six months of treatment

CHECKLIST OF ALL ACTIVITIES OF IPSYD TEAM WITH SUPPORTED PATIENTS *TW;v15;20140711*

Z Code:_____ **Date of diagnosis:**_____ **Date of recruitment:**_____

Treatment start date:_____ **Healthpost:**_____ **Key:** *Outcome : -9 = impossible; -1 = pending; E = complete; P = in process*
Types of TB: P = pulmonary; EP = extrapulmonary
Resistance profile: S = fully sensitive; M = MDR; R = resistant not MD

Approx Mth	Step	Activity	Outcome	Initials	Date	Notes / Comments
Third	Additional home visit 1 "AHV1" ("high risk" families)	53. Enquire why family were unable to attend community meetings (explore problems)				
		54. Ask about symptoms in contacts or patients and if anyone has symptoms, encourage them to go to the health post (although there is no specific project incentive for this)				
		55. Leave sample tubes for those with symptoms if necessary (wide topped containers)				
		56. Review understanding of treatment and the importance of adherece				
		57. Invite the family to attend the next interactive community meeting				
	Work in the healthpost and using the project registry	58. CONDITION OF CASH TRANSFER COMPLETED: Confirm attendance of 100% of the household at ≥1 community meeting, sign and deliver the incentives card to the administrator of the project to make the corresponding payment				NOTE: If the condition is complete, write in the incentives card aswell
		59. (Prior to AHV2) Check patient adherence				
		60. (Prior to AHV2) Check adherence of relevant contacts				
		61. (Prior to AHV2) Speak with a) facilitator b) healthpost staff to find out if any surmountable family problems exist				
		62. Ask the family about their relationship with the facilitator and vice versa (good/normal/bad)				
Fourth	Additional home visit 2 "AHV2" (one month following AHV1)	63. Ask why they were unable to attend community meetings (explore issues) and if they did attend ask how they found it				
		64. Ask if there are any symptomatic contacts or patient and if there are encourage them to attend the healthpost (although no project incentive is given for doing this)				
		65. Leave tubes for those with symptoms if necessary (wide topped containers)				
		66. Revise the understanding of treatment and the importance of adherence				
		67. Invite the family to attend the next interactive community meeting				
		68. If following this visit, the family is still unable to complete their conditions of attendance at community meetings or have other specific problems, organise a revision of their case in the MDT IPSYD meeting				
	Work in the healthpost and using the project registry	69. CONDITION OF CASH TRANSFER COMPLETED: Confirm that after their first 50 doses, the patient completed the following 24 doses (approximately 2 months), sign and deliver the patient's "incentives card" oto the IPSYD team administrator to make the corresponding payment				74 doses in total (NOTE: If the condition is complete, write in the incentives card aswell)
		70. If after taking their first 50 doses, the patient has not completed their subsequent 24 doses, coordinate with the patient's facilitator				
		71. Monitor adherence to chemoprophylaxis of the contacts and if they are not adhering, coordinate with the facilitator				
Fifth and Sixth	Additional home visit >3 (programmed and individualised)	72. Ask why they were unable to attend community meetings (explore issues) and if they did attend ask how they found it				
		73. Ask if there are any symptomatic contacts or patient and if there are encourage them to attend the healthpost (although no project incentive is given for doing this)				
		74. Leave sample tubes for those with symptoms if necessary (wide topped containers)				
		75. Revise the understanding of treatment and the importance of adherence				
		76. Invite the family to attend the next interactive community meeting				
		77. If following this visit, the family is still unable to complete their conditions of attendance at community meetings or have other specific problems, organise a revision of their case in the MDT IPSYD meeting				

Document 1e: Checklist of activities with supported TB patients from six months to end of treatment

CHECKLIST OF ALL ACTIVITIES OF IPSYD TEAM WITH SUPPORTED PATIENTS

TW;v15;20140711

Z Code:_____ **Date of diagnosis:**_____ **Date of recruitment:**_____

Treatment start date:_____ **Healthpost:**_____ **Key:** *Outcome : -9 = impossible; -1 = pending; E = complete; P = in process*
Types of TB: P = pulmonary; EP = extrapulmonary
Resistance profile: S = fully sensitive; M = MDR; R = resistant not MD

Approx mth	Step	Activity	Outcome	Initials	Date	Notes / Comments
Sixth to Ninth	*Work in the healthpost and using the project registry*	78. CONDITION OF THE CASH TRANSFER COMPLETED: Confirm that the patient has completed their subsequent 24 doses of treatment (approximately 2 months), sign and deliver the patient's incentives card to the IPSYD administrator in order to make the appropriate transfer				98 doses in total (NOTE: If the condition is complete, write in the incentives card aswell)
		79. If the patient has not completed the subsequent 24 doses, coordinate with their facilitator				
		80. Verify in the national TB program cards if the contacts that started chemoprophylaxis have completed the same				
		81. CONDITION OF CASH TRANSFER COMPLETED: If between 80-100% of contacts that started chemoprophylaxis have finished the same and the patient has finished their treatment, sign and deliver the incentives card to the IPSYD adnimistrator in orderto make the appropriate transfer				NOTE: If the condition is complete, write in the incentives card aswell
		82. If the appropriate contacts have not completed their chemoprophylaxis, coordinate with the patient's facilitator				
Six to 24 months	*Work in the healthpost and using the project registry*	83. CONDITION OF CASH TRANSFER COMPLETED: If the patient has HIV, aftter 6 months of treatment, confirm that the patient is still taking their medicine and each 24 doses completed, sign and deliver the incentives card to the IPSYD administrator to make the appropriate transfer. Note: it is essential to maintain these patients momentum and spirit so that they are able to compelte their treatment over the long term (there are two boxes just in case the patient reaches 10 months of treatment)				NOTE: If the condition is complete, write in the incentives card aswell
						NOTE: If the condition is complete, write in the incentives card aswell
		84. CONDITION OF TRANSFER COMPLETED: If the patient has MDR TB, after 6 months of treatment, keep confirming that the patient is continuing htier treatment and each 50 doses taken, sign and deliver the patient's incentive card to the IPSYD administrator to make the appropriate transfer. Note: it is essential to maintain these patients momentum and spirit so that they are able to compelte their treatment over the long term (there are two boxes just in case the patient reaches 24 months of treatment or more)				NOTE: If condition is complete, write in the incentives card aswell
						NOTE: If condition is complete, write in the incentives card aswell
						NOTE: If condition is complete, write in the incentives card aswell
						NOTE: If condition is complete, write in the incentives card aswell
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						NOTE: If condition is complete, write in the incentives card aswell
		85. Make sure that all the activities checklists are completed				
24 months	*Final follow-up visit (6 months in pilot, 24 months in CRESIPT)*	86. Follow-up questionnaire				
		87. Recover the sputum sample or saliva for the prevalence survey from all household members				
		88. Deliver the sputum samples to our laboratory				
		89. Encourage any symptomatic household members to attend the health post				
		90. Deliver the results of the sputum sample from the prevalence survey to the health post				
		91. Update, double-check, ad complete all the checklists of activities including this one and the patient's incentive card				
>24 months	***Finalise folder***	92. Ensure that the completed folder of the patient and family has been double-digitized				

Document 2: Daily attendance and project costs form

DAILY IPSYD TEAM ATTENDANCE AND PROJECT COSTS FORM *v14/TW/20140711*

Team member:_____

***Key (see the corresponding box below)**

Principal place of activity

1. Patient's house	5. Field laboratory	
2. CENFOLAB	6. University laboratory	
3. Healthpost/hospital	7. Place of work of participant	
4. PRISMA	8. Bank	9. Other (specify)

Activity Code

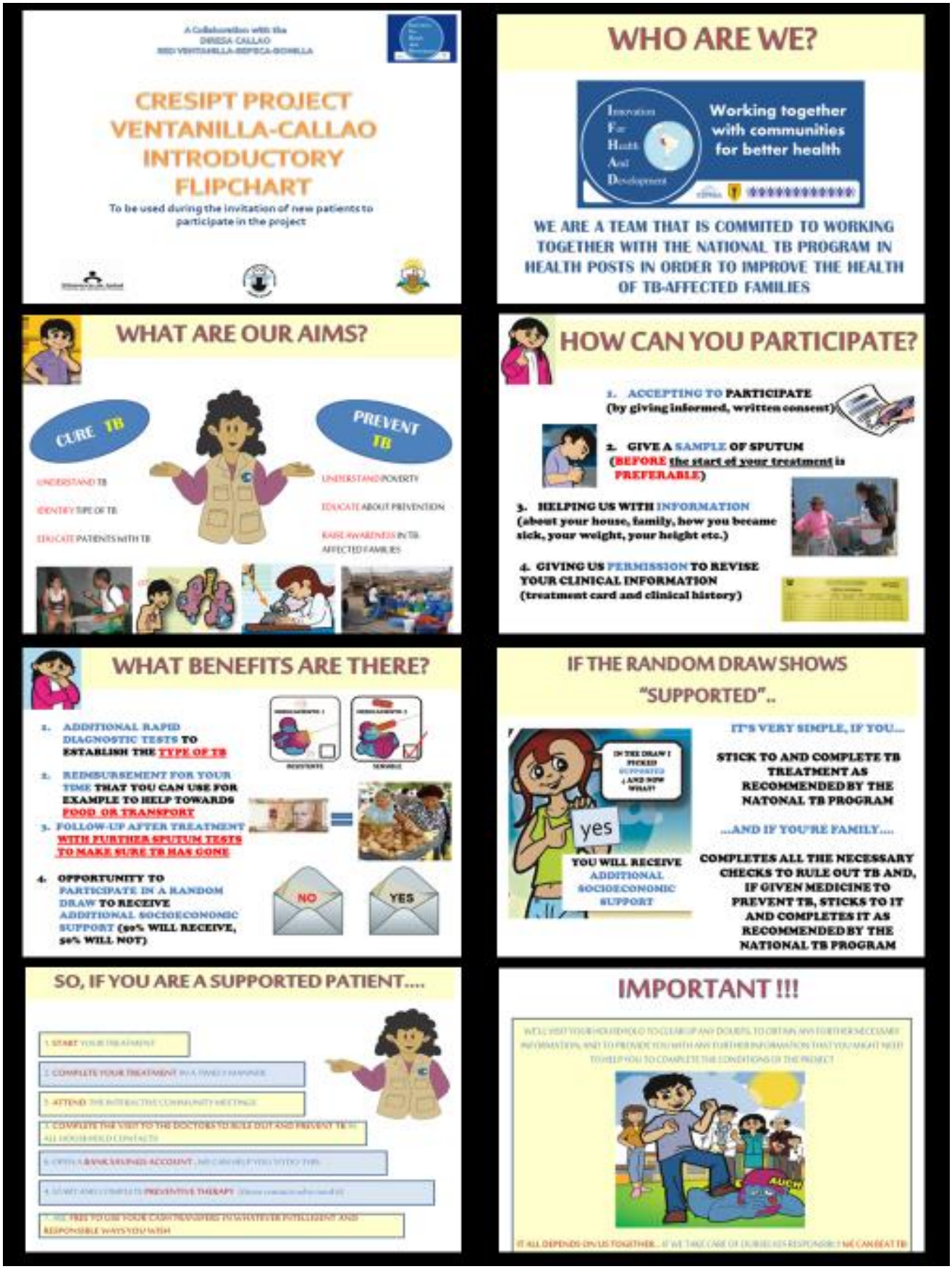
IN THE HEALTH POSTS	*HOME VISITS*	*OTHERS (OFFICE / MEETINGS / PERSONAL)*
1. Identify new patients	9. Home visit (indicate which type of the following visits: IHV/AHV1/AHV2/AHV3 etc)	12. Pick up / purchase of materials for PRISMA / Cenfolab / University
2. Recruitment	10. Home visit for final follow-up or estimations	16. Training or meeting with facilitators
3. Meeting in the healthpost	11. Home visit for other reason (e.g. inviting patient)	17. Accompany patients to their bank appointment
5. Pulling / review of treatment cards	*INTERACTIVE COMMUNITY MEETING*	18. Meeting / presentation of the field team (any)
6. Delivery of sputum results 7. Collecting sputum from patient	4. Doing a community meeting (only the reponsible team member needs to write the patients/contacts involved and the total money spent on the meeting - this should be the same as the total in the table on the register of the community meeting)	19. Work in PRISMA / Cenfolab (including paperwork)
8. Deliver sputum field/uni labs	13. Pick up / purchase materials for the community meeting	21. Break/lunch (of team member)
20. Time spent waiting for patient or healthcare personnel	14. Organization / pick up / purchase / prepare snack for the community meeting	22. Other (specify)
24. Short follow-up questionnaire 25. Final follow-up questionnaire	15. Organization / coordination / preparation of the place in which the community meeting takes place	23. Medical appointment / consultation of team member

