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Cost of tuberculosis treatment in low- and middle-income countries: systematic review and meta-regression

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SUMMARY

BACKGROUND: Despite a scarcity of tuberculosis (TB) cost data, a substantial body of evidence has been accumulating for drug-susceptible TB (DS-TB) treatment. In this study, we review unit costs for DS-TB treatment from a provider's perspective. We also examine factors driving cost variations and extrapolate unit costs across low- and middle-income countries (LMICs).

METHODS: We searched published and grey literature for any empirically collected TB cost estimates. We selected a subgroup of estimates looking at DS-TB treatment. We extracted information on activities and inputs included. We standardised costs into an average per person-month, fitted a multi-level regression model and cross-validated country-level predictions. We then extrapolated estimates for facility-based, directly observed DS-TB treatment across countries.

RESULTS: We included 95 cost estimates from 28 studies across 17 countries. Costs predictions were sensitive to characteristics such as delivery mode, whether hospitalisation was included, and inputs accounted for, as well as gross domestic product per capita. Extrapolation results are presented with uncertainty intervals (UIs) for LMICs. Predicted median costs per 6 months of treatment were US$315.30 (95% CI US$222.60–US$417.20) for low-income, US$527.10 (95% CI US$395.70–US$743.70) for lower middle-income and US$896.40 (95% CI US$654.00–US$1214.40) for upper middle-income countries.

CONCLUSIONS: Our study provides country-level DS-TB treatment cost estimates suitable for priority setting. These estimates, while not standing as a substitute for local high-quality primary data, can inform global, regional and national exercises.

KEY WORDS: cost; tuberculosis; first-line treatment; LMIC; systematic review

IN 2017, APPROXIMATELY 10 million people developed tuberculosis (TB), with an estimated 1.9 million deaths due to TB globally.[1] To accelerate progress in reducing this TB burden, the World Health Organization (WHO) has set targets of 95% reduction in TB deaths compared to 2015 rates, and 90% reduction in TB incidence rates to less than 10 TB cases per 100 000 population by 2035.[2] Achieving these targets will require a scale-up of current services, as well as the introduction of new technologies.[3] These expansions to national TB programmes will stretch current TB budgets.[2] Estimates of costs of healthcare provision are a key component of economic evaluations, budgeting and planning when considering the introduction of new technologies or the expansion of interventions and services. However, cost data for TB services and interventions available globally remains scarce and a concern to analysts and policy makers alike.[2]

The Global Health Cost Consortium (GHCC) was established to improve the quality and availability of costs estimates for HIV and TB, with two main products. The first product is a comprehensive unit cost study repository (UCSR) summarising and standardising existing cost data from a systematic review of all literature to date in HIV and TB.[4] The second product is a reference case to improve methods and reporting of costing studies for estimating the costs of global health services and interventions.[5]

For TB, in addition to this updated effort by GHCC, 10 systematic reviews have been published addressing different aspects of cost data. Four systematic reviews summarised evidence on patient-incurred costs in various settings,[6–9] stressing the elevated financial burden and risk faced by TB patients and their households. From a provider perspective, there have been seven systematic reviews.

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These reviews covered various aspects of service delivery: treatment costs for drug-susceptible and multidrug-resistant TB for centralised and decentralised services;[6,10,11] costs of diagnostic and monitoring tests and algorithms;[12,13] and costs of TB-related services when patients are co-infected with HIV.[14,15] The studies converge in concluding that there is a scarcity of data and a need for standardisation of costing methods going forward.

The aim of the present study is to examine the current evidence base on TB costs to explore whether it could be used to estimate costs in countries with data scarcity. We reviewed and standardised unit costs for treatment of drug-susceptible TB from a provider's perspective where a substantial body of evidence has been accumulating. We examined the factors driving cost variation and then assessed the extent to which TB cost data currently available can be used to estimate unit costs across low- and middle-income countries (LMICs).

METHODS

This systematic review was conducted and is reported following the principles of the PRISMA statement,[16] provided in the Supplementary Data (Supplementary Table S1). There was no protocol published for this analysis; however, the methods for the development of the Unit Cost Study Repository (UCSR), the basis of data included, covering searches, article selection, and data extraction, are presented in detail elsewhere.[17]

Ethical approval was not required for this study, as it pertains to secondary data analysis only.

