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Dynamic modelling of improved diagnostic testing for drug-resistant tuberculosis in high burden settings

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Abstract

Background Limited diagnostic testing for drug-resistant TB (DR-TB) may lead to high rates of misdiagnosis and undertreatment. Current diagnostic tests focus only on detection of rifampicin-resistant TB (RR-TB). This study aims to determine the impact of improved diagnostic testing for a wider range of drug resistance on DR-TB outcomes in high-burden TB settings, using the Philippines and Thailand as case studies.

Methods A dynamic compartmental model was designed to simulate population level TB transmission, accounting for acquired drug resistance from treatment failure of drug susceptible TB. Three scenarios were analyzed: (1) Use of GeneXpert MTB/RIF on all presumptive TB cases (Status Quo); (2) GeneXpert MTB/RIF + GeneXpert XDR, (3) GeneXpert MTB/RIF + targeted Next Generation Sequencing (tNGS). Scenarios were modelled over a 10-year period, from 2025 to 2034.

Results Compared to the status quo, Scenario 2 results in a fourfold increase in annual DR-TB cases diagnosed in the Philippines and a fivefold increase in Thailand. DR-TB treatment failure decreases by 20% in the Philippines and 23% in Thailand. Scenario 3 further increases DR-TB case detection, reducing DR-TB treatment failure by 26% in the Philippines and 29% in Thailand. Reductions in DR-TB incidence and mortality ranged from 3 to 6%.

Conclusion The use of GeneXpert XDR or tNGS as an additional diagnostic test for DR-TB significantly improves DR-TB case detection and reduces treatment failure, supporting their consideration for use in high burden settings. These findings highlight the importance of detecting a wider range of TB resistance in addition to RR-TB, the potential impact these improved diagnostic tests can have on DR-TB outcomes, and the need for additional research on cost-effectiveness of these interventions.

Keywords Tuberculosis, Drug resistance, Infectious disease modelling, Diagnostic testing, Acquired drug resistance, High-burden settings

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Background

Tuberculosis (TB) remains a serious public health concern in Southeast Asia, a region that accounts for 46% of incident cases worldwide and an estimated 170,000 drug-resistant TB cases in 2022 [1]. Drug-resistant tuberculosis (DR-TB) poses a major challenge to global prevention and elimination efforts. Early and accurate diagnosis and susceptibility profiling are critical for timely and optimal treatment. Scaling up the use of modern diagnostics is identified as a priority action to achieve the 2030 End TB Goals [2].

Current WHO guidelines recommend using GeneXpert (Xpert MTB/RIF or Xpert Ultra) as the initial diagnostic test for adults and children with signs and symptoms of pulmonary TB, as it detects rifampicin-resistant TB (RR-TB) [3]. However, isoniazid-resistant rifampicin-susceptible TB (Hr-TB) has a higher prevalence globally and is not detected by rapid molecular diagnostic tests currently used in most high-burden settings [4]. The misdiagnosis and treatment of Hr-TB with first-line drugs results in increased treatment failure and mortality [5, 6]. Modelling studies have shown that treatment failure for Hr-TB can also lead to amplification of drug resistance, thereby contributing to higher rates of multidrug-resistant TB (MDR-TB) [7, 8].

GeneXpert XDR and targeted Next-Generation Sequencing (tNGS) are identified as potential front-line diagnostic tools to detect a wider range of drug resistance, including Hr-TB [9, 10]. GeneXpert XDR can detect resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectables (amikacin, kanamycin, capreomycin) [3]. Targeted NGS can detect resistance to at least 13 anti-TB drugs, including newly introduced treatment regimens with bedaquiline (BDQ), with the flexibility to update tNGS assays to include additional targets for detecting novel resistance mutations as they emerge [11, 12].

This study aims to use dynamic modelling to determine the impact of improved diagnostic testing on DR-TB outcomes in high-burden TB settings, using the Philippines and Thailand as case studies. According to 2022 WHO estimates, TB incidence in the Philippines is approximately 638 per 100,000 population, compared to 155 per 100,000 population in Thailand. Drug resistance is reported as RR/MDR-TB incidence, at 27 per 100,000 population in the Philippines and 3.7 per 100,000 population in Thailand [1]. Building on previous models of TB transmission [7, 13–15], the proposed model will account for all forms of DR-TB in addition to RR/MDR-TB, as well as acquired drug resistance resulting from treatment failure of drug-susceptible TB (DS-TB). The key output of the model will be to measure the impact of different DR-TB diagnostic tools and strategies on DR-TB diagnosis, treatment failure, prevalence, incidence, and mortality over a 10-year period.

Methods

A deterministic differential equation model was developed using Vensim DSS v10.1.4 (see Fig. 1). The model distinguishes fourteen subpopulations: (1) susceptible to TB infection (S); (2) exposed with early latent DS-TB (L_{AS}); (3) exposed with DS-TB in late latency (L_{BS}); (4) exposed with early latent DR-TB (L_{AR}); (5) exposed with DR-TB in late latency (L_{BR}); (6) active, undiagnosed DS-TB (I_S); (7) active, undiagnosed DR-TB (I_R); (8) active, correctly diagnosed DS-TB (D_S); (9) active, correctly diagnosed DR-TB (D_R); (10) DR-TB incorrectly diagnosed as DS-TB (D_X); (11) correctly treated DS-TB (T_S); (12) correctly treated DR-TB (T_R); (13) incorrectly treated DR-TB (T_x); and (14) successfully completed TB treatment and considered recovered (R). The total population size N(t) is the sum of the population across all fourteen stocks:

$$\begin{aligned} N(t) = {} & S(t) + L_{AS}(t) + L_{BS}(t) + L_{AR}(t) \\ & + L_{BR}(t) + I_S(t) + I_R(t) + D_S(t) \\ & + D_R(t) + D_X(t) + T_S(t) \\ & + T_R(t) + T_X(t) + R(t) \end{aligned} \quad (1)$$

