

Assessing the Impact of M72/AS01E Vaccination on  
Tuberculosis Burden in Cambodia



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## Abstract

**Introduction** While improvements in tuberculosis detection and treatment have been achieved, Cambodia still fall short of achieving tuberculosis elimination.

**Objective** The main objective of this study was to assess the impact of the M72/AE01S vaccine on tuberculosis cases in Cambodia.

**Methods** We developed an age-stratified compartmental model. The model was fitted to the observed cases in Cambodia. Results were forecast over 10 years to assess the vaccine's impact on the cumulative cases and mortality in 2035 relative to 2025.

**Results** At a coverage rate of 25%, the vaccine demonstrates a case reduction of approximately 2%. Notably, even though the vaccine is not administered to children, there is a corresponding decrease in cases among this group.

**Conclusion** Results from our model suggest that the M72/AE01S vaccine can substantially reduce tuberculosis cases over 12 years; however, it may be insufficient alone if Cambodia is to progress towards tuberculosis elimination.

**Keyword** Age-stratified compartmental model, tuberculosis, M72/AE01S

# 1 Introduction

## 1.1 Background

Tuberculosis (TB) is usually a treatable and preventable infectious disease caused by *Mycobacterium tuberculosis* (1). It is spread when people with contagious TB expel the bacteria into the air (e.g. by coughing). The risk of developing the disease following infection is highest within the first 2 years, at approximately 5%. After this period, it is significantly lower and can remain elevated for the remainder of one's lifetime (2). Despite this, nearly a quarter of the global population is estimated to have been infected with TB (3).

In 2023, TB returned as the primary cause of morbidity and mortality globally from a single infectious agent, following three years in which coronavirus disease (COVID-19) had been the leading cause (3). In the same year, around 10.8 million people fell ill and 1.25 million died from TB worldwide (3). TB exists in all countries and affects all age groups. It is the top killer of HIV-positive people and also a significant source of deaths related to antimicrobial resistance (3).

TB remains a critical public health challenge in Southeast Asia (SEA), accounting for more than 45% of the annual global TB incidence (3). The region had more than 4.8 million people infected with TB, and over 600000 died (not including TB + HIV mortality) due to this disease in 2022 (3). This part of the continent also faces a high burden of multidrug-resistant and rifampicin-resistant TB (MDR-/rr-TB). The estimated incidence of MDR-/rr-TB in 2022 was 170000 (3). Drug resistance is a daunting hindrance to TB care and prevention worldwide, making it more challenging and longer to treat, with inferior results for patients (3).

Six countries in the Southeast Asian (SEA) region, including India, Indonesia, Myanmar, Bangladesh, Thailand, and the Democratic People's Republic of Korea, have a high global burden of TB (3). Although Cambodia is not one of the six, it is still facing devastating public health challenges due to the TB burden. Several factors contribute to this burden in the country, including high population density and limited healthcare resources, which lead to a high prevalence and rapid transmission rates.

## 1.2 Tuberculosis in Cambodia

For many years, Cambodia has made tangible progress towards achieving the End TB Strategy targets, with 500000 TB patients cured and an estimated 400000 deaths prevented since 2000 (3). The health authorities in Cambodia have invested in screening people more actively in high-risk societies, including older population groups, marginalised communities, and contacts of individuals with bacteriologically confirmed TB (3). While there is evidence indicating that TB incidence and mortality in the country had been falling before the COVID-19 pandemic, there is uncertainty about meeting the Sustainable Development Goals target to end the tuberculosis epidemic by 2030 (4).

Antimicrobial resistance (AMR) is a growing concern, which has led to an increase in TB spread, severe illness, and death in Cambodia (3). The World Health Organisation (WHO) has estimated that this silent pandemic is expected to cause 5.2 million deaths and cost the country US\$148 billion between 2020 and 2030 (3). With funding being frozen by the United States, TB programmes, particularly community-based interventions in Cambodia, will further increase the TB burden (5). Due to the staffing loss and service delivery disruption, an estimated 10000 patients with drug-sensitive TB, 300 patients with MDR-TB and 10000 individuals receiving TB preventive treatment (TPT) are experiencing treatment interruptions (5).

Therefore, the government must find a more conducive and affordable way to tackle the country's TB challenges. A literature review has demonstrated that new TB vaccines will play a crucial role in accelerating the decline of TB and achieving its elimination (4).

The country has implemented several measures to combat TB, including the SAHACA project, which partners with Khana and has proven effective in active case finding through community mobilisation. Instead of providing a hospital-based TB program, Cambodia has transformed the scheme to offer free, universal access to TB care and treatment at the community level (6). The country has invested in advanced diagnostics and the management of drug-resistant TB. New testing approaches, such as Xpert Ultra and liquid culture (MGIT), are used, ensuring faster and more accurate results. The efforts of the National Centre for Tuberculosis and Leprosy Control (CENAT) and its partners to expand TB control activities have resulted in rates of bacteriologically confirmed TB declining by 45% between the national TB prevalence surveys conducted in 2002 and 2011 (7).

TB prevention approaches in Cambodia include implementing the Bacillus Calmette-Guerin (BCG) vaccination as part of the national childhood immunisation program. Vaccinated children are safeguarded from catching the most severe forms of TB (meningitis and disseminated TB disease), but not against contracting it from an infectious person, such as a family member (7). While studies suggest that BCG vaccination at birth effectively prevents pulmonary TB in young children, it offers limited protection in adolescents and adults (8). Of the total global number of individuals who develop TB disease each year, about 90% are adults, with more cases among men than women (3).

Consequently, boosting immunoprotection in older populations is crucial. Several TB vaccine candidates are in development (9). GlaxoSmithKline developed a promising vaccine, the M72/AS01E, in partnership with AERAS. The M72/AS01E is the most promising candidate (10). A Phase 2b trial was conducted in several African countries, along with its three-year follow-up (11). It demonstrated that M72/AS01E elicited a strong immune response and reduced the progression to pulmonary TB in adults with latent TB infection, providing protection for at least three years (4). Notably, a South African study projected that M72/AS01E vaccination could avert approximately 80% more TB cases and deaths by 2050 than BCG revaccination (4). Other developed vaccines, such as the H56, ID93, and M72 subunit vaccines, are designed to offer pre-exposure and post-exposure protection (10).

Current modelling (11) has indicated that M72/AS01E vaccination and BCG revaccination could be cost-effective in India for different vaccine features and execution approaches (4). Nevertheless, the vaccine implementation's likely impact and costs are expected to be country-specific (12). Research conducted on the effect of the TB vaccine in China, South Africa, and India showed that the significance of vaccine characteristics and their impact

depended on the epidemiology in each country (12). Since the M72/AS01E vaccine is protective against pulmonary TB in adults, it can potentially reduce drug-resistant tuberculosis by reducing transmission and averting the need for antibiotics (13).

No published research has evaluated the benefits of introducing the M72/AS01E vaccine in Cambodia. Most studies have been conducted in African countries (14), and while a Phase 3 clinical trial is underway in several countries (15), Cambodia is not among them. This underscores the need for localised research to determine the vaccine's feasibility in the Cambodian settings. Introducing the vaccine in the country could potentially enhance TB control efforts by providing additional protection to the most affected group, namely the older age groups. Given the high TB burden and the limitations of current prevention strategies, this proposed research addresses a critical gap that could provide essential data to inform policy decisions and enhance TB control efforts in the country.

Specifically, the study aims to assess the potential impact of M72/AS01E vaccination in Cambodia, focusing on cure rates, treatment adherence, and drug resistance across different socioeconomic groups. This evaluation will provide valuable insights into how the new vaccine could complement existing TB prevention strategies, assess its effectiveness, and inform national TB control strategies in low-income settings.

## 2. Methods

### 2.1 Data

TB incidence, treatment rates, prevalence data, and mortality estimates from 2018 to 2024 were obtained from the Annual Tuberculosis Report published by the Ministry of Health in the Kingdom of Cambodia. The data from 2000 to 2017 were taken from the WHO. TB data values and sources are recorded in the Supplementary material.

### 2.2 Model Structure

We developed an age-stratified mathematical model of TB in Cambodia. The model is an extension of prior models of TB vaccination. It explains infection with *M. Tuberculosis*, the transition of TB disease, and treatment and diagnosis, stratified by age.

The model divides the population into two groups: the children's group, comprising individuals aged 0 to 9 years, with six states; and the adult group, comprising individuals aged 10 years and above, with six compartments. The total population is the sum of all states in these two groups. Several significant assumptions underlie the model's construction. Key assumptions are given below, and the rest are outlined in the supplementary:

**(A1):** All infants are susceptible. Taking into consideration that infants who were born in 2000 to untreated TB-infected women may have lower birth weights and, in rare cases, be born with tuberculosis, it can be concluded that all these infants were potentially susceptible to tuberculosis (16).