Search strategy, selection of studies and standardisation of cost estimates

Our search and article selection process included three steps. First, we searched the UCSR.[4] Briefly, for TB-related costs, a systematic search of the published literature in PubMed, EMBASE, EconLit, Cochrane, National Health Service Economic Evaluation Database; and the Cost-Effectiveness Analysis Registry was done in July 2016 using broad searches, including economic terms (e.g., 'cost', 'economic' or 'financial'), disease-related terms (e.g., 'TB', 'tuberculosis, 'MDR', 'XDR') and intervention-specific keywords (e.g., 'treatment', 'DOTS', 'isoniazid preventive therapy', 'patient cost'). These searches were then updated to include two additional databases, Web of Science and Literatura Latinoamericana en Ciencias de la Salud (LILACS) in March 2017. There were no exclusions based on language or intervention type. Grey literature, experts in the field and the reference lists of previous systematic reviews were also consulted. All studies presenting empirically collected TB cost data from a provider or patient perspective in low, lower-middle and upper middle-income countries covering the period from January 1990 to March 2017 were included in the UCSR. Second, we updated the UCSR searches in February 2019 and retrieved all studies presenting empirically collected TB cost data from a provider or patient perspective in LMICs covering the period from March 2017 to February 2019 using the same searches and inclusion criteria. Finally, from all the studies retrieved, we selected a subset of studies presenting cost data from a provider perspective published since 2000 for drug-susceptible TB treatment. We also restricted this review to those studies presenting TB treatment using a standard 6-month rifampicin-containing regimen, i.e., 2-month intensive phase including isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a 4-month continuation phase of isoniazid and rifampicin only.

Two authors screened all articles retrieved and verified eligibility of those included in the review. From the studies included, we extracted information describing the study setting and costing method such as country, intervention description, including service delivery characteristics, the year when the authors reported data being analysed and targeted population. We also extracted data describing the cost inputs included in the unit cost estimates to assess the risk of bias in individual estimates. The primary outcome of interest was unit costs, defined as cost per person treated for the full duration of the treatment, including both the intensive and continuation phases. We converted all cost estimates into United States dollars ($US) using the exchange rate for the year of the study, then standardised them into 2017 $US using US gross domestic product (GDP) price deflator. Finally, we calculated an average cost per person-month of treatment by dividing the episode cost by 6 months' treatment duration.

Data analysis

We tested eight random effects multi-level regression models (specifications can be found in Supplementary Table S2). Covariates were defined at two levels: country-level and study-level. The following country-level variables were included in our analysis: TB case detection rate[18] (now treatment coverage) and HIV prevalence[19] (for the year when the authors reported data being analysed in each study) as indicators of local burden and programme size and performance for TB and local burden for HIV; antiretroviral treatment (ART) coverage in 2017, as opposed to year-specific coverage for two reasons: 1) it represents an indicator of local investments in vertical programmes and 2) data for studies before year 2005 were patchy. Finally, we added GDP per capita[20] (for the year when the authors reported data being analysed in each study) as often associated with health service cost variation. Second-order terms for HIV prevalence and antiretroviral therapy (ART)

coverage were also tested in the models to normalise these variables, as the relationship between HIV prevalence/ART coverage and mean cost was found to shift from linear to quadratic after a certain point. We included four variables related to the characteristics of the unit cost estimate describing service delivery modalities that are relevant to treatment cost variation. The first variable indicated whether hospitalisation costs were included. Hospitalisation costs come from hospitalisation being recommended as part of the treatment. The second variable is related to whether the TB treatment strategy followed was directly observed treatment (DOT), self-reported by authors. The third variable relates to the inputs included in the cost estimate, for example, whether or not capital costs had been included in the estimate presented. The final variable indicated the location of treatment delivery, whether facility-based or community-based. The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) were estimated to select the model with the best fit. Lower values of BIC or AIC indicate a better fit for the model.

Our selected model was specified as follows:

$$\log(cost)_{iy} = \alpha + \beta_1 TBcdr_y + \beta_2 \log(GDPpc)_y + \beta_3 HIV_y + \beta_4 HOSP_i + \beta_5 NDOT_i + \beta_6 COMM_i + \beta_7 INPUT_i + u_{iy} + \varepsilon_{iy}$$