The Susceptible population is infected by DS-TB or DR-TB at a rate of $\beta_S\left(\frac{I_S}{N}\right)$ or $\beta_R\left(\frac{I_R}{N}\right)$, respectively, and moves into the early latency phase L_A. The indicator β represents the transmission coefficient, which is the average number of contacts per year multiplied by the probability of contracting TB from TB-positive contact. Flow from the Recovered to Susceptible stock occurs at rate (γ), allowing for TB reinfection after recovery. The crude birth rate (η) and the crude death rate (μ) are used to account for overall population change over time. The equation for the Susceptible population (S) is defined as:

$$\frac{dS}{dt} = \eta N - S\beta_S\left(\frac{I_S}{N}\right) - S\beta_R\left(\frac{I_R}{N}\right) + \gamma R - \mu S \quad (2)$$

Previous studies have determined that tuberculosis models that employ two latent compartments, one for fast activation and one for slow activation, can reproduce TB latency dynamics more accurately, according to observed empirical data [16, 17]. The model presented herein, therefore, includes an early latency stock (L_A) and a subsequent late latency stock (L_B) to allow for both fast and slow activation, respectively, to the infected compartment (I). Due to the length of late latency, reinfection may occur in latent stock L_B in the context of high

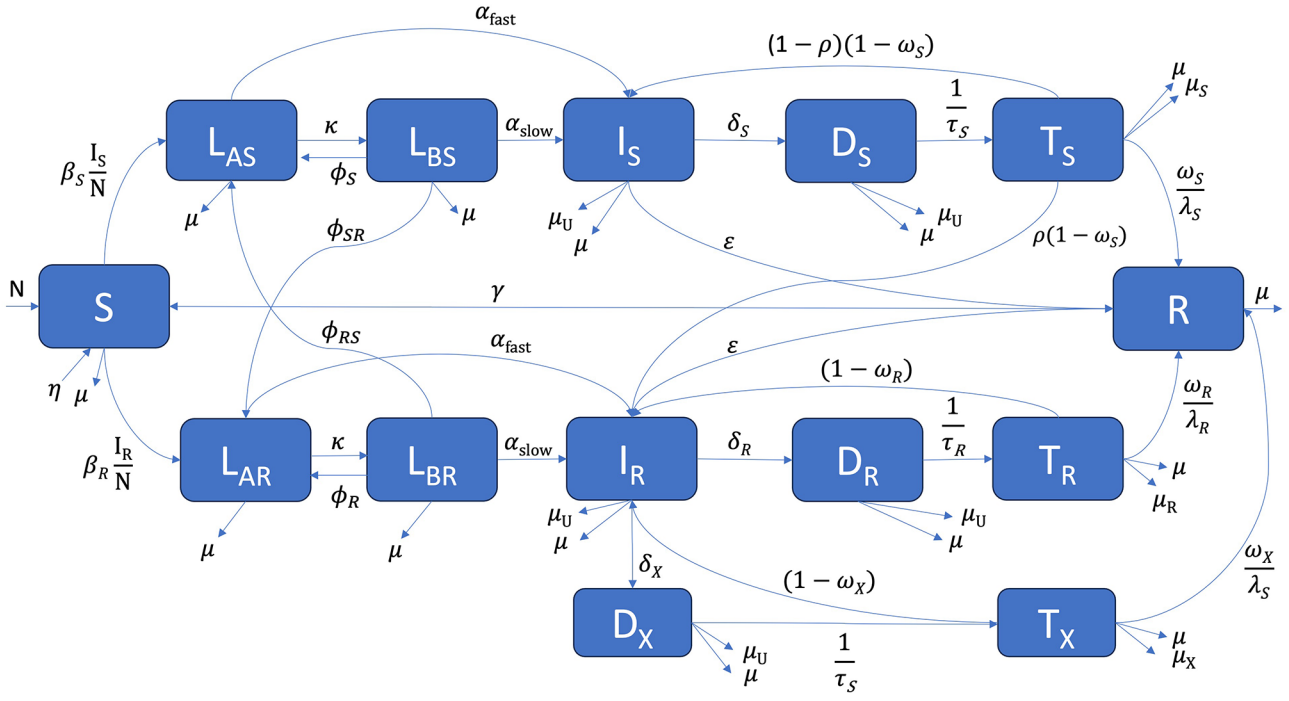


Fig. 1 Dynamic compartmental model structure. S = susceptible population, L_A = latent population, L_B = population in late latency, I = infected population, D = diagnosed population, T = treated population, R = recovered population, N = initial population, η = crude birth rate, μ = crude death rate, μ_u = mortality rate from untreated TB, β = transmission coefficient, α_{fast} = fast activation rate, α_{slow} = slow activation rate, κ = progression to late latency, ϵ = rate of spontaneous self-cure, δ = rate of diagnosis, τ = time to treatment, ω = treatment success rate, ρ = proportion of acquired resistance, and γ = loss of immunity. Subscripts $_{S, R}$ and $_X$ denote stocks and transitions related to DS-TB, DR-TB, and DR-TB diagnosed and treated as DS-TB, respectively

endemicity and repeated exposure, resulting in flow back to initial latency stock L_A at rate ϕ, defined as follows:

$$\phi_S = \mathrm{Y} L_{BS} \beta_S \left(\frac{I_S}{N}\right) \quad (3)$$

$$\phi_R = \mathrm{Y} L_{BR} \beta_R \left(\frac{I_R}{N}\right) \quad (4)$$

$$\phi_{SR} = \mathrm{Y} L_{BS} \beta_R \left(\frac{I_R}{N}\right) \quad (5)$$

$$\phi_{RS} = \mathrm{Y} L_{BR} \beta_S \left(\frac{I_S}{N}\right) \quad (6)$$

TB cases either undergo fast activation (α_{fast}) and flow from early latency (L_A) to Infected stocks, or else undergo progression to late latency at rate κ. From late latency (L_B), TB cases undergo slow activation (α_{slow}) to being Infected. The following equations describe the subpopulations in early latency (L_A) and late latency (L_B):

