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Comparing disease specific catastrophic cost estimates using longitudinal and cross-sectional designs: The example of tuberculosis

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ABSTRACT

Background: There has been an increasing interest in assessing disease-specific catastrophic costs incurred by affected households as part of economic evaluations and to inform joint social/health policies for vulnerable groups. Although the longitudinal study design is the gold standard for estimating disease-specific household costs, many assessments are implemented with a cross-sectional design for pragmatic reasons. We aimed at identifying the potential biases of a cross-sectional design for estimating household cost, using the example of tuberculosis (TB), and exploring optimal approaches for sampling and interpolating cross-sectional cost data to estimate household costs.

Methods: Data on patient incurred costs, household income and coping strategies were collected from TB patients in Negros Occidental and Cebu in the Philippines between November 2018 and October 2020. The data collection tools were developed by adapting WHO *Tuberculosis Patient Cost Surveys: A Handbook* into a longitudinal study design. TB-specific catastrophic cost estimates were compared between longitudinal and simulated cross-sectional designs using different random samples from different times points in treatment (intensive and continuation phases).

Results: A total of 530 adult TB patients were enrolled upon TB diagnosis in this study. Using the longitudinal design, the catastrophic cost estimate for TB-affected households was 69 % using the output approach. The catastrophic cost estimates with the simulated cross-sectional design were affected by the reduction and recovery in household income during the episode of TB care and ranged from 40 to 55 %.

Conclusion: Using longitudinally collected costs incurred by TB-affected households, we illustrated the potential limitations and implications of estimating household costs using a cross-sectional design. Not capturing changes in household income at multiple time points during the episode of the disease and estimating from inappropriate samples may result in biases that underestimates catastrophic cost.

1. Introduction

Tuberculosis (TB) is a chronic disease that requires a minimum of 6 months treatment (The World Health Organization, 2022a). The risk of TB infection and disease is associated with poverty, together with poor care-seeking behaviour, delay in diagnosis, and poor treatment adherence and the development of drug-resistant TB (DR-TB) (Wingfield et al., 2014; Carter et al., 2018; Foster et al., 2015). Despite free TB services available in public health facilities, TB patients usually incur large costs for care seeking, diagnosis, and treatment. The costs include not only out-of-pocket (OOP) payments for direct medical costs, but also direct non-medical costs such as transportation, food or nutritional

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supplements and indirect costs such as income loss (Laurence et al., 2015; Tanimura et al., 2014; Barter et al., 2012). TB also impacts poverty as it can reduce the physical ability to work, and as a result lead to income loss (Foster et al., 2015; Laurence et al., 2015; Tanimura et al., 2014). In addition, households being affected by long-term diseases such as TB usually mobilize their money for treatments by dissaving, selling assets, or taking loans, making them poorer and trapped in the cycle of poverty (Sauerborn et al., 1996), which can have a long-term economic impact on TB patients and their households (Mudzengi et al., 2017).

In 2013, the World Health Organization (WHO) set the End TB Strategy, and one target of the strategy is "to ensure that no family is burdened with catastrophic expenses due to TB" (The World Health Organization, 2013). To capture the current situation of TB associated household costs and monitor the progress to toward achieving this target, WHO supports countries to conduct baseline and periodic TB patient cost surveys (The World Health Organization, 2017). National TB patient cost surveys have already been conducted so far in 31 countries (The World Health Organization, 2023).

In 2015, WHO produced a generic protocol and data collection tool (field testing version) which was later refined and published as a handbook in 2017 (The World Health Organization, 2017). This handbook has also been adapted for use in other disease specific studies assessing societal and catastrophic costs. The WHO recommended using a cross sectional design for the estimation of this target, given that it is commonly measured using population wide surveys. WHO then applied different approaches to estimate total costs incurred for TB services compared to that used for "catastrophic health expenditure" in the general population (The World Health Organization, 2017). All the national surveys were designed and conducted as cross-sectional studies due to feasibility and practicality; smaller survey budget required, shorter duration of data collection, and no follow-up interviews required, compared to longitudinal designs. TB treatment has two phases, the intensive and continuation phase, which are treated with different regimens and different frequency of monitoring by providers. The estimation of direct costs (i.e. direct medical and non-medical costs) is based on an assumption that the frequency of health service utilization and expenditure within a treatment phase is consistent. Direct costs for the last facility visit by visit type (i.e. collection of TB drugs, directly observed therapy (DOT), follow-up by clinicians) were being captured, and then scaled up to the entire duration of the phase using the frequency of health service utilization. The direct costs for the treatment phase that are not captured directly are extrapolated based on the median costs estimated from the data of other patients in that treatment phase (The World Health Organization, 2017).

Indirect costs are estimated through two different methods: the output approach and human capital approach (The World Health Organization, 2017). The output approach relies on self-reported household income before and during the TB episode, while the human capital approach uses reported time spent for care seeking and treatment during a TB episode multiplied by an individual hourly income estimated from reported income and working hours.

This study aims to assess the differences in the costs using the output approach between the longitudinal and cross-sectional methods, and to identify methodological improvements in the WHO recommended national TB patient cost surveys. We compare estimates of total costs and the prevalence of catastrophic costs between the longitudinal and cross-sectional designs. Our analysis aims at highlighting limitations and implications of the current guideline for assessing catastrophic costs due to TB using a cross-sectional design, which can also inform methods for other diseases.

2. Methods

2.1. Study setting and population

The estimated TB incidence in the Philippines was 650 per 100,000 in 2021 (The World Health Organization, 2018, 2022b), and The Philippines has been classified by the WHO as one of the 30 high TB burden countries for both drug-susceptible TB (DS-TB) and multidrug-resistant and rifampicin resistant TB (MDR/RR-TB) (The World Health Organization, 2018, 2022b; Hargreaves et al., 2011). The National Tuberculosis Control Program (NTP) conducted a nationwide TB patient cost survey in the Philippines between 2015 and 2017 using the WHO recommended cross-sectional design and cost extrapolation method (The World Health Organization, 2017; Drummond, 2005). The results of the survey found 42.4 % (95 % confidence interval (95 % CI) 40.2–44.6 %) of TB patients' households faced catastrophic costs (The World Health Organization, 2022b; Florentino et al., 2022; Yamanaka et al., 2023).