where

- *cost* is the average unit cost (per person-month of treatment) in 2017 $US, log-transformed to account for a right-skewed distribution;
- $i = (1, \ldots, I)$ refers to the individual studies
- $y = (1, \ldots, Y)$ refers to year of data-country pairs
- *TBcdr* is the TB case detection rate. It is expressed as a proportion to reflect the number of new and relapsed TB cases notified to the WHO divided by the estimated number of incident TB cases in a given year and country. All data were collated based on the year when the authors reported data being collected or analysed in each study or, if not this was not available, year of publication (y).
- *GDPpc* is the GDP divided by mid-year population[20] to produce GDP per capita in current $US. All data were reported based on the year when the authors reported data being analysed in each study (y).
- *HIV* is the HIV prevalence among adults (15–49 years) as a proportion. All data were reported based on the year when the authors reported data being analysed in each study (y).
- *HOSP* is a variable for inclusion of hospitalisation costs for each study. It is equal to 1 if hospitalisation costs have been included in the estimates.
- *NDOT* is a dummy variable to indicate the treatment modality for each study. It is equal to 1 for non-DOT.
- COMM is a variable indicating the location of service delivery for each study. It is equal to 1 if the treatment is delivered in the community.
- INPUT is a dummy variable to indicate whether the authors included all key inputs in their estimate (i.e., capital, personnel and recurrent costs)
- u_{iy} is the between-study error, ε_{iy} is the within-study error.

We first tested for heterogeneity using a Hausman test and determined that a random effects model was appropriate. We employed the *xtreg* and *xtmixed* commands in STATA (StataCorp, College Station, TX, USA) using random effects and maximum likelihood estimation to fit a random intercept model, but we opted to use the *xtmixed* for further prediction as more appropriate due to the nature of our data sources: 1) studies performed in a variety of countries and time points; and 2) different settings and delivery of interventions in each study. In the Supplementary Data, we provide a visual representation of the observed vs. the predicted values using the best-fit model that indicates that the *xtmixed* approach provided a better fit and estimates than the *xtreg* approach (Supplementary Figure S1).

To check the predictive validity of our model, we could either remove single data points and check the prediction from the model fit to the rest of the data or we could remove all data points for each country and use the data from the remaining countries to do the same prediction. We chose the second cross-validation check of the predictive accuracy of the selected model because our aim was to predict across countries. After cross-validation checks, we then used our best fit model and local covariates to predict median cost per person-month of first line TB treatment using DOT, including all inputs (i.e., capital, personnel and recurrent costs) without hospitalisation as the most common delivery option, and the one providing the best predictive power across LMICs.

RESULTS

Of the 17 312 studies identified after duplications were removed, we assessed abstracts and full texts from 843 studies (six articles were not reviewed as we did not have access to the full text[21–26]). Of the 205 studies presenting empirically collected TB cost data, we excluded 80 articles reporting only costs incurred by patients and their households. A total of 96 studies reported costs from a provider perspective for interventions and services other than first-line standardised treatment for drug-susceptible TB and were also excluded. In total, 29 studies published between 2000 and 2018 contributing 106 unit costs across 19