$$\frac{dL_{AS}}{dt} = \mathrm{S}\beta_S \left(\frac{I_S}{N}\right) - \kappa L_{AS} + \phi L_{BS} \beta_S \left(\frac{I_S}{N}\right) - \alpha_{fast} L_{AS} - \mu L_{AS} \quad (7)$$

$$\frac{dL_{BS}}{dt} = \kappa L_{AS} - \alpha_{slow} L_{BS} - \phi L_{BS} \beta_S \left(\frac{I_S}{N}\right) - \mu L_{BS} \quad (8)$$

$$\frac{dL_{AR}}{dt} = \mathrm{S}\beta_R \left(\frac{I_R}{N}\right) - \kappa L_{AR} + \phi L_{BR} \beta_R \left(\frac{I_R}{N}\right) - \alpha_{fast} L_{AR} - \mu L_{AR} \quad (9)$$

$$\frac{dL_{BR}}{dt} = \kappa L_{AR} - \alpha_{slow} L_{BR} - \phi L_{BR} \beta_R \left(\frac{I_R}{N}\right) - \mu L_{BR} \quad (10)$$

Once infected, individuals may naturally recover or 'spontaneously self-cure' at rate (ε) and move to the recovered stock (R), die from untreated TB (μ_u) or from other causes of mortality (μ), or else be diagnosed with TB and move to the diagnosed compartment (D). TB cases that have experienced treatment failure may flow from the Treated stock (T) back to the Infected stock (I) at rate (1 - ω), where ω represents treatment success. This flow is also affected by the rate of acquired resistance (ρ), which determines the proportion of treated DS-TB cases (T_S) that develop active, undiagnosed DR-TB (I_R).

$$\frac{dI_S}{dt} = \alpha_{fast} L_{AS} + \alpha_{slow} L_{BS} - \varepsilon I_S - I_S \delta_S + \mathrm{T_S}(1-\rho)(1-\omega \mathrm{S}) - \mu I_S - \mu_U I_S \quad (11)$$

$$\begin{aligned}\frac{dI_R}{dt} &= \alpha_{fast}L_{AR} + \alpha_{slow}L_{BR} - \varepsilon I_R \\ &\quad - I_R\delta_{\mathrm{R}} - I_R\delta_{\mathrm{X}} + \mathrm{T_s}\rho\,(1-\omega_{\mathrm{S}}) \\ &\quad + T_R(1-\omega_{\mathrm{R}}) - \mu I_R - \mu_U I_R\end{aligned} \tag{12}$$

For diagnosis of DS-TB, the annual case detection rate C is used, based on annual data for the Philippines and Thailand from the 2023 WHO Global Tuberculosis Report. For diagnosis of DR-TB, the case detection rate is modified by ν, the proportion of cases tested with a rapid diagnostic at time of diagnosis, the sensitivity of the diagnostic test used (θ), and the rate of empiric diagnosis (E), which is the proportion of DR-TB diagnosed in the absence of a rapid diagnostic test. Most importantly, DR-TB diagnosis is dependent on detectable resistance (σ), which is the proportion of DR-TB cases that can be detected by the rapid diagnostic used. The diagnosis rates for DS-TB (δ_{S}), DR-TB (δ_{R}) and DR-TB mis-diagnosed as DS-TB (δ_{X}) are defined as:

$$\delta_{\mathrm{S}} = \mathrm{C}\,(1-\varepsilon) \tag{13}$$

$$\delta_{\mathrm{R}} = \mathrm{C}\,(1-\varepsilon)*(\nu\sigma\theta + \mathrm{C} - \mathrm{E}\nu) \tag{14}$$

$$\delta_{\mathrm{X}} = \mathrm{C}\,(1-\varepsilon)*(1-\nu\sigma\theta - \mathrm{E} + \mathrm{E}\nu) \tag{15}$$

The following equations describe the populations diagnosed and treated for DS-TB, DR-TB and DR-TB mis-diagnosed and treated as DS-TB:

$$\frac{dD_S}{dt} = I_S\delta_{\mathrm{S}} - D_S\left(\frac{1}{\tau_{\mathrm{S}}}\right) - \mu D_S - \mu_U D_S \tag{16}$$

$$\frac{dD_R}{dt} = I_R\delta_{\mathrm{R}} - D_R\left(\frac{1}{\tau_{\mathrm{R}}}\right) - \mu D_R - \mu_U D_R \tag{17}$$

$$\frac{dD_X}{dt} = I_R\delta_{\mathrm{X}} - D_X\left(\frac{1}{\tau_{\mathrm{S}}}\right) - \mu D_X - \mu_U D_X \tag{18}$$

$$\begin{aligned}\frac{dT_S}{dt} &= D_S\left(\frac{1}{\tau_{\mathrm{S}}}\right) - \mathrm{T_S}\,(1-\rho)\,(1-\omega_{\mathrm{S}}) \\ &\quad - \mathrm{T_s}\rho\,(1-\omega_{\mathrm{S}}) - T_S\left(\frac{\omega_{\mathrm{S}}}{\lambda_{\mathrm{S}}}\right) - \mu T_S - \mu_S T_S\end{aligned} \tag{19}$$

$$\begin{aligned}\frac{dT_R}{dt} &= D_R\left(\frac{1}{\tau_{\mathrm{R}}}\right) - \mathrm{T_R}\,(1-\omega_{\mathrm{R}}) \\ &\quad - T_R\left(\frac{\omega_{\mathrm{R}}}{\lambda_{\mathrm{R}}}\right) - \mu T_R - \mu_R T_R\end{aligned} \tag{20}$$

$$\begin{aligned}\frac{dT_X}{dt} &= D_X\left(\frac{1}{\tau_{\mathrm{S}}}\right) - \mathrm{T_X}\,(1-\omega_{\mathrm{X}}) \\ &\quad - T_X\left(\frac{\omega_{\mathrm{X}}}{\lambda_{\mathrm{X}}}\right) - \mu T_X - \mu_X T_X\end{aligned} \tag{21}$$