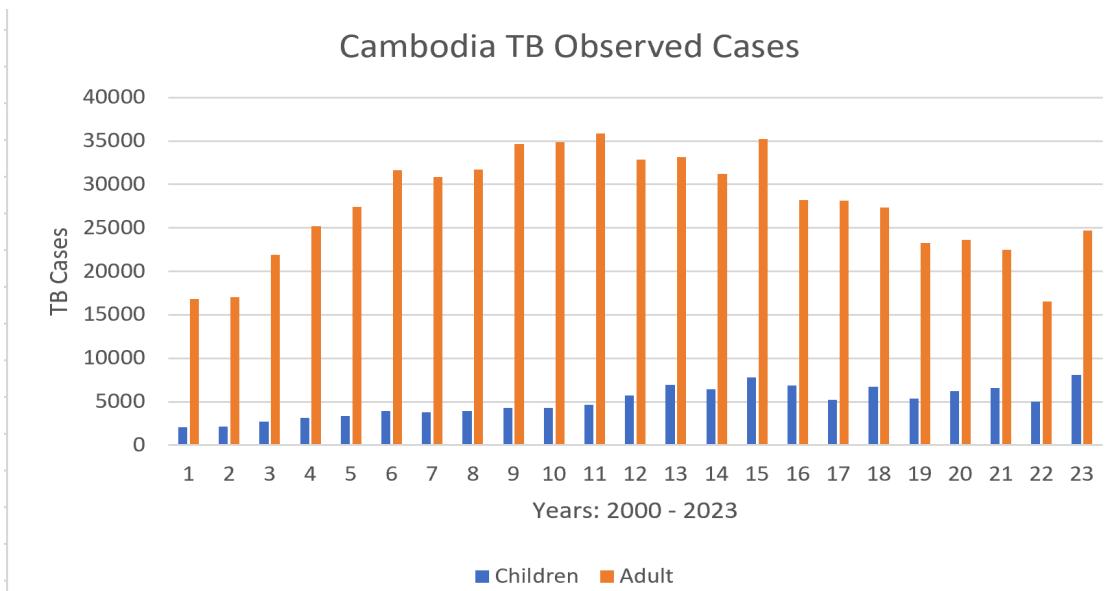
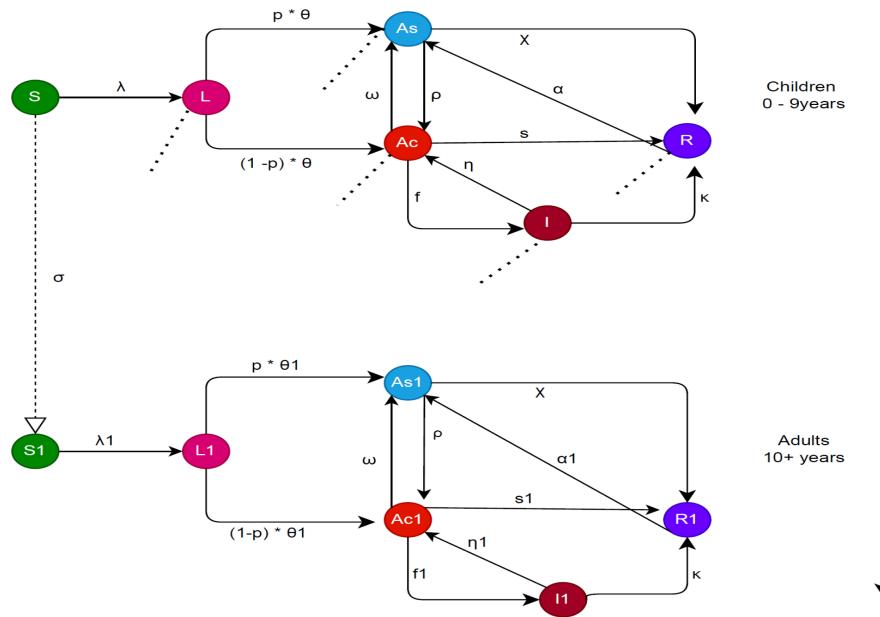
**(A2):** Reinfection with tuberculosis. Reinfection refers to the acquisition of a new infection after exposure to the same or potentially different strains of TB bacteria. We assume one strain: pulmonary TB. The probability of successful infection for reinfection is lower than that of primary infection, due to immunity gained through either infection or recovery.

**(A3):** Cambodia has shown low cases of multidrug-resistant tuberculosis, hence we did not include these in our model.

Our model construction is stated as follows. We begin by assuming that all individuals in the susceptible state progress to the latent state at a force of infection  $\lambda$ . The latent state from past papers (4, 11) is divided into three categories; however, due to a lack of data for our model, we decided to have one latent state (17). Individuals in the latent state then progress to a disease state, classified into subclinical and clinical disease, before diagnosis and treatment. Individuals in the subclinical state may either progress to clinical disease or recover naturally over time.

Furthermore, individuals in the clinical disease state who receive treatment may adhere to it and recover, or not adhere and then relapse. Those in the relapse group may eventually recover and move to the recovered compartment. Considering the possibility of reinfection, individuals in the recovered compartment may be reinfected by those in the infected compartment and move back to the relapse state. Lastly, compartments in the children's group experience a decrease due to ageing, and we assume that the total death rate equals the birth rate to maintain a constant population.

The model structure is depicted in Figure 1, and the full details of the TB model structure, including equations and parameter values, are provided in the Supplementary material.



**Figure 1: Tuberculosis natural history model structure and cases**

*Abbreviations:*  $S_i$  = Susceptible-Naive;  $L_i$  = Latent (recently infected),  $A_{si}$  = Subclinical Disease,  $A_{ci}$  = Clinical Disease,  $I_i$  = Relapse(failed-treatment), and  $R_i$  = Recovered. Subscript  $i = 1$ , and  $i \neq 1$  represents adults and children states respectively.

The model structure (Figure 1) delineates several compartments in the progression of TB. The Cambodian population is divided into classes:  $S$  = Susceptible-Naive;  $L$  = Latent (recently infected),  $A_s$  = Subclinical Disease,  $A_c$  = Clinical Disease,  $I$  = Relapse(failed-treatment),  $R$  = Recovered. Individuals with no history of exposure or infection with Mycobacterium tuberculosis (M.tb) ( $S$ ) can be infected at a rate  $\lambda$  and advance to the Latent compartment ( $L$ ). Once in  $L$ , individuals can either (i) advance rapidly to Subclinical Disease ( $A_s$ ), or (ii) progress to the clinical disease state ( $A_c$ ).

Individuals in the Subclinical Disease class ( $A_s$ ) are assumed to be infectious, but with higher infectiousness compared to those with clinical disease (4) and are supposed to show no symptoms of TB. These individuals may progress to Clinical disease ( $A_c$ ) or may naturally recover from the disease to the recovered state ( $R$ ). Those individuals in the state ( $A_c$ ) are infectious and display symptoms. They will be diagnosed and started on treatment. The model presents potential outcomes for clinically active TB patients: (i) cure or successful completion of treatment ( $s, s_1$ ), (ii) treatment failure ( $f, f_1$ ), and (iii) mortality attributed to TB ( $\mu_{sev}, \mu_{sev1}$ ) or natural death ( $\mu, \mu_1$ ).

Those who complete treatment and get cured move to  $R$ , while those who do not adhere to treatment relapse to  $I$ . Once in a relapse state, individuals may go back to clinical disease or eventually recover. Individuals in the child states are assumed, on average, to transition to their respective adult states after ten years at a rate  $\sigma$ . Additionally, those in the recovered groups may suffer a recurrence at a rate  $\alpha$ , transitioning back to being subclinically infected.

The equations of the TB model are as follows:

The ageing parameter was only included in the susceptible equations for simplicity. Full model equations are provided in the supplementary.

*Age i ≠ 1*

$$\frac{dS}{dt} = B - (\sigma + \mu)S$$

$$\frac{dL_i}{dt} = \lambda S_i - (\theta_i + \mu_i)L_i$$

$$\frac{dAs_i}{dt} = p\theta_i + \omega Ac_i + \alpha_i R_i - (\rho + \chi + \mu_i)As_i$$

$$\frac{dAc_i}{dt} = (1 - p)\theta_i + \rho As_i + \eta_i I_i - (f_i + s_i + \omega + \mu_{sev_i} + \mu_i)Ac_i$$

$$\frac{dI_i}{dt} = f_i Ac_i - (\eta_i + \mu_i + \kappa)I_i$$

$$\frac{dR_i}{dt} = \chi As_i + \kappa I_i + s_i Ac_i - (\alpha_i + \mu_i)R_i$$

$$\mu_{sev_i} + f_i + s_i = 1$$

### 2.2.1 Model Fitting

The model was executed using Stan and the rstan package for R, which allows for the identification and estimation of Bayesian models. We generated 4,000 samples from the posterior distributions of each quantity of interest. Point estimates were computed as the mean of these distributions, and credible intervals were calculated as the 97.5th and 2.5th percentiles of the distributions.

