Evaluating the impact of cash transfers on tuberculosis (ExaCT TB): a stepped wedge cluster randomised controlled trial

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Shareable abstract (@ERSpublications)
Cash transfers can be feasibly delivered to people at risk for TB to support adherence to care. While rates of treatment initiation remained unchanged, cash transfers supported increased referral and completion of testing for this at-risk population. https://bit.ly/3Ahx9yB

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Abstract

Background Mitigating financial barriers to tuberculosis (TB) diagnosis and treatment is a core priority of the global TB agenda. We evaluated the impact of a cash transfer intervention on completion of TB testing and treatment initiation in Uganda.

Methods We conducted a pragmatic complete stepped wedge randomised trial of a one-time unconditional cash transfer at 10 health centres between September 2019 and March 2020. People referred for sputum-based TB testing were enrolled to receive UGX 20 000 (~USD 5.39) upon sputum submission. The primary outcome was the number initiating treatment for micro-bacteriologically confirmed TB within 2 weeks of initial evaluation. The primary analysis included cluster-level intent-to-treat and per-protocol analyses using negative binomial regression.

Results 4288 people were eligible. The number diagnosed with TB initiating treatment was higher in the intervention period *versus* the pre-intervention period (adjusted rate ratio (aRR)=1.34) with a 95% CI of 0.62–2.91 (p=0.46), indicating a wide range of plausible true intervention effects. More were referred for TB testing (aRR=2.60, 95% CI 1.86–3.62; p<0.001) and completed TB testing (aRR=3.22, 95% CI 1.37–7.60; p=0.007) per National Guidelines. Results were similar but attenuated in per-protocol analyses. Surveys revealed that while the cash transfer supported testing completion, it was insufficient to address long-term underlying social/economic barriers.

Interpretation While it is uncertain whether a single unconditional cash transfer increased the number of people diagnosed and treated for TB, it did support higher completion of diagnostic evaluation in a programmatic setting. A one-time cash transfer may offset some but not all of the social/economic barriers to improving TB diagnosis outcomes.

Introduction

Background and objectives

Prompt diagnosis and treatment of tuberculosis (TB) patients is essential to making progress towards ending TB. Not only were 4 million of the estimated 10 million new TB cases in 2021 not accounted for, but also high rates of pre-treatment loss to follow-up plagued those that were identified [1, 2]. The failure to address economic barriers faced by patients is a principal reason why those who present to health facilities do not complete the cascade of care for TB diagnostic evaluation [3–5]. TB disproportionately affects the poorest and most vulnerable populations [6, 7], leading to substantial losses in productivity for already poor individuals (3–4 months of work), families (30% of yearly household earnings) and countries

(4–7% of gross domestic product) [8]. Accessing TB diagnostic services poses a serious risk to individuals' and households' socioeconomic status.

In Uganda, a low-income and high-TB burden country, 51% of people seeking care for TB symptoms face catastrophic costs (>20% of annual household income) due to high direct non-medical costs such as transportation and opportunity costs such as lost wages [5, 9–11]. These costs and negative financial consequences make adults with presumed TB less likely to complete testing and initiate treatment [7]. Social and structural determinants of health – such as food insecurity, poor housing and environmental conditions, geographic and cultural barriers to healthcare access – are also common and contribute to a lower likelihood of TB diagnosis and treatment initiation [12–14]. Unfortunately, better diagnostics alone do not mitigate these factors [5].

Person-centred approaches that address underlying social determinants of TB are thus needed. Cash transfers, both used as incentives or as components of a social protection strategy, are a promising person-centred approach to improving TB outcomes [15, 16]. Cash transfers have been shown to improve public health outcomes in a variety of diseases and conditions including HIV [17], maternal mortality [18], childhood immunisations [19] and neglected tropical diseases [20]. Increasing evidence demonstrates that cash transfers can be an important component of treatment strategies to improve TB treatment completion and cure rates in programmatic settings [21–24]. In Uganda, even modest cash transfers were universally acceptable to support TB care services [25]. However, it is not known if cash transfers or other social protection strategies reduce pre-treatment loss to follow-up. We sought to assess the feasibility and potential effectiveness of a cash transfer intervention on completion of TB diagnostic evaluation and treatment initiation in a programmatic setting.