The following equation describes the Recovered population (R) that has successfully completed TB treatment and is considered cured:

$$\begin{aligned}\frac{dR}{dt} &= \varepsilon I_S + \varepsilon I_R + T_S\left(\frac{\omega_{\mathrm{S}}}{\lambda_{\mathrm{S}}}\right) \\ &\quad + T_R\left(\frac{\omega_{\mathrm{R}}}{\lambda_{\mathrm{R}}}\right) + T_X\left(\frac{\omega_{\mathrm{X}}}{\lambda_{\mathrm{X}}}\right) - \gamma R - \mu R\end{aligned} \tag{22}$$

Model calibration

The model was calibrated to estimated TB incidence and reported diagnosis and treatment rates for the Philippines and Thailand from 2010 to 2019, as published in the WHO Global Tuberculosis Report, 2023. Data from 2020 to 2022 were not utilized due to the impact of COVID-19 on TB detection and treatment during this period and is expected to revert to pre-COVID-19 rates. Epidemiological parameters were used from published literature on tuberculosis transmission dynamics, as summarized in Table 1. DR-TB prevalence was calibrated to most recent national drug resistance survey data for TB (see Supplemental Material, Table S1). Calibrated data and future projections for key outcomes from 2010 to 2034 are shown in Fig. 2 for the three diagnostic testing scenarios in the Philippines and Thailand.

Diagnostic testing scenarios

To investigate the impact of using different diagnostic tools, three scenarios are proposed for analysis: (1) Status quo, representing the use of GeneXpert MTB/RIF on all presumptive TB cases; (2) GeneXpert MTB/RIF+GeneXpert XDR, and; (3) GeneXpert MTB/RIF+tNGS. In all scenarios, GeneXpert MTB/RIF remains the initial diagnostic for detection of *Mycobacterium tuberculosis*, with GeneXpert XDR and tNGS proposed as additional tests for more comprehensive detection of DR-TB.

The intervention for Scenario 2 and 3 is simulated to be implemented in 2024, with outcomes modelled across a 10-year period from 2025 to 2034. Results are summarized in Table 2 to compare outcomes across each scenario for DR-TB diagnosis, mortality, treatment failure, incidence, and prevalence by 2034.

The value for Detectable resistance (σ) reflects country specific RR/MDR-TB rates in Scenario 1, is increased to 80% in Scenario 2 to reflect GeneXpert XDR capacity to detect a wider range of drug resistance and is further increased to 98% in Scenario 3 to reflect even higher DR-TB detection capacity of tNGS. In Scenario 1,

Table 1 Estimation of parameters

Parameter	Description	Estimated value, Philippines	Estimated value, Thailand	Source
$N_{(0)}$	Initial population (2010)	95,000,000	68,000,000	[18]
η	Crude birth rate	Annual data	Annual data	[18]
μ	Crude death rate	Annual data	Annual data	[18]
β_S	Transmission coefficient DS-TB	11	1.4	Fitted
β_R	Transmission coefficient DR-TB	7	1.4	Fitted
α_{fast}	Fast activation rate	0.0826	0.0826	[16]
α_{slow}	Slow activation rate	0.0049	0.0049	Fitted
κ	Progression to late latency	0.872	0.872	[16]
Υ	Risk of reinfection once infected	0.21	0.21	[7]
ε	Spontaneous self-cure	0.20	0.20	[7, 19]
ρ	Rate of acquired resistance	0.20	0.20	[20]
C	Case detection rate	Annual data	Annual data	[1]
θ	Sensitivity of initial diagnostic	0.96	0.96	[3]
σ	Detectable resistance	Survey data	Survey data	[21–25]
ν	Proportion of cases tested with rapid diagnostic at time of diagnosis	Annual data	Annual data	[1]
E	Empiric diagnosis DR-TB	0.04	0.01	Fitted
τ_S	Time to treatment DS-TB	5 days	5 days	[26]
τ_R	Time to treatment DR-TB	7 days	7 days	[26]
ω_S	Treatment success rate DS-TB	Annual data	Annual data	[1]
ω_R	Treatment success rate DR-TB	Annual data	Annual data	[1]
ω_X	Treatment success rate DR-TB treated as DS-TB	0.70	0.70	[5, 8]
λ_S	Length of DS-TB treatment	0.55 years	0.50 years	Fitted
λ_R	Length of DR-TB treatment	0.75 years	0.60 years	Fitted
μ_U	Mortality untreated TB	0.20	0.20	[7, 13]
μ_S	Mortality DS-TB	0.01	0.10	[1]
μ_R	Mortality DR-TB	0.12	0.21	[1]
μ_X	Mortality DR-TB treated as DS-TB	0.14	0.28	[6, 8]
γ	Loss of immunity	0.1	0.1	[14]

detectable resistance represents the proportion of DR-TB cases that can be detected with the current use of GeneXpert MTB/RIF. This value is calibrated to DR-TB case detection and adjusted to be in line with most recent drug resistance survey estimates for RR/MDR-TB prevalence (see Supplemental Material, Table S1), resulting in baseline detection of 18% and 15% of overall DR-TB cases in the Philippines and Thailand, respectively. Non-rifampicin-resistant strains of TB are not detected, such as resistance to commonly used first-line drugs including isoniazid, ethambutol, or pyrazinamide, as well as resistance to fluoroquinolones and second-line injectables. Accounting for test sensitivity and ability to detect additional strains of DR-TB, the use of GeneXpert XDR in Scenario 2 increases the proportion of detectable resistance to 80%, and the use of tNGS in Scenario 3 increases detectable resistance to 98%. Both tests had comparable pooled specificity for detection of resistance across all targeted TB drugs, at 96% for tNGS and 98% for GeneXpert XDR [3].