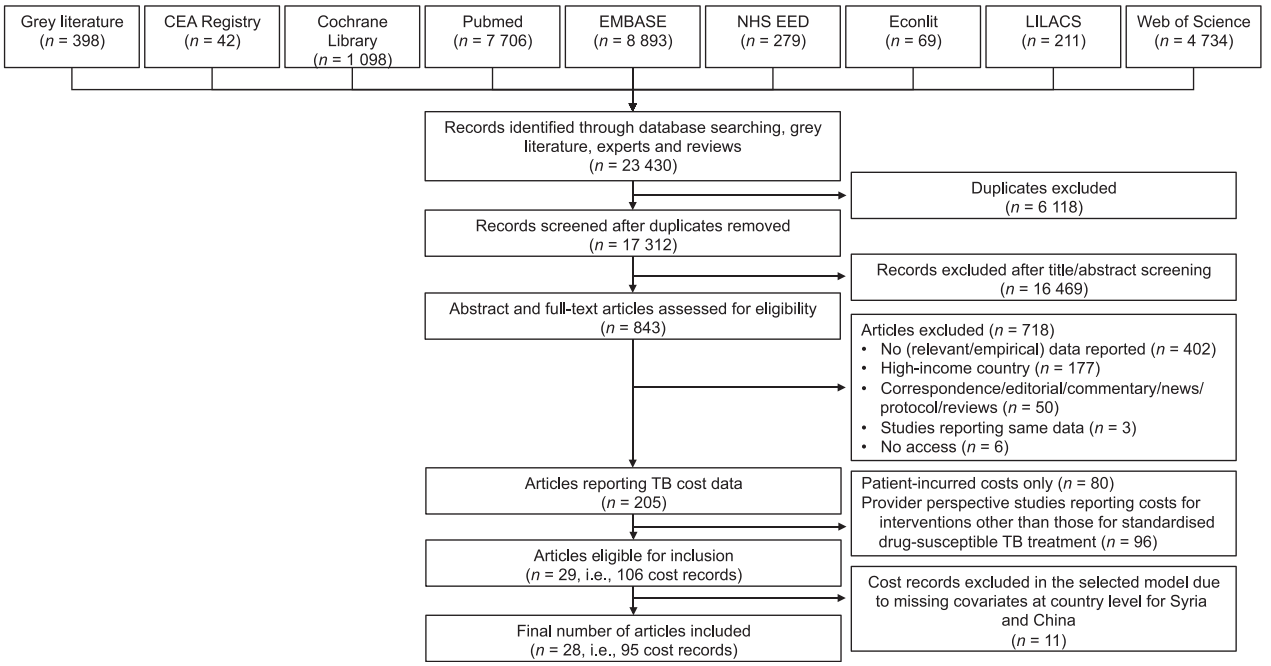

Figure 1 Search results and article selection. CEA = cost-effectiveness analysis; TB = tuberculosis; NHS = National Health Service; EED = Economic Evaluation Database; LILACS = Literatura Latinoamericana en Ciencias de la Salud; TB = tuberculosis.

countries were eligible for inclusion (Figure 1). Unit costs from China and Syria were then excluded in the complete dataset for analysis, as there was no information available for HIV prevalence for the year when the authors reported data in these two countries. Our final dataset included 28 studies from 17 countries and reported a total of 95 unit costs.[27–54] These estimates (as well as all other TB unit costs for different interventions) can be found online by country in the UCSR of the Global Health Cost Repository (available from: https://ghcosting.org/pages/data/ucsr/app/).

In Supplementary Table S3, we describe characteristics from the studies included and in Supplementary Table S4, we present the characteristics of the unit costs. Unit cost availability is not uniformly distributed across countries – some countries, like South Africa,[28,36,48,49] have more information available than others (Figure 2). Most studies estimated costs under a DOT strategy either facility-based ($n = 25$) or community-based ($n = 15$). In addition to six studies disaggregating costs by smear status of the patient, another six studies restricted the population studied to smear-positive patients.[28,29,34,35,38,39,41,45,47,49,51,53] Two additional costing studies took place alongside the trials.[31,45] Costing methods and allocation approaches of shared resources varied between studies. While most studies reported cost estimates, including all relevant costs inputs (capital, personnel and recurrent costs), six studies excluded some aspects of capital costs.[34,38,40.43,46,53] Variation was found in the activities included and the valuation decisions when accounting for the time of community health workers/volunteers. Variation was also observed in the inclusion of diagnosis, treatment and management of adverse drug events and hospitalisations. Only one study excluded all laboratory costs (diagnosis and monitoring)[2,7] while another included diagnosis as part of the treatment unit cost reported.[41] Two studies reported treatment for adverse drug reactions.[49,54] Overall larger variation in the inclusion of hospitalisation costs was observed. In some settings, hospitalisation was recommended as part of the standard of care evaluated, like in the Russian Federation, and represented a high proportion of the costs.[33,35,36,41,52] In other settings, hospitalisation was not a requirement, but its costs were included if patients needed to be hospitalised during their treatment. Finally, most unit costs were reported as cost per patient treated, except for four papers looking at cost per patient completing treatment[28,44,50,52] and one study reporting costs per patient successfully treated.[45] Looking at the distribution of unit costs (Figure 3), studies that included hospitalisation costs and facility-based service delivery had higher unit costs compared to those not including hospitalisation costs or community-based service delivery.

Our next step was to examine the potential drivers of unit costs within a regression framework. We ran various models, presented in Supplementary Table S1. The best fitted model is presented in the Table. Our model results show a statistically significant positive association between unit cost and GDP per capita, all inputs included and hospitalisation, while community-based services are negatively associated with unit costs (Table). The coefficients presented can