Methods

Trial design

We conducted a pragmatic, open label, complete stepped wedge randomised trial of a one-time unconditional cash transfer intervention in 10 community health centres across eight districts in Uganda. Study rollout and data collection period occurred over the course of 6 months, from September 2019 to March 2020 (supplementary figure S1). The trial employed a repeated cross-sectional design; each 1-month time period captured different people initiating evaluation for TB. Of note, the study design was modified due to COVID-19-related disruptions (supplementary methods).

Participants

Individuals in the target population were ⩾18 years of age and initiating evaluation for pulmonary TB. People were excluded if they: 1) had sputum collected for monitoring of response to anti-TB therapy; 2) had sputum collected as part of active, community-based case finding (*e.g.*, contact tracing, community outreach); 3) were referred to a study health centre for TB treatment after a diagnosis had been established elsewhere; or 4) were started on treatment for extrapulmonary TB only. Among the target population, we considered clients eligible for the cash transfer intervention if they had evidence of sputum-based testing for pulmonary TB. This included those: 1) confirmed as having been tested in the facility laboratory register; 2) indicated referred for Xpert in the facility presumptive TB register; 3) confirmed as treated for TB in the facility treatment register; or 4) who had completed the laboratory requisition form included in their medical record.

Sites

Study staff reviewed 2015 TB testing and treatment data reported to the Uganda National TB and Leprosy Program (NTLP) to identify health centres that met eligibility criteria, focusing on those within 150 km of Kampala for feasibility purposes. Eligible health centres included those with sufficient volume of TB testing based on standard (multi-day) sputum smear microscopy and/or Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA, USA) [26]. 10 of 122 eligible health centres were selected based on feasibility and statistical considerations with National TB programme officers, health centre in-charges and the trial statistician input.

The trial was approved by the institutional review boards at Makerere University School of Public Health and the University of California San Francisco, and by the Uganda National Council for Science and Technology including a waiver of written informed consent for enrolling in the intervention and accessing routinely collected demographic and clinical information among all participants. Those found to be eligible for the cash transfer intervention were provided with all relevant details about study participation at the time of enrolment and assented to participation. Written informed consent was obtained for participation in

post-intervention surveys. The trial is registered with the Pan-African Clinical Trials Registry (PACTR201906852160014).

Interventions

Routine care

The conventional approach to TB diagnostic evaluation at health centres in Uganda involves collection of a spot specimen for Xpert testing, a semi-automated rapid point-of-care PCR-based assay that is recommended as the first line test for diagnosing pulmonary TB where available. Consultation for results and treatment initiation generally require additional health centre visits. People presenting for TB diagnostic evaluation or treatment do not routinely receive any social or economic support from health centres.

Intervention

An unconditional cash transfer intervention of UGX 20 000 in value was provided to all eligible people undergoing sputum-based testing for pulmonary TB during the intervention period at participating health centres *via* mobile money (in October 2020, USD 1 ≈ UGX 3710; UGX 20 000 ≈ USD 5.4). Eligible people were enrolled into the cash transfer intervention by health centre laboratory technicians at the time they submitted a sputum sample for TB testing. The cash transfer was distributed using a local mobile money aggregator approved by the Uganda Communications Commission (Beyonic, https://beyonic.com/). The intervention was introduced to relevant health centre staff during a 1 to 2 days of training at the beginning of the buffer month (supplementary methods).

Sociodemographic, clinical and laboratory data were collected at all health centres from all participants from the following sources: 1) NTLP presumptive TB registers; 2) laboratory registers; 3) TB treatment registers; and 4) Xpert laboratory requisition forms as described elsewhere [26]. A subset of study participants were purposively selected to complete a survey, which collected costs of accessing TB diagnostic evaluation services and perceptions of whether the intervention targeted known socioeconomic barriers to TB care. Surveys were conducted by a trained research staff member, who called the participant using their provided phone number, assessed for interest in survey participation, received informed consent and administered the survey.