Sensitivity analysis

The sensitivity analysis was first conducted using univariate analysis for 18 parameters listed in Table 1, with +/-25% variation in parameter values (See Supplemental Material, Table S2). Holding other parameter values constant across 1000 simulations, one-way sensitivity analysis was performed to determine which parameters have the greatest impact on key outcomes related to DR-TB incidence, diagnosis, mortality, and treatment failure. Six parameters resulted in the highest variation from the mean (>14% variation for the Philippines and >5% for Thailand) for at least one key outcome and were selected for multivariate analysis (see Fig. 3). To estimate variability in key outcomes from simultaneous variation in parameters, multivariate sensitivity analysis was conducted for each scenario to determine 95% confidence interval (95% CI) and minimum and maximum range for reported results (see Table 2).

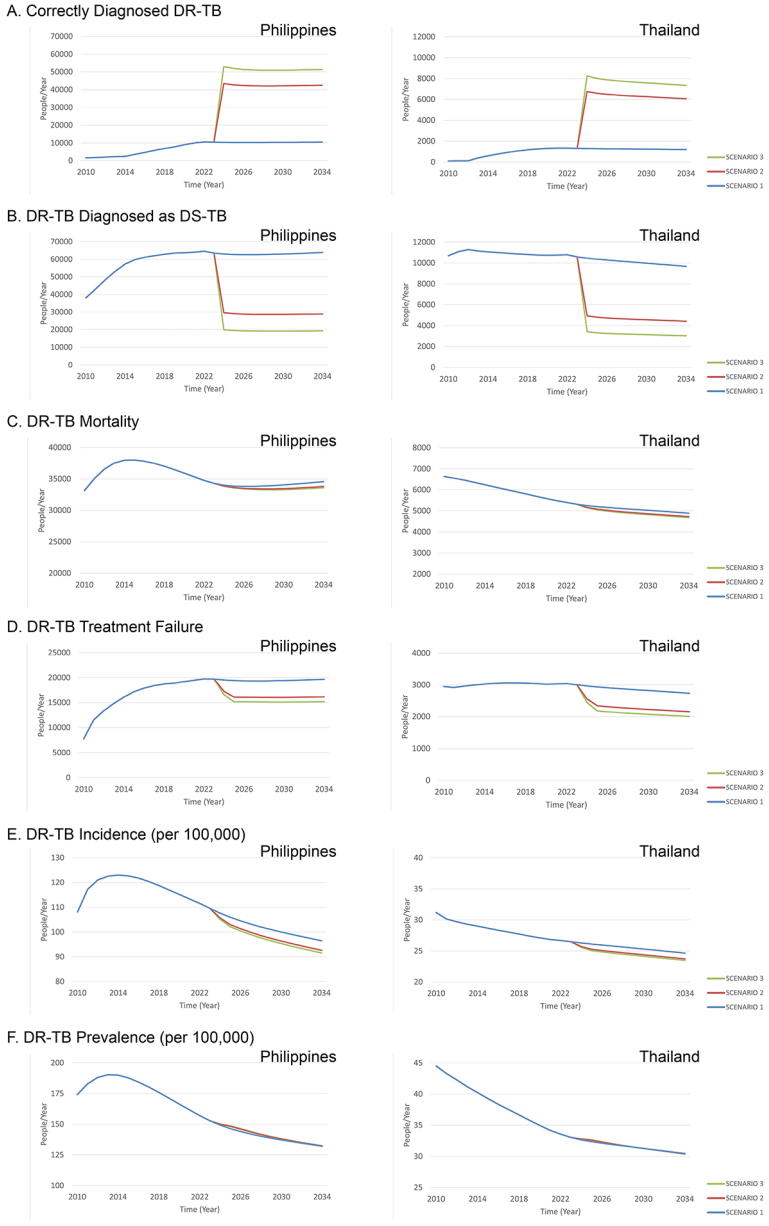


Fig. 2 Modelling outcomes for Scenarios 1, 2 and 3. Results have been modelled across six key outcomes: (**A**) Correctly diagnosed DR-TB, (**B**) DR-TB Misdiagnosed as DS-TB, (**C**) DR-TB Mortality, (**D**) DR-TB Treatment Failure, (**E**) DR-TB Incidence and (**F**) DR-TB Prevalence. Scenario 1, shown in blue, represents baseline data for current use of GeneXpert MTB/RIF. Scenario 2, shown in red, represents use of GeneXpert XDR and Scenario 3, shown in green, represents use of tNGS. Scenarios 2 and 3 are implemented starting in 2024, with results modelled across 10-years from 2025 to 2034

Results

In Scenario 1, Status quo, the use of GeneXpert MTB/RIF is limited to detection of RR/MDR-TB which represents less than 20% of overall DR-TB cases. As a result, more than 60,000 and 10,000 DR-TB cases are misdiagnosed and undertreated as DS-TB with first-line TB drugs each year in the Philippines and Thailand, respectively.