Final outcome

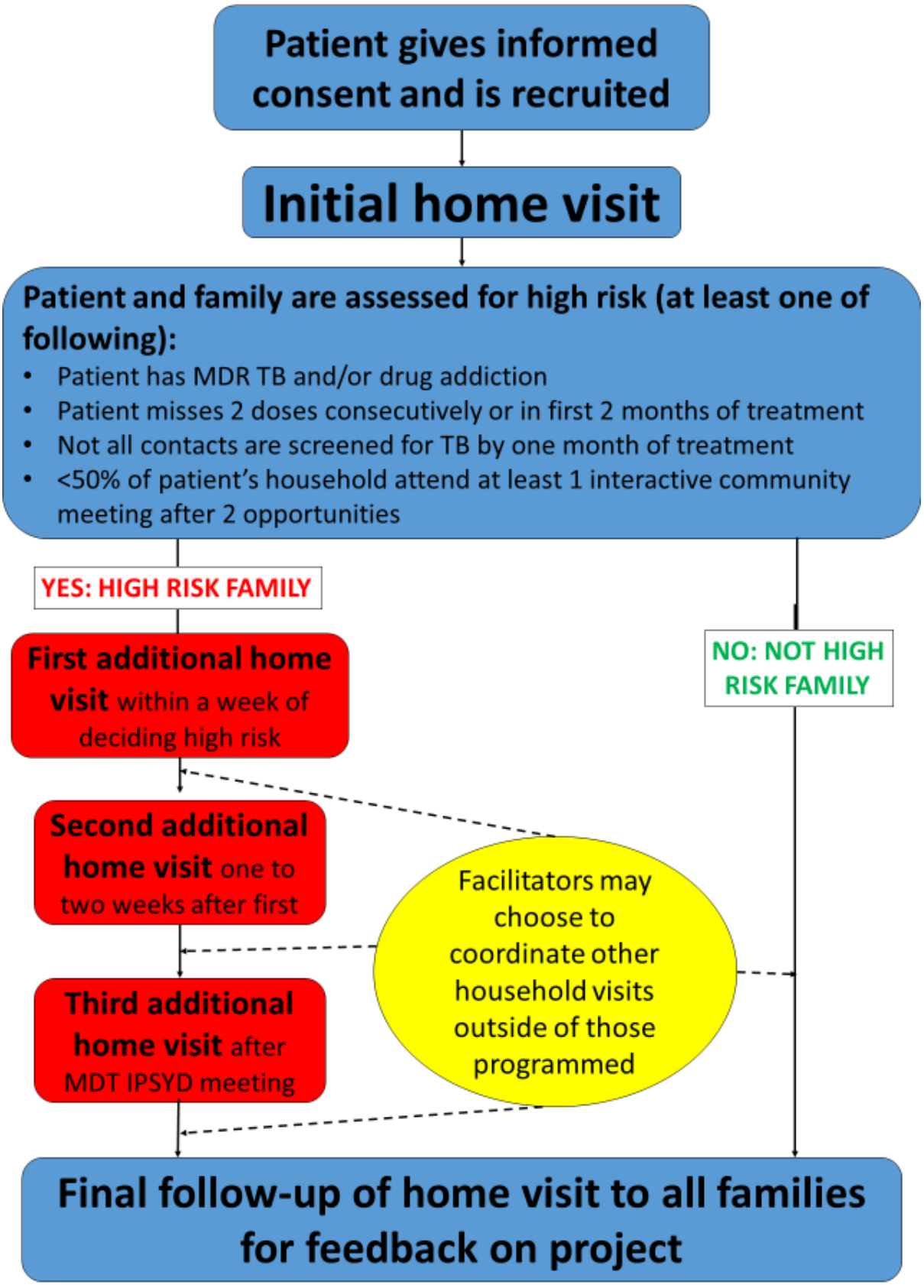
-1	Incomplete but possible
-9	Incomplete and impossible
E	Effective
P	In process
B	Time organised

Date	Principal place of activity*	Health post	Code of house involved in activity	Patient involved in the activity (yes=1; no=0; line= not applicable)	Number of contacts involved in the activity (line=no applicable; 0=none)	In the case of a community meeting, number of members of the family participating minus children who were looked after by baby sitter (line=not applicable 0 = none)	Actual time that the activity started	Time that activity was planned to start	Actual time activity ended	Activity*	Cost (Peruvian soles) of TRANSPORT OF TEAM MEMBER (only work-related transport)	Cost (Peruvian soles) of TRANSPORT OF PATIENT, CONTACTS, FACILITATORS OR OTHERS	Cost or equivalent value (Peruvian soles) for MATERIALS used or FOOD provided for COMMUNITY MEETING / or photocopies (patient registration books/treatment cards/others)	Final outcome* (please don't put "OK" as a response)

Document 3: Introductory educational flipchart for recruitment



Document 4: Flowchart for household visits



Document 5: Example Interactive Community Workshop Guide

INTERACTIVE COMMUNITY MEETING: EDUCATIONAL WORKSHOP AND TB CLUB Nº 1

HEALTH POST CIUDAD PACHACUTEC

"WORKING TOGETHER WITH COMMUNITIES TOWARDS GOOD HEALTH FOR ALL"
Friday 7th March2014

General Objective:

- Improve the cure, prevention and control of TB (both non-MDR and MDR) in households and communities affected by TB.

Specific Objectives:

- Ensure that patients and their household contacts understand in general terms simple methods for the prevention and control of TB
- Create a culture of responsible saving and spending to promote social and economic development.
- Educate about the conditional cash transfers and how they relate to completing the objective of the Peruvian National TB Program.
- Reduce stigma, combat depression and increase empowerment.
- Achieve that all participants recognise and value their own personal characteristics and reinforce positive feelings about themselves

Outputs:

- The participants define, in their own words, the questions and answers from the roulette wheel relating to TB.
- The participants recognise and put into practice the messages about domestic economy (household spending and saving).
- The participants recognise their treatment objectives and learn how to exercise their rights as people affected by TB.
- The participants, of their own volition, comply with the health post personnel requests with respect to treatment of TB patients and prevention of TB in household contacts.
- The participants actively participate in the community activities of the IPSYD team and CRESIPT project.
- The participants are able to improve their outlook on how they approach having TB and feelings relating to stigma.

IPSYD team members responsible: Tom Wingfield, Marco Tovar, Rosario Montoya, equipo CRESIPT

Location: Auditorium of the Health Post Ciudad Pachacutec.

PROCESS AND THEME	OBJETIVE	CONTENT	METHOD / TECHNIQUE	TIME	MATERIALS	LEAD PERSONNEL	OUTPUT
PRIOR ACTIVITIES	Preparation of space in which the interactive community meeting will occur.	Group the seating in a circle with all seats facing the "Prize-giving Roulette."	Participatory	60 min. (13:30-14:30)	Chairs, table, projector, laptop, plugs and extension cables, White board or similar pens, paper, flip chart, balloons, etc.	Whole CRESIPT team	Space prepared and ready to receive the participants. The attendance list will have been previously generated by the Project administrator and must be updated and finalised by the end of the meeting
Reception of the participants	Register all participants attending	Previously generated register	Participatory	30 min. (14:30 - 15:00)	Register Pens Relevant list of those who need to receive cash transfer after attending Namebadges	Carlos (PAC) Rosario Sosa Pilar Tapia	The register will be completed which includes the participants reimbursement for travel expenses (must sign). In addition, the document listing those requiring cash transfer must also be completed Participants will be identified by name badge which will have an additional number "1" or "2" assigned
Welcome and introductory presentation	Presentation of the outline of the session's program	Themes visited, personnel, timing	Presentation	7 min	Copies of the community meeting program Projector & laptop	Dr. Marco Tovar and Dr Tom Wingfield	The participants are orientated to the central themes of the community meeting.
Group activitiy	Generate trust and remove inhibitions	The participants are grouped according to the number assigned previously to them on their namebadge	Participatory, interactive	8-10 min	Clear space in order to split group into two	Charo Montoya Pilar Tapia	The participants get to know each other in order for further communication to be facilitated
The ABC of Tuberculosis (First hour)	Orientate the participants about TB Make sure that the participants have relevant supporting Reading materials that they can review in their own time	Definition of TB Transmission of TB Types of TB Diagnosis of TB Treatment Adherence Prevention of TB Risk factors Importance of active case-finding in TB Information leaflets	Participatory Key ideas	10 min.	Roulette with questions and responses to the key themes. Projector and Laptop Community meeting materials (Booklets, slides, flip chart) Reading material	Carlos Pozo Dr. Tom Wingfield Dr. Tovar Charo Montoya Rosario Sosa Frank Fernandez	The participants respond in teams to the roulette questions and respond with the asistance of written posters to the questions The image and key message are displayed on the projector screen Those participants taking part in the game receive useful materials at the end (notebook, writing materials etc) The participants are encouraged to show the Reading material provided to their household members unable to attend the community meeting