In this segment, we estimated the key parameters of our age-specific mathematical model of TB transmission dynamics. Estimating parameters is significant in modelling, as it involves inferring values from observed data to predict or understand transmission dynamics (18). We estimated the key parameters using the annual TB cases data, given in the supplementary file, from 2000 to 2023. By deploying the Markov Chain Monte Carlo (MCMC) method in stan, the model generated age-specific TB cases (for infectious TB classes), which were subsequently compared to observed annual cases. For each parameter, the prior distributions were given based on either literature data or an initial guess of the parameters. These priors, modelled as log-normal distributions, enclosed our uncertainty before incorporating the observed data. The posterior distributions were acquired by updating the priors with the observed data.

We assumed throughout the fitting that the empirical reporting rate was 100%; thus, once cases were detected, they were recorded. We use MCMC to estimate parameter values and a Poisson log-likelihood to evaluate the model fit. Simulations were run for 250 years to achieve equilibrium during the fitting process. Unfortunately, the model stabilises at lower values compared to the observed data. We ultimately used the estimated values from this to fit our model. The warm-up phase consisted of the first 1000 iterations for each chain, with fitting

conducted using four chains of 2000 total iterations each (1000 sampling iterations after the warm-up) on the observed period (2000–2023). This was followed by a 12-year forecasting period (2024–2035).

The prior distributions of each estimated parameter used in this model are presented in Table 1, along with the summary statistics of the parameter estimates obtained from the MCMC. A complete list of parameters and their sources can be found in the S1.

*Table 1:* Prior and Posterior Distributions for Key Model Parameter

Parameter	Definition	Prior Distribution	Posterior				
			Mean	Lower Bound (2.5%)	Upper Bound (97.5%)	Effective Sample Size	R.hat
$\theta$	Rate of progression to disease for children.	lognormal( log (0.3), 0.5)	0.13	0.11	0.15	57	1.06
$\theta_1$	Rate of progression to disease for adults.	lognormal( log (0.5), 0.5)	0.03	0.03	0.03	600	1
$s$	Successful treatment rate for children.	dirichlet([2, 12, 1]')	0.64	0.41	0.94	44	1
$s_1$	Successful treatment rate for adults.	dirichlet([2, 12, 1]')	0.77	0.70	0.95	192	1.02
$f$	Failure treatment rate for children.	-	0.03	0.003	0.07	54	1.07

$f_1$	Failure treatment rate for adults.	-	0.01	0.002	0.03	968	1
$\omega$	Rate of reactivation from clinical to subclinical disease	lognormal( log (0.008), 0.3)	0.003	0.002	0.005	1585	1
$\rho$	Rate of reactivation from subclinical to clinical disease	lognormal( log (0.3), 0.5)	0.30	0.30	0.30	2116	1
$\mu_{sev}$	TB mortality rate in children.	-	0.01	0.0001	0.02	143	1.02
$\mu_{sev_1}$	TB mortality rate in adults.	-	0.01	0.0002	0.02	275	1.02
$L$	Children with latent TB in 2000.	lognormal( log (11000), 0.2)	10744	9671	11891	137	1.03
$L_1$	Adults with latent TB in 2000.	lognormal( log (450000), 0.2)	441843	425125	458573	611	1
$\beta$	Transmission rate for adults.	lognormal( log (2.5), 0.8)	2.07	2	2.12	860	1
$\alpha$	Rate of relapse from recovery for children.	lognormal( log (0.02), 0.3)	0.11	0.09	0.15	118	1.03
$\alpha_1$	Rate of relapse from recovery for adults	lognormal( log (0.015), 0.3)	0.002	0.001	0.003	695	1
$\eta$	Rate of reactivation from relapse to	lognormal( log (0.03), 0.3)	0.03	0.02	0.06	1053	1

	clinical disease for children						
$\eta_1$	Rate of reactivation from relapse to clinical disease for adults	lognormal( log (0.025), 0.3)	0.03	0.01	0.04	1834	1

## 2.1 Scenario analysis and sensitivity analysis

The fitted age-based model was used to analyse the impact of the M72/AS01E vaccine. We run three scenarios: the baseline scenario, which reflects the current condition with a few interventions, taking into account the lack of funding(5).

The executive order signed by the US President in January 2025 to suspend all US foreign aid has resulted in profound consequences for the TB programme in Cambodia, particularly community-based interventions like the Community Mobilisation Initiatives to End TB Phase 2 (COMMIT2), which has been terminated effective 26 February 2025(5).

Second, we run two scenarios for the M72/AS01E vaccine with 25% and 75% coverage. For both scenarios and the baseline, we assumed 100% test sensitivity.

A new 2.9 million pounds program, SHIFT-TB (Strengthening Health Systems through Integrated Risk Factor Intervention and Tuberculosis (TB) Case-Finding), is underway in the country to tackle tuberculosis, led by KHANA in collaboration with local and international partners, including the University of Sydney and the National University of Singapore(19). The

launch of SHIFT-TB comes at a critical time to fill the gap left by the withdrawal of major donors, such as USAID, and maintain the momentum.

All scenarios were executed with a warm-up period of 300 iterations for each chain. Fitting was performed using four chains, each consisting of a total of 700 iterations, which included 400 sampling iterations following the warm-up.

### 3 Results

#### 3.1 Scenario analysis

The vaccination scenarios were implemented from 2026 to 2035 for the adult group, which includes adolescents and adults. In these scenarios, a periodic re-vaccination strategy was implemented, with campaigns assumed to be provided every 3 years starting in 2026. We explored routine vaccine coverage of 25% and 75% of the target populations. Only people with latent disease were included for vaccination. We assumed that M72/AS01E vaccination was applied universally to the adult group without pre-vaccination screening, with vaccine effectiveness calculated as the product of vaccination coverage, vaccine efficacy (50%), and time-dependent protection status accounting for waning immunity.

The model applies the full vaccine effect to the adult latent TB compartment (L1), implicitly assuming that vaccination targets the relevant population with latent infection. This approach reflects a universal vaccination strategy where M72/AS01E is administered to all adolescents and adults in the target population, with the vaccine effect directly modifying the progression rate from latent to active tuberculosis in the adult compartments.

*Table 2:* Predicted cases for both the baseline and M72/AS01E vaccine at low coverage

Year	Baseline	Low coverage(25%)	% Change=((Baseline - Low Coverage) / Baseline) × 100
2026	33141	33129	0.04
2027	33559	33351	0.62

2028	34032	33383	1.91
2029	34566	33768	2.31
2030	35159	34221	2.67
2031	35810	34739	2.99
2032	36516	35318	3.28
2033	37273	35952	3.54
2034	38082	36637	3.79
2035	38940	37370	4.03

At a coverage rate of 25%, the vaccine demonstrates a case reduction of approximately 2%. Notably, even though the vaccine is not administered to children, there is a corresponding decrease in cases among this group, as shown in Figures 6 and 7. Unfortunately, we were unable to conduct the final scenario due to time constraints in running the model, but we believe the potential impact would be considerably greater.

### 3.2 Sensitivity analysis

We had planned to conduct two distinct sensitivity analyses. The first was designed to evaluate the anticipated impact of the interventions under varying conditions. This involved altering the intervention's effect parameters, vaccination effect, transmission rates, and treatment outcomes for individuals using a one-at-a-time approach. The second analysis aimed to assess the model's robustness against uncertainties in the fixed parameters, where we varied these parameters by  $\pm 10\%$  of their baseline values in 5% increments. For both sensitivity analyses, we intended to quantify sensitivity as the percentage change in the 12-year cumulative cases relative to the baseline parameters. Unfortunately, due to time constraints and difficulties in fitting the model to the observed data satisfactorily, we were unable to carry out the sensitivity analyses.

## 4 Discussion

This study utilises an age-based compartmental model to simulate the dynamics of tuberculosis (TB) transmission in Cambodia, stratifying the population into age groups (children aged 0-5 years and adults aged 6 years and older) across twelve epidemiological states. Transitions between these states are governed by biologically plausible parameters, including progression rates, reactivation probabilities, and treatment outcomes. This age-stratified approach is particularly pertinent to Cambodia's epidemiological landscape, where childhood TB poses a significant burden, and transmission patterns vary considerably between age groups due to differences in exposure risks, immune responses, and case detection rates. The model features a smooth sigmoid transition function for each of the three interventions employed, offering a more realistic representation of policy decision-making and scale-up processes that correspond with Cambodia's gradual healthcare system strengthening efforts over the past two decades.