The use of GeneXpert XDR in Scenario 2 increases the proportion of detectable resistance to 80%, resulting in immediate and sustained improvements, from 2024 onwards, in the diagnosis of DR-TB compared to Scenario 1 (Fig. 2A: Correctly Diagnosed DR-TB). By 2034, this translates to a fourfold increase in annual DR-TB cases diagnosed in the Philippines (from 10,870 to 43,500 cases) and a fivefold increase in Thailand (from 1,219 to 6,081 cases); the majority of which are Hr-TB cases that would not have otherwise been detected. The increase in DR-TB detection is coupled with a proportionate reduction in DR-TB cases misdiagnosed and subsequently undertreated as DS-TB (Fig. 2B: DR-TB diagnosed as DS-TB).

Table 2 Key outcomes across scenarios. Mean values for six key DR-TB outcomes are reported, along with 95% confidence interval (CI) range and minimum and maximum values. Baseline values are reported (2019) as well as outcome values for year 2034 for each of the three diagnostic testing scenarios.

Outcome	Year	Philippines				Thailand			
		Baseline	Scenario 1	Scenario 2	Scenario 3	Baseline	Scenario 1	Scenario 2	Scenario 3
		2019	2034	2034	2034	2019	2034	2034	2034
Diagnosed DR-TB *(people/year)*	Mean	7,896	10,870	43,500	52,447	1280	1219	6081	7354
	95% CI	110	200	733	863	17	17	73	85
	Min	4,316	5,117	20,875	25,630	683	648	3519	4356
	Max	15,241	25,948	94,632	111,143	2262	2207	9775	11,442
DR-TB Mis-diagnosed as DS-TB *(people/year)*	Mean	64,586	66,203	29,885	19,942	10,837	9767	4437	3041
	95% CI	833	1,172	516	346	119	112	49	34
	Min	38,240	34,026	15,534	10,319	6986	6153	2790	1891
	Max	118,982	158,864	64,974	42,146	16,438	15,186	6888	4786
DR-TB Mortality *(people/year)*	Mean	37,036	35,804	34,871	34,660	5732	4930	4745	4699
	95% CI	451	613	572	568	60	54	48	47
	Min	22,794	18,688	18,422	18,305	3806	3199	3195	3193
	Max	64,823	81,791	72,245	69,839	8398	7415	6808	6774
DR-TB Treatment Failure *(people/year)*	Mean	19,788	21,177	16,851	15,720	3157	2851	2193	2026
	95% CI	527	641	363	300	80	74	38	29
	Min	5,351	5,335	6,644	6,981	941	824	1052	1104
	Max	53,252	73,363	46,062	39,373	6771	6257	3994	3470
DR-TB Incidence *(people/year)*	Mean	131,176	136,123	129,809	128,191	19,746	17,693	16,946	16,758
	95% CI	1,636	2,350	2,102	2,052	203	191	168	163
	Min	79,667	69,589	70,345	70,014	13,232	11,532	11,750	11,807
	Max	229,852	308,273	265,455	256,898	28,395	26,180	23,418	22,777
DR-TB Prevalence *(people)*	Mean	191,633	186,242	185,547	185,571	25,802	21,867	21,733	21,715
	95% CI	2,338	3,189	3,027	3,016	268	239	221	219
	Min	117,671	97,485	99,287	99,513	17,166	14,214	14,650	14,764
	Max	336,130	426,616	385,822	375,450	37,707	32,801	31,142	31,281

As a result of accurate initial diagnosis of DR-TB, there is also a marked reduction in DR-TB treatment failure, which decreases by 20% in the Philippines and 23% in Thailand (Fig. 2D: DR-TB treatment failure). Total DR-TB Mortality (Fig. 2C) and Treatment failure (Fig. 2D) are summed across all DR-TB cases (Fig. 2A and B), which include correctly diagnosed DR-TB cases as well as DR-TB cases mis-diagnosed as DS-TB.

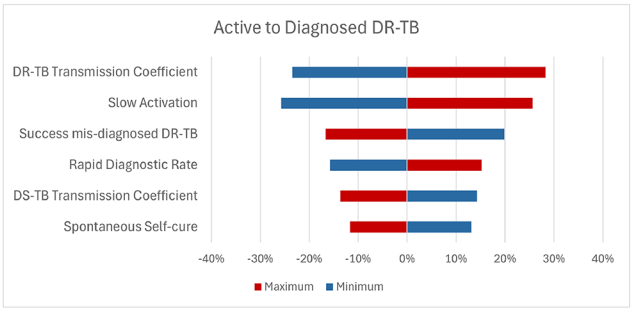
In Scenario 3, the use of tNGS would allow for the detection of 98% of DR-TB cases, which would result in over 52,000 cases detected in the Philippines and over 7,000 cases detected in Thailand annually by 2034. In Scenario 3, treatment failure decreases by 26% in the Philippines and 29% in Thailand.

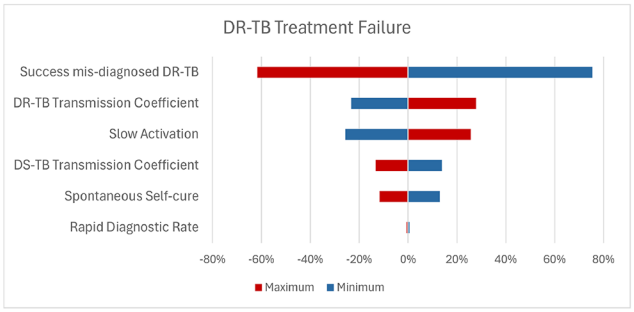
Trends in DR-TB incidence and mortality are the same as those of DR-TB treatment failure, showing a slight downward trend by 2034. Scenario 1 has the least number of DR-TB cases diagnosed (Fig. 2A), which results in the highest rates of DR-TB mortality (Fig. 2C) and, because of undetected DR-TB cases that continue to infect others in the population over time, leads to the highest DR-TB incidence (Fig. 2E). As expected, increased DR-TB diagnosis rates in Scenarios 2 and 3 are associated with lower DR-TB mortality and lower DR-TB incidence, as more DR-TB cases receive appropriate treatment and are prevented from infecting others in the population. In the Philippines, DR-TB mortality is reduced by 3%, and DR-TB incidence is reduced by 5% in Scenario 2 and 6% in Scenario 3. In Thailand, both DR-TB mortality and DR-TB incidence are reduced by 4% in Scenario 2 and 5% in Scenario 3.

