Title: Cost-Effectiveness of Expanded Diagnostic Testing for Drug Resistant Tuberculosis in High Burden Settings

Supplemental Material

Contents:

I. Model Parameters. These thirteen parameters were run in univariate sensitivity analysis. Six of these parameters (marked with an *) were included as part of the total 15 indicators used for the multivariate probabilistic sensitivity analysis.

Parameter	Philippines	Thailand	Source
Transmission coefficient DS-TB*	11	1.4	Fitted
Transmission coefficient DR-TB	7	1.4	Fitted
Fast activation rate*	0.0826	0.0826	[1]
Slow activation rate*	0.0049	0.0049	Fitted
Progression to late latency*	0.872	0.872	[1]
Risk of reinfection once infected	0.21	0.21	[2]
Spontaneous self-cure*	0.20	0.20	[2,3]
Rate of acquired resistance	0.20	0.20	[4]
Case detection rate*	Annual data	Annual data	[5]
Empiric diagnosis DR-TB	0.04	0.01	Fitted
Treatment success rate DR-TB treated as DS-TB	0.70	0.70	[6,7]
Mortality DR-TB treated as DS-TB	0.14	0.28	[6,8]
Loss of immunity	0.1	0.1	[9]

*These parameters were used in multivariable probabilistic sensitivity analysis.

II. Calculation of GeneXpert XDR diagnostic test cost

The diagnostic cost for GeneXpert XDR was based on the costing analysis for GeneXpert MTB/RIF, conducted by Capeding et. al.[10] Costs were transformed from $2017 USD to $2025 USD with 3.9% annual inflation. The cost of consumables, or GeneXpert cartridges, has reduced in price since 2017. The updated Xpert MTB/RIF pricing is taken from the Department of Health procurement award in 2024, using an exchange rate of 1 PHP: $0.017 USD and 3.9% annual inflation to calculate 2025 price. For GeneXpert XDR, all categories are assumed equal to GeneXpert MTB/RIF 2025 costs, except for consumables. The GeneXpert XDR cartridge price is based on Global Fund price estimates in 2023.

Table S2: Calculation of GeneXpert MTB/RIF and GeneXpert XDR diagnostic test cost

	GeneXpert MTB/RIF		**GeneXpert XDR**
Category	USD$ (2017)	USD$ (2025)	USD$ (2025)
Capital	1.27	1.72	1.72
Consumables	16.41	14.59[1]	19.80[2]
Overhead	1.15	1.56	1.56
Staff	0.66	0.90	0.90
Total	**19.49**	**18.77**	**23.98**

[1] Republic of the Philippines, Department of Health. Notice of Award for Cartridge-Based Nucleic Acid Amplification Test Reagent for MTB/RIF Cartridges under IB No. 2023-282. Posted January 4, 2024. https://doh.gov.ph/cartridge-based-nucleic-acid-amplification-test-reagent-for-mtb-rif-cartridges-under-ib-no-2023-282/

[2] Briefing Note: New Pricing for Cepheid GeneXpert Tuberculosis Testing. 19 October 2023. The Global Fund. https://www.theglobalfund.org/media/13442/operational_2023-10-cepheid-genexpert-tb-testing_briefingnote_en.pdf

III. Calculation of Targeted NGS (tNGS) diagnostic test cost

For the calculation of cost for tNGS applied as a diagnostic tool for TB, a breakdown of costs was conducted using broad categories as outlined by the WHO Genomics costing tool (https://www.who.int/publications/i/item/9789240090866). Although originally intended for costing of SARS-CoV-2 genomic surveillance, categories and costs have been modified below for TB.

Table S3: Summary of costs for tNGS as a diagnostic tool for DR-TB

Cost Categories	**Cost per sample $USD**	**Source**
Reagents	100	Global Health Access Catalogue
Equipment (amortized over 10 years)	1.28 – 2.46	Illumina quotation, NTRL Budget Proposal
Consumables (library prep and QC)	40.27	RITM (see table S3)
Personnel	1.17	Estimated (see table S4)
Facility and Transport	5 - 10	Estimated
TOTAL	**148 - 154**	

The cost of reagents is USD$100 per sample, as quoted in the Global Health Access catalogue for the cost of Illumina Deeplex for MiSeq. The equipment cost is quoted from Illumina as the cost for a MiSeq machine, which is $221,000. For amortization of equipment costs, the lifetime was assumed to be 10 years with an annual interest rate of 6.5%, equaling an annual amortized cost of $30,742. Assuming a throughput of 12,000 (minimum) to 24,000 (maximum) samples per year, this equipment cost is estimated to be USD$1.28 - $2.46 per sample.