Three key interventions illustrate the evolution of Cambodia's tuberculosis (TB) control strategy: the implementation of Community-based directly observed therapy (DOT) from 2000 to 2023, Active Case Finding (ACF) programs from 2005 to 2035, and Tuberculosis Preventive Treatment (TPT) targeting high-risk populations. These interventions reflect a complex temporal pattern shaped by policy changes and resource constraints. The DOTS initiative highlights the systematic rollout of standardised treatment protocols in alignment with WHO recommendations. In contrast, ACF signifies Cambodia's intensified efforts to uncover undiagnosed cases among high-risk communities and within healthcare facilities. The TPT intervention employs a data-driven approach to forecast future trends, allowing the model to learn from historical implementation patterns—such as the scale-up from 2000 to 2014, the

decline from 2014 to 2021, likely due to COVID-19 disruptions, and the subsequent recovery between 2021 and 2023. This parameterisation acknowledges the dynamic nature of public health interventions, resource availability, and competing health priorities prevalent in low- and middle-income countries, such as Cambodia.

The vaccine showed a significant reduction in cases, approximately 2% if administered at 25% coverage. This might be a huge gain, but we believe that at 75% coverage, the reduction in cases will be higher.

This model addresses several gaps in the existing tuberculosis (TB) modelling literature, particularly in its incorporation of age-specific dynamics and flexible intervention trajectories. However, it has notable limitations that deserve attention. The model assumes homogeneous mixing within age groups and does not consider spatial heterogeneity or high-risk subpopulations, such as individuals living with HIV, diabetics, or household contacts of active TB cases. These factors are critical in understanding TB epidemiology in Cambodia, where significant rates of HIV co-infection and household transmission contribute substantially to the childhood TB burden. Unlike more sophisticated models, such as those by (18,20), this framework does not explicitly account for drug resistance dynamics or differentiate between pulmonary and extrapulmonary TB. This lack of distinction may lead to an underestimation of the complexities surrounding Cambodia's TB epidemic, particularly given the increasing challenges posed by multidrug-resistant TB.

Furthermore, while treatment outcome probabilities are estimated as simplex parameters, they may not fully reflect the heterogeneity in treatment responses across different patient populations. The reporting rate parameters also assume stable surveillance systems, despite

known variations in case detection capacity across provinces in Cambodia. Computational limitations influenced our modelling approach. We were restricted to 4000 posterior samples (4 chains  $\times$  1000 iterations), which may have reduced the precision of our parameter estimates. Time constraints also prevented thorough sensitivity analyses to evaluate the model's robustness against alternative specifications or assumptions. Future research should prioritise extended sampling and systematic sensitivity testing to improve model uncertainty characterisation and validate key findings.

Future research should also consider incorporating network-based transmission models, explicit drug resistance compartments, cost-benefit analysis, and province-level heterogeneity to enhance the effectiveness of targeted interventions and inform resource allocation decisions.

The model's primary strength lies in its ability to combine epidemiological realism with policy-relevant flexibility, making it especially valuable for planning and evaluating Cambodia's tuberculosis (TB) program. Its Bayesian framework, utilising informative priors, allows for robust parameter estimation, even when data is limited. Additionally, the smooth intervention functions and learnable future trends yield realistic projections that are essential for medium-term strategic planning.

The age-stratified structure of the model directly addresses the World Health Organisation's End TB strategy, focusing on childhood TB to enable policymakers to assess interventions aimed at specific age groups and understand intergenerational transmission dynamics (21). The model's capacity to quantify uncertainty through credible intervals is vital for risk-informed decision-making in resource-constrained environments. Furthermore, this is the first study done

to evaluate the impact of the M72/AS01E vaccine specifically in Cambodia.

## **Author contributions**

Conceptualisation: 1091538	Data curation: 1091538
Formal Analysis: 1091538	Supervision: BD, K
Methodology: 1091538	Writing - review & editing: 1091538
Writing - original draft: 1091538	

## **Competing interest**

The author declares no competing interests.

## **Financial disclosure**

The author received no specific funding for this work

## **Supplementary Information captions**

S1: Data and methods. In-depth discussion of data source and model implementation.

## **Availability statement**

### **Data**

We utilised publicly available data from the Annual Tuberculosis Report, published by the Ministry of Health in the Kingdom of Cambodia, and data from 2000 to 2017 were sourced from the WHO.

### **Code**

All code used in this study has been made publicly available on GitHub (<https://github.com/1091538MGH>). Additional details are also available in the supplementary materials (S1)

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## Figures

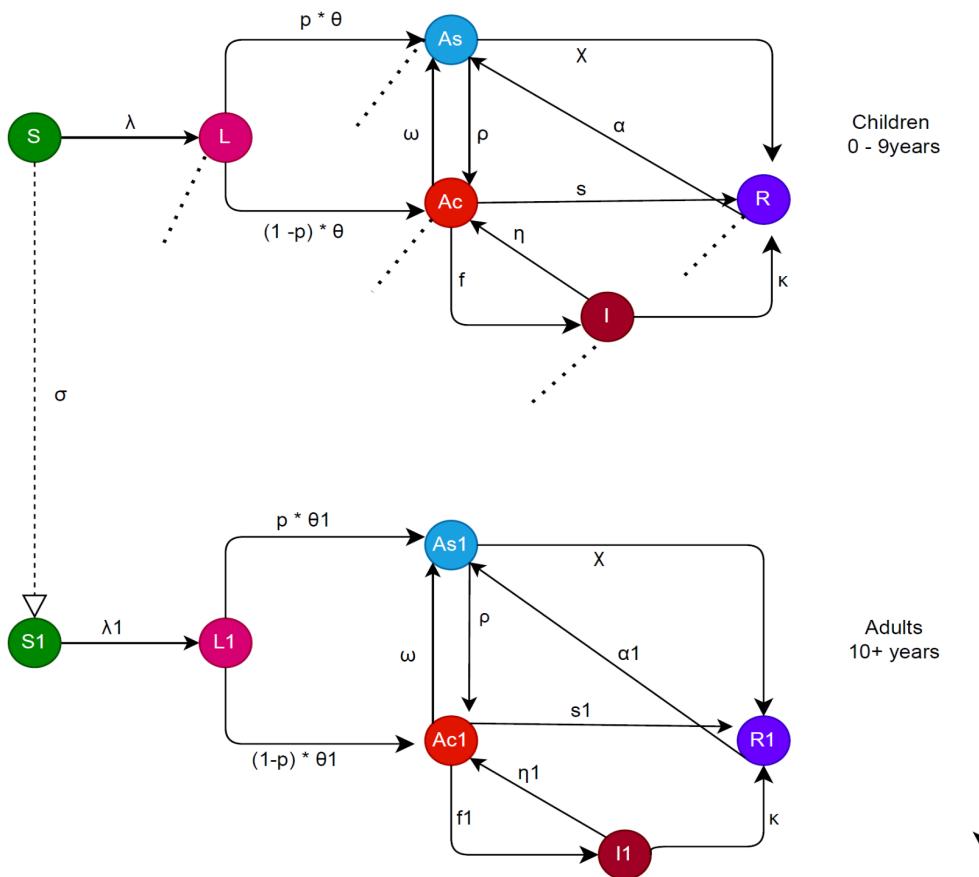
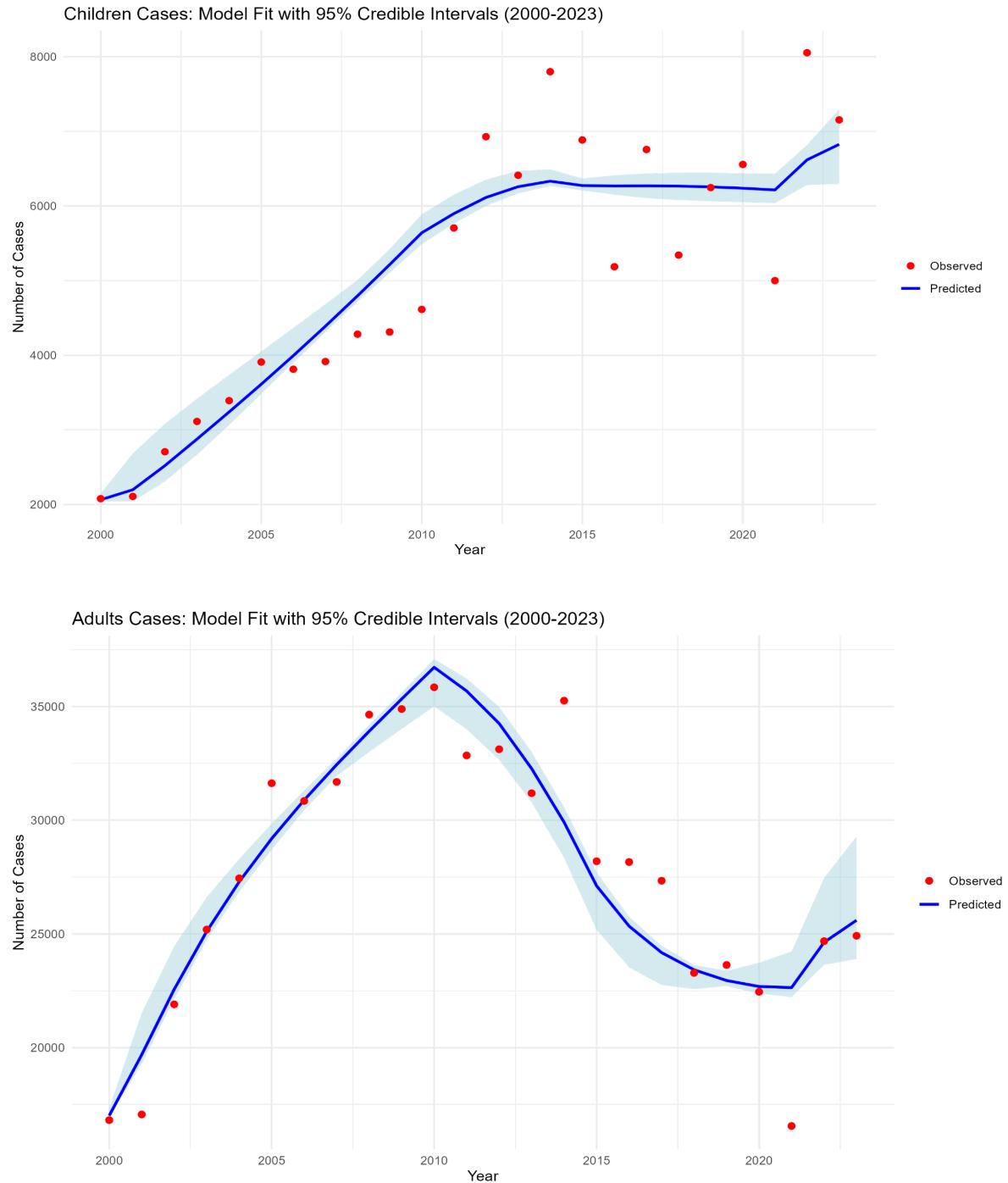