Our study was conducted as a nested sub-study of an ongoing longitudinal study aimed to measure the effects of malnutrition and diabetes in patients with TB in Manila, Negros Occidental and Cebu, the Philippines, and to investigate associations with treatment outcome through potential effects on treatment compliance, drug side effects, glycaemic control, weight gain and nutrition during treatment and cell-mediated immune responses (**Appendix 1**). Part of our nested sub-study was to assess the change in costs, income and coping mechanisms before TB diagnosis through to completion of TB treatment, and to assess the difference in costs incurred by TB patients with and without diabetes (Yamanaka et al., 2024). It was conducted in Negros Occidental and Cebu in the Philippines. Negros Occidental is a province in the Western Visayas Region, located in the south-eastern area of the Philippines and categorized as a rural area with a population size of 2.6 million. Cebu is a province of the Central Visayas Region with the second largest city (Cebu city) in the Philippines and categorized as an urban area. We used a sub-sample of 11 health facilities and hospitals located in those two regions. All study sites in Cebu (urban setting) and Negros Occidental (rural setting) used for the main study were also used in our sub-study. The main objective of this sub-study was to compare patient costs incurred by TB patients (and their households) with versus without comorbid diabetes. Assuming a 90 % consent rate and 91 % treatment completion rate, we expected to collect patient cost data from a total of 502 people with TB. Given 9–12 % of the cohort were estimated to have diabetes (45–60 people) (White et al., 2020), we estimated that our sample size of 502 people with TB was sufficiently powered to detect a minimum 17 % increase in total costs, based on a 2011 diabetes patient cost study in Thailand (Chatterjee et al., 2011; Riewpaiboon et al., 2011).

The eligibility criteria of the main study were pulmonary TB patients aged 18 years or older. Although HIV positive TB patients were included in the main study, they were excluded in this sub-study to exclude the financial impact from TB-HIV coinfection. Therefore, costing study participants were TB patients from the main study enrolled between November 2018 and March 2020, and all the data collection was completed by October 2020.

2.2. Study design and data collection

We collected data on patient incurred costs, income, health service utilization, coping mechanisms and social consequences of TB at four time points as part of the ongoing main study (Ferrer et al., 2021). The patient was interviewed at: 1) the start of TB treatment, 2) the end of the

TB intensive phase (month 2 for DS-TB and month 4 for DR-TB), 3) the midpoint of the TB continuation phase (month 4 for DS-TB and month 7.5 for DR-TB), and 4) the end of the TB continuation phase (month 6 for DS-TB and month 9 for DR-TB). For DS-TB and DR-TB, the TB continuation phase lasts longer (4 months and 7 months) than the TB intensive phase (2 months and 4 months), respectively, and patients usually return to work during the TB continuation phase due to physical recovery and resolution of TB symptoms. This informed the two timepoints for data collection in the TB continuation phase of our study.

Research nurses were based at each study site as interviewers to recruit study participants from the main study into this patient cost study. Prior to being deployed to each study site, research nurses received a five-day training on the survey instrument, process of informed consent, TB infection control measures, ethical considerations, and pilot data collection. While patients from the main study at each study site were waiting to be seen, a research nurse explained the purpose of the patient cost study and shared an information sheet. Patients who agreed to participant in the research and signed the informed consent form were enrolled. Data collection for patient costs, household income and coping strategies was conducted by the trained research nurses via 30–45 min in-person interviews at each participant's home and by telephone during the period of COVID-19 lockdowns when it was difficult to have face-to-face interviews.

The data collection tool was adapted from the national TB patient cost survey in the Philippines (Florentino et al., 2022), and this in turn was based on the WHO guideline for national TB patient cost surveys (The World Health Organization, 2017). Costs consisted of direct medical costs (e.g. medical consultation fees, and costs for drugs, diagnostic tests before starting treatment, monitoring tests, hospitalization, and DOT), direct non-medical costs (e.g. costs for transportation, food and supplements, and accommodation), and indirect costs (e.g. income losses due to illness when too unwell to work and costs for a care giver). The data collection included household income and assets, health service utilization, coping mechanisms and social consequences of TB. Other socio demographic and clinical information such as age, sex, education level, TB diagnosis, body mass index (BMI) were extracted from the main study.

2.3. Data analysis

Data were collected and entered at the time of the interviews via tablet-based questionnaires using Open Data Kit (ODK) and ODK collect. Data cleaning and processing, statistical analyses, and data visualizations were performed using R4.2.0. Data monitoring and validation were performed on a weekly basis, and identified missing data was collected by follow-up phone calls and entered into the database using R coding. Mean with standard deviation (SD) and 95 % confidence intervals (CI), and median with inter-quartile range (IQR) were used for continuous data, and frequency and proportions (%) were used for categorical data. All results were stratified based on diabetes status at the time of TB diagnosis. Statistical differences between patients with DS-TB and DR-TB were tested using a chi-square test for categorical data such as demographic and clinical characteristics and the *t*-test or Kruskal–Wallis test for continuous data such as income, health service utilization and cost data. Fisher's exact test was performed for statistical differences in the proportion of catastrophic costs between the longitudinal and cross-sectional designs. Statistical significance was defined as a p-value less than 0.05. Data on costs and income were collected in Philippine Pesos (Php) and later converted into US$ for analysis at the rate of Php 51.19 per US$ 1, which was the average UN Operational Rate of Exchange during the data collection period (November 2018–October 2020).

2.4. Catastrophic cost estimates using the longitudinal study design

Using longitudinal data, costs per phase were first interpolated backwards for the period since the last interview using the data on costs incurred for the last visit by purpose of visits (i.e. DOT, medical follow-up and drug pick-up) multiplied by the frequency of each visit type during each phase. Only for hospitalizations, the duration, reasons and incurred costs for each hospitalization were collected separately considering the individuality of costs of hospitalizations. Then total costs were estimated by summing the costs per phase. Catastrophic cost due to TB was defined as total costs, consisting of direct medical and non-medical costs and indirect costs, exceeding 20 % of ability to pay (i.e. annual household income of TB patients) as per the WHO definition (The World Health Organization, 2017). Following the method used for the Philippines national TB patient cost survey, our study used the output approach as the primary method for estimating indirect cost (differences in self-reported household income before having TB symptoms and at the time of each data collection). A secondary approach, estimating indirect costs using the human capital approach, was used and the results of the two approaches compared (see further details in **Appendix 2**). Reported annual household income prior to TB diagnosis was used as a primary indicator for ability to pay (denominator for estimating catastrophic costs due to TB, output approach). For TB-affected households reporting zero income before having TB, annual household income was imputed using a regression model based on household assets, and the imputed value was used as the denominator for catastrophic costs (**Appendix 3**).

2.5. Simulating catastrophic cost estimates collected using the cross-sectional design

The total longitudinal patient costs over the full course of treatment were compared with results from a simulated cross-sectional design.