Outcomes

The primary outcome represented completion of the care cascade among those accessing the health centre who were ultimately diagnosed with TB, calculated as the number of people initiated on treatment for microbiologically confirmed TB within 2 weeks of presenting to the health centre for TB evaluation. Secondary outcomes were defined by key steps along the cascade of TB diagnostic evaluation, and included key milestones representing quality of service delivery from initiation of testing at the health centre to completion of the care cascade among those with TB. These steps included: 1) the number referred for TB testing; 2) the number who completed TB testing if referred; 3) the number diagnosed with microbiologically confirmed TB; 4) the number treated for TB if diagnosed; and 5) the number with favourable treatment outcomes (including treatment completion). Time to treatment initiation was defined as the number of days between the date of presentation to the health centre for initial evaluation and the date of documented TB treatment initiation.

Sample size

Our sample size calculations used appropriate formulae for stepped wedge trial designs. A type I error of 5% and 80% power was assumed. 7 months of pre-trial data from 2018 to 2019 collected from participating health centres suggested an intracluster correlation coefficient of 0.11, a geometric mean number of people initiating treatment within 14 days of 2.22 (95% CI 1.80–2.74) and standard deviation (SD) of 2.09. Given these assumptions, a sample size of 240 people diagnosed with microbiologically confirmed TB was needed in order to detect a minimum odds ratio between pre-intervention and intervention periods of 1.09.

Randomisation

Eligible health centres were randomised using a simple, unrestricted two-stage process. First, they were matched into clusters based on pre-randomisation data of patient volume. Second, clusters were randomly assigned into the sequence order in which they would switch into the intervention period during a stakeholder-led randomisation ceremony whereby health centre representatives chose a numbered ball from an opaque bag, indicating their sequence order. Owing to the nature of the intervention, masking of participants and providers was not possible.

Statistical methods

We summarised participant clinical, demographic, cost characteristics, implementation outcomes and survey results using counts and proportions for categorical variables, and means and SD for continuous data. We assessed underlying secular trends in our primary outcome measure for each health centre and cluster in both pre-intervention and intervention exposure periods using individual-level participant data using cluster-period mixed effects regression models (supplementary methods) [27, 28].

We performed cluster-level analyses to assess the effect of the intervention strategy on trial outcomes using both the intent-to-treat (ITT) and per-protocol study populations. The ITT analysis estimated the overall effect of the intervention while the per-protocol analysis aimed to assess the effect of the cash transfer among those who actually received it. The comparator group included people in the pre-intervention period who otherwise met trial eligibility criteria (figure 1). Secular trends were assessed and found to be insignificant (supplementary results). Multivariate negative binomial regression analyses estimated adjusted rate ratios (aRRs) and corresponding 95% confidence intervals and adjusted for clustering by health centre. Final models included the following cluster-level covariates: health centre location (peri-urban *versus* rural), mean age, proportion male, proportion HIV positive and trial month [28]. Socioeconomic indicators are not routinely collected at health centres and therefore not available for analysis. However, rurality may account for socioeconomic differences between the populations of people accessing care at different health centres. An exploratory sensitivity analysis estimated the direct effect of the intervention and included all data from the intervention period from all health centres and people eligible to receive the cash transfer (supplementary methods). Analyses were conducted using Stata v16 (StataCorp, College Station, TX, USA).

Results

During the study period, 6152 people underwent TB testing at one of the 10 participating health centres, and 5460 (89%) were in the target population. Among those in the target population, 5101 (93%) had evidence of sputum-based testing for pulmonary TB and thus were eligible for the cash transfer intervention. There was an equal allocation of months to pre-intervention and intervention conditions, with 30 in each period (figure 1). Of all those found to be in the target population and eligible for the cash transfer intervention, 1143 (37%), 813 (16%, data not analysed) and 3145 (73%) individuals were evaluated in the pre-intervention, buffer and intervention periods, respectively (figure 1).

People evaluated during the pre-intervention and intervention periods were similar except for lower proportions with HIV (25.9% *versus* 42.0%) and confirmed TB (3.6% *versus* 8.1%) in the intervention period (table 1). Reasons for exclusion in ITT or per-protocol groups are described in figure 1.