Figure 1: **Age-based model diagram.** Individuals are divided into twelve distinct natural states.



**Figure 2: Model vs observed data.** The figure shows the predicted annual number of tuberculosis cases for both child and adult groups, against the observed data. Shaded areas represent 95% credible intervals.

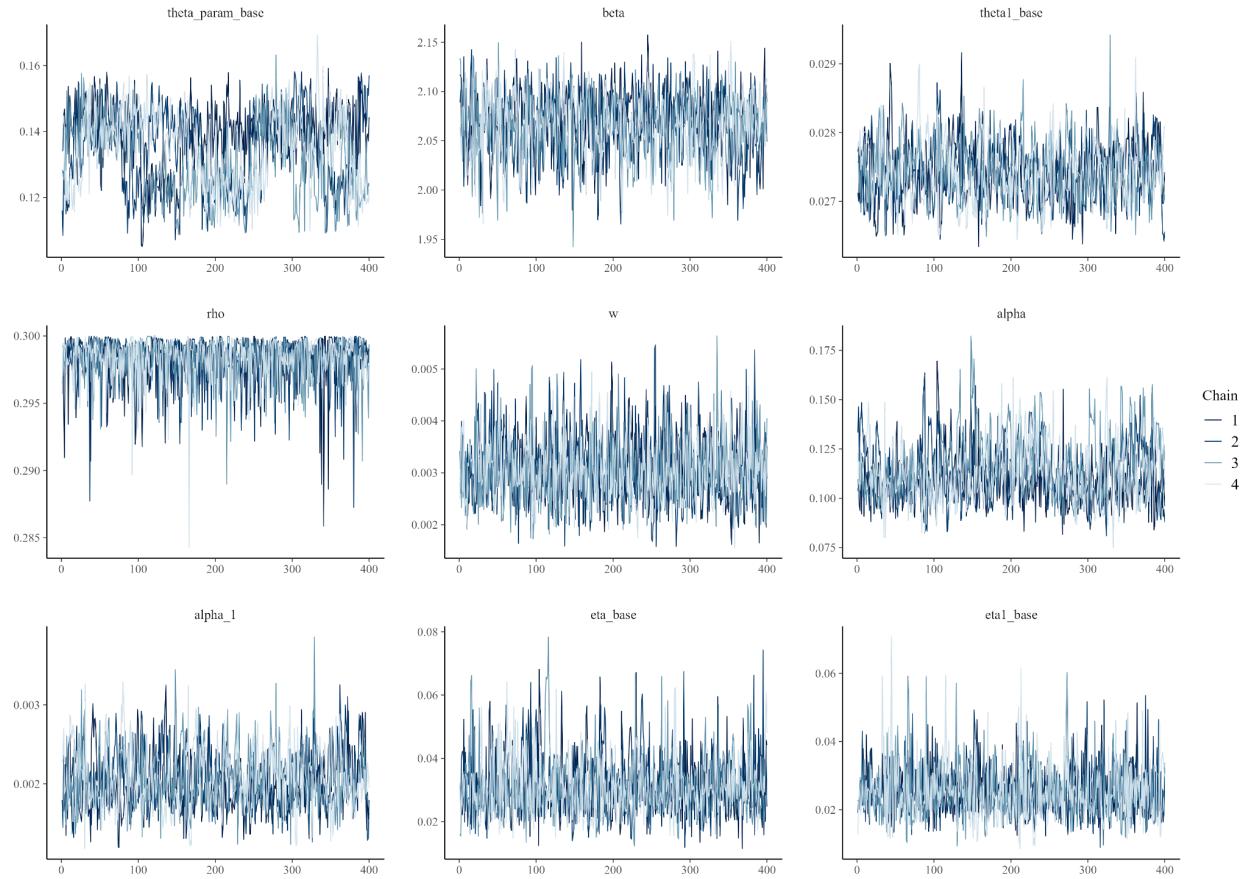


Figure 3: Trace plots for key parameters indicate good chain mixing, though the `thera_param` parameter exhibits instability. Increased iterations are recommended.