In the simulated cross-sectional method, the aim was to simulate incurred expenses per patient at one time point only (either end of intensive phase or middle of continuation phase). To achieve this, we randomly sampled patients from our sample and allocated them to two groups; either those for whom data would have been collected at the end of the intensive phase and or in the middle of the continuation phase in accordance with WHO guidance. We then produced different samples for different proportions of patients in the intensive and continuation phases, respectively (i.e. 20 %:80 % (proportion 1), 35 %:65 % (proportion 2), 50 %:50 % (proportion 3)). The selection of these proportion combinations was based on the most commonly reported proportions used in published national TB patient cost surveys conducted using the WHO recommended methodology (**Appendix 4**) (Florentino et al., 2022; Viney et al., 2019, 2021; Chittamany et al., 2020; Timire et al., 2021; Kirubi et al., 2021; Pedrazzoli et al., 2018; Aia et al., 2022; Kilale et al., 2022; Traore et al., 2022; Muttamba et al., 2020; Aung et al., 2021; Kaswa et al., 2021). Proportion 1 was adopted to replicate the sampling of the Philippines national TB patient cost survey. Proportion 2 was adopted to present the ideal proportion of patients in the cross-sectional design given that the majority of TB patients have DS-TB, which has a 2-month TB intensive phase (33.3 %) and 4-month TB continuation phase (66.6 %), which results in the ratio of 33.3 %:66.6 %. Proportion 3 was adopted to replicate some national surveys that applied a higher proportion of patients in the TB intensive phase (e.g. Mongolia survey purposively applied 50 %:50 % in the sampling) (**Appendix 4**).

Thereafter the direct medical and non-medical costs of the non-sampled treatment phase were extrapolated based on the median costs

estimated from other patients in that treatment phase, following the methodology used for national patient cost surveys (The World Health Organization, 2017). In this extrapolation process for the direct costs, differences in the costs by drug-resistance status and with/without experience of hospitalization were considered.

2.6. Ethical considerations

Ethical approval for the main study, including approval for this sub-study, was obtained from the St. Cabrini Medical Center-Asian Eye Institute Ethics Review Committee (SCMC-AEI ERC) (ERC #2018-008). Ethical approvals were also obtained from the Ethics Review Committee of the WHO Regional Office for the Western Pacific (Ref: 2019.18.PHL.4.STB) and the Ethics Review Committee at the London School of Hygiene and Tropical Medicine and Nagasaki University. In addition to the ethics approvals, we obtained an endorsement letter from National TB Control Programme, Department of Health, the Philippines, to conduct this study. A written consent form was obtained from all participants before the commencement of the interview. The informed consent signed by all participants explicitly stated that only the principal investigator (PI) and co-PIs would have access to the study dataset.

3. Results

3.1. Study population

A total of 530 adult TB patients were enrolled upon TB diagnosis in this study. Of these, 443 patients (83.6 %) were enrolled in the first-line TB treatment (DS-TB patients) and 87 patients (16.4 %) were enrolled in MDR/RR-TB treatment (DR-TB patients) (Table 1). Most of the study participants completed TB treatment (79.4 %) while 15.6 % had loss-to-follow-up, 1.2 % had treatment failure, and 3.9 % died during TB treatment. Therefore, data from all four data collection timepoints were obtained for 445 participants (84 %), which has been the basis for the analysis in Table 3 onwards.

The proportion of participants with no education was less among DR-TB patients (DS-TB: 34.1 %, DR-TB: 21.8 %, $p = 0.041$). The proportion of participants receiving treatment support (facility or community DOT) while in DR-TB treatment was higher throughout TB treatment (intensive phase: DS-TB 17.3 %, DS-TB: 97.0 %; middle of continuation phase: DS-TB 14.9 %, DR-TB: 88.1 %; end of continuation phase: DS-TB 13.0 %, DR-TB 92.5 %; $p < 0.001$) (Table 1).

Households for both DS-TB and DR-TB patients reported a substantial decline in household income at the time of TB diagnosis and during TB treatment. For DS-TB patients, the mean reported monthly household income before having TB symptoms was USD 183 (95 %CI: USD 152–215), and it reduced to USD 77 (95 %CI: USD 64–89) at TB diagnosis and USD 8 (95 %CI: 6–10) at the end of the intensive phase. The reported household income increased to USD 194 (95 %CI: USD 159–229) and USD 189 (95 %CI: USD 155–223) during the middle and at the end of the continuation phase, respectively. For DR-TB patients, the mean reported monthly household income before having TB symptoms was USD 250 (USD 182–319), decreasing to USD 99 (USD 64–134) at TB diagnosis and USD 13 (USD 2–23) at the end of the intensive phase. The reported household income increased to USD 204 (USD 149–259) and USD 250 (USD 182–319) during the middle and at the end of the continuation phase, respectively (Table 1).

The proportion of patients receiving the social support package was higher in DR-TB patients throughout TB treatment (intensive phase: DS-TB 3.3 %, DR-TB: 86.8 %; middle of continuation phase: DS-TB 4.8 %, DR-TB: 94.3 %; end of continuation phase: DS-TB 3.6 %, DR-TB 96.2 %; $p < 0.001$ at all the time points). There was no statistical significance between the proportion of DS-TB and DR-TB patients receiving the conditional cash transfer (CCT) programme. The CCT programme was received by 16.0 % (95 %CI: 12.8–19.7 %) of TB-affected households before TB diagnosis, and the proportion remained constant throughout TB treatment (TB diagnosis: 15.5 % (95 %CI: 12.4–19.2 %), the end of intensive phase: 16.9 % (95 %CI: 13.6–20.6 %), the middle of continuation phase: 15.5 % (95 %CI: 19.7–12.8 %), the end of continuation phase: 14.6 % (95 %CI: 11.8–18.5 %)) (Table 1).

The mean total number of visits for TB services amongst all participants was 90.5 visits, with 5.1 visits occurring for care seeking before TB diagnosis. People with DR-TB had more frequent visits in total (DR-TB: 418.0, DS-TB: 47.1, $p < 0.001$) compared to people with DS-TB (Table 1). There were significant differences ($p < 0.001$) in the number of visits for TB services by treatment phase and by purpose of visit between people with DR-TB and DS-TB.

Among the three main cost categories for TB services, the costs were predominantly driven by indirect costs throughout a TB episode. For DS-TB patients, the proportion of income loss out of total costs incurred before TB diagnosis was 73.8 %, 94.4 % in the intensive phase, 81.4 % and 84.9 % in the middle and end of the continuation phase. For DR-TB patients, the proportion was 51.0 % before TB diagnosis, 89.1 % in the intensive phase, 76.9 % and 72.1 % in the middle and end of the continuation phase, while the proportion of direct medical costs was also high at 31.0 %.