PROCESS AND THEME	OBJETIVE	CONTENT	METHOD / TECHNIQUE	TIME	MATERIALS	LEAD PERSONNEL	OUTPUT
Domestic economy	Motivate the participants concerning the importance of responsible spending and saving.	Examine how money is spent within households Expound the importance of a budget Saving for future expenses (forward thinking)	Participatory Key Ideas	10 min.	Roulette with questions and responses to the key themes. Community meeting materials (Booklets, slides, flip chart) Reading material concerning saving	Carlos Pozo Dr. Tom Wingfield Pilar Tapia	The participants describe how money is spent in the home and recognise the main sources of income. The participants consider the importance of making a household budget. They show and make an example of a household budget. The participants recognise how to plan for unexpected spending/events.
Conditional cash transfers into a bank account	The participants are informed about the essential requisites for receiving the conditional cash transfers Encourage and inform the patients and their family of the importance of agreeing to and committing to the programmed activities	1. WHAT ARE THE CONDITIONS FOR RECEIVING THE CASH TRANSFERS? Sputum simple (preferentially prior to treatment - will receive doublé incentive). Home visit in the first week following treatment start Interactive community meetings: Workshops. TB Club Evaluation by the National TB Program: medical consultation, preventive therapy, treatment of TB including treatment of new household cases. Adherence to treatment for cure Household contacts complete preventive therapy (6 mths isoniazid) 2. HOW DO YOU ACHIEVE THE CONDITIONS? Active participation at interactive community meetings by all household members at at least one session. Complete treatment in a timely manner with good adherence as detailed in the incentives card. Become facilitator: On completing project and program early conditions, actively participating in interactive community meetings, having a vocation and time available	Participatory Key ideas Participatory Key ideas	10 min. 10 min.	Roulette with questions and responses to the key themes. Community meeting materials (Booklets, slides, flip chart) Reading material including incentives card Incentives card	Carlos Pozo Dr. Tom Wingfield Carlos Pozo Dr. Tom Wingfield	The participants participate actively in the roulette game All the patients provide a sputum simple at the appropriate time The participants collaborate by providing suitable times for a household visit. The participants agree to participate in the interactive community meetings and invite other members of their household. The participants attend their TB clinic visits for treatment or ruling out TB in a timely manner. All participants that have relevant household contacts (especially children <5) have started preventive therapy or treatment for TB as indicated by the healthpost. All the patients are adherent to their TB treatment. All children and other relevant contacts on preventive therapy are adhering and ensure that any contacts who still have not had their TB screening appointment, arrange it All participants have a copy of the incentives card. Keep an eye out for candidates (self-elected or elected by the team) who meet criteria for and are keen to become facilitators

PROCESS AND THEME	OBJETIVE	CONTENT	METHOD / TECHNIQUE	TIME	MATERIALS	LEAD PERSONNEL	OUTPUT
Conditional cash transfers into a bank account	Reinforce the potential positive outcomes of adherence etc	3. IF YOU MANAGE TO COMPLETE THE CONDITIONS WHAT HAPPENS? ○ There should be less risk of treatment failure and more chance of cure with good adherence and completion of treatment ○ Screening for TB and giving preventive therapy in contacts.may prevent them getting TB disease ○ This applies especially to children. With respect to the IPSYD Project benefits: ○ You'll gain a DOUBLE incentive ○ You will have the opportunity to join us as a facilitator ○ By participating in the community meetings you'll receive education about TB. ○ You will be able to take part in the TB Club's to reduce stigma	Participatory Key ideas	5 min.	Roulette with key questions.	Carlos Pozo Dr. Tom Wingfield	Motivate the patients to adhere to treatment and follow National TB Program guidance Ensure that 100% of household contacts attend their screening medical consultation and receive and complete preventive therapy as necessary 100% of <5 year olds start their preventive therapy The participants complete each condition of the IPSYD Project and receive all the relevant benefits
Stigma (Part 1) What are stigma, empowerment, and TB clubs?	1. Educate patients and their contacts about self-stigma and empowerment 2. Introduce the theme of TB clubs – their aim, background and effectiveness 3. Motivate participation	What is stigma? What causes stigma? What are the effects of stigma? What are the different types of stigma? Enacted, anticipated, elf-stigma What is being empowered? What is a TB Cub? Proven to be successful, the clubs are a safe and compassionate place in which we can share feelings and experiences	Participatory	10 mins	Drawings of Becerra in powerpoint that reflect the patient's doubts and worries at the beginning of treatment contrasted with their hope and positivity at the end of successful treatment	Dr Tom Wingfield	The participants increase their sense of self-esteem To feel better about ourselves as TB-affected people Fight for our rights Understand why we feel as we do Understand why others treat us the way they do To make living with TB easier To complete TB treatment and get cured
Part 2: Stigma Part 3: Empowerment - "¿How can we beat stigma?"	Help the participants to identify the different ways in which TB-related stigmas has affected their lives and explore how this made them feel. Help participants to identify how they can confront stigma through their own actions	Relaxing music / welcome / review of the agreements of the TB club (see guide) Motivational ice breaker. This could be Hot (see document 1), Las Balsas (see Document 2) o Head to head (Document 3) TB Club (see guide) Facilitator prepares flipchart with 3 columns to fill: "Empowerment", "Rights", "Responsibilities"	Participatory Active (learn through doing) Participatory Active (learn through doing)	30 mins 30 mins	Necessary Becerra stigma and empowerment drawings (there are 18 in total) Power point (possibly) TB Club agreements Flip chart with marker pens	Frank Fernandez Mari Haro Doug Huff Tom Wingfield Frank Fernandez Doug Huff	"Exercise our rights" "Take responsibility for our health and lives" "Educate and train ourselves" "Be self-sufficient" "Have self-confidence and self-esteem" "Earn money" "Work together and support each other to improve"

Document 6: Example of program of interactive community meeting

Document 7: Key learning themes of educational workshops and activities

Rather than have educational workshops that developed one specific theme concerning TB each time over months, we decided that we would make the workshops into activities involving core themes that would always be touched upon. This meant that a patient or household contact who attended just one workshop and did not attend further would learn the important points about TB. In addition, for patients or contacts who attended multiple workshops the content although repeated would not be tiresome as it would be presented in a different way every time. Some related presentations are available from our website, www.ifhad.org. We aimed to keep language simple and not overload participants with technical or extensive detail, therefore the themes and responses are not exhaustive. The key themes we covered were as follows (numbers indicate what we felt to be the most important aspects of each theme).

TB infection, disease and control

1. What are some ways in which TB disease can be prevented?
    - Including how TB is transmitted
    - Cough hygiene; Ventilation; Nutrition; Reduce avoiding overcrowding
2. What are risk factors for getting TB disease?
    - Extremes of age; Overcrowding; Poverty; Malnutrition; Specific illnesses: Diabetes, HIV, Alcoholism
3. TB, TB diagnosis and TB treatment
    - Different types of TB (MDR/sensitive, pulmonary/extrapulmonary)
    - Diagnosis of TB (including simple explanations of smear, culture, and molecular tests)
    - Phases of treatment, duration of treatment and differing treatments depending on resistance or other factors (e.g. HIV)
    - Free treatment provided by government
    - Integral medical attention (e.g. with maternal health, psychology etc) and patients' rights
    - Healthcare workers' and the TB program's responsibility
4. Adherence to treatment
    - Education and reminders necessary
    - Increase likelihood of cure
    - Decrease likelihood of developing resistance or failing treatment
    - Support from the IPSYD project and family members

- Reducing the hidden economic burden of treatment with cash transfers

Household spending and saving

1. What do we need to do to make a household budget and spend/save responsibly?
    - List of all household income
    - List of all household spending (including travel, education, and food)
    - Sources of unexpected expenditure (including illness and loss of work)
    - Payment of debts
    - Saving with anticipation
    - Avoid spending more than one earns
    - Money-generating ideas

2. What are our sources of household income?
    - Income of husband/wife/head of household
    - Income of other household member or relative
    - Small own business or other work (e.g. caring for children, washing clothes)
    - Family business
    - Cooperative (e.g. making artesanía, canteen)
    - Non-cash income (e.g. in return for food or board)

The IPSYD project and conditional cash transfers

1. With regards to the IPSYD project, what do I have to do to receive my conditional bank transfers?
    - Open a bank account (with our assistance)
    - Give us a sputum sample to perform a molecular test and give you a rapid resistance test result
    - Allow us to visit your home, finish the questionnaire if necessary and list your household contacts
    - Adhere to TB treatment until completion
    - Screen household contacts for TB disease
    - Contacts needing preventive therapy (medicine to prevent TB) and those requiring treatment, start, adhere to, and finish treatment

Activities for interactive learning concerning the above themes (pictures and plans available from www.ifhad.org)

1. **Prize-giving roulette** – Participants are split into two teams and take turns spinning a roulette detailing the main themes. Questions concerning the theme landed on are asked of each team and they have to find the appropriate answer from posters hanging around the area in which the meeting is taking place. Correct answers get a point, the answers are discussed and both teams receive individual small gifts at the end.

2. **Advance and win!** – the participants are split into two teams and a team representative stands at the start of a short path made of different coloured tiles. Each tile represents a theme. The teams roll a dice with colours on each side to see which questions they answer. The questions are presented on posters with writing and representative pictures for those who can't read and the team whose turn it is decide on an answer. A correct answer means the team can move forward one tile but if incorrect the questions passes to the other side.

3. **Word play** – the participants are split into two teams. They are given a number of large cards that each contain a separate word. The separate words when ordered correctly form a sentence related to TB knowledge (e.g. TB can be transmitted through the air), or household economics (e.g. Making a household budget is a good way to save money). Each round corresponds to a different theme. The team that makes the sentence first and reads it out together the to the arbitrator wins a point. The team with the most points by the end are the winners.

4. **Snap TB with Memory!** - participants are split into three teams. A pre-prepared board contains a number of black squares. Behind each square is a picture relating to an aspect of TB (e.g. transmission, TB treatment) or household finances (e.g. opening a bank account). The teams approach the board and, taking it in turns, choose two black squares to reveal the picture behind. If the pictures match then they get asked a related question by the arbitrator. If they answer the question correctly, they collect the two cards (1 point) and the go passes to the next team. If they answer the question incorrectly, the two remaining teams have the opportunity to answer the question for bonus points.

5. **Making fun of TB** - The participants are split into two teams. Prior to the game, 54 large playing cards have been designed with 3 "suits assigned to 17

each of the cards. The logos cover ABC of TB, domestic finances, and the conditional cash transfer incentives of the socioeconomic intervention. There are also 3 jokers. Each group is dealt 6 cards and elects a person to play for them. The players from two of the teams sit down at a table visible to everyone. The aim is to get three cards of the same suit. Once the player does this they put the three cards on the table and will answer two questions about that subject. The first question is worth two points with a bonus question worth one point. Once one round of questions has been played the players switch over.

6. **This is war….against TB!** – This game follows the outline of a popular TV show in Peru. Candidates are split into two teams and a member from each team approaches a buzzer with a hand behind their back. A question is shown on the slide show (if projector available) or on a poster. The question is a "starter question" concerning wither ABC of TB, domestic finances, and the conditional cash transfers. The player that buzzes soon gets to answer the question (without conferring with their team). If they get the starter question right then they get two points and rejoin their team and answer two further related bonus questions for a point each. If they get the starter question wrong then the opportunity to answer goes to the other player (without conferring). If they answer the question right then they reget two points, rejoin their team and their team gets the chance to answer the two bonus questions for a point each. The winner is the team with the most points when the questions are exhausted

Document 8: technical guide on setting up a TB Club

Developed by Doug Huff, Psych. Frank Fernandez, and Tom Wingfield

Summary for facilitators

Contents of TB Club Theme 1: Explaining the clubs and stigma (10 minutes at the end of the educational workshop)

Contents of TB Club Theme 2: Personal experience (first 30 minutes of the club)

Contents of TB Club Theme 3: Empowerment

(Second 30 minutes of the club)

Support Materials 1-4 for activity

Becerra Drawings and Explanations

TB Clubs: a reference for the facilitators

BRIEF SUMMARY

Each interactive community meeting will consist of 2 parts which will each last about an hour:

1) Educational workshop:

a) 50 minutes concerning TB and the Project goals, plus

b) 10 minutes of an introduction to stigma (Contents TB Club)

2) TB Club

a) 30 minutes: Stigma (Contents of TB Club Theme 2)

b) 30 minutes: Empowerment (Contents of TB Club Theme 3)

Why do we need TB Clubs?

- TB Clubs are a way to share experiences and therefore reduce feelings of isolation and stigma
- Many countries of the world (from Nicaragua in Latina America to Ethiopia in Africa) already have TB Clubs with success: these Clubs work!
- Given that the TB Clubs are "for TB-affected people and by TB-affected people" they will deal with the key themes in the lives of TB-affected families

How do TB Clubs work?