In the ITT analysis, the cash transfer intervention increased the number of people with confirmed TB initiating TB treatment within 14 days of sputum submission; however the confidence interval we derived indicated a wide range of plausible true intervention effects (aRR 1.34, 95% CI 0.62–2.91, p=0.46; table 2). In the intervention period, more people were referred for TB testing (aRR=2.60, 95% CI 1.86–3.62; p<0.001) and completed testing per National Guidelines (aRR=3.22, 95% CI 1.37–7.60; p=0.01). The number of people diagnosed with TB and the number who had a favourable TB treatment outcome were similar across pre-intervention and intervention periods. Results were similar in the per-protocol analysis (table 2).

When comparing people in the intervention period who actually received the cash transfer (n=2212) *versus* those who did not (n=933), there was no difference in the primary outcome (aRR=1.40, 95% CI 0.50–3.95; p=0.52). However, the numbers of people referred for testing (aRR=1.85, CI 1.18–2.89; p=0.01), completing testing (aRR=1.82, 95% CI 1.02–3.27; p=0.04) and with favourable treatment outcomes (aRR=1.96, 95% CI 1.02–3.75; p=0.04) were significantly higher (supplementary table).

The number diagnosed with confirmed TB increased by about fourfold (aRR=3.70, 95% CI 1.78–7.68, p<0.001) among individuals who had knowledge of the cash transfer regardless of receipt of cash (n=2541) as compared with those not enrolled (had no knowledge of the intervention; n=604). Similarly, more people completed testing (aRR=2.91, 95% CI 1.30–6.54; p=0.01), were diagnosed with confirmed TB (aRR=3.59, 95% CI 1.79–7.18; p<0.001) and had favourable treatment outcomes (aRR=3.92, 95% CI 1.84–8.33; p<0.001).

Survey results (n=192) (table 3) suggested that the cash transfer made it easier to access TB care by facilitating transportation (n=173, 90%) and that receiving supports like cash transfers allow people to prioritise returning to the health centre (n=180, 94%). Almost 75% of respondents anticipated using