3.2. Comparison of total costs between longitudinal and simulated cross-sectional designs

The methodological differences between the longitudinal and cross-sectional designs for assessing TB patient costs were summarized in Table 2. With the output approach, using longitudinal data, the mean total cost was estimated as USD 932 (95 %CI: USD 798–1066). However, the mean total costs estimated using the cross-sectional design was based on the proportion of patients in the intensive and continuation phases. It was USD 680 (95 %CI: USD 566–794) for proportion 1, USD 928 (95 %CI: USD 710–1146) for proportion 2, and USD 1113 (95 %CI: USD 878–1348) for proportion 3 (Table 3). Income loss was the main contributor to differences between the longitudinal and cross-sectional designs. Income loss was estimated at USD 802 (95 %CI: USD 672–932) with the longitudinal method, while the cross-sectional methods estimated USD 550 (95 %CI: USD 440–660), USD 788 (95 % CI: USD 573–1002) and USD 975 (95 %CI: USD 744–1206) for proportions 1, 2 and 3 respectively (Table 3).

3.3. Comparison of TB-affected households facing catastrophic costs

Using the output approach and longitudinal method, 69.0 % (95 % CI: 64.7–73.3 %) of TB-affected households incurred costs >20 % of annual household income (Fig. 1).

With the cross-sectional method, 39.7 % (95 %CI: 35.2–44.2 %) of TB-affected households faced catastrophic costs for proportion 1, which was lower than that for proportion 2 (47.9 %, 95 %CI: 43.4–52.5 %) and for proportion 3 (54.6 %, 95 %CI: 50.1–59.2 %). Statistically significant differences ($p < 0.001$) were observed between the catastrophic costs using the longitudinal and cross-sectional designs for proportions 1, 2 and 3 and also within the cross-sectional design (between proportions 1 and 2, and proportions 2 and 3).

Table 1
Demographic, clinical, and economic characteristics of study participants in Negros Occidental and Cebu, the Philippines by drug resistance status.

		Drug-susceptible TB		Drug-resistant TB		All TB patients		p-value
		N	**(%)**	**N**	**(%)**	**N**	**(%)**	
Total		**443**	**83.6 %**	**87**	**16.4 %**	**530**	**100 %**	
Demographic characteristics								
Sex	Female	133	30.0 %	21	24.1 %	154	29.1 %	0.329
Age group	18–24	69	15.6 %	10	11.5 %	79	14.9 %	0.092
	25–34	74	16.7 %	15	17.2 %	89	16.8 %	
	35–44	61	13.8 %	17	19.5 %	78	14.7 %	
	45–54	85	19.2 %	25	28.7 %	110	20.8 %	
	55–64	82	18.5 %	13	14.9 %	95	17.9 %	
	≥65	72	16.3 %	7	8.1 %	79	14.9 %	
Education level	No education/Primary	151	34.1 %	19	21.8 %	170	32.1 %	0.041
	High school	213	48.1 %	45	51.7 %	258	48.7 %	
	University or higher/Vocational	79	17.8 %	23	26.4 %	102	19.3 %	
Insurance status	No insurance	125	28.2 %	28	32.2 %	153	28.9 %	0.479
	PhilHealth	194	43.8 %	32	36.8 %	226	42.6 %	
	GSIS/SSS (insurance for formal employment)	124	28.0 %	27	31.0 %	151	28.5 %	
Household size		5 (1–14)		4 (1–14)		5 (1–14)		
Employment status before TB	Employed (Formal)	88	19.9 %	23	26.4 %	111	20.9 %	0.140
	Employed (Informal)	171	38.6 %	29	33.3 %	200	37.7 %	
	Unemployed	150	33.9 %	33	37.9 %	183	34.5 %	
	Student/Retired	34	7.7 %	2	2.3 %	36	6.8 %	
Primary income earner	Yes	209	47.2 %	46	52.9 %	255	48.1 %	0.393
Clinical characteristics								
Diabetes status at TB diagnosis	With diabetes	112	25.3 %	32	36.8 %	144	27.2 %	0.038
Treatment history	New	322	73.4 %	24	27.6 %	346	65.8 %	<0.001
	Relapse	111	25.3 %	46	52.9 %	157	29.9 %	
	Retreatment	5	1.1 %	10	11.5 %	15	2.9 %	
	Unknown	0	0.0 %	5	5.8 %	5	1.0 %	
Body mass index (kg/m^2)	≥18.5	254	57.5 %	44	50.6 %	298	56.3 %	0.286
Diagnostic delay (>4weeks)		308	69.5 %	69	79.3 %	377	71.1 %	0.087
Duration of TB treatment (weeks)	Intensive phase: Mean, SD	8	1.2	18	2.8	10	3.9	<0.001
	Continuation phase: Mean, SD	16	1.5	22	2.0	17	2.4	<0.001
Hospitalized due to TB		39	8.8 %	13	14.9 %	52	9.8 %	0.118
Treatment supports in intensive phase	Self-administered	340	82.7 %	2	3.0 %	342	71.6 %	<0.001
	With treatment partner	71	17.3 %	65	97.0 %	136	28.5 %	
Treatment supports in middle of continuation phase	Self-administered	338	85.1 %	7	11.9 %	345	75.7 %	<0.001
	With treatment partner	59	14.9 %	52	88.1 %	111	24.3 %	
Treatment supports in end of continuation phase	Self-administered	341	87.0 %	4	7.6 %	345	77.5 %	<0.001
	With treatment partner	51	13.0 %	49	92.5 %	100	22.5 %	
Financial status		**Mean**	**95 % CI**	**Mean**	**95 % CI**	**Mean**	**95 % CI**	
Self-reported monthly household Income (in US$)	Before onset of TB symptoms	183.4	(151.7–215.2)	179.0	(139.2–218.8)	182.7	(155.4–210.0)	0.865
	At the time of TB diagnosis	76.7	(64.3–89.1)	98.6	(63.8–133.5)	80.3	(68.4–92.1)	0.245
	At the end of intensive phase	8.0	(5.8–10.1)	12.5	(1.8–23.2)	8.6	(6.2–11.0)	0.420
	At the middle of continuation phase	194.0	(158.6–229.4)	203.8	(148.9–258.8)	195.3	(163.6–226.9)	0.768
	At the end of continuation phase	189.3	(155.4–223.2)	250.2	(181.5–318.9)	196.5	(165.5–227.6)	0.120
Social supports for TB patients	Before TB diagnosis	0.3	(0.04–1.8)	20.8	(11.7–34.1)	2.7	(4.7–1.5)	<0.001
	Intensive phase	3.3	(1.9–5.6)	86.8	(74.4–93.7)	13.3	(16.8–10.4)	<0.001
	Middle of continuation phase	4.8	(3.1–7.5)	94.3	(83.5–98.2)	15.5	(19.2–12.4)	<0.001
	End of continuation phase	3.6	(2.1–6.0)	96.2	(85.7–99.1)	14.6	(18.2–11.6)	<0.001
Conditional cash transfer for poor	Before TB diagnosis	16.3	(13.0–20.3)	13.2	(6.3–25.6)	16.0	(19.7–12.8)	0.561
	Intensive phase	15.6	(12.3–19.5)	15.1	(7.6–27.8)	15.5	(19.2–12.4)	0.930
	Middle of continuation phase	16.8	(13.4–20.9)	17.0	(8.9–29.9)	16.9	(20.6–13.6)	0.979
	End of continuation phase	15.1	(11.8–19.0)	13.2	(6.3–25.6)	14.8	(18.5–11.8)	0.723
Health service utilization (times of facility visits)		**Mean**	**95 % CI**	**Mean**	**95 % CI**	**Mean**	**95 % CI**	
Before TB diagnosis	Care seeking	5.1	(4.9–5.3)	5.8	(5.1–6.6)	5.1	(4.9–5.3)	0.033
Intensive phase	Medical follow-up	0.7	(0.7–0.8)	3.2	(2.3–4.1)	1.0	(0.9–1.2)	<0.001
	Drug pickup	6.9	(6.3–7.6)	97.0	(83.1–110.8)	17.5	(14.3–20.7)	<0.001
	Directly observed therapy	9.1	(6.9–11.3)	117.7	(109.2–126.1)	21.8	(17.9–25.7)	<0.001
Middle of continuation phase	Medical follow-up	0.4	(0.4–0.5)	1.8	(1.5–2.0)	0.6	(0.5–0.6)	<0.001
	Drug pickup	5.7	(5.2–6.2)	43.5	(33.6–53.3)	10.1	(8.4–11.8)	<0.001
	Directly observed therapy	7.3	(5.5–9.1)	59.4	(50.0–68.8)	13.4	(10.9–15.9)	<0.001
End of continuation phase	Medical follow-up	0.6	(0.6–0.7)	1.7	(1.4–2.0)	0.7	(0.7–0.8)	<0.001
	Drug pickup	5.3	(5.0–5.6)	31.7	(22.5–41.0)	8.4	(7.0–9.8)	<0.001
	Directly observed therapy	5.9	(4.3–7.6)	56.2	(47.7–64.8)	11.8	(9.5–14.2)	<0.001
Total (before TB diagnosis until end of continuation phase)		47.1	(41.6–52.6)	418.0	(383.8–452.1)	90.5	(77.7–103.2)	<0.001