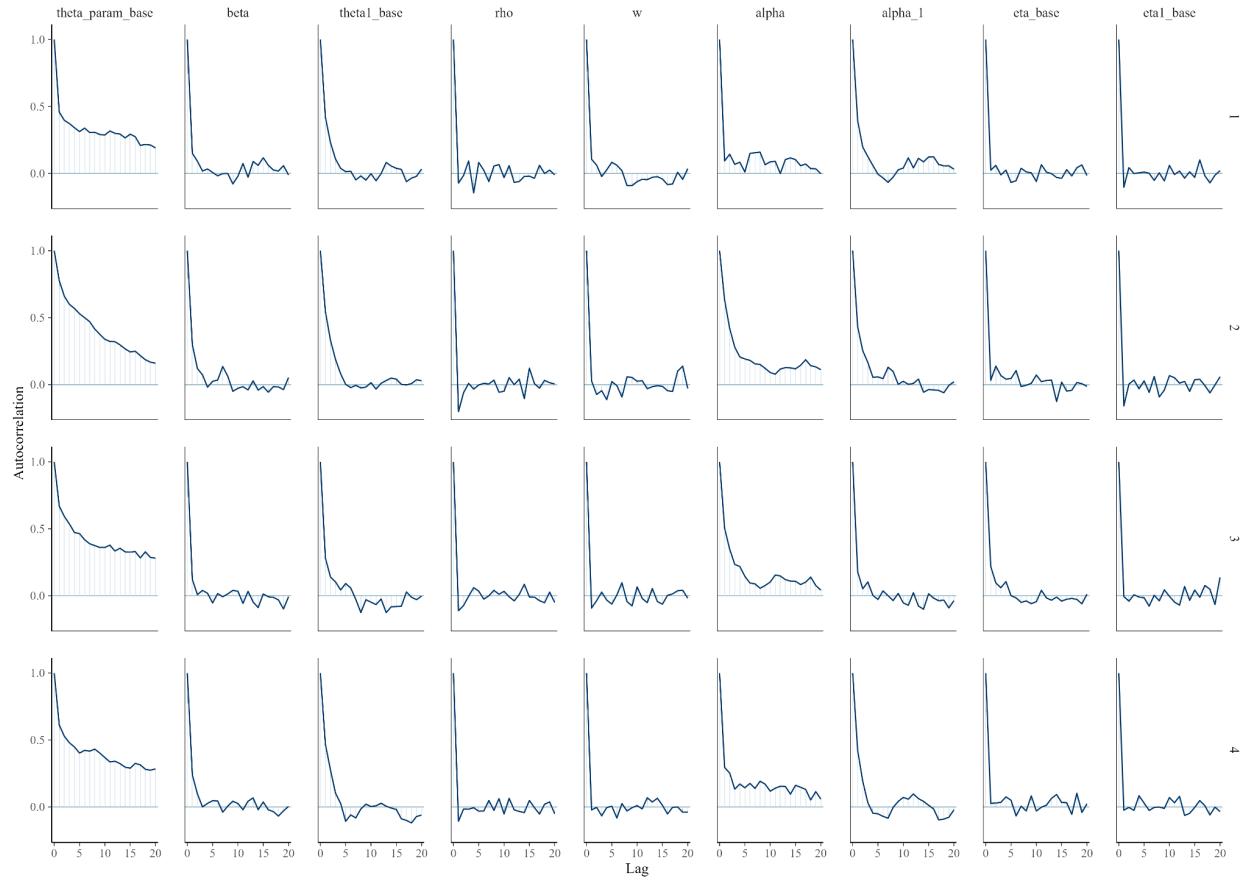


Figure 4: Autocorrelation for all parameters except `theta_param_base` shows a rapid decline to zero, indicating efficient sampling. It is advisable to increase iterations.

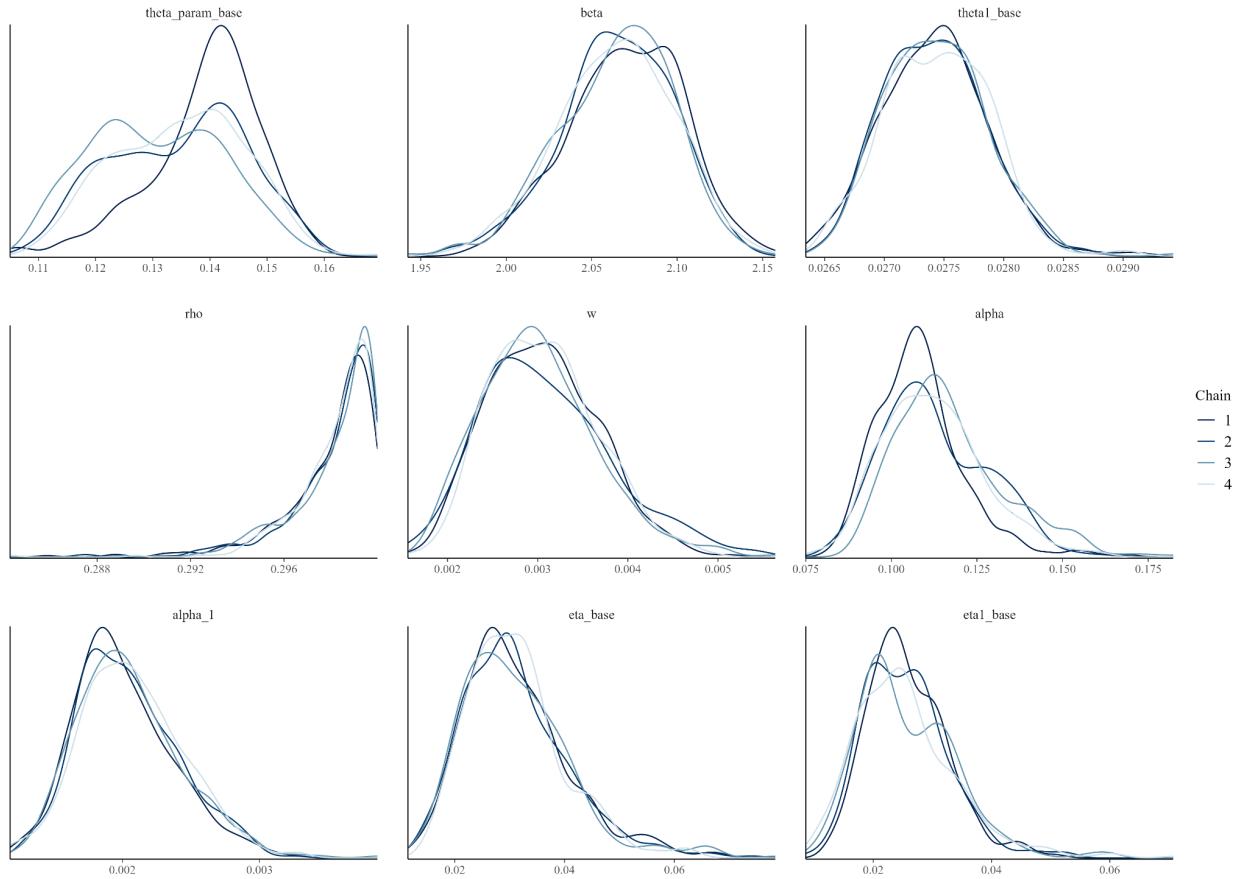


Figure 5: Posterior distribution. All chains produce very similar density curves, indicating good convergence. However, for  $\text{theta\_param}$ , the four chains are exploring slightly different posterior distributions. More iterations are recommended.