- With the support of a facilitator, the groups will talk about the themes surrounding TB including stigma and empowerment
- The materials that we are going to use in the TB Clubs such as drawings and interactive jigsaws are guiding talking points
- To facilitate communication networks between our TB Club members and to be more in keeping with their personal experiences we will separate groups in to patients (two groups, one male and one female) and contacts
- The TB Clubs will last for approximately one hour
- We want to improve the TB Clubs and therefore will continuously be asking for both TB Club Member and facilitator feedback of what we did well and what we could do better

What is a TB Club and what are a TB Club's goals?

- TB Clubs are a space free of prejudice in which we can:
    - Share experiences
    - Express ourselves
    - Explore the theme of stigma
    - Learn to empower ourselves as TB-affected people
- TB Clubs are facilitated by facilitators and IPSYD team members but directed by the Club itself

What are the agreements of the TB Club?

- All of us in the TB Club have the right to speak
- All of us in the TB Club should have the opportunity to speak
- Nobody needs to speak if they do not wish to, it is not a requirement
- We must respect the opinions of all members of the TB Club (even if we were to have a difference of opinion)
- We must listen to all TB Club members when they speak and not interrupt
- What is said in the TB Club stays in the TB Club: it is completely confidential (of course, it would be great if the messages from the TB Club concerning stigma and empowerment were spread by TB Club members in the community but without revealing any personal details of other TB Club members)

Open questions about the Becerra drawings (pages 64-70) to start conversations and sharing of points of view:

- What can you see in the drawing? (describe)
- What do you think the people in the drawing (patient / family / health personnel) are feeling and or thinking?
- How do you feel when you see this drawing? Why do you feel like that?
- Is there anyone here who has had a similar experience or has known somebody who has had a similar experience? Would you share that experience with the group?
- Does anyone who was listening have any comments about what they've just heard from their friends in the TB Club or any other comments?

Content of TB Club Theme 1:

Introduction to stigma, empowerment and the TB Clubs at the end of the educational workshop

- **Title:** "What is Stigma, Empowerment, and TB Clubs?"
- **Time:** 10-15 minutes at the end of the first hour of the interactive community meetings before starting the hour of the TB Clubs
- **Goals: 3**
    1. Educate TB patients and their contacts to TB Self-Stigma & Empowerment
    2. Introduce TB Clubs – their purpose, history, effectiveness
    3. Motivate participation
- **Materials:**
    - Becerra drawings on powerpoint and copy in hand: #2, 13
- **Facilitator Presentation:**
- **"What is Stigma?":**
    - Stigma is:
        - the negative thoughts, behaviors, and judgments some people have towards others they think they are somehow "different" and therefore less valuable or less worthy human beings
            - in our case the "difference" is a health problem -- TB
        - stigma can cause feelings of exclusion, rejection, blame, shame, or worthlessness
    - Stigma can have many layers and affect each person in varied ways for many different reasons e.g.
        - being poor or unemployed, being a woman, not having much education, belonging to a certain group of people or being from a certain part of the country, or having an illness or disability
    - Stigma is a process
        - everyone learns how to stigmatize, from the time they are children
        - it is how we recognize the differences between people
        - it is considered a normal part of life and is not bad in itself
        - but when we say a person that is different is a bad person because of the difference then the process becomes harmful, damaging, and painful to others
    - **"What Causes Stigma?":**
    - stigma is caused by fear, misunderstanding, and misinformation
    - the most common cause is fear e.g.
        - fear of getting TB and it's harmful health effects

        - fear of missing work or being fired
        - fear of being rejected by family members and friends
        - fear of being isolated and excluded from social events
        - fear of being discovered to have TB and being stigmatized
- **"What are the Effects of Stigma?":**
    - stigma can affect each person in different ways for different reasons
    - it can cause feelings of sadness, loneliness, worthlessness, shame, guilt, and fear
    - these feelings cause stress, which causes more harmful health effects in addition to the TB
    - when people are afraid others will discover they have TB they often hide or conceal their TB to avoid stigma and the painful feelings that come with it
    - Concealing prevents them for getting diagnosed, receiving treatment, and becoming cured
- **"What are the different types of Stigma?":**
    - there are 3 types of stigma:
        1. enacted stigma
        2. anticipated stigma
        3. self-stigma
    - **Enacted Stigma:**
        - is the physical or verbal expression of stigma
        - in our case it is the comments or behaviors people make towards us because we have TB
        - it is a form of discrimination
        - it occurs in our homes, neighborhoods, markets, churches, at work, on TV, in the government, in the health care system
        - because so many people practice this form of stigma in so many ways and in so many places it is very hard to change – it can take many years to change people's attitudes and believes, and then not everyone will change
    - **Anticipated Stigma:**
        - is the type of stigma we think others will have towards us if they suspect or discover we have TB
        - sometimes we don't have to actually experience stigma – we just assume other people will have these stigma thoughts and feelings about us
        - we become fearful that others will discover we have TB and stigmatize or discriminate against us

        - to avoid these fears and painful feelings we Conceal our symptoms of TB and avoid getting diagnosed or receiving or completing treatment
    - **Self-Stigma:**
        - is the type of stigma we apply to ourselves
        - the influence of stigma can be so strong we may begin to believe the negative thoughts and attitudes we think others have about us are true
        - we may begin to think it is our own fault we have TB, or that we have done something wrong or bad to deserve TB
        - we may begin to believe we are less valuable human beings than others and not deserving of respect, dignity and rights like other people
        - when we accept and believe these untrue judgments about us this is called Self-Stigma
        - self-stigma occurs when we believe and accept the stigma & discrimination other people have toward us is true
        - because stigma is painful we may try to avoid the pain by isolating ourselves from other people, avoiding our friends and relatives, not participating in social events
        - this can make us feel more sad, lonely, depressed, and hopeless
        - we may feel abandoned by our family and friends, at the time we most need their help and support
        - self-stigma this is the most harmful of the 3 types of stigma
        - but self-stigma is also the type of stigma we ourselves can do something about, we can control, we can resist
        - when we learn to resist self-stigma we can resist all 3 types of stigma and become empowered
- **"What is being Empowered?":**
    - Empowerment is participating in activities that increase our ability to make changes in our lives
    - it is having the ability to recognize and solve problems that affect our lives
    - it is having a say in decisions that affect our lives and being listened to
    - it is being recognized and respected as human beings of worth and value, as equal citizens with equal rights
    - and being able to use our rights to improve our lives and the lives of our family, friends, and community
    - we can learn to become empowered and resist TB stigma by participating in TB Clubs

- **“What are TB Clubs?”:**
  - TB Clubs are special support groups for men and women with TB
  - they have been used successfully to resist TB stigma and help empower people with TB in other countries around the world for 20 years
  - they are a safe, supportive place where we can share our thoughts, feelings, experiences, and concerns without fear and without being judged
  - a place where we can learn more about self-stigma and empowerment, and practice the skills to resist stigma
  - a place where we can learn to:
    - feel better about ourselves
    - stand-up for ourselves
    - understand why we feel the way we do
    - understand why people behave the way they do towards us
    - make living with TB easier
    - complete TB treatment and become cured

Contents of the TB Club Theme 2: Personal experience of stigma

- **Title:** "How has TB Stigma affected our lives?"
- **Time:** 30 minutes
- **Goal:** Help people identify the different ways they have been affected by TB stigma and how TB stigma makes them feel
- **Materials:**
    - Becerra drawings: #1, 2, 3, 4, 11, 12, 13
        - may use HC staff and children drawings if theme arises spontaneously from group
    - flipchart/stand/markers
    - TB Club Agreement
- **Process:**
    - Facilitator: Reiterates the welcome and opening of the TB Club
    - Facilitator: reviews TB Club Agreement
    - Facilitator: can decide to put relaxing instrumental music on in the background as a relaxation technique
    - Facilitator: to break the ice and get people interacting, the facilitator may want to do an activity with the group (Activity Materials 1-3)
    - Club members choose a drawing that shows a past or current event that they or a family member or a friend may have experienced
    - Club members think quietly to themselves for several minutes about how this event made or makes them or a family member or a friend feel
    - Facilitator acknowledges how hard it may be to share painful experiences and feelings, that it requires trust in ourselves and each other, and that through this process we can learn how to overcome stigma
- **Questions/Discussion:**
    - Facilitator asks if any Club member would like to share their drawing and how their own experience is similar in some way to the drawing

        - if there are no volunteers Facilitator may lead by selecting a drawing and sharing their personal experience and feelings associated with that drawing
    - Facilitator should be certain Club members talk about their feelings associated with their experience, not just the facts of the experience, by asking when necessary: “how did this make you feel”?
    - Facilitator gives every Club member an opportunity to share
- **Closing Messages:**
    - Facilitator asks group “what important things have we learned from our experiences and feelings?”
    - Facilitator writes key summary words on flipchart
    - Facilitator says:
        - “these stories help us understand how some people may judge and condemn people with TB” or blame people for having TB as if it were their own fault”
        - “these stories also shows us how it feels to be stigmatized -- it can be painful and make us feel like outcasts, strangers, unwanted, unnoticed, as if we are not human anymore”
        - “feeling stigmatized can hurt our health in addition to what the illness causes”
        - “but we can learn to overcome self-stigma with Empowerment which we will talk about in the second half hour”
- **Facilitator offers to speak with anyone who would like to talk more during, the sign-out session**

Contents of TB Club Theme 3: Empowerment

- **Title:** "How can we overcome Stigma?"
- **Time:** 30 minutes
- **Goal:** Help people identify how to respond to stigma though individual action
- **Materials:**
    - Becerra drawings: #1, 2, 3, 4, 5, 11, 12, 13
        - may use HC staff and children drawings if theme arises spontaneously from group
    - flipchart/stand/markers
    - TB Club Agreement
- **Process:**
    - There are many different ways to facilitate a TB club, the following listed are certain examples
    - The facilitator can decide to perform an activity to break the ice and get people moving (Document 1-3)
    - The facilitator can put some relaxing instrumental music in the background to relax the participants
    - Facilitator reviews TB Club Agreement
    - Facilitator prepares flipchart page divided into 3 columns labeled "Empowerment", "Rights", "Responsibilities/Duties"

- **Questions/Discussion:**
    - Facilitator gives every Club member an opportunity to share
    - Facilitator asks Club members to think about and share their ideas about "Empowerment" and writes them on flipchart e.g.
        - "standing up for your rights"
        - "taking responsibility for your health and/or life"
        - "getting training or education"
        - "being self-reliant -- standing on your own 2 feet"
        - "being self-confident"
        - "earning money"
        - "working together to support each other/change things"
    - Facilitator asks Club members to think about and share their ideas about "Rights" and writes them on flipchart e.g.
        - the right to be treated with respect and dignity
        - the right to participate (have a say) in decisions that affect our lives
        - the right to not be discriminated against in any form because we have TB
            - at home:
                - the right to be with our family and friends
                - the right not to be evicted from our house by our family or landlord because we have TB

- at work: the right to work and not to lose our job because we have TB
- in the community:
  - the right to buy and sell food or goods
  - the right to attend school, church, or social events
  - the right to organize and attend support groups
  - right to the same quality health care and information as others receive
  - the right to participate (have a say) in decisions about our health care and TB treatment, ask questions, get answers