Diagnostic delay: Duration from start having TB symptoms until TB diagnosis.

Table 2
Characteristics of longitudinal versus cross-sectional study design for patient cost data collection.

Characteristic	Longitudinal study (our study)	Cross-sectional study (national TB patient cost surveys)
Sample population	Patients newly diagnosed with TB	Patients receiving TB treatment (at least initial 14 days of the current treatment phase)
Duration of study	Enrolment period plus follow-up period (at least 6 months for DS-TB and 9 months for DR-TB)	Depending on TB burden in study sites, on average 4–6 months
Example for length of data collection	2 years for the sample size of 530	3–6 months for the sample size of 500–1300
Number of data collection points	At least 4 times per patient to assess changes in income, costs, and coping mechanisms over time. (e.g. at TB diagnosis, during intensive phase, and during continuation phase)	Single time point per patient, interviewed during either intensive phase (costs before and during TB diagnosis, and during intensive phase) or continuation phase (costs during continuation phase).
Missing data	More due to dropout (84 % completion rate for 4 interviews, >90 % of participants without missing data at each time point) (e.g. refuse to participate, moveout from study areas, death, loss to follow-up) during follow-up period.	Less (>90 % of participants without missing data) (have missing data only to specific questions for which participants refuse to answer)
Recall bias	1 week to 1 month for the recall period	maximum 3–9 months for the recall period for income before TB diagnosis
Estimation of total costs	Interpolation of costs in each treatment phase based on data from same patient over period of TB episode.	Extrapolation of reported costs to estimate costs incurred during the phase in which patients were not interviewed. (e.g. costs incurred during continuation phase for patients who were in intensive phase at the time of interview)

Table 3
Detail of costs incurred per TB-affected households, by design, mean (95 %CI), output approach.

TB patient costs, US$			Longitudinal			Cross-sectional								
						Proportion of patients in intensive and continuation phases								
						20:80			35:65			50:50		
			Mean	(95 % CI)	%	Mean	(95 % CI)	%	Mean	(95 % CI)	%	Mean	(95 % CI)	%
Pre-TB diagnosis	Direct medical costs		28.7	(20.1–37.3)	3.1 %	13.9	(12.4–15.3)	2.0 %	16.1	(14.3–17.9)	1.7 %	16.7	(14.9–18.4)	1.5 %
	Direct non-medical costs		29.1	(24.3–33.9)	3.1 %	18.4	(17.1–19.6)	2.7 %	20.3	(17.8–22.9)	2.2 %	23.4	(19.6–27.1)	2.1 %
	Income loss		219.3	(161.2–277.4)	23.5 %	125.8	(89.6–161.9)	18.5 %	179.7	(126.9–232.5)	19.4 %	263.7	(180.6–346.9)	23.7 %
Post-TB diagnosis	Direct medical costs	Drug pickup	0.05	(0–0.1)	0.0 %	0.002	(0–0.006)	0.0003 %	0.004	(0–0.009)	0.0004 %	0.01	(0.001–0.02)	0.001 %
		Directly observed therapy	0.0	(0.0–0.0)	0.0 %	0.0	(0.0–0.0)	0.0 %	0.0	(0.0–0.0)	0.0 %	0.0	(0.0–0.0)	0.0 %
		Follow-up	1.8	(0.9–2.6)	0.2 %	1.5	(0.5–2.5)	0.2 %	2.1	(0.9–3.2)	0.2 %	1.2	(0.2–2.2)	0.1 %
		Hospitalization	1.8	(0–4.3)	0.2 %	2.7	(0–6.3)	0.4 %	2.2	(0–5.7)	0.2 %	2.0	(0–4.8)	0.2 %
	Direct non-medical costs	Accommodation	0.06	(0–0.1)	0.0 %	0.5	(0.2–0.8)	0.1 %	0.3	(0.2–0.4)	0.0 %	0.4	(0.2–0.7)	0.0 %
		Food	3.6	(2.6–4.6)	0.4 %	7.6	(4.0–11.1)	1.1 %	7.6	(3.6–11.6)	0.8 %	6.9	(3.5–10.4)	0.6 %
		Travel	19.2	(16.2–22.1)	2.1 %	33.2	(24.7–41.7)	4.9 %	32.7	(22.0–43.3)	3.5 %	34.7	(22.6–46.7)	3.1 %
		Nutrition supplement	45.8	(40.0–51.7)	4.9 %	52.1	(44.3–59.8)	7.7 %	59.0	(49.9–68.1)	6.4 %	52.4	(44.6–60.2)	4.7 %
	Income loss		582.7	(493.3–672.1)	62.5 %	424.2	(341.9–506.5)	62.4 %	607.9	(434.1–781.7)	65.5 %	711.3	(534.7–887.8)	63.9 %
Total direct medical costs			32.3	(23.3–41.3)	3.5 %	18.1	(13.7–22.5)	2.7 %	20.3	(16.0–24.7)	2.2 %	19.9	(16.5–23.3)	1.8 %
Total direct non-medical costs			97.7	(87.6–107.8)	10.5 %	111.7	(97.0–126.4)	16.4 %	119.9	(101.7–138.1)	12.9 %	117.9	(0–135.9)	10.6 %
Total income loss			802.0	(672.0–932.1)	86.1 %	550.0	(439.5–660.4)	80.9 %	787.7	(572.9–1002.4)	84.9 %	975.0	(743.9–1206.1)	87.6 %
Total cost			932.0	(798.4–1065.7)	100.0 %	679.8	(565.8–793.7)	100.0 %	927.9	(710.0–1145.7)	100.0 %	1112.8	(877.7–1347.8)	100.0 %