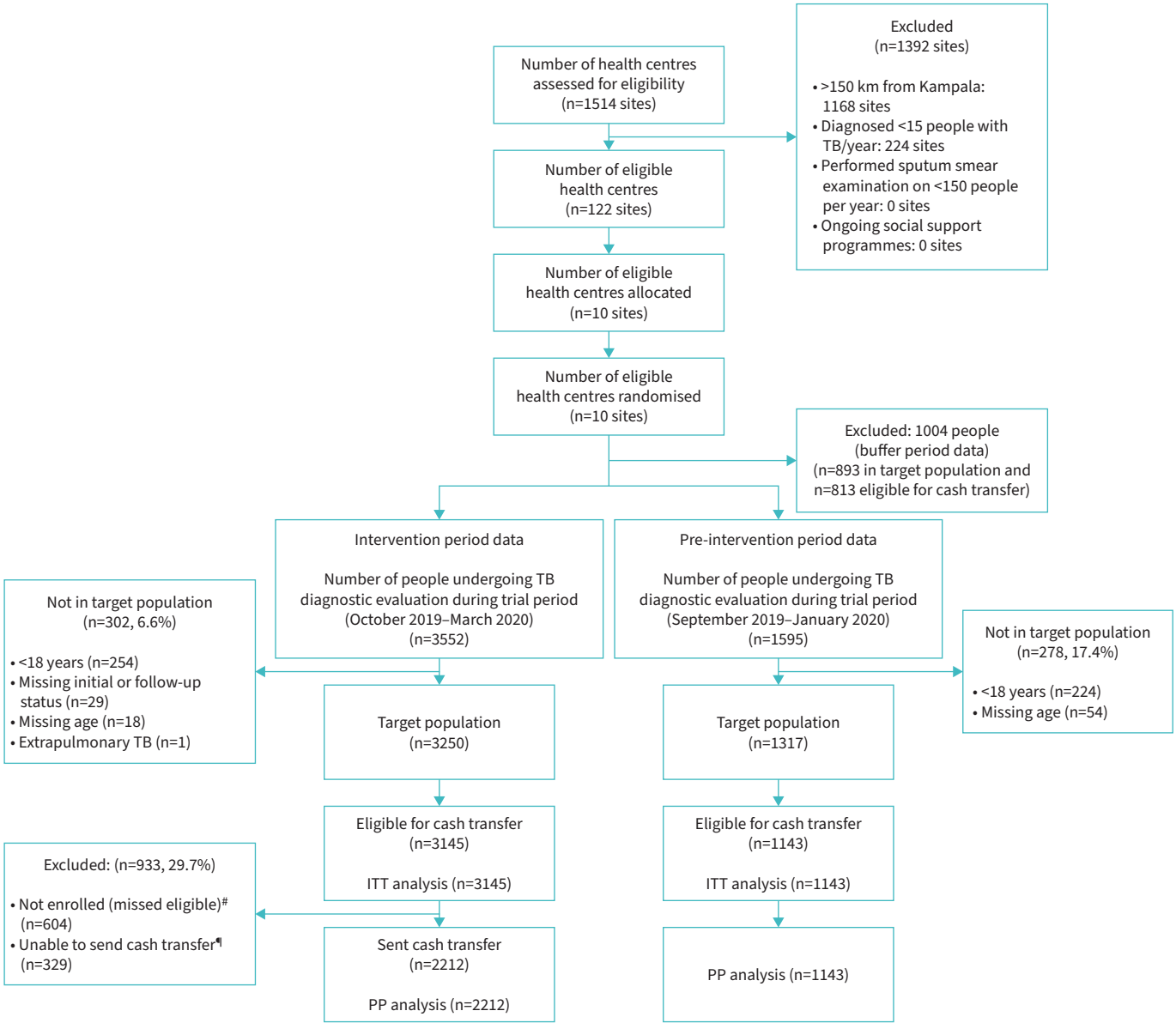

FIGURE 1 CONSORT flow diagram. Over the course of the study period spanning from 1 September 2019 to 31 March 2020, 6152 people sought TB care at one of the 10 participating health facilities (pre-intervention (n=1595), buffer (n=1004), intervention (n=3250)). 5460 people were in the target population for the study, of whom 5101 had evidence of sputum-based testing for pulmonary tuberculosis (TB) and thus were eligible for the cash transfer intervention. The 1004 people evaluated for TB during the buffer period included 813 people eligible for the cash transfer. All buffer period data were excluded from all data analyses. The 4288 people in the pre-intervention (n=1143) and intervention (n=3145) periods who were in the target population and eligible for the cash transfer intervention comprised the intent-to-treat (ITT) population. The per-protocol (PP) population (n=3355) included the 1143 people eligible for the cash transfer in the pre-intervention period and those in the intervention period who were ultimately sent the cash transfer (n=2212). #: we excluded from the PP analysis those who were found eligible for the cash transfer according to health facility register data but were not enrolled in the study according to study logbooks (missed eligible; n=604). ¶: we excluded from the PP analysis those who we were unable to send the cash transfer (n=329) because of: 1) name and mobile money number mismatch (n=195); or 2) missing, invalid or unregistered mobile money number provided at study registration (n=134).

negative financial coping strategies (dissaving, such as selling an asset, taking out a loan or borrowing savings) without the cash transfer (n=129, 72%), and this proportion increased with increasing poverty (poorest: n=41 (84%), poor: n=36 (75%), not poor: n=61 (64%); p=0.03, supplementary results). Most survey participants (n=122, 63%), however, felt the cash transfer was not enough to protect their households from new or worsening impoverishment.

TABLE 1 Participant baseline clinical and demographic characteristics by study population and study period

	Intent-to-treat population[#]		Per-protocol population[¶]		Buffer period
	Pre-intervention	Intervention	Pre-intervention	Intervention	
Patients n	1143	3145	1143	2212	813
Age years	41.7±15.9	37.0±14.4	41.7±15.9	36.0±14.0	39.0±16.2
Female	668 (58.4)	1841 (58.6)	668 (58.4)	1275 (57.6)	443 (54.5)
Rural health centre	783 (68.5)	2492 (79.2)	783 (68.5)	1857 (84.0)	630 (77.5)
HIV positive[+]	438 (42.0)	792 (25.9)	438 (42.0)	476 (21.8)	267 (32.8)
Confirmed TB	93 (8.1)	112 (3.6)	93 (8.1)	66 (3.0)	38 (4.7)
Treated among MTB positive	78 (83.9)	100 (89.3)	78 (83.9)	57 (86.4)	31 (81.6)

Data are presented as mean±SD or n (%) unless otherwise indicated. TB: tuberculosis; MTB: *Mycobacterium tuberculosis*. [#]: n=4288; [¶]: n=3145; [+]: HIV status available for n=4105 participants.