- Facilitator asks Club members to think of and share their ideas about "Responsibilities/Duties" and writes them on flipchart e.g.
  - the duty to protect our families, friends, and the community from getting TB
  - the duty to take all our medicines, complete TB treatment, become cured
  - the duty to help other people who may have TB become diagnosed, receive and complete treatment, become cured
  - the duty not to stigmatize/discriminate against others
- Facilitator asks Club members to think about and share their ideas about what kind of actions they might take to "Empower themselves" and writes them on flipchart e.g.
  - do not self-stigmatize e.g.
    - resist accepting and believing the negative stigma thoughts others have towards us because we have TB e.g.
      - it is not our fault we have TB, we did not want to get TB, we have done nothing wrong to deserve having TB
    - believe that we are good, valuable people, worthy of love and deserving of the same rights others have
    - remember -- "we are good people with a bad illness, not bad people because we have TB"
  - talk with and educate other people about TB stigma/discrimination e.g.
    - family members, friends, neighbors, co-workers, health care workers
    - explain to others what stigma is, how it hurts people, how it prevents people from receiving treatment and becoming cured, how it is a form of discrimination
    - correct myths & misinformation about TB when you hear people repeating it
    - talk openly to others about your knowledge, experience, and feelings about TB
  - support our fellow Club members and any TB patient in fighting against TB stigma, completing TB treatment, and becoming cured e.g.
    - visit TB patients in their homes

        - help TB patients get to healthpost visits and take their medicines daily
        - encourage to speak openly with healthpost doctors, nurses, and TB Facilitators about questions they have about their TB, their treatment or medicines, and any bad side effects they are having from the medicines
    - speak out against TB stigma/discrimination when we see or feel we or others are being stigmatized/discriminated against because of TB e.g.
        - stand up for our rights when we think they are being denied or not being considered
        - be a role model: watch our own thoughts and words and don't stigmatize others

- **Closing Messages:**
    - Facilitator asks group "what important things have we learned from our experiences and feelings?"
    - Facilitator writes key summary words on flipchart e.g.
        - do not self-stigmatize: resist, believe, remember
        - educate: explain, correct, talk openly
        - support: visit, help, encourage
        - speak-out, stand-up, be a role model
    - To finish: The facilitator can decide to finish with handshakes or "abrazotherapy" (essentially, shaking hands or hugging each member as comfortable / appropriate)
    - Facilitator: can reinforce the session asking the Club to update or exchange numbers for people who wish to continue their conversations. The facilitator offers to speak with anyone who would like to talk more during, the sign-out session

SUPPORT MATERIAL 1

ACTIVITY: HOP (3-4 minutes)

OBJECTIVE:
Integrate and motivate the members to improve communication and maintain the attention of all the members participating, creating a favourable and friendly environment.

GROUP SIZE:
The number of members participating is not specific. This activity can be performed with all types of groups (children, adolescents, and adults).

TIME REQUIRED:
3 minutes approximately although this depends on the number participating in the activity

MATERIAL:
None specific.

PLACE:
This activity can be performed as much in open as in closed spaces, without requiring a large space.

DEVELOPING THE ACTIVITY:
The participants are asked to listen to objects that belong to a certain group (number, fruit, colours, country or group). People raise their hands if they hear an object that belongs to the group and say “hop”. If they get it right then they will accumulate points and if they get it wrong then they will accumulate negative points and the facilitator can make a pretend “punishment” for the losers or round of applause for the winners.

SUPPORT MATERIAL 2

ACTIVITY: THE RAFTS (3-4 minutes)

OBJECTIVE:
Integrate and motivate the members to improve communication and maintain the attention of all the members participating, looking for leaders and creating a favourable and friendly environment.

GROUP SIZE:
The number of members participating is not specific. This activity can be performed with all types of groups (children, adolescents, and adults).

TIME REQUIRED:
3 minutes approximately although this depends on the number participating in the activity

MATERIAL:
None specific.

PLACE:
This activity can be performed as much in open as in closed spaces, without requiring a large space.

DEVELOPMENT OF ACTIVITY:
The participants are informed: Let's imagine that we're in the sea and only those castaways that are in boats of 2 are going to be saved…followed by 3, then 4, 5, 6 and so on successively (or backwards, mixed etc).

SUPPORT MATERIAL 3

ACTIVITY: HEAD TO HEAD (3-4 minutes)

OBJECTIVE:
Integrate and motivate the members to facilitate interaction and work in groups

GROUP SIZE:
The number of members participating is not specific. This activity can be performed with all types of groups (children, adolescents, and adults).

TIME REQUIRED:
3 minutes approximately although this depends on the number participating in the activity

MATERIAL:
None specific.

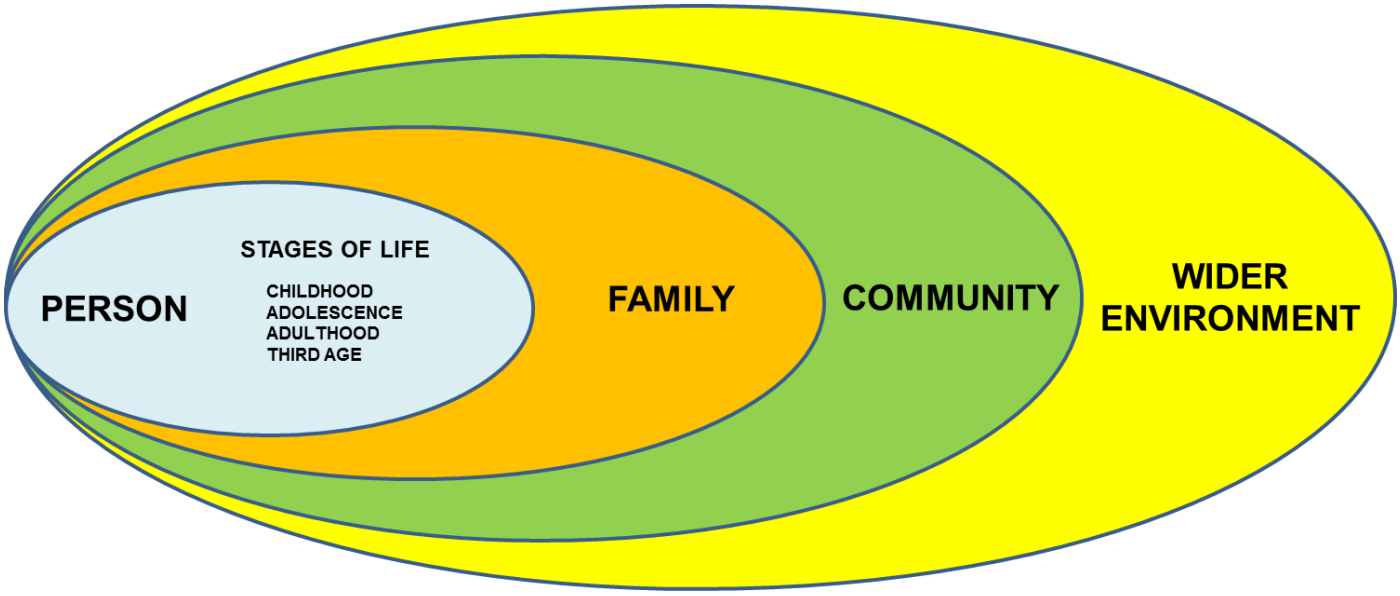
PLACE:
This activity can be performed as much in open as in closed spaces, without requiring a large space.

DEVELOPMENT OF ACTIVITY: The facilitator will ask the participants to form pairs and then motivating them by joining body parts. Instructions: Nose to nose, eye to eye, elbow to elbow, cheek to cheek, foot to foot, head to toe, hand to hand, arm to arm, belly to belly, back to back, hand to ear etc
¡Make your own connections! You can make variations on a theme.

FRANK FERNANDEZ
PSICÓLOGO

SUPPORT MATERIAL 4

Psychological concept: Stages and levels of life



Let's consider 3 ways in which people deal with the issues facing them:

1) Think responds to the question What?
What thoughts do I have (as a person), what do my family and those close to me think (family), what do others around me at work, in the street, in church, think (community), what is the general feeling "out there" (wider environment)
2) Feel responds to the question How?
What we feel about ourselves, personal and internalized emotions (person), what feelings and emotions arise at home that may help or hinder the fight against stigma (family) how do people in the community around me manage their emotions and feelings (community), what is the general feeling "out there" (wider environment)
3) Act responds to the question When? Where?
When and where can I act against stigma (person), when and where would my family and household challenge stigma (family) where and when in the community and in the general population (community and wider environment)

The Becerra drawings - explanation & points for conversation

DRAWINGS 1-12: STIGMA (FIRST PART OF THE TB CLUB)

Drawing 1:

Usefulness: This drawing shows a lady that has her own business, an eatery. She is or was a TB patient. The drawing illustrates both stigma and loss of household income.

¿What can we see? The lady is trying to sell her food to a pair of young men who appear to be rejecting her offer and laughing at her. We may presume that this maltreatment relates to ignorance and enacted stigma by the men against the lady regarding her diagnosis.

Points for conversation: Has anyone in the Club experienced a similar situation such as loss of work, reduction of income? This may lead to conversations concerning human rights, and how to combat TB costs (including cash transfers).

Drawing 2:

Usefulness: This drawing encompasses stigma in its various forms and is great to start conversation and to introduce the theme of stigma. The drawing is the opposite of drawing 13 that shows empowerment, like a "before/after" TB.

¿What can we see? A young man with TB who appears sad with many current issues passing through his mind: loss of work and family, disapproval from a respected figure, and feelings of isolation.

Points for conversation: What can people see in the picture? Why have people treated the young man like this? Is there anyone in the Club who can relate to any one of the thoughts passing through this man's head?

Drawing 3:

Usefulness: This drawing is highly important and has a high educational value because it can be interpreted in various ways: TB transmission on public transport and beyond, active case-finding, and stigma against or logical avoidance of people with a chronic cough

¿What can we see? A man coughing on public transport. The coaster / bus is overfull with many people of different ages and with all Windows closed that increases the risk of TB transmission. The young man has noticed the other gentleman's cough and seems surprise and scared.

Points for conversation: How is TB transmitted? What can we do to decrease the risk of transmission seen in the drawing? What advice would you give to the coughing chap?

Drawing 4:

Usefulness: The value of this drawing is to focus on the stigma that exists in the home. It concerns relationships within the family, TB transmission and nutrition. In this way, it is similar to drawing 2.
What can we see? A TB patient is sat apart from his family at home during dinner. He still has a cough.
Points for conversation: Is there anyone in the Club who can identify with what is happening in the drawing? What can we do at home to reduce the risk of TB transmission? At home, how can we avoid our relative with TB feeling stigmatized? Does TB transmission risk stay the same throughout treatment?

Drawing 5:

Usefulness: This drawing is meant to identify with younger people in school or college. With respect to adolescents, it also refers to the stigma that relates to being a TB contact. *What can we see?* A pupil is sitting apart in the corner of his class. The other students are laughing at him and even the teacher appears annoyed by his presence. The pupil is isolated from class and may be a TB patient or contact.
Points for conversation: (Try to ensure that the younger people of the group have a chance to talk) Is there anyone who identifies with what they see? Is what's going on in the picture fair? How can we prevent this type of maltreatment in schools and colleges?