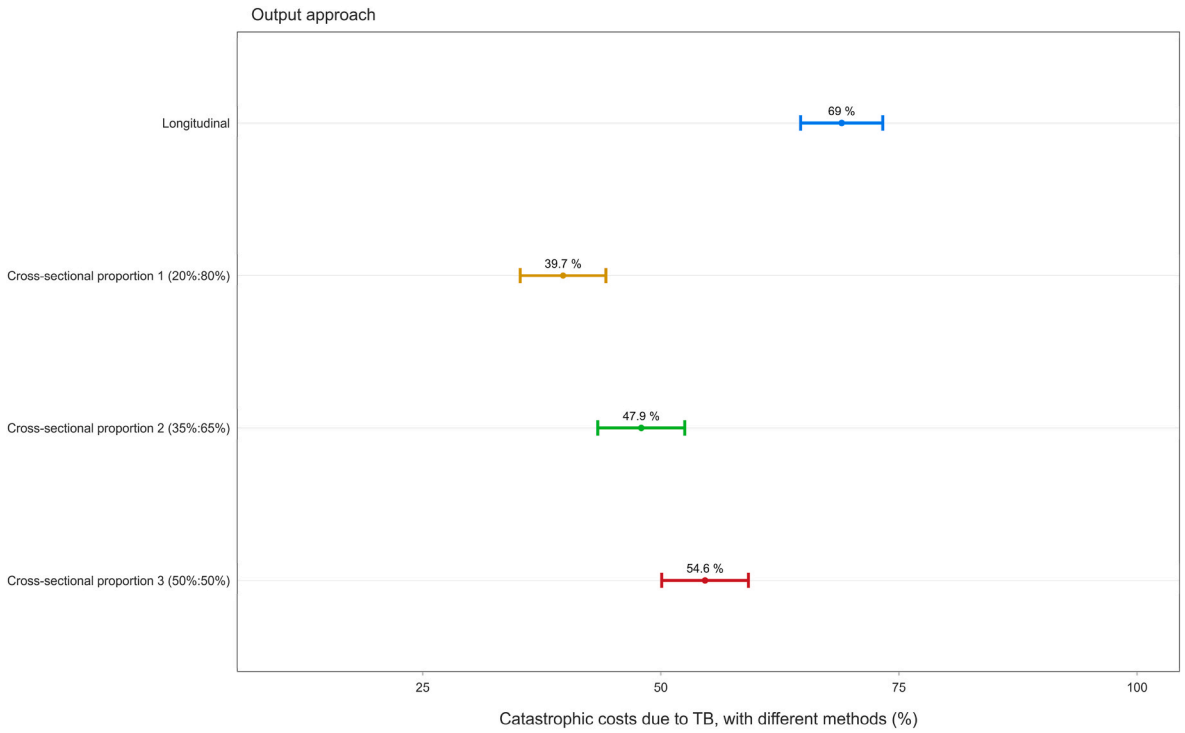

Fig. 1. Percentage of TB-affected households facing catastrophic costs (>20 % of annual household income).

3.4. Coping mechanisms and social consequences

Half (50.3 %) of TB-affected households relied on either dissaving, loans, or selling household assets to cope with the financial burden prior to TB diagnosis (Fig. 2). The proportion decreased to 20.2 % in the intensive phase and 11.0 % and 11.7 % during the middle and at the end of the continuation phase. Among the three coping mechanisms, taking loans was the most common, at 32.6 % before TB diagnosis, 15.3 % in the intensive phase, and 7.9 % and 9.9 % during the middle and at the end of the continuation phase, respectively.

Job loss was the most encountered social consequence of TB, with nearly half of households experiencing job loss before TB diagnosis (46.1 %) and during the intensive phase (40.9 %). Food insecurity was greatest amongst households during the intensive phase (7.6 %), but social exclusion was greatest before TB diagnosis (12.8 %).

4. Discussion

4.1. Key findings

Our analysis highlighted the potential bias of estimating disease-specific catastrophic costs using a cross-sectional design. We found that catastrophic cost estimates of TB were underestimated with the cross-sectional approach compared to the longitudinal approach. The catastrophic cost estimates with the cross-sectional approach were considerably affected by the proportion of patients taken from each treatment phase. Our analysis with a simulated cross-sectional approach showed that the catastrophic cost estimates ranged from 40 % to 55 % according to the proportion of patients selected in the intensive versus continuation phase. This is due to an inherent failure in the cross-sectional design to capture changes in household income during a TB episode because the changes experienced during the intensive phase are typically reduced by 95 % but increased by 7 %–8 % during the continuation phase, compared to household income prior to TB symptoms.