For calculation of consumables, a list of materials is included below, converted from local currency (PHP) to $USD. The total cost is USD$4,027 for library preparation for 100 reactions. Total cost of consumables is approximately USD$40.27 per sample.

Table S4: Estimates for cost of consumables for tNGS of TB samples (100 reactions)

Item	Unit	Reactions Per Kit	Qty to Procure	Unit Price (PHP)	Total (PHP)	Total (USD)
Tube, Strips, clear, 8-tube, without caps, low profile, 0.2 mL 300 strips/box	Strip	NA	2	16,183.75	32,367.50	568.65
Tube, Strips, optical, ultraclear, Dome cap, 8-cap, 0.2 mL, 120 strips/pack, 10 packs/box	Strip	NA	1	9,350.00	9,350.00	164.27
Pipette tip, 1000 uL, aerosol-resistant, racked, sterile, nuclease-free, low retention (96 tips/rack; 10 racks/box)	Box	NA	1	11,500.00	11,500.00	202.04
Pipette tip, 200 uL, aerosol-resistant, racked, sterile, nuclease-free, low retention (96 tips/rack; 10 racks/box)	Box	NA	2	10,250.00	20,500.00	360.15
Micropipette Tips, 200G uL, Genomic Micropipette tips, 96 tips/rack, 10 racks/box	Box	NA	1	9,350.00	9,350.00	164.27
Pipette tip, 10 uL, aerosol-resistant, racked, sterile, nuclease-free, low retention (96 tips/rack; 10 racks/box)	Box	NA	2	8,125.00	16,250.00	285.49
Tube, Microcentrifuge, 1.5 mL, Polypropylene, Clear, Non-Sterile, SnapLock cap, 500 tubes/pack, 10 packs/case	Pack	NA	1	10,625.00	10,625.00	186.67
Tube, Microcentrifuge, 2.0 mL, Microtube with Locking-Cap, Round Bottom, Slight-Stiff-Touch, Natural, Polypropylene, Autoclavable, Flat Top with Scale, RNase/DNase/human-DNA free, 1000 tubes/bag, 5 bags/case	Pack	NA	1	11,000.00	11,000.00	193.25
Alcohol, Ethanol, absolute, Analytical grade, 2.5 L/bottle	Bottle	NA	1	2,000.00	2,000.00	35.14
Water, Type 1, Molecular Biology Grade, Protease-Free, DNase-Free, RNase-Free, membrane-filtered, 500ml / Bottle (Invitrogen, UltraPure Catalog No. 10977-015)	Bottle	NA	1	4,726.25	4,726.25	83.03
Buffer EB, 250 mL per bottle	Bottle	NA	1	11,750.00	11,750.00	206.43
Water, Type 1, Molecular Biology Grade, Protease-Free, DNase-Free, RNase-Free, membrane-filtered, 500ml / Bottle (Invitrogen, UltraPure Catalog No. 10977-015)	Bottle	NA	19	89,798.75	89,798.75	1577.63
TOTAL					₱229,217.50	$4,027.01

To calculate personnel costs, an estimate of personnel required to conduct tNGS sequencing was costed according to local salary rates. These were multiplied by estimated full-time equivalent (FTE) hours required, with 1 FTE representing a standard 40-hour work week. Annual costs in PHP were converted to $USD using an exchange rate of 1 PHP: $0.017 USD. Each team of personnel, representing 6.1FTE, represents an annual cost of USD$56,046. Each team is estimated to sequence 48,000 TB samples per year for an average cost of USD$1.17 per sample.

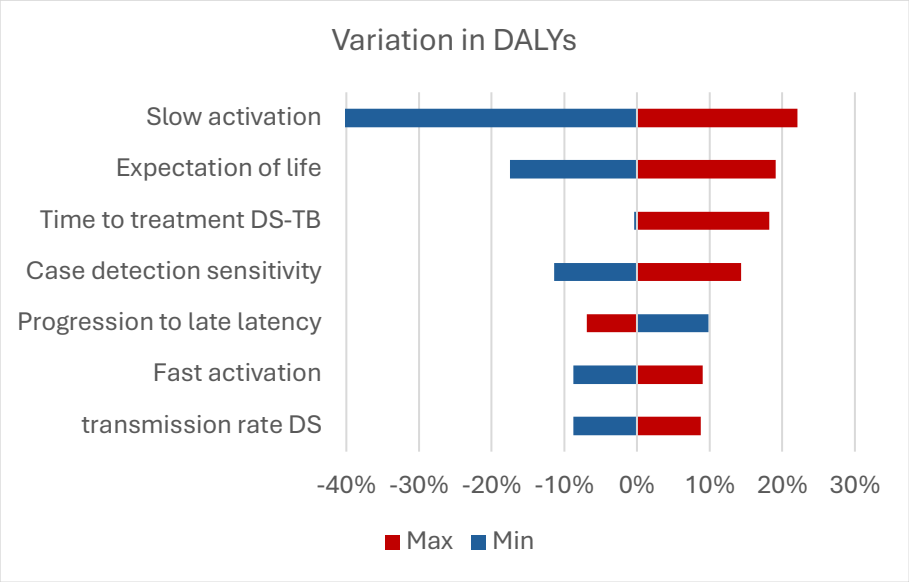
Table S5: Estimating personnel costs for tNGS of TB samples