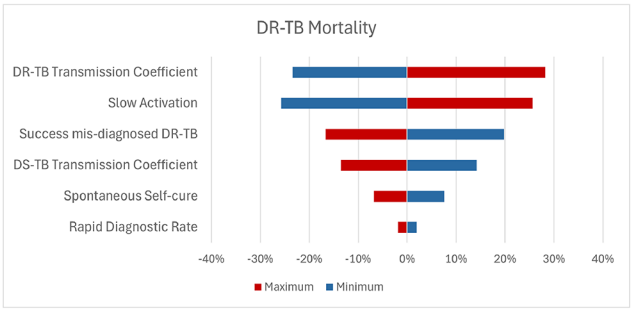
In terms of DR-TB prevalence (Fig. 2F), the large increases in DR-TB diagnosis lead to initial increases in DR-TB prevalence, as observed in Scenarios 2 and 3. Since case detection rates are held constant as an independent variable from the diagnostic testing intervention, DR-TB cases are moving from misdiagnosed to correctly diagnosed with little change in the absolute number of cases. However, this initial increase in prevalence is balanced out over time by reductions in DR-TB mortality and incidence, resulting in a small overall reduction (<1% in both countries) in total DR-TB prevalence by 2034.

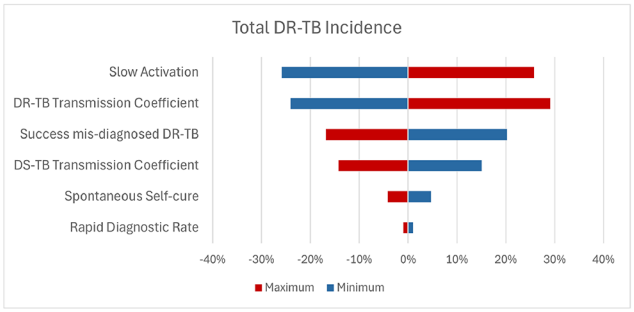
Outcomes were most sensitive to variation in DR-TB transmission coefficient, DS-TB transmission coefficient, slow activation rate, the success rate for DR-TB misdiagnosed and treated as DS-TB, and the proportion of cases receiving rapid diagnostic. Results from the univariate analysis are shown in Fig. 3 as tornado graphs for each

The Philippines

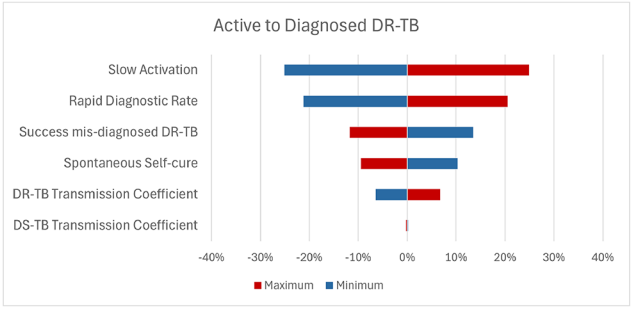


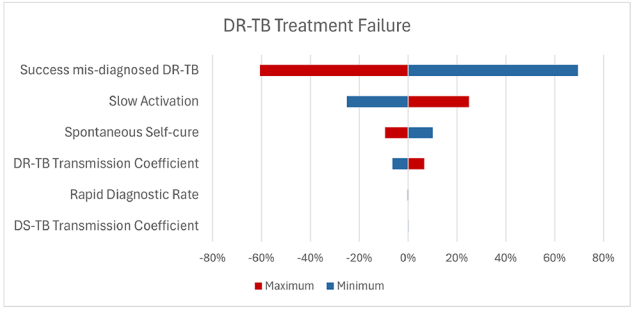


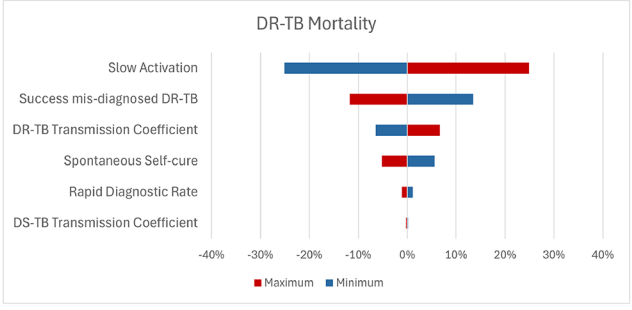




Thailand







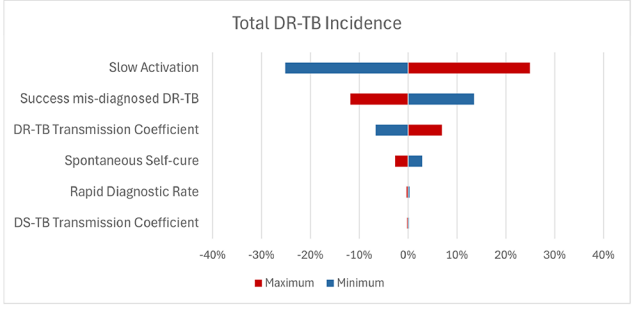


Fig. 3 Tornado plots for one-way sensitivity analysis. Results are shown separately for the Philippines and Thailand. The six parameters that resulted in greatest variation from the mean are shown: DR transmission coefficient, DS transmission coefficient, Slow activation, Rapid diagnostic rate, Success mis-diagnosed DR-TB and Spontaneous self-cure. Bars show the percentage variation from the mean by 2034 for each outcome, with ±25% variation in that parameter. "*Success mis-diagnosed DR-TB*" refers to the treatment success rate for DR-TB cases mis-diagnosed and treated as DS-TB

outcome in 2034. Results from the multivariate analysis conducted with simultaneous variation across these six key parameters are summarized in Table 2.