4.2. Redesigning national TB patient cost surveys for robust evaluation of indirect costs

In the longitudinal approach, the changes in household income (and incurred income loss) can be captured by having multiple data collection points. However, in the WHO recommended cross-sectional design, the changes cannot be captured as the income loss during TB treatment is calculated based on the difference in income between before having TB symptoms and at the time of TB diagnosis (The World Health Organization, 2017). In our study, TB-affected households were more financially vulnerable during pre-diagnosis and the TB intensive phase, with their household income recovering in the TB continuation phase to that of the level before having TB symptoms. In line with the changes in household income, the proportions of households using savings and taking loans were also high during these periods. In this situation, with the cross-sectional design, income loss is overestimated for those in the TB intensive phase and underestimated for those in the continuation phase.

However, there is a trade-off with these inaccurate estimates and using a longitudinal design which requires a longer duration for study implementation, more frequent data collection, and a larger budget. In resource-limited settings, it is not always feasible to estimate catastrophic costs using the longitudinal design and the cross-sectional design must be used. Our findings indicate that care should be taken when interpretating cross-sectional patient cost surveys. Indirect costs were the main cost driver in 13 national TB patient cost surveys out of 31 completed (The World Health Organization, 2023), which highlights why robust evaluation of indirect costs is essential in assessing TB patient costs. One option for the cross-sectional design is to enrol TB patients while in the TB continuation phase only to allow an assessment of household income before TB, during TB diagnosis, in the TB intensive and continuation phases, even though this increases the risk of recall bias. A study in Nepal that compared the results of TB patient cost between the longitudinal and cross-sectional approaches suggested that in resource-constrained settings where a longitudinal study design is not feasible, one-time data collection in the TB continuation phase would provide more accurate cost estimates (Bengey et al., 2023). Another

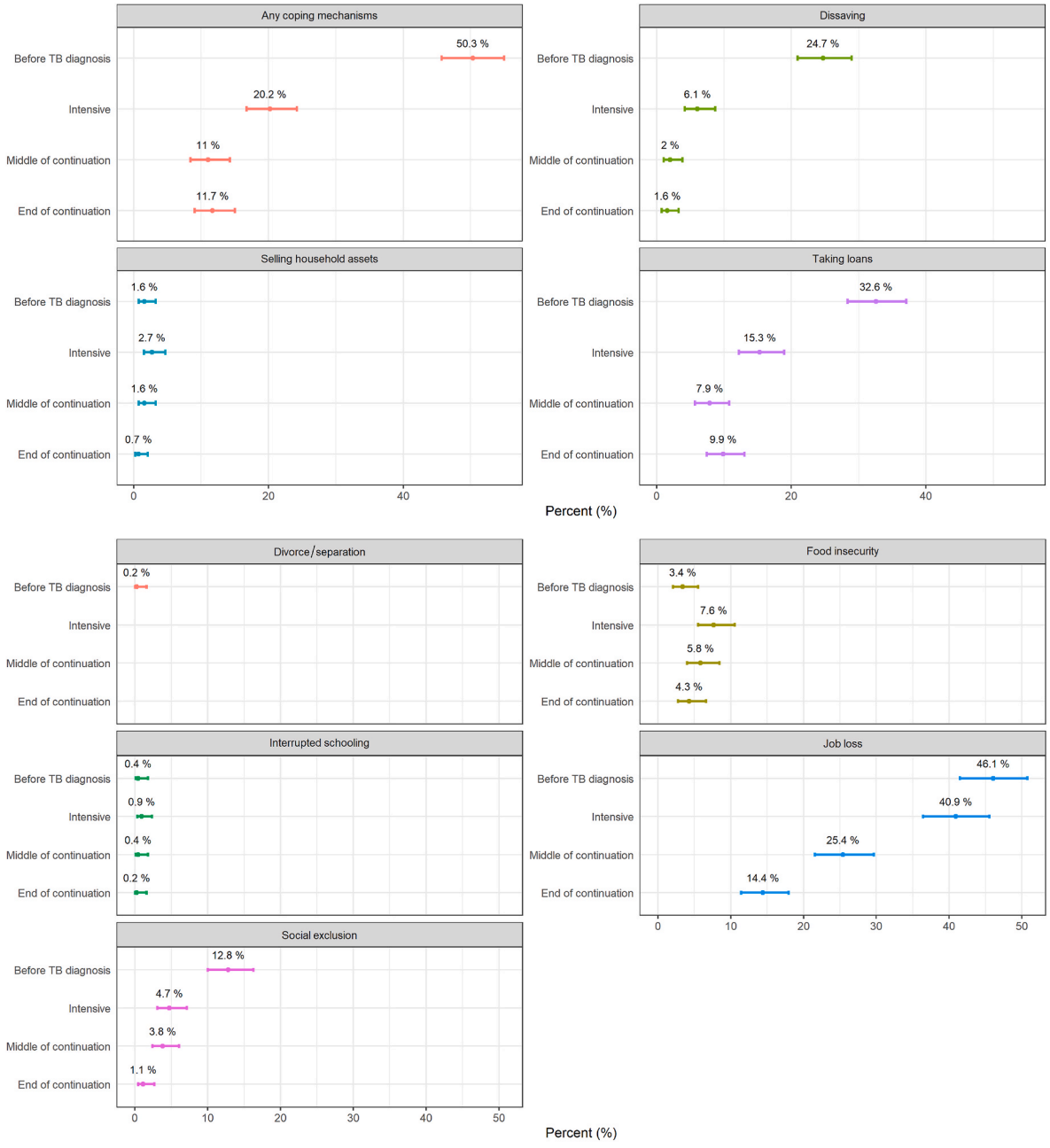

Fig. 2. Coping mechanisms and social consequences due to TB. *interrupted schooling includes both children in households and patients themselves

option is to consider national TB patient cost surveys using a feasible longitudinal design. Although the longitudinal approach requires additional time and financial resources and may increase the risk of attrition bias, it provides a more robust evaluation of costs and income per person across an episode of TB (Evans et al., 2021; Guo et al., 2013). Our study conducted data collection at four time points during an episode of TB, and another longitudinal TB patient cost study (TB Sequel) collected data at 0, 2, 6, 12 and 24 months, which is likely not feasible in resource-limited settings (Evans et al., 2021). Therefore, WHO guidelines for conducting national TB patient cost surveys could explore a more feasible option for a longitudinal approach, such as two data collection timepoints: once in each of the intensive and continuation phases.