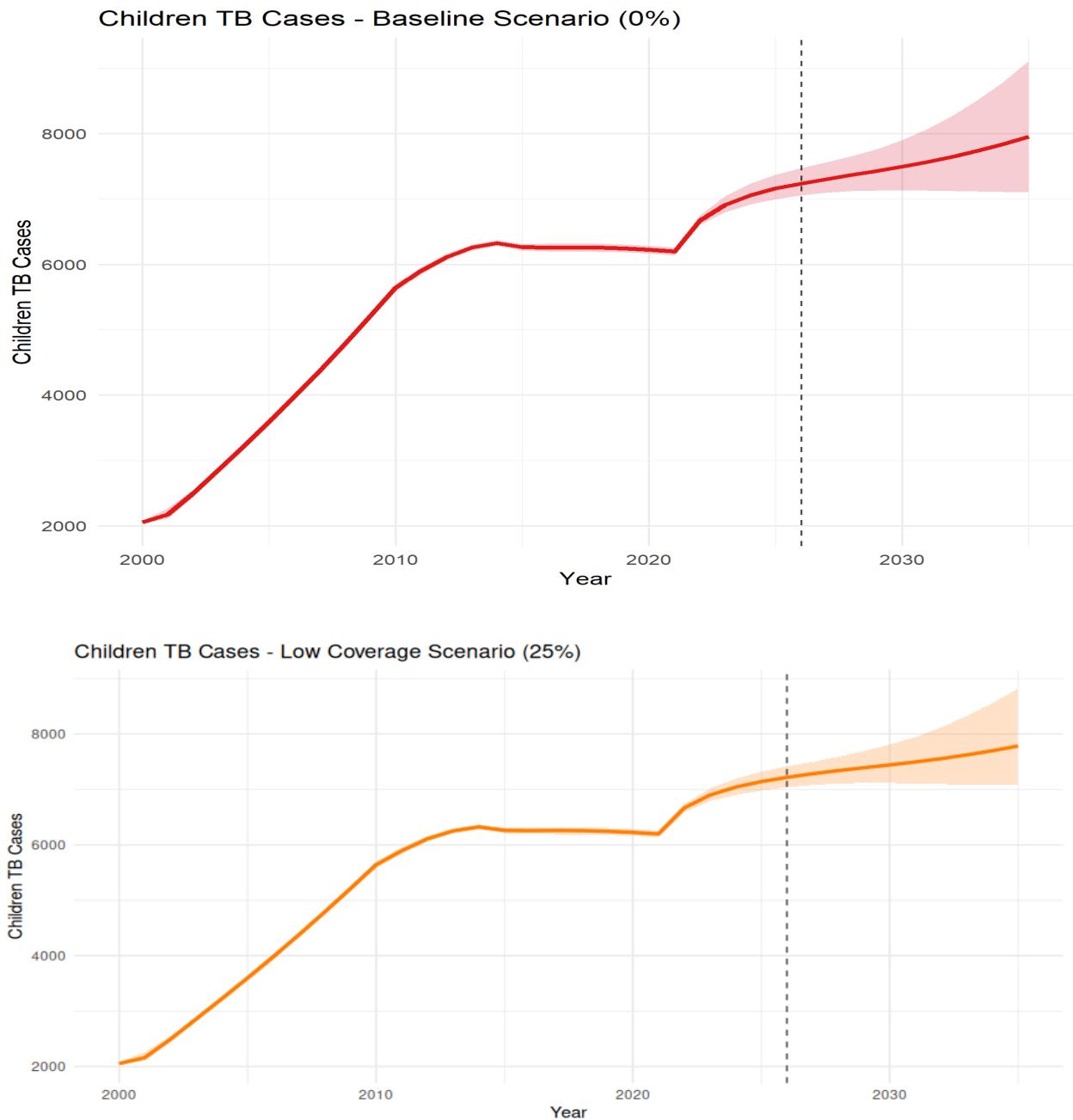


Figure 6: Predicted case Baseline vs Low coverage(25%) for children

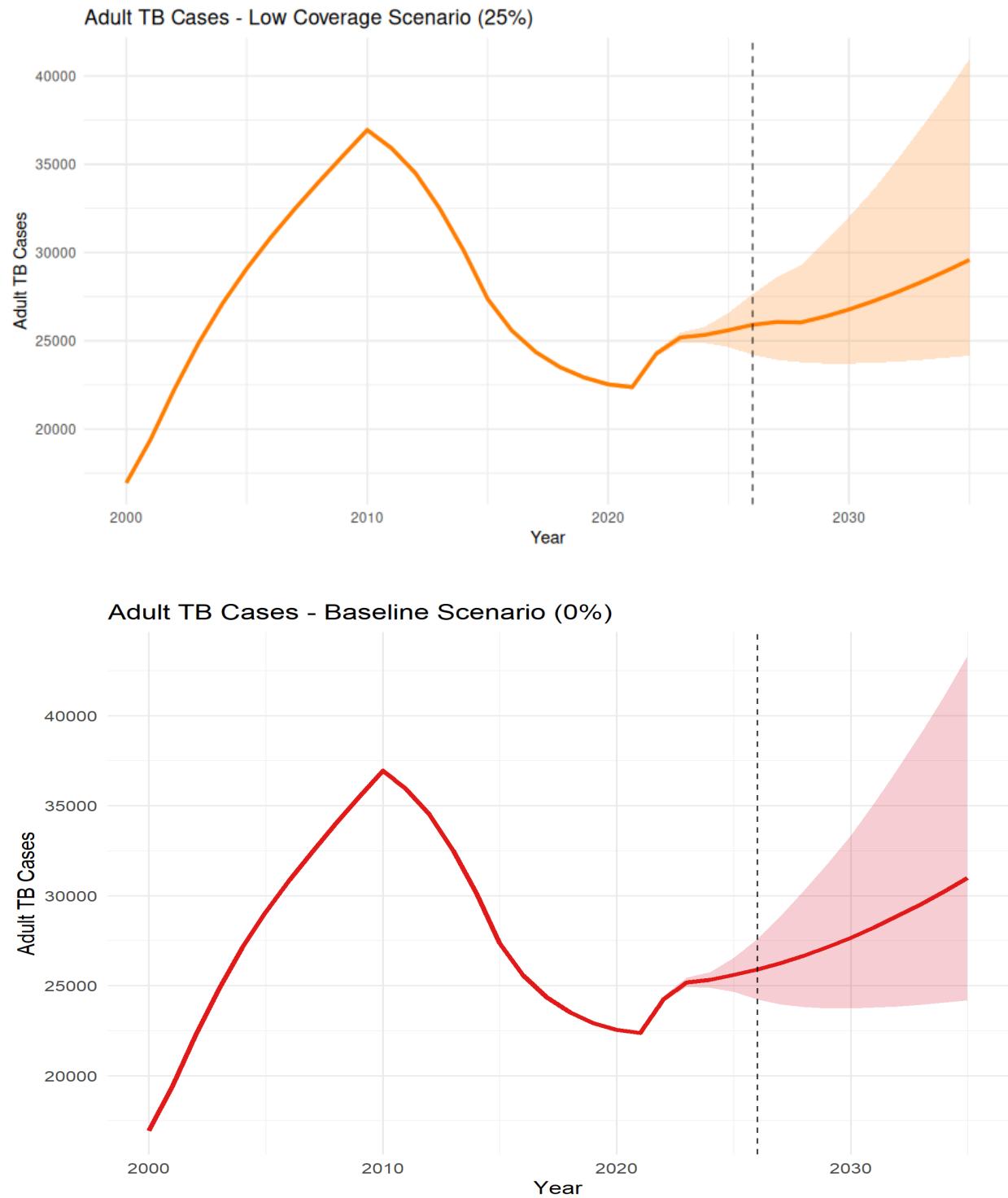


Figure 7: Predicted case Baseline vs Low coverage(25%) for adults

## 1. Model structure

We developed an age-stratified dynamic transmission model to assess the potential impact of M72/AS01E vaccination in Cambodia.

The model is extended from the model described in (4,22) with additional structure to represent relapse, progression, and treatment. The natural history of tuberculosis is described below (section 1.1).

### 1.1 TB Natural history model structure and equations

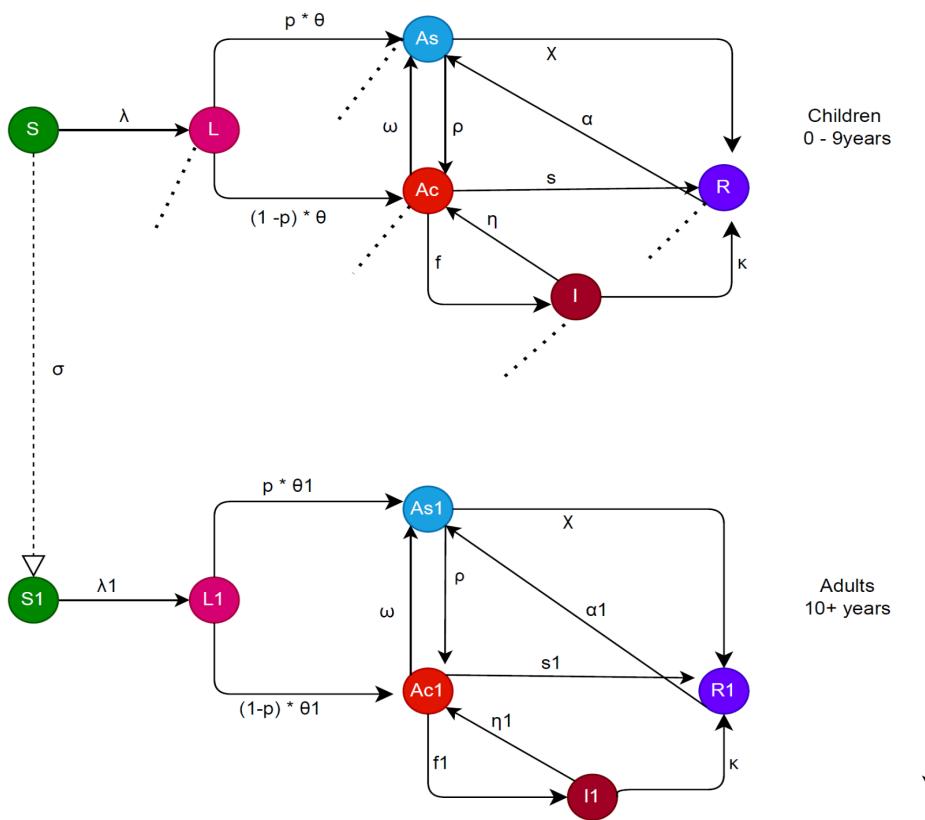
Our TB structure (Figure S1.1) divides the population into classes (S = Susceptible-Naive; L = Latent (recently infected),  $A_s$  = Subclinical Disease,  $A_c$  = Clinical Disease, I= Relapse(failed-treatment), R = Recovered).

Individuals with no history of exposure or infection with *Mycobacterium tuberculosis* (M.tb) (S) can be infected at a rate  $\lambda$  and advance to the Latent compartment (L). Once in L, a proportion of individuals progress to either clinical disease ( $A_c$ ) or subclinical disease ( $A_s$ ) , assuming no direct reversion to the susceptible state. The proportion that progresses to clinical disease is believed to be greater than 50% as shown from the dataset.