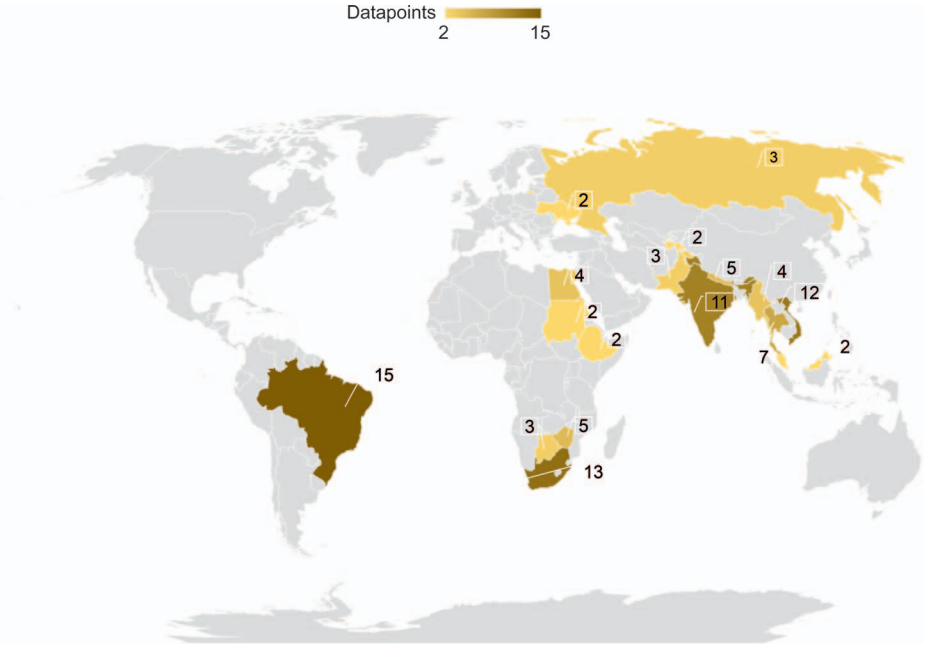

Figure 2 Availability of unit costs by country for the treatment of drug-susceptible tuberculosis.

be interpreted, for example, as a 1% increase in TB case detection rate being associated with a statistically non-significant 0.2% increase in average unit cost per person-month of treatment, whereas a 1% increase in GDP per capita per year was associated with a statistically significant 0.44% increase in average unit cost per person-month of treatment. We found a high correlation ($r = 0.92$) between observed and predicted values for the selected model (Figure 4).

In the Supplementary Data (Supplementary Figure S2), we present the validation results for the prediction model. We observed a variation in performance by setting. The model performs better in settings with facility-based DOT costs for drug-susceptible TB without hospitalisation than in those settings where hospitalisation is included or where service delivery happens in the community. Finally, in Supplementary Table S5, we present a table with predicted unit costs with 95% confidence intervals for all LMICs. Our predicted median costs per 6 months of treatment are for low-income (US$315.30, 95% CI US $222.60–US$417.20), lower middle-income (US$527.10, 95% CI US $395.70–US$743.70) and upper middle-income (US$896.40, 95% CI US $654.00–US$1214.40) countries.

DISCUSSION

This review provides an up-to-date overview of primary data available for first-line treatment of drug-susceptible TB in LMICs. We also put forward a multi-level regression analysis of standardised costs to model and extrapolated to other countries without data, controlling for epidemiological and socio-economic differences between settings and service delivery.

We found that unit costs for drug-susceptible TB treatment were positively associated with GDP per capita, inputs included and hospitalisation, while community-based services were negatively associated. Our prediction model performed well for facility-based DOT costs for drug-susceptible TB without hospitalisation; however, it performed worse in those settings where hospitalisation is included or where service delivery happens in the community. This may be due to variations in hospitalisation duration and/or procedures that patients underwent during hospitalisation, and secondly, due to the variations in the valuation of community health workers or volunteers time.

This study improves previous models in that it accounts for within- and between-study variance using a multi-level approach to regression for extrapolation in facility-based DOT costs. When comparing our median predicted cost per 6 months of treatment for low-income (US$315.30), lower middle-income (US$527.10) and upper middle-income (US$896.40) countries with previously published estimates (US$258.00, US$273.00, US$840.00, respectively),[6] we predict higher overall medians, with the difference becoming smaller as income increases. This may be because we are predicting only complete estimates for a 6-month duration in facility-based DOT service delivery models without hospitalisation and the previous systematic review did not control for the impact of predicting estimates for full duration, hospitalisation policy or inputs included in the cost