Discussion

Our results demonstrate that a modest one-time unconditional cash transfer can be feasibly delivered to people at health centres undergoing evaluation for TB in a high-burden, low-income setting. While the effect of this cash transfer on our epidemiological outcome of treatment initiation among those diagnosed with TB was not significant (ITT: aRR 1.34, 95% CI 0.62–2.91, p=0.46; per-protocol: aRR=0.77, 95% CI 0.34–1.73, p=0.53), our findings demonstrate that this cash transfer did improve adherence to care. Our intervention increased the rate of completion for each step along the TB diagnostic cascade of care from referral for sputum-based testing to sputum submission to completion/results of microbiologic tests by two- to fourfold. These findings suggest that cash transfers are a feasible strategy for supporting people at risk for TB in completing the often arduous process associated with obtaining a diagnosis for their symptoms. Our survey results further support this assertion; 94% of survey participants agreed that the cash transfer helped them change their decision-making and return to the health centre.

We explored the mechanism of action of our cash transfer affecting TB diagnostic evaluation through several analyses. Our per-protocol analysis found that enrolment into the cash transfer intervention led to greater numbers referred for TB testing, completing testing, diagnosed with TB and with favourable treatment outcomes (table 2). We conducted an exploratory sensitivity analysis designed to estimate the direct effect of enrolment into the intervention and found that the number of people with TB who initiated treatment was significantly greater among those in that group compared to those who were eligible but not enrolled and therefore had no knowledge of the cash transfer. In addition, our survey results suggest that while the cash transfer we implemented may have motivated or facilitated return to the health centre,

TABLE 2 Cash transfer impact on primary and secondary outcomes, intent-to-treat (ITT) (n=4288) and per-protocol (PP) (n=3355) populations

Outcomes	Unadjusted effect estimate		Adjusted effect estimate[#]	
	Rate ratio (95% CI)	p-value	Rate ratio (95% CI)	p-value
ITT analysis				
Treatment initiation (14 days)	1.17 (0.80–1.70)	0.42	1.34 (0.62–2.91)	0.46
Referred for TB testing	2.75 (2.13–3.55)	<0.001	2.60 (1.86–3.62)	<0.001
Completion of TB testing	2.88 (1.98–4.18)	<0.001	3.22 (1.37–7.60)	0.007
Diagnosed with MTB	1.20 (0.83–1.74)	0.32	1.50 (0.80–2.79)	0.21
Treatment cure/completion	1.31 (0.86–2.00)	0.21	1.42 (0.59–3.43)	0.44
PP analysis: receipt of cash transfer				
Treatment initiation (14 days)	0.63 (0.36–1.09)	0.10	0.77 (0.34–1.73)	0.53
Referred for TB testing	1.94 (1.42–2.64)	<0.001	1.88 (1.34–2.63)	<0.001
Completion of TB testing	2.04 (1.32–3.15)	0.001	2.43 (1.16–5.12)	0.02
Diagnosed with MTB	0.71 (0.43–1.17)	0.18	1.07 (0.50–2.28)	0.87
Treatment cure/completion	0.81 (0.45–1.45)	0.48	0.95 (0.37–2.49)	0.93

TB: tuberculosis; MTB: *Mycobacterium tuberculosis*. [#]: adjusted for mean age, proportion male (log transformed), proportion HIV positive (log transformed), health centre location (peri-urban *versus* rural) and trial month.