Individuals in the Subclinical Disease class ( $A_s$ ) are assumed to be infectious, but with lower infectiousness compared to those with clinical disease and are supposed to show no symptoms of

TB. These individuals may progress to clinical disease ( $A_c$ ) or may naturally recover from the disease to the recovered state (R). Individuals in the clinical disease state are infectious and displaying symptoms. Cambodia has shown higher percentages of those with clinical TB receiving treatment(23). Patients in the clinical group are assumed to receive treatment. Those who complete treatment and get cured move to R, while those who do not adhere to treatment relapse to I. Individuals in the relapse compartment will either reactivate symptoms or recover. Individuals in the recovered state may become reinfected and revert to the subclinical group. Moreover, individuals in R classes are partially protected against reinfection (compared to those in the S state) through immunity gained from successful treatment. There is natural death in all compartments, and excess mortality due to TB may happen in clinical disease states.

The model is also stratified into two age groups: children aged 0 to 9 years and adults aged 10 years and above. Those in the children's group are assumed to progress to the adults' group after 10 years.



**Figure S1.1** Tuberculosis natural history model structure

*Abbreviations:*  $S_i$  = Susceptible-Naive;  $L_i$  = Latent (recently infected),  $As_i$  = Subclinical Disease,  $Ac_i$  = Clinical Disease,  $I_i$  = Relapse (failed-treatment) and  $R_i$  = Recovered. Subscripts  $i \neq 1$  and  $i = 1$  represent children's states and adults' states, respectively.

### Total population

$$P = S_i + L_i + As_i + Ac_i + I_i + R_i$$

### Children equations $i \neq 1$

$$\frac{dS}{dt} = B - (\sigma + \mu)S$$

$$\frac{dL}{dt} = \lambda S - (\theta + \sigma + \mu)L$$

$$\begin{aligned}
\frac{dAs}{dt} &= p\theta L + \omega Ac + \alpha R - (\rho + \sigma + \mu + \chi)As \\
\frac{dAc}{dt} &= (1 - p)\theta L + \rho As + \eta I - (\omega + f + s + \sigma + \mu + \mu_{sev})Ac \\
\frac{dI}{dt} &= fAc - (\eta + \mu + \kappa)I \\
\frac{dR}{dt} &= sAc + \chi As + \kappa I - (\alpha + \mu)R \\
f + s + \mu_{sev} &= 1 \\
B &= \mu_{sev} Ac + \mu_{sev_1} Ac_1 + \mu P + \mu_1 P_1
\end{aligned}$$

**Adult equations**  $i = 1$

$$\begin{aligned}
\frac{dS_1}{dt} &= \sigma S - (\lambda + \mu_1)S_1 \\
\frac{dL_1}{dt} &= \sigma L + \lambda S_1 - (\theta_1 + \mu_1)L_1 \\
\frac{dAs_1}{dt} &= \sigma As + p\theta_1 L_1 + \omega Ac_1 - (\rho + \mu_1 + \chi)As_1 \\
\frac{dAc_1}{dt} &= \sigma Ac + (1 - p)\theta_1 L_1 + \alpha_1 R_1 - (\omega + \mu_1 + \mu_{sev_1} + f_1 + s_1)Ac_1
\end{aligned}$$

$$\begin{aligned}
\frac{dI_1}{dt} &= \sigma I + f_1 Ac_1 - (\kappa + \eta_1 + \mu_1)I_1 \\
\frac{dR_1}{dt} &= \sigma R + s_1 Ac_1 + \chi As_1 + \kappa I_1 - (\alpha_1 + \mu_1)R_1 \\
f_1 + s_1 + \mu_{sev_1} &= 1
\end{aligned}$$

The description of the compartments is explained in Table S1.1.

**Table S1.1 TB model compartments**

State	Description
S	Total children who are susceptible to TB infection
L	Total children who have recently been infected with Latent TB
As	Total children who are infected with subclinical TB (no symptoms)
Ac	Total children who are infected with clinical TB (showing symptoms)
I	Total children who relapse after unsuccessful treatment
R	Total children who recovered after a successful treatment
$S_1$	Total adults who are susceptible to TB infection
$L_1$	Total adults who have recently been infected with Latent TB
$As_1$	Total adults who are infected with subclinical TB (no symptoms)
$Ac_1$	Total adults who are infected with clinical TB (showing symptoms)
$I_1$	Total adults who relapse after unsuccessful treatment
$R_1$	Total adults who recovered after a successful treatment
Total Population (P)	$S + L + As + Ac + I + R + S_1 + L_1 + As_1 + Ac_1 + I_1 + R_1$

Key assumptions made for our model are as follows:

1. We assume that only  $As_1$  and  $Ac_1$  are infectious
2. The adult group cases include multidrug-resistant tuberculosis, but were not specifically included as compartments.
3. Birth rate and death rate were equalised to ensure population stability.

4. The proportion of individuals who develop clinical disease was assumed to be more than 50%.

## 2. Parameters

The parameters used in the TB model structure are described in Section 2.1. The table provides sources, definitions, and information on whether the parameter is static or variable, as well as whether it varies by age or time during model calibration.

The parameter ranges stated are priors fitted during calibration in a Bayesian analysis. We assume that all values inside the prior range are equally likely. The initial ranges were pre-specified based on a literature review and the calibration process.

### 2.1 TB model parameter values and data sources

**Table S2.2 TB model parameter values and sources**

Description	Units	Symbol	Prior	Fixed or Varying During Calibration	Age Varying	Time Varying	Source
<i>Births and deaths (including on-treatment mortality)</i>							
Natural mortality rate	Per year	$\mu_i$	( 1/71 ; 1/66 )	Fixed	Yes; value for children is greater than value for adults	No	[ 3 ]
Birth rate	Per year		-	Equation	No	Yes	calculated
Mortality rate for clinical tuberculosis disease	Per year	$\mu_{sev_i}$	( 0.0001 - 0.02 )	Varying	Yes; value for children is greater than the value for adults	Yes because $\mu_{sev_i}$ varies	[ 3,4 ]
<i>Natural History</i>							

Force of infection	Per year	$\lambda$	-	Fixed Equation	Yes; age-specific contact rates	Yes	calculated
Transmission Probability	Per person per year	$\beta$	( 2 - 2.12 )	Varying	No ; assumed only adults can transmit	Yes	[ 1 ]
Proportion developing Subclinical disease	Per year	p	0.53	Fixed	No	No	Averaged from data
Infectiousness of subclinical relative to Clinical tuberculosis	-	$\Gamma$	0.68	Fixed	No	No	[ 3,4 ]
Rate progression to disease by age	Per person per year	$\theta_i$	( 0.03 - 0.15 )	Varying	Yes; value for children is less than value for adults	No	[ 2,5 ]
Rate of progression from As to Ac	Per person per year	$\rho$	0.3	Varying	No	No	Assumed
Aging	Per person per year	$\sigma$	0.2	Fixed	No	No	Assumed
Rate of relapse from R	Per person per year	$\alpha_i$	( 0.001 - 0.15 )	Varying	Yes; value for children is less than value for adults	No	[ 6,7 ]
Rate of reactivation from I to Ac	Per year	$n_i$	( 0.01 - 0.06 )	Varying	Yes; value for children is less than value for adults	Yes	[ 1 ]
Natural cure and treatment outcomes							
Rate of natural cure from Ac to As	Per person per year	$\omega$	( 0.002 - 0.005 )	Varying	No	No	[ 8,9 ]
Rate of natural cure from As to R	Per year	$\chi$	0.1	Fixed	No	No	[ 2 ]
Rate of natural cure from I to R	Per year	$\kappa$	0.85	Fixed	No	No	[ 1 ]

Treatment success	Per year	$s_i$	( 0.41 - 0.95 )	Varying	Yes; value for children is greater than value for adults	Yes	[12,13]
Treatment failure	Per year	$f_i$	( 0.002 - 0.07 )	Varying	Yes; value for children is less than value for adults	Yes	[3,13]

### 3. Model simulation

Cambodia has shown more than 83% of TB treatment initiation (33) over the past years. The treatment initiation rate determines the progression from clinical TB to the on-treatment compartment. In our model, we assumed that once patients are notified as clinically ill, they receive treatment; hence, there is no separate state for treatment. We implemented three interventions: active case finding (ACT), TB preventive therapy (TPT), and community DOTS, using linear interpolation. For the baseline model, without the vaccine, the interventions were implemented as follows: ACT from 2005 to 2035 due to the availability of funding (19). TPT from 2008 to 2035 (19) and DOTS from 2000 to 2025, due to funding cuts by the US (5).

Our model has three possible results after receiving treatment: death, treatment completion and cured ( progress to the R state ), and treatment failure ( transition to the relapse state ). The outcomes are estimated during calibration, ensuring that they sum up to one for each age group.

#### 4. M72/AS01E Vaccine

The M72/AS01E vaccine was specifically