Drawing 6:

Usefulness: This drawing is centred more around females. It describes distinct fears: risk of transmission to children, relatives and partners, and opinions of friends/community
¿What can we see? A lady is considering all her fears about TB: infecting her children, rejection by her husband, gossiping of friends. From her point of view, having TB means that she is going to ruin other people's lives.
Points for conversation: (Try to ensure that the women of the group speak) How can we reduce the risk of infecting children and how are we going to check that they don't have TB? Should we explain about TB to children? How does TB affect relationships between a couple?

Drawing 7:

Usefulness: This drawing is about the stigma that we come across even in healthposts. So, it's important that no TB program health personnel are present in the Clubs so patients can freely express themselves.

¿What can we see? The healthcare professional is signalling (without looking) that the patient should keep away from her and leave his sample. The patient appears shamefaced and upset. Ironically, in the background a poster can be seen that talks of the rights of TB patients: perhaps the healthcare professional should take note!

Points for Conversation: Can someone share their experience of the healthpost (good/bad)? ¿What are the healthposts' responsibilities and the patient's rights?

Drawing 8:

Usefulness: This drawing deals with active case finding and how couples' relationships may be affected by TB.

¿What can we see? A man that probably has TB who has a severe cough. His partner seems to realise that perhaps he has TB. Due to that, she asks him to keep away from her. He covers his mouth and looks ashamed. It seems unclear whether she suggests to him to go and get checked to rule out TB or not.

Points for conversation: How are relationships between couples affected by TB? What are the different ways in which someone can react to finding out that their partner has TB? How can we face and resolve such problems like TB as a couple?

Drawing 9:

Usefulness: This drawing deals with the way in which TB can affect young people in school or college. It goes together well with Drawing 5, especially in a group consisting mainly of young people / adolescents.

¿What can we see? In the foreground, a group of boys is playing football, happily. In the middle, there is a boy with a cough. It looks like the group to the right are making fun of the coughing boy.

Points for conversation: (Try to ensure that the younger people in the group talk) Is the stigma that we see in the picture a form of bullying? How can we confront the problem of stigma in schools, especially relating to TB?

Drawing 10:

Usefulness: This drawing deals with the stigma that can be found in the health posts. So, it's important that there are no TB program personnel in the Clubs in order that the TB patients can express themselves freely. This drawing relates very well with drawing 7.

¿What can we see? The healthcare professional is covering her mouth and turning her back on the patients in the waiting room. Ironically, in the background there is a poster concerning the clinical journey of TB patients: the healthcare professional should take note!

Points for conversation: Can someone tell us about their experience in the healthpost (good/bad)? What are the healthpost's responsibilities and the patient's rights?

Drawing 11

Usefulness: This is an emotive example of the negative effects of TB and stigma as much from healthpost personnel as in the community. Use it cautiously.

¿What can we see? We can see a family taking their relative (who appears to have TB) to the healthpost in a wheelbarrow. We may imagine that the patient's clinical episode is severe given his weakness. Also, the family appears poor given the mode of transporting their relative. Sadly, members of the public and the guard are watching and gossiping about the scene.

Points for conversation: How can we avoid a scene such as this? (prompt diagnosis, active case finding etc)?

Drawing 12

Usefulness: Stigma even exists between patients. Sometimes people with TB can be differentiated as they have to use a different entrance at the healthpost or give a sputum simple etc. The drawing also touches on the issue of confidentiality.

¿What can we see? A division can be seen between the 3 patients on the right and the patient on the left with suspected TB. The ladies are whispering about her and the man seems to hear by chance about the possible diagnosis. The TB patient looks sad and ashamed.

Points for conversation: Doe this situation really occur in the healthposts? Why? What could we as TB affected people and the healthpost do to overcome this problem?

DRAWINGS 13-18: EMPOWERMENT (SECOND PART OF THE TB CLUB)

Drawing 13

Usefulness: This drawing, the opposite of drawing 2, is essential with respect to the empowerment section. In it we find the positive aspectes relating to adherence and cure of TB. The drawing encompasses all the things which our socioeconomic intervention aims to combat.

¿What can we see? The same young man, contrary to what we saw in drawing 2, appears happy: he is thinking about his cure, finding/continuing work, having loving family, and that now he is a facilitator supporting others (CRUCIAL POINT FOR CONVERSATION).

Points for conversation: How did this young man's life become positive? How can we do the same?

Drawing 14

Usefulness: This drawing is the opposite to drawing 8. We can also appreciate how important support from people at home is (be it wife, husband, relative or friend). Besides this, we can also note the importance of active case finding to prevent TB (the wife in this case has less risk of getting infected and her husband a greater chance of cure)

¿What can we see? The lady is worried about her husband's or relative's cough. So, they go together to the health post to promptly get diagnosed and start treatment!

Points for conversation: ¿What do we do if a relative, friend, or other person has a cough? What is active case-finding and how can it benefit a facilitator by doing it?

Drawing 15

Usefulness: This drawing captures empowerment. It is an example of leaving behind self-stigma and learning to respect oneself.

¿What can we see? A confident woman says to other women she knows that she is going to take her anti-TB treatment. While a couple of the women seem shocked, the lady on the left seems calm and free of prejudice.

Points for conversation: Is having TB our fault? Is there any one amongst us who wants to have TB? When do TB patients stop being contagious? Would any of you speak so freely as this lady? If so/not, why?

Drawing 16

Usefulness: This drawing would be most usefully employed towards the end of the TB Club. It encompasses the whole of the positive process of the TB Club: sharing, belonging, and mutual support.

¿What can we see? There is a TB Club functioning well. Its members are interacting and sharing their experiences and listening actively. In the background, we can appreciate the TB Club agreements and the empowerment solutions.

Points for conversation: Which parts of the TB Club have been the most informative / useful for you? What have we learnt in today's TB Club? What are we going to do if we confront stigma in the Street / healthpost / home?

Drawing 17

Usefulness: This drawing illustrates the part of our intervention in which patients can become a facilitator and support other patients recently diagnosed. Active case finding is also a crucial part to this process.

¿What can we see? A facilitator / member of the IPSYD team is sharing her positive experience in order to empower and encourage other new patients.

Points of conversation: What advice would you give to a patient newly diagnosed with TB today? As patients and ex-patients or people affected by TB, what experiences have we had that might be useful to share?

Drawing 18

Usefulness: This picture encompasses all the support necessary to empower us to fight against stigma and get cured. The sources of support are various and we must not forget that there is always someone on which we can count. The patients can count on us.

¿What can we see? Active case finding by partner/relative, friends offering support, the staff of the healthpost and the patient working in conjunction to cure TB, and the avoidance of transmitting TB at home.

Points for conversation: Who can we personally count on to support us? ¿Before our sputum test become negative, how can we avoid transmitting TB in the first weeks of treatment?

Strategies for using the Becerra drawings

As we have seen, the drawings can be grouped according to the major themes on which they are focused. This may be of great value as, remember, we will be dividing TB Clubs into male patients, female patients, and contacts (both sexes) according to their differing experiences. It is also worthwhile remembering that the age of members of the TB Club will vary a lot from very young or adolescent to elderly patients.

If there is anyone in the Club that has already attended many interactive community meetings, then: a) they can help alot regarding the dynamic of the group and b) they can be specifically asked to choose a drawing about which they have not spoken or a drawing about which they have talked previously but now their opinion / experience has changed and they may want to revisit the theme.

Drawings about patients

- Female patients – Number 6 & 15
- Male patients – Numbers 8 & 14
- Patients of either sex – Numbers 1, 3, 4, 7, 10 & 11

Drawings about stigma related to the healthpost / healthcare facility

- Numbers 7, 10, and 11

Before and after / juxtaposing drawings

- Number 2 with 13
- Number 6 with 15
- Number 8 with 14

Drawings focusing on contacts

- Numbers 3, 4, 5, 9, and 12

Drawings focusing on children

- Numbers 5 and 9

Drawings concerning empowerment

- Numbers 13 to 18

NB: The Becerra drawings were adapted from original drawings from the resource "Understanding and challenging TB stigma: a toolkit for action" from the Zambart project. This resource can be accessed and is freely available to download from http://targets.lshtm.ac.uk/resources/Publications/TB_and_Stigma_Eng2.pdf

Document 9: Feedback form for interactive community meetings

IPSYD PROJECT INTERACTIVE COMMUNITY MEETING FEEDBACK FORM

v7/TW/20140711

Date of interactive community meeting:_____ Healthpost of interactive community meeting:_____

1. How many IPSYD interactive community meetings have you participated including today's meeting? (circle your answer please)	1	2	3	4	5	6	More than 6

2. How would you describe your experience at the IPSYD interactive community meetings with respect to the following….?	Very good	Good	Neither good nor bad / don't know	Bad	Very bad
					
2a. Information prior to the meeting					
2b. Reading material provided					
2c. The meeting's overall organisation					
2d. The attitude of our staff					
2e. The activities of the educational workshop					
2f. The activities of the TB Club					
2g. The reimbursement for transport costs					
2h. The refreshment provided					

3. Would you recommend to another TB-affected family that they attend the IPSYD interactive community meetings? (circle your answer please)	Yes 	No 	Don't know 
4. If you didn't receive an economic incentive, would you still attend an IPSYD interactive community meeting anyway? (circle your answer please)	Yes 	No 	Don't know 
5. Will you continue to attend the IPSYD interactive community meetings? (circle your answer please)	Yes 	No 	Don't know 
6. Do you think you will practice outside of the IPSYD interactive community meeting what you learnt today? (circle your answer please)	Yes 	No 	Don't know 

7. What were some positive aspects of this IPSYD interactive community meeting?	
8. What were some negative aspects of this IPSYD interactive community meeting?	
9. What would you recommend to us to improve the IPSYD interactive community meetings?	

MANY THANKS FOR PARTICIPATING IN THIS IPSYD INTERACTIVE COMMUNITY MEETING, PLEASE NOW APPROACH ONE OF OUR STAFF WHO WILL AWARD YOU A CERTIFICATE OF ATTENDANCE. WE LOOK FORWARD TO SEEING YOU AGAIN THE NEXT TIME!