TABLE 3 Results of a post-intervention explanatory survey aimed at identifying perceptions of the utility of the cash transfer (n=192)

	Strongly agree/agree, n (%)
Barrier: transport	
The cash made it easier to obtain or pay for transport to and from the clinic	173 (90)
The cash was not enough to facilitate your transport to or from the clinic	50 (26)
Barrier: food	
The cash transfer made it easier to obtain or pay for food	128 (66)
Without the cash transfer you would have had to go without or reduce food for your family	39 (20)
Barrier: decision-making	
Receiving incentives like cash transfers is useful in helping change your decision-making about going to the clinic	180 (94)
Knowing about the cash transfer made it easier to return to the clinic	169 (88)
Knowing about the cash transfer affected your decision to come back to the clinic	156 (81)
The cash transfer did not address your reasons for deciding to complete diagnostic evaluation or start treatment	102 (53)
Barrier: financial security	
Without the cash, you would need to take out a loan/borrow money/sell an asset to cover costs to return to clinic	129 (72)
The cash was not enough to protect you and your household from losing income or becoming poor (or poorer)	122 (63)
The cash improved or helped your household's income	54 (28)
The cash allowed you to feel more secure in your position in your community	16 (8)
Cash transfer: structure	
Amount: The amount of cash transfer was not enough to affect decision to finish testing in clinic	55 (29)
Timing: The cash was provided too late to affect decision to complete diagnostic evaluation or to begin treatment	27 (14)

it may not have been sufficient in size or frequency to address underlying poverty associated determinants that affect treatment initiation for those who have TB. Taken together, these findings suggest that enabling diagnostic evaluation with cash transfers is feasible, but that to improve epidemiological outcomes (*i.e.* treatment initiation) TB-affected individuals may require more durable multicomponent social and economic supports to address their unmet needs across the cascade of care.

These findings add nuance to the growing evidence demonstrating the effectiveness of cash transfers for supporting treatment adherence and cure/completion for TB-affected people. While several systematic reviews of cash transfers describe the positive effects of these interventions during the treatment phase of care [21, 22], the majority of these cash transfer schemes utilised different structures such as conditionalities, recurrent payments of moderate amounts through the course of treatment, or linkage to other existing social protection programmes. Our research suggests that there may be something different about the function and effectiveness of cash transfers at different stages in the process of TB care.

Unfortunately, our study, like many others, was interrupted by the COVID-19 pandemic, potentially affecting the robustness of our sample size estimation (supplementary methods). In addition, the country-wide lockdown measures implemented in Uganda might have made it such that those with TB symptoms who would have otherwise accessed the health centre to ascertain a diagnosis may have never presented for evaluation. These individuals would not have been included in our study. Empirical data from 58 health centres in Uganda, including the 10 health centres included in this study, found that TB case notifications significantly decreased after the implementation of the lockdown period [29]. Finally, we elected to use an epidemiological outcome, the number of people with microbiologically confirmed TB who initiate treatment within 14 days, as the primary outcome. While this outcome may be important in elaborating how the intervention mitigates disease transmission or morbidity, TB itself is a rare outcome even in a high-burden setting. Instead, focusing on completion of testing may have been a more relevant primary outcome.

Strengths of our study include integration of both implementation and effectiveness outcomes into our analysis, allowing us to understand the effect of cash transfers on improving completion of critical steps in the diagnostic cascade of care for TB. Second, our intervention was informed by context-specific formative research which identified essential person-centred barriers to TB diagnostic evaluation (transportation costs, lost income) [5] and identified a feasible and appropriately structured intervention to address those challenges using theory-informed methods [25]. We used post-intervention surveys to provide important insight into the how and why our intervention did and did not work. These results will be the foundation for considering ways to refine the intervention to improve overall population outcomes and those of target sociodemographic subgroups.

This study highlights the potential need for interventions that target underlying determinants rooted in poverty. Such interventions, described as social protection interventions, are designed to protect individuals from social and economic risk, and are one of the three pillars of the World Health Organization (WHO) End TB Strategy [30] as well as a key component of the United Nation's Sustainable Development Goals agenda [31, 32]. Our results support the need for additional research that identifies and evaluates feasible TB-specific social protection interventions that may be programmatically implemented and scaled to address the needs of TB-affected individuals in all phases of their care.

Provenance: Submitted article, peer reviewed.

This study is registered at https://pactr.samrc.ac.za/ with identifier number PACTR201906852160014.

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