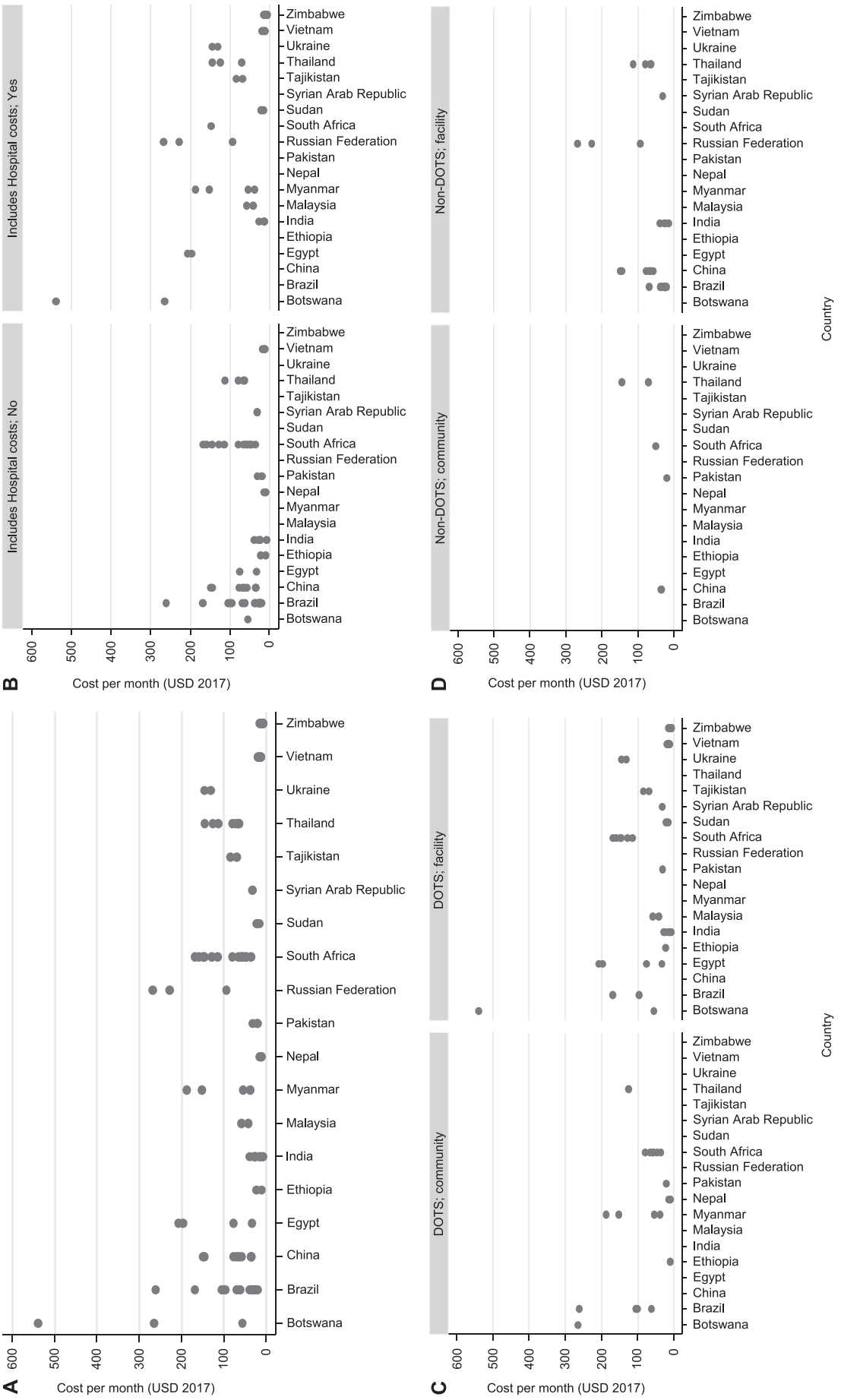

Figure 3 Distribution of observed values for selected variables. Panel **A)** all unit costs distribution by country; Panel **B)** unit costs distribution by hospitalisation costs included; Panel **C)** DOTS treatment unit costs distribution by location; Panel **D)** non-DOTS treatment unit costs distribution by location.