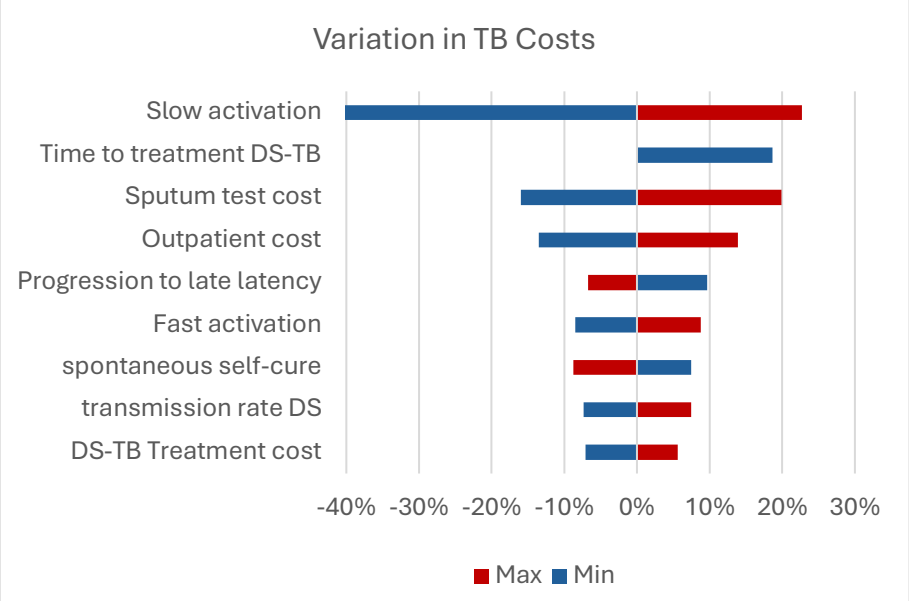
Personnel	**Salary rate (PHP)**	**Unit**	**FTE**	**Annual Cost PHP**	**Annual Cost $USD**
Medical Technician	40,000	Per month	2	960,000	16,320
Sequencing Personnel	40,000	Per month	2	960,000	16,320
Bioinformatician	40,000	Per month	1	480,000	8,160
Medical officer	60,000	Per month	1	720,000	12,240
Clinical pathologist	850	Per hour	0.1	176,800	3,006
TOTAL			**6.1**	**3,296,800**	**56,046**

IV. Univariate Sensitivity Analysis

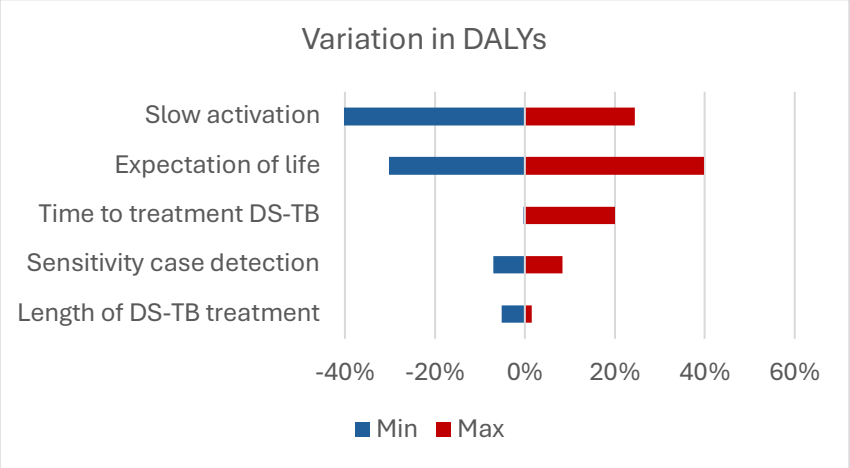
Univariate sensitivity analysis was conducted on 40 study parameters. The parameters that caused the largest variation in values for DALYs and Costs are shown below for the Philippines and Thailand.