Document 10: DOUBLE incentives card

DOUBLE INCENTIVES CARD

TW;v18;20140711

	Condition	What you and your household members are required to do to receive a DOUBLE incentive	What you will receive in Soles	What the facilitator will receive in Soles	What the health post will receive	Date condition completed in the field	Signature of responsible field team member	Date of double digitation of completion of condition in PRISMA	Signature of administrator completing double digitation	Date bank transfer made (virtually)	Signature of staff member reponsible for transfer	Bank transfer code / number
Double incentive	SPUTUM SAMPLE	Give a sputum sample prior to starting treatment and complete the questionnaire with the research nurse. The national TB program must have registered you in your health posts TB patient register.	40	10	Materials for work undertaken by the TB program equal to an amount of 20 soles					NA	NA	NA
	HOME VISIT	In the first week following recruitment to our project, allow us to visit your house, complete the questionnaire (if necessary), and list all the people who live in the same house as you	50	10	NA							
	COMMUNITY MEETINGS	By 3 months following recruitment, you and all (100%) of the people that we listed as living in the same house as you attend at least 1 IPSYD community meeting	100	20	NA							
	MEDICAL APPOINTMENT OR SPUTUM SAMPLE WITH RESULT AND START OF MEDICINE IF NECESSARY	All (100%) of the people registeredas living in the same house as you attend their medical appointment or give a sputum sample (that has a result) to rule out TB. Those people who need to take medicine to prevent TB (chemoprophylaxis) or TB treatment, must have started it. Contacts who do not need to take such treatment must be confirmed in the medical treatment cards	150	30	NA							
	ADHERENCE TO TREATMENT	SENSITIVE/NON-MDR PATIENTS (INCLUDING THOSE WITH HIV), DURING THE FIRST 50 DOSES OF TREATMENT: each 25 doses (approximately each month) of TB treatment taken missing no more than 2 doses	50	10	NA							
		MDR PATIENTS, DURING THE FIRST 150 DOSES OF TREATMENT (APPROXIMATELY 6 MONTHS): each 25 doses (approximately each month) of TB treatment taken missing no more than 2 doses	50	10	NA							
		SENSITIVE/NON-MDR PATIENTS (INCLUDING THOSE WITH HIV), AFTER THE FIRST 50 DOSES OF TREATMENT TO THE END OF TREATMENT: each 24 doses (approximately two months) of TB treatment taken missing no more than 1 dose	50	10	NA							
		MDR PATIENTS, AFTER THE FIRST 150 DOSES OF TREATMENT UNTIL THE END OF TREATMENT: each 50 doses (approximately two month) of TB treatment taken missing no more than 2 doses	50	10	NA							
	COMPLETION OF CHEMOTHERAPY AND TB TREATMENT	You complete your TB treatment and all (100%) of the people who live with you who started chemoprophylaxis to prevent TB, finish their chemoprophylaxis	100	20	NA							

Document 11: SIMPLE incentives card

	Condition	What you and your household members are required to do to receive a SIMPLE incentive	What you will receive in Soles	What the facilitator will receive in Soles	What the health post will receive	Date condition completed in the field	Signature of responsible field team member	Date of double digitation of completion of condition in PRISMA	Signature of administrator completing double digitation	Date bank transfer made (virtually)	Signature of staff member reponsible for transfer	Bank transfer code / number
Simple incentive	SPUTUM SAMPLE	Give a sputum sample as soon as possible after starting treatment and complete the questionnaire with the research nurse. The national TB program must have registered you in your health posts TB patient register.	20	5	Materials for work undertaken by the TB program equal to an amount of 20 soles					NA	NA	NA
	HOME VISIT	In the first month following recruitment to our project,allow us to visit your house, complete the questionnaire (if necessary), and list all the people who live in the same house as you	25	5	NA							
	COMMUNITY MEETINGS	By 5 months following recruitment, you and all (100%) of the people that we listed as living in the same house as you attend at least 1 IPSYD community meeting	50	10	NA							
	MEDICAL APPOINTMENT OR SPUTUM SAMPLE WITH RESULT AND START OF MEDICINE IF NECESSARY	>80% of the people registered to live in the same house as you attend their medical appointment or give a sputum sample (which has a result) to rule out TB. Those people who need to take medicine to prevent TB (chemoprophylaxis) or TB treatment, must have started it. Contacts who do not need to take such treatment must be confirmed in the medical treatment cards	75	15	NA							
	ADHERENCE TO TREATMENT	SENSITIVE/NON-MDR PATIENTS (INCLUDING PEOPLE WITH HIV), DURING THE FIRST 50 DOSES OF TREATMENT: each 25 doses (approximately each month) of TB treatment taken missing equal to or more than 3 doses	25	5	NA							
		MDR PATIENTS, DURING THE FIRST 150 DOSES OF TREATMENT (APPROXIMATELY 6 MONTHS): each 25 doses (approximately each month) of TB treatment taken missing equal to or more than 3 doses	25	5	NA							
		SENSITIVE/NON-MDR PATIENTS (INCLUDING PEOPLE WITH HIV), AFTER THE FIRST 50 DOSES OF TREATMENT TO END OF TREATMENT: each 24 doses (approximately two months) of TB treatment taken missing equal to or more than 2 doses	25	5	NA							
		MDR PATIENTS, AFTER THE FIRST 150 DOSES OF TREATMENT UNTIL THE END OF TREATMENT: each 50 doses (approximately two month) of TB treatment taken missing equal to or more than 3 doses	25	5	NA							
	COMPLETION OF CHEMOTHERAPY AND TB TREATMENT	You complete your treatment and 80% or more of the people who live with you who started chemoprophylaxis to prevent TB, finish their chemoprophylaxis	50	10	NA							

Document 12: Reading material for patients opening their bank accounts

BANK ACCOUNTS FOR IPSYD CONDITIONAL CASH TRANSFERS

In order to receive your economic incentives following successful completion of TB program and IPSYD project goals by you and your family, we need you to have a bank account ("Zero Maintenance") with MI BANCO. This process will make the cash transfers more secure: you can be sure they'll arrive!

REQUIREMENTS FOR OPENING A SAVINGS ACCOUNT

1. Have a valid and current ID document (with a copy) and be 16 years old or more
2. We will accompany you to attend the bank to open the account in person
3. You don't have to pay or deposit anything to open your bank account

IMPORTANT:

1. It is advisable to practice your signature from your ID document at home as it has to match with your signature in the bank. Also, please think about what your 4 number secret code might be for your bank card might be (it's the code you'll need to take money out of cash machines). **IT'S ADVISABLE TO NEVER SHOW THE SECRET CODE OF YOU CARD TO ANYONE.**
2. If you aren't able to sign your name you can still have a bank account. All that is needed is your digital fingerprint, 2 color photographs of you and a person to accompany you. The **accompanying person** cannot be a family member but can be a trusted friend or neighbour. They will need to accompany you each time you withdraw money

STEPS TO OPEN YOUR BANK ACCOUNT

1. Go to the bank with your ID card and get a ticket for the tellers. This ticket has a number that will appear on the screens above the bank counters indicating the next number in the queue. If this number is yours, approach the window whose number is shown next to yours and they will attend to you

2. When its your turn and you approach the window, take with you your ID card and ask to open a "zero maintenance savings account"

3. The bank staff will take a copy of your ID card and will give you some documents to sign (after eading thoroughly), then they will give you your bank card and they will ask you to put in your 4 digit secret code. Finally, they will give you a sheet of paper showing your savings account number (we will require a copy of this to make the payments to your account and you can keep the original).

Vs 11ago14

INCENTIVES / BENEFITS

You can withdraw money from Mi Banco cash machiness, Mi Banco branches teller windows and smaller Mi Banco agencies without any additional fees. We want to let you know that whenever we make the appropriate transfers there is a delay of approximately 3 working days until the money reaches your account. However, please remember that **YOU WILL ONLY RECEIVE THE CASH TRANSFERS IF YOU COMPLETE THE AIMS DETAILED IN YOUR INCENTIVES CARD**

YOUR SAVINGS ACCOUNT IS NOT ONLY FOR THE IPSYD PROJECT INCENTIVES

You can use the account to save your own money and also that of other people (friends, relatives) if they deposit it in your account. Your savings account will only stop working and be closed if you don't use it at all for over a year

MI BANCO Branches

Ventanilla: Av Principal Mz C Lte 13 Zona Comercial
Opening Hours: From Monday to Friday 9:00am to 6:00pm, Saturdays 9:00am to 12:00pm

Callao:
Callao 1: Av Elmer Faucett 306-310-314 Urb La Colonial
Callao 2: Av Saenz Peña N° 924
Callao 3: Av Argentina 3093-2557 MINKA
Opening Hours: From Monday to Friday 9:00am to 6:00pm, Saturdays 9:00am to 12:00pm

DATE OF APPOINTMENT:.....TIME:.....

BRANCH:.....

Vs 5mayo14

Document 13: IPSYD Facilitator Training Process

IPSYD Team Facilitators: Role, recruitment, and selection

Who are facilitators?

- A facilitator is a person, normally a patient or ex-patient, who has a vocation to support families affected by TB.
- The term "facilitator" is equivalent to "promoter".

What does a facilitator do?

- The specific role of a facilitator is to support families affected by TB to complete the TB program goals and receive the corresponding conditional cash transfers of the IPSYD project. This is achieved through meeting with patients/contacts in the healthpost, home visits, and leading interactive community meetings (educational workshops and TB clubs)
- Facilitators will only work with "supported" patients and their families

How are facilitators selected?

- Facilitators are selected by the adequate completion of their own conditions with respect to the TB program. This means that a patients who doesn't take their own medicine and whose contacts don't attend the healthpost for their TB screening will not be invited to train to be a facilitator
- Those selected to become facilitators will also have shown good interpersonal and communication skills
- Beside completing their own conditions, a facilitator will be a person with a strong commitment to and vocation towards TB patients and their families
- A facilitator will need to have sufficient availability to appropriately complete their important role

How are facilitators trained?

- The IPSYD team has developed a facilitator training plan. Within the plan, apart from practical sessions observing and running a home visit and interactive community meeting, every month we offer a half-day training day that consists of:
    - General learning concerning TB: the bacteria, transmission, treatment, contacts
    - Explanation of the IPSYD project and conditional cash transfers
    - Explanation of the work of the research nurses, research nurse assistants, and facilitators of the IPSYD project
    - Educational and psychological workshop: working in teams, leadership, and interaction/communication
- One can only become a facilitator after attending a half-day training session, two home visits and two interactive community meetings (the first as observers and the second as active members/leaders of the IPSYD team)

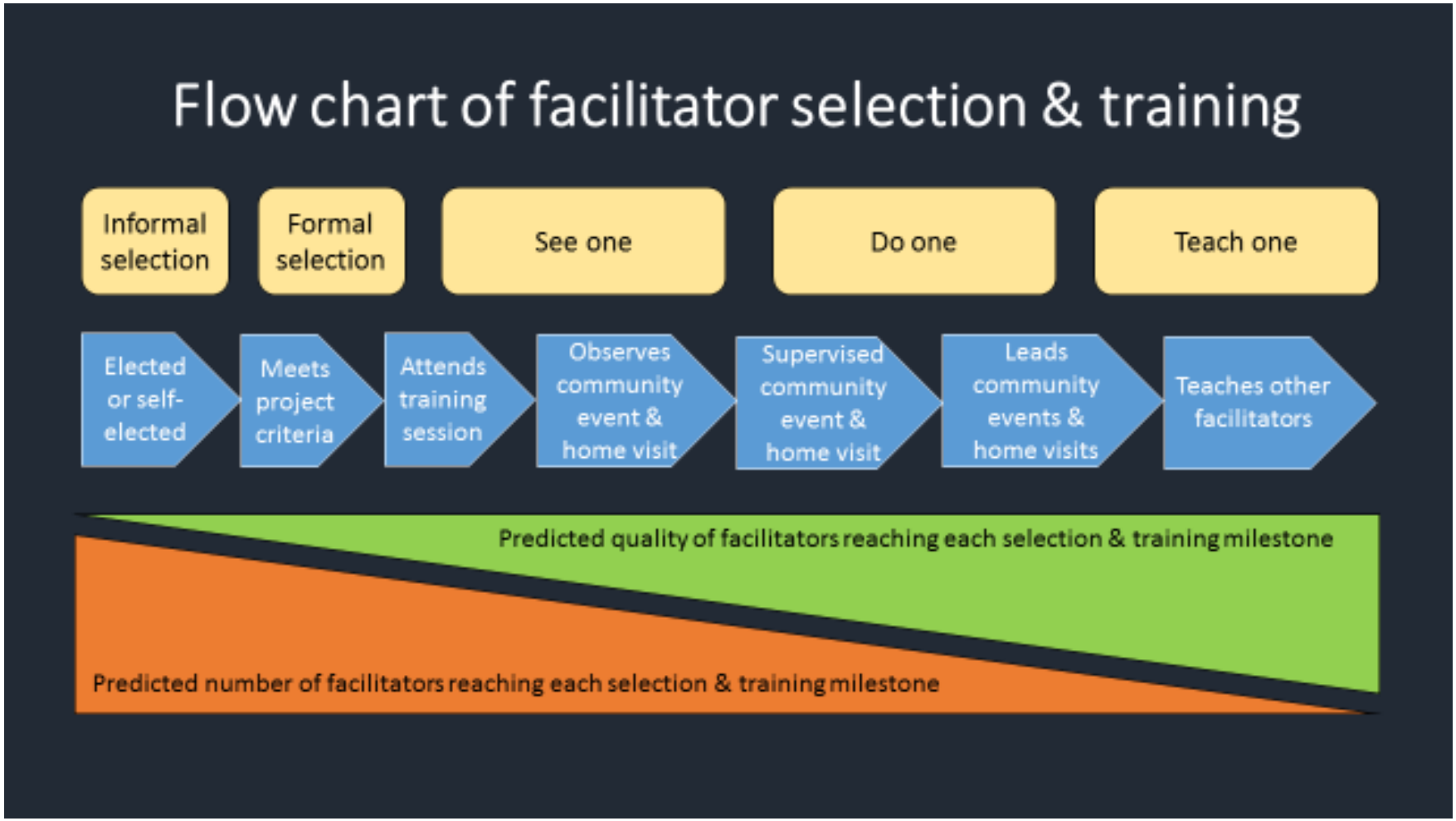
What type of reimbursement/payment will a facilitator receive for their work?