Table Multilevel regression model results (95 data points)

Variables	Descriptive statistics *n* (%)	Model results β (95%CI)	*P* value
TB case detection rate* at year *y*,† mean ± SD	64.1 ± 24.8	0.002 (−0.007 to 0.011)	0.658
Log (GDP per capita at year *y*†), $US, mean ± SD	2961.1 ± 3 247.3‡	0.444 (0.226 to 0.662)	<0.001§
HIV prevalence at year *y*†, %, mean ± SD	4.7 ± 8.2	0.016 (−0.011 to 0.043)	0.247
Includes hospital costs, yes	36 (40.5)	0.460 (0.168 to 0.751)	0.002§
DOTS, no	24 (26.9)	−0.283 (−0.573 to 0.007)	0.056
Community-based (reference: facility-based)	27 (28.4)	−0.401 (−0.691 to −0.111)	0.007§
Included all key input cost, yes	72 (75.8)	1.571 (1.005 to 2.137)	<0.001§
Constant		−0.955 (−2.423 to 0.513)	0.202

* We used the case detection rate as it was reported at the time of the studies; however, this is now being referred to as 'treatment coverage'. It is expressed as a proportion to reflect the number of new and relapsed TB cases notified to the WHO divided by the estimated number of incident TB cases in a given year and country.
† Year when the authors reported data that were analysed in each study.
‡ Mean GDP per capita.
§ Statistically significant.
CI = confidence interval; TB = tuberculosis; SD = standard deviation; GDP = gross domestic product; HIV = human immunodeficiency virus.

estimates. We also present uncertainty around our extrapolated estimates, which helps contextualise the quality of the data available informing these predicted values.

There are some limitations in this study. First, we limited the analysis to first-line treatment costs from a health service perspective. These estimates are presented aggregated. If disaggregated by HIV status, the predictions will allow for more granularity in prioritisation exercises. However, we were not able to expand the analysis in such way with the data currently available (for more information on the literature available on HIV-TB costs, we refer to de Siqueira-Filha et al.[14]). Overall, there is an urgent need to expand this analysis to other services and interventions in TB, such as treatment for drug-resistant TB, diagnosis and prevention. TB patients tend to face substantial costs that were not included. Second, we did not include variables known to be important drivers of costs in the model specifications—such as scale. This is because the data available did not provide enough detail to allow for this. In the future, a more detailed specification and appropriate standardisation of units will allow for more precision in the predictions. Finally, there is an important uncertainty reflected in the width of confidence intervals of our estimates; while the estimates will be useful in informing cost-effectiveness analyses, they may lack the precision needed for budgeting and planning purposes.

Our study confirms that TB treatment for drug-susceptible TB is a low-cost intervention in most

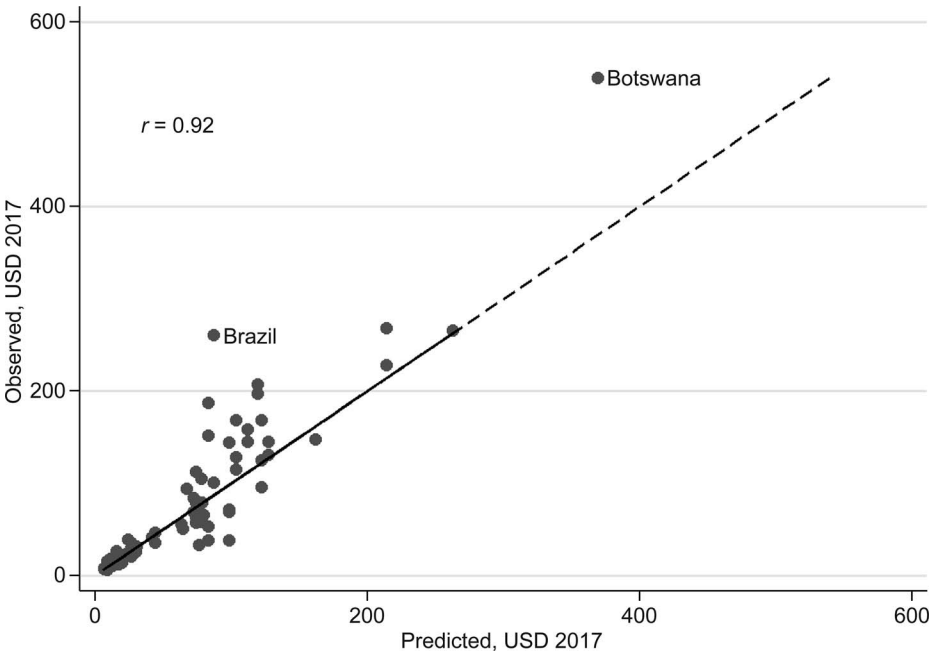

Figure 4 Observed vs. predicted estimates for all unit costs using the best fit model. This figure presents the relationship between observed data points as reported in the studies and the estimates predicted by the statistical model. The correlation coefficient (*r*) measures the strength and direction of a linear relationship.

settings. It is hoped that these estimates can inform global, regional and national priority setting exercises, not as a substitute for local, good-quality primary data, but as informed estimates when local primary data are not available. These broad estimates can be updated using the regression proposed once more primary data are available from large, country-led data collection exercises.