4.3. Required recommendations for sampling

The absence of an official recommendation about the sample proportions to be obtained in the TB intensive and continuation phases for national surveys using the cross-sectional design resulted in large differences, varying from 19 % in the Philippines to 53 % in Solomon Islands (The World Health Organization, 2017). This may have resulted in under or overestimation of indirect costs. Given the majority of TB patients globally have DS-TB and the treatment requires 2 months for the intensive phase and 4 months for the continuation phase (The World Health Organization, 2022a, 2022b), the appropriate proportion of patients in the intensive phase would be around 33.3 %. And given that 2.5 % of global TB notifications are DR-TB, with shorter treatment regimens typically lasting 4 months for the intensive phase and 5 months for the continuation phase, the appropriate proportion is 33.6 % (The World Health Organization, 2022). For the WHO-recommended surveys, since the proportion of patients with DR-TB varies by country, it can be recommended that the ideal sampling proportion needs to be defined using the latest statistics around TB notifications (https://worldhealthorg.shinyapps.io/tb_profiles/). In the case of the Philippines, out of 444,987 total cases notified in 2022, 9916 cases (2.2 %) were MDR/RR-TB, and therefore, the ideal proportion of patients in the intensive phase is estimated as 33.6 % assuming all MDR/RR-TB patients are on treatment with the shorter 9-month regimen. For countries with a large number of (pre-)extensively drug-resistant TB (XDR-TB) and/or extrapulmonary TB, the proportion of notifications may need to be considered as the treatment for (pre-)XDR-TB and extrapulmonary TB takes longer than that for pulmonary DS-TB. Our findings suggests that the catastrophic cost estimates in studies that enrolled more than 33.6 % of participants from the intensive phase and applied the output approach (i.e. 50 % or more in Kenya, Solomon Islands, Uganda, Vietnam, and Zimbabwe) might have been overestimated (**Appendix 3**). Surveys that under-sampled patients in the intensive phase (i.e. 19 % in the Philippines) may have underestimated the catastrophic costs. Hence our study findings highlight the need for an official recommendation by WHO.

4.4. Inconsistency between recommendations and implementations

We found that the mean total costs incurred by TB-affected households was USD 932, and of these costs 24 % (USD 219) was indirect costs borne during care seeking before TB diagnosis. More than 70 % of our study participants took four weeks or more from the onset of TB symptoms until the diagnosis of TB, and therefore the long duration of care seeking and the consequent delay in TB diagnosis resulted in income loss even before diagnosis of the disease. This result is consistent with a previous systematic review of TB patient cost studies showing that indirect costs before TB diagnosis accounted for 26 % of total costs (Tanimura et al., 2014). The WHO recommendation clearly states *"Use self-reported household income at three points in time (before the onset of TB symptoms, at the time of diagnosis and during the "current" treatment phase) to estimate income change before and during the TB episode"*. However, the implementation is being conducted differently for surveys using the output approach. As we summarize in Appendix 4, the majority of national surveys used the output approach for estimating indirect costs, but none of them included income loss before TB diagnosis (Florentino et al., 2022; Viney et al., 2019, 2021; Chittamany et al., 2020; Timire et al., 2021; Pedrazzoli et al., 2018; Aia et al., 2022; Aung et al., 2021; Nhung et al., 2018). This inconsistency between the recommendation and the implementation can be also observed in a recent WHO publication *"National surveys of costs faced by tuberculosis patients and their households 2015–2021"* (The World Health Organization, 2022c). In part 2, 20 country profiles are presented, and for those using the output approach, the publication was unable to present income loss before TB diagnosis. The exclusion of indirect costs before TB diagnosis may have a considerable impact on catastrophic cost estimates since it lowers the catastrophic cost estimates. Yet of 14 publications of national TB patient cost surveys implemented using a cross-sectional design, nine surveys applied the output approach as a method for estimating indirect costs (Florentino et al., 2022; Viney et al., 2019, 2021; Chittamany et al., 2020; Timire et al., 2021; Pedrazzoli et al., 2018; Aia et al., 2022; Aung et al., 2021; Nhung et al., 2018). Our analyses re-highlights the impact of indirect costs before TB diagnosis and the need to correct the inconsistency between the recommended method and the implementation in national TB patient cost surveys.

4.5. Limitations

This study had several limitations. First, this study was conducted using 11 health facilities located in urban (Cebu) and rural (Negros) settings in the Philippines, and therefore, the results and findings cannot be generalized. Changes in household income, coping mechanism, and social consequences of a disease could be markedly different by country and local contexts. Although the reduction and recovery in household income and in social consequences in our findings are observed in a longitudinal study in Vietnam, the pattern was not identified in another longitudinal study that assessed the catastrophic cost estimates for TB in Nepal (Vo et al., 2021; Gurung et al., 2021). Second, in this study, 16 % of participants were not able to complete four data collection time points due to drop out from TB treatment or study participation, and therefore, results of catastrophic cost estimates might be affected by attrition bias. Also, the dropout rate in the longitudinal design will be an issue if the study design is applied to a national survey since the WHO recommended national surveys require a much larger sample size (i.e. around 800-1000 or more), and a high dropout rate may result in extension of survey duration. The issue needs to be carefully considered especially for countries with mobile populations. Third, although the longitudinal study design allowed multiple interviews during a TB episode with less recall bias compared to a cross sectional study, this study assessed costs from the onset of TB symptoms to the completion of TB treatment. Therefore, financial loss due to TB-related sequalae and/or prolonged social consequences after TB treatment were not investigated in this study. Fourth, self-reported income was used as the ability to pay measure in the catastrophic cost estimates in this study. However, the use of self-reported income can induce the underestimation of the catastrophic cost compared to methods with the asset linking approach or income estimates using the national average (Sweeney et al., 2018). Furthermore, though household consumption/expenditure is considered the gold standard for estimating ability to pay (Wagstaff and Lindelow, 2014; DeJuan and Seater, 1999), we did not explore this method. Further studies developing and validating a consumption/expenditure-based measure will contribute to the improvement of the measurement of ability to pay in the catastrophic cost estimates.

5. Conclusion

Using longitudinal data of costs incurred by TB-affected households, we illustrated the potential limitations and implications of estimating indirect costs using a cross-sectional design and the output approach in the catastrophic cost estimates. Excluding possible changes in household income during the treatment of the disease and an inappropriate sampling balance from the different treatment phases will potentially underestimate catastrophic costs. Our findings can contribute to improvements in the recommendations and guidelines provided by the WHO Task Force for conducting national TB patient cost surveys to assess TB-specific catastrophic costs.

CRediT authorship contribution statement

Takuya Yamanaka: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mary Christine Castro:** Resources, Project administration, Investigation. **Julius Patrick Ferrer:** Resources, Project administration, Investigation. **Sharon E. Cox:** Writing – review & editing, Funding acquisition, Conceptualization. **Yoko V. Laurence:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Anna Vassall:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2024.116631.

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