- Each time that a patient completes a condition and receives a bank transfer, the corresponding facilitator (i.e. who supports that family) also receives a bank transfer (of approximately 20% the value of that the patient receives, Document 15)
- A facilitator can support more than one family at the same time in their community
- For the main part, facilitators are going to work in the same community in which they live. Due to this, facilitators will not normally receive a reimbursement for their transport given that it is hoped they will be within walking distance of their patients' houses

What are the criteria by which a facilitator will not be able to continue working with the IPSYD team?

- A facilitator will be unable to continue their work with the IPSYD team when they are unable to adequately carry out their role (Figure):
    - Anonymous feedback of their patients reveals low output or a lack of courtesy
    - A facilitator cannot maintain confidentiality of their patients
    - In cases of dishonesty, robbery, or falsification of reports or documents
    - In cases of the facilitator threatening behaviour or bribery of the patients and/or their family

Flow Chart of Facilitator Training



Specific roles of facilitators

Goal	Method	Desired result
Support and coordinate with the IPSYD research nurses and research nurse technicians to carry out day-to-day project activities	• To have frequent meetings in the healthpost • To undertake household visits to families failing to meet their conditions outside of those realised by the nurses • Organise and undertake interactive community meetings in their community • Collect sputum samples during the prevalence survey	• Expand the reach of the IPSYD team • Support patients and their families to comply with the TB program norms and receive their incentives • Measure the impact of our intervention with respect to the TB rates in supported versus comparison communities
Help patients and their families to identify and express emotions, needs, desires and concerns	• Facilitators can share their personal experiences: benefits, difficulties, advice to achieve success • Lead the TB Clubs using activities developed by the IPSYD team	• Active participation by all participants in the TB Club and Educational Workshop • TB Club that functions independently (even post IPSYD intervention) • Recruitment of other facilitators
Support patients and their contacts to adhere to the TB program norms of adherence and successful completion of treatment and adherence	• Leadership of TB Clubs • Home visits • Meetings in the healthpost • Education and companionship	• Increase adherence and treatment completion • Increase empowerment
Support patients and their families to reduce the personal barriers with which to meet the challenge of adherence and treatment completion	• To assist during TB Club so that the participants can identify and express any emotions and beliefs that might prevent good treatment adherence and completion	• Reduce stigma • Increase empowerment • Increase adherence and treatment completion
Monitor and document attendance at the interactive community meetings	• Good documentation • Feedback	• Identification of participants at high risk of not completing the conditions • Stimulate participation
Train new facilitators	• Organise and lead facilitator training	• Create sustainable and transferable facilitator training

Document 14: Example of facilitator training session material

FACILITATOR TRAINING: GENERIC METHODOLOGICAL GUIDE

"WORKING TOGETHER WITH COMMUNITIES TOWARDS HEALTH"

General objectives:

- Train new facilitators from the supported communities in order that they may start working with new TB patients and their families
- Through an educational session and professional/psychological workshop, offer the participants a formal, transferable and certified training, which will be essential for their work with the project but also may be useful as future evidence of professional development

Specific objectives (in brackets the existing project materials revised in each objective are shown):

- Ensure that the participants have a general understanding of the methods of TB prevention and control aswell as TB treatment and adherence (Patient mini-flipchart)
- Ensure that the participants understand the TB Program goals underlying the IPSYD project conditions for the conditional cash transfers (Incentives card)
- Revise the key messages concerning responsible spending and saving (Project handout and bank handouts and materials)
- Educate the participants about their role as facilitators and the role of the other members of the IPSYD team (IPSYD Project team activity checklist)
- Involve the participants in a psychological/professional workshop and activity concerning working in teams, leadership and interaction (Summary of TB Clubs previously prepared by Frank Fernandez, and role play activities by Tom Wingfield)
- Ensure that the participants understand, value and are able to draw on their own personal characteristics with respect to becoming facilitator and reinforce the positive feelings they have about themselves (throughout the session and final feedback)

Outputs:

- Prior to the training session, each potential participant must receive the Reading material (incentives card, mini-flipchart or handout, bank material, and IPSYD team field activity check list)
- At the beginning, the participants do an exam consisting of 10 multiple choice questions
- The participants define and answer in their own words the educational questions from the educational workshop activity
- The participants value and put into practice the messages concerning home economy and reflect such messages on a flipchart
- The participants take the same 10 question multiple choice exam that they did at the beginning of the session
- The participants receive a formal certificate at the end of the training detailing the educational aspects covered (TB, home economy, working in teams, leadership, interaction and communication) and give feedback to improve the session

Responsible members of the team: Tom Wingfield, Marco Tovar, Rosario Montoya, Frank Fernandez, Douglas Huff and the IPSYD team

PROCESS /THEME	OBJECTIVE	CONTENT	METHODS	TIME	MATERIALS	STAFF MEMBER	OUTPUT
Prior activities	Preparation of the space in which to develop the training session	Group the seats in an appropriate manner and get projector set up	Participative	60 min. (13:30-14:30)	Chairs, table, projector, laptop, plugs and extension, pens, paper, balloons, etc.	IPSYD team	Prepared and appropriate space ready to receive participants and undertake activities Pre- and post-training examination
Reception of participants and pre-course exam	Register all the participants Ensure participants complete the 10 question precourse exam	Registration Precourse exam	Participative	15 min. (14:45 - 15:00)	Attendance sheet Pencils Printed attendance sheet (generated from database) Precourse exam Name bade	Tom and Charo Assistance from existing facilitators	Attendance register completed by each participant IPSYD team members explain the precourse test to the facilitators and assist them if they have any questions The participants can be identified by name with their badges and get to know one another
Welcome greeting and presentation	Present the contents of the training day	Themes and times, presenters	Presentation	5 min	Copy of program of the training day Projector and laptop	Tom	The participants are orientated to the central themes of the training day and are encouraged in the fact that they have been chosen to be facilitators
Group activity	Generate confidence and break the ice	Group the participants according to a number previously list on their name badge	Activity, participative	5 min	Free and appropriate space with which to organise the two groups	Charito	The participants feel more at ease with each other and have more confidence amongst the group
Education workshop about the IPSYD team, peoples roles and the roles of the facilitators	Orientate the participants around TB and conditional cash transfers Explain how the IPSYD project functions Explain what is the role of the facilitator and how they can benefit	Revision of TB Incentives Spending and saving responsibly The role of our team and the facilitators	Participative and activity Presentation and activity Presentation and activity Presentation	15 min 15 mins 15 mins 15 mins	Powerpoint and posters, pens, paper, mini-flip chart as a reference Incentives card (poster-size or PPT) Bank leaflet Cards with key team activities ordered	Pilar / Mari Haro Natalie / Charito Charo / Carlos Tom	Powerpoint with appropriate answers Incentives card with incentives covered and the participants have to guess what the incentive is (for example, doses missed etc) The group notes positive and negative things that the patients and their families can buy with the incentives Place all the activities cards in the appropriate place in the appropriate time from recruitment to final follow-up. Take a photo at the end
Professional/psychological workshop: being a facilitator	Focus on the abilities needed to complete the role of facilitator successfully	Working in a team, leadership and communication Facilitating TB Clubs: ho to facilitate!	Presentation and activity Presentation and activity (role play of Tb Club)	25 mins 35 mins	Projector, laptop, slides Roleplay guide / techniques to use during TB Clubs	Tom Mari Haro / Jessica / Charito Tom	Explore what a team is. Generate a list of abilities that make a person work well in teams. Do a role play of a TB Club planting different participants to act out difficult aspects. Critique good things and things to be improved about the practice
Feedback, postcourse exam, close and certificates	Repeat the exam post-course to reinforce messages learnt Summarise session	Post-course exam (revise together) Certificates	Participative	20 mins	Pencils and exam	Tom and Charo	Leave with the feeling of having learnt something and have the evidence of such learning in hand (certificates). Reinforce the key themes prior to leaving

Document 14: Facilitator training (cont.)

Role play: Training new facilitators to run TB Clubs: a practical session

Roles of participants:

- IPSYD Facilitator Supervisor/Trainer:
  - Supports and advised the supervisor in training

- Facilitator in training:
  - During the role play supports and facilitates the TB Club members to express their thoughts and feelings about living with or being affected by TB
  - Asks the TB Club members to describe the Becerra drawings to stimulate conversation if necessary

- 2/4 people undertake the role of TB Club members (i.e. pretend to be patients below – can vary)
  - Club Member #1:
    - Woman, 26 years old, a mother of a daughter of 2 years old
    - Her husband mistreats her at home and ignores her
    - She would love to share these feelings but is ashamed and upset
  - Club Member #2:
    - 40 year old male
    - Is annoyed because he has lost his job (he believes due to his TB diagnosis)
    - He speaks out angrily and dominates the conversation
  - Club Member #3:
    - Woman or man 15 years of age
    - Doesn't identify with the other Tb Club members, thinks they're old fogeys
    - Appears extemely bored and speaks on his phone
  - Club Member #4:
    - Woman, 60 years old
    - Doesn't seem to understand the TB Club or the pictures she's shown
    - Responds in an inappropriate way to questions asked due to lack of understanding

- Observer who notes and feeds back at the end:
  - What did the facilitator in training do well?
  - What could the facilitator in training do to improve the results of the TB Club?

After 10 minutes, everyone changes roles and the practice TB Club is repeated (i.e. the observer becomes a patient, a patient becomes a facilitator in training leading the Club, and a facilitator in training becomes an observer etc).

Appendix 2: Bound copy of “Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru.” PLOS Medicine. 2014 Jul 15;11(7):e1001675. doi: 10.1371/journal.pmed.1001675

Appendix 3: Bound copy of “The seasonality of tuberculosis, sunlight, vitamin D, and household crowding.” J Infect Dis. 2014 Sep 1;210(5):774-83. doi: 10.1093/infdis/jiu121. Epub 2014 Mar 4

Appendix 4: Bound copy of “Designing and implementing a socioeconomic intervention to enhance TB control: operational evidence from the CRESIPT project in Peru.” BMC Public Health. 2015 Aug 21;15(1):810. doi: 10.1186/s12889-015-2128-0

END OF THESIS