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All authors have declared that they have no competing interests. GBG is currently employed by Sanofi Pasteur as Regional Lead for vaccine epidemiology and modelling in Europe and does not work in any project related to tuberculosis. The work presented here was done during GBG's employment at London School of Hygiene & Tropical Medicine (London, UK).

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : En dépit de la rareté des données relatives au coût de la tuberculose (TB), un ensemble substantiel de preuves s'accumule en ce qui concerne le traitement de la TB pharmacosensible (DS-TB). Dans cette étude, nous revoyons les coûts unitaires du traitement de la DS-TB selon la perspective du prestataire de soins. Nous examinons également les facteurs à l'origine des variations de coût et extrapolons les coûts unitaires dans les pays à revenu faible et modéré (LMIC).

MÉTHODE : Nous avons recherché dans la littérature publiée et parallèle toutes les estimations de coût de la TB recueillies empiriquement. Nous avons sélectionné un sous groupe des estimations relatives au traitement de la DS-TB. Nous avons extrait des informations relatives aux activités et intrants inclus. Nous avons standardisé les coûts dans une moyenne par personne-mois, adapté un modèle de régression multiniveaux et contre validé les prédictions au niveau des pays. Nous avons alors extrapolé les estimations relatives au traitement de la DS-TB par DOTS en structures de santé dans les différents pays.

RÉSULTATS : Nous avons inclus 95 estimations de 28 études dans 17 pays. Les prédictions de coût ont été sensibles à des caractéristiques comme le mode de prestation, l'inclusion d'une hospitalisation, et les intrants ainsi qu'au produit national brut per capita. Les résultats de l'extrapolation sont présentés avec une incertitude pour les LMIC. Les coûts médians prédits pour six mois de traitement ont été de US$315,30 (US$222,60–US$417,20) pour les pays à revenu faible, US$527,10 (US$395,70–US$743,70) pour les pays à revenu moyen faible, et US$896,40 (US$654,00–US$1214,40) pour les pays à revenu intermédiaire supérieur.

CONCLUSION : Notre étude fournit des estimations de coût du traitement de la DS-TB par pays adaptée à l'établissement de priorités. Ces estimations, qui ne sont toutefois pas un substitut à des données primaires locales de grande qualité, peuvent informer les exercices mondiaux, régionaux et nationaux.

RESUMEN

MARCO DE REFERENCIA: A pesar de la escasez de datos sobre el costo de la tuberculosis (TB), se ha acumulado suficiente evidencia en el caso del tratamiento de la TB sensible a los medicamentos (DS-TB). En este estudio, revisamos sistemáticament los costos unitarios para el tratamiento de DS-TB desde la perspectiva de un proveedor. También examinamos los factores influyentes en la variación de los costos y extrapolamos los costos unitarios en los países de ingresos bajos y medianos (LMIC).

MÉTODO: Se realizaron búsquedas en la literatura publicada y no publicada to identificar cualquier estimación empírica de costos de TB. De este group, seleccionamos un subgrupo de estimaciones que analizan el tratamiento de DS-TB. Información sobre actividades e insumos incluidos fue extraida. Estandarizamos los costos a un promedio por persona por mes. Ajustamos un modelo de regresión multinivel a la muestra de costs y validamos las predicciones a nivel de país. Finalmente, extrapolamos las estimaciones para el tratamiento directamente observado de la DS-TB en las facilidades a los países restantes.

RESULTADOS: Se incluyeron 95 estimaciones de costos a partir de 28 estudios en 17 países. Las predicciones de costos varian dependiendo de características como el tipo de servicio, si el costo de la hospitalización fue incluida y los insumos incluidos, así como el producto interno bruto per cápita. Los resultados de extrapolación se presentan con incertidumbre para los LMIC. Los costos promedios por seis meses de tratamiento fueron US$315,30 (US$222,60–US$417,20) en países de ingresos bajos, US$527,10 (US$395,70–US$743.70) en países de ingresos medianos bajos y US$896,40 (US$654,00–US$1214,40) en países de ingresos medianos altos.

CONCLUSIONES: Nuestro estudio presenta estimaciones de costos de tratamiento de la DS-TB nacionales adecuadas para establecer prioridades. Estas estimaciones, aunque no son un sustituto de datos primaries y locales de alta calidad, pueden informar ejercicios globales, regionales y nacionales.