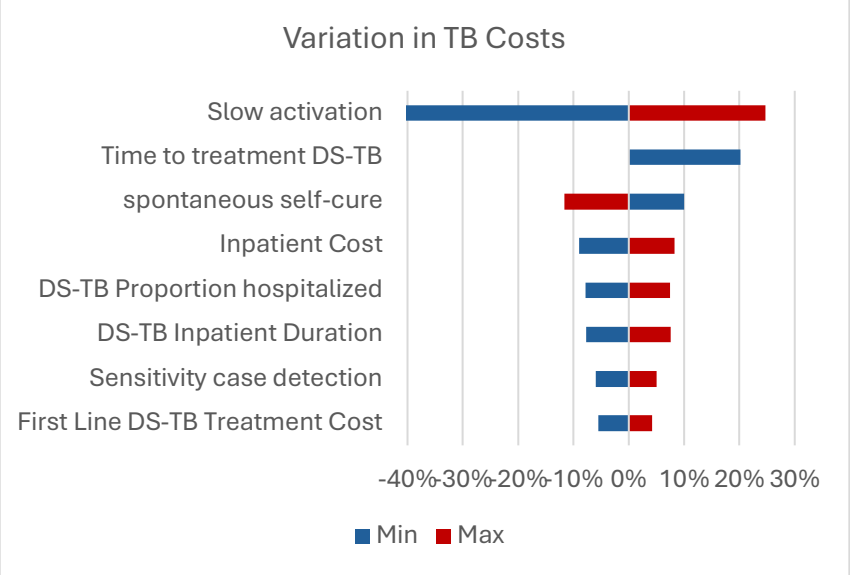
Philippines





Thailand


Variation in DALYs
Slow activation
Expectation of life
Time to treatment DS-TB
Sensitivity case detection
Length of DS-TB treatment
-40%
-20%
0%
20%
40%
60%
Min
Max


Variation in TB Costs
Slow activation
Time to treatment DS-TB
spontaneous self-cure
Inpatient Cost
DS-TB Proportion hospitalized
DS-TB Inpatient Duration
Sensitivity case detection
First Line DS-TB Treatment Cost
-40%
-30%
-20%
-10%
0%
10%
20%
30%
Min
Max

References:

1 Menzies, N. A. *et al.* Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. *Lancet Infect Dis* **18**, e228-e238 (2018). https://doi.org/10.1016/S1473-3099(18)30134-8

2 Karmakar, M., Ragonnet, R., Ascher, D. B., Trauer, J. M. & Denholm, J. T. Estimating tuberculosis drug resistance amplification rates in high-burden settings. *BMC Infect Dis* **22**, 82 (2022). https://doi.org/10.1186/s12879-022-07067-1

3 Ragonnet, R. *et al.* Revisiting the Natural History of Pulmonary Tuberculosis: A Bayesian Estimation of Natural Recovery and Mortality Rates. *Clin Infect Dis* **73**, e88-e96 (2021). https://doi.org/10.1093/cid/ciaa602

4 Sharma, A. *et al.* Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. *Lancet Infect Dis* **17**, 707-715 (2017). https://doi.org/10.1016/S1473-3099(17)30247-5

5 Global Tuberculosis Report. (World Health Organization, Geneva, 2024).

6 Romanowski, K. *et al.* The impact of improved detection and treatment of isoniazid resistant tuberculosis on prevalence of multi-drug resistant tuberculosis: A modelling study. *PLoS One* **14**, e0211355 (2019). https://doi.org/10.1371/journal.pone.0211355

7 Gegia, M., Winters, N., Benedetti, A., van Soolingen, D. & Menzies, D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* **17**, 223-234 (2017). https://doi.org/10.1016/S1473-3099(16)30407-8

8 Zurcher, K. *et al.* Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: a multicentre cohort study. *Lancet Infect Dis* **19**, 298-307 (2019). https://doi.org/10.1016/S1473-3099(18)30673-X

9 Kuddus, M. A., McBryde, E. S., Adekunle, A. I., White, L. J. & Meehan, M. T. Mathematical analysis of a two-strain tuberculosis model in Bangladesh. *Sci Rep* **12**, 3634 (2022). https://doi.org/10.1038/s41598-022-07536-2

10 Capeding, T. P. J. *et al.* Cost of TB prevention and treatment in the Philippines in 2017. *Int J Tuberc Lung Dis* **26**, 392-398 (2022). https://doi.org/10.5588/ijtld.21.0622