Discussion

Results from this modelling study demonstrate how improving diagnostic testing to detect a wider range of TB resistance in high burden settings, in line with the capability of newer diagnostic tools such as GeneXpert XDR and tNGS, can have an immediate and significant impact in increasing accurate DR-TB detection, leading to large reductions in DR-TB treatment failure. These modelling results have also highlighted the magnitude of DR-TB cases misdiagnosed and undertreated as DS-TB due to the limitation of current diagnostic tests which focus only on rifampicin-resistant TB.

Using case-studies for the Philippines and Thailand, this study has illustrated the importance of diagnostic testing for DR-TB detection in high-burden settings. Although the Philippines has higher TB incidence and prevalence than Thailand, both countries demonstrated a large impact in DR-TB diagnosis and reductions in treatment failure with improved diagnostic testing, proportional to overall DR-TB cases. It is also important to note that although the transmission coefficient in Thailand was lower than in the Philippines, it did not differ between DS-TB and DR-TB (Table 1). This suggests that at lower transmission rates, the effect of reduced fitness of DR-TB is less pronounced, which supports findings from other modelling studies which indicate decreased prevalence of TB can lead to an increased proportion of DR-TB strains [20, 27]. Therefore, while DR-TB prevention efforts are important in the Philippines due to the sheer volume of cases requiring accurate diagnosis and treatment, DR-TB prevention efforts in Thailand would impact a larger proportion of overall TB burden despite the smaller absolute number of cases.

Surprisingly, univariate sensitivity analysis revealed that the rate of acquired drug resistance, or treatment failure of DS-TB resulting in DR-TB, was not a significant factor in overall DR-TB outcomes. The volume of cases that acquire drug resistance is impacted by treatment failure and, due to the high rates of treatment success for DS-TB in both the Philippines (87% in 2019) and Thailand (85% in 2019), the proportion of DS-TB cases that fail treatment and result in acquired drug resistance is low, making this a weak contributor to overall DT-TB outcomes. Instead, the treatment success rate for misdiagnosed DR-TB, which was calibrated to 70% for both the Philippines and Thailand, was identified as a key parameter. This indicates that reducing treatment failure of misdiagnosed DR-TB treated as DS-TB would have a large influence on overall DR-TB outcomes and may potentially impact rates of MDR-TB through reduced amplification of resistance.

Future studies on the cost of implementing improved TB diagnostic tests such as GeneXpert XDR and tNGS will be essential to determine the cost effectiveness of these interventions in high burden settings. While tNGS can detect a wider range of drug resistance than GeneXpert XDR, sequencing technology remains expensive, especially in resource-limited settings, and would require additional training and expertise on testing protocols and interpretation of results [28], whereas many countries are already familiar with the GeneXpert platform. These tradeoffs will influence which diagnostic test, or potential combination of tests, would be most cost effective in reducing DR-TB outcomes over time. Future studies could also investigate the marginal benefits of targeting additional diagnostic tests on high-risk groups for DR-TB, including previously treated TB cases and patients with TB co-morbidities such as human immunodeficiency virus (HIV) or diabetes.

Several assumptions were made to balance model simplicity with accuracy. The model does not include age or comorbidities with TB, which may affect transmission rates as well as diagnosis and treatment outcomes. The model is focused on pulmonary TB transmission and therefore does not include extra-pulmonary TB data or the effect of BCG vaccination which does not protect against pulmonary TB. The model does not account for loss to follow up during treatment, as all patients are accounted for in one of four treatment outcomes: relapse, acquired resistance, recovery or death. The model does not differentiate between new cases and previously treated TB cases within the "Active TB" stock, which may affect their rates of diagnosis and treatment outcomes. The model is performed on the total country population and does not account for migration or sub-national factors such as population density or socioeconomic status, which may affect TB transmission. Finally, the model was calibrated to WHO reports and therefore the accuracy of model estimates are dependent on the accuracy of reported country data.

Despite these limitations, results from this dynamic modelling have several policy implications. First, there is a clear need for improved TB diagnostic testing, early in the diagnostic pathway, to detect TB drug resistance prior to treatment to prevent DR-TB treatment failure and potential amplification of resistance. In addition, accurate detection of Hr-TB could incentivize countries to adopt modified treatment regimens for patients with Hr-TB, as recommended by WHO in 2018, to further reduce DR-TB treatment failure and mortality. Finally, these findings highlight the importance of detecting a wider range of TB resistance given limited current and forecasted availability of anti-TB drugs, and to protect the introduction of new treatment protocols in the region. To address these many concerns, the use of GeneXpert XDR or tNGS as an additional diagnostic test for DR-TB can significantly improve DR-TB case detection and treatment outcomes, supporting their consideration for use in high burden settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10027-6.

Supplementary Material 1

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Author contributions
MG contributed to the conceptualization, investigation, methodology, formal analysis, visualization and writing the original draft. JPA contributed to the conceptualization, methodology, formal analysis, and reviewing and editing. DL, RB, FT, SM, and WS contributed to the conceptualization, validation, investigation and review and editing. DM contributed to the conceptualization, methodology, supervision and reviewing and editing. All authors read and approved the final manuscript.

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Data availability
The datasets analysed during the current study are publicly available in the WHO Global Tuberculosis Program repository (https://www.who.int/teams/global-tuberculosis-programme/data).

Declarations

Ethics approval and consent to participate
Not applicable. No participant data was collected for this study. The study was granted exemption from IRB review from the Duke-NUS Departmental Ethics Review Committee (Reference: DERC-19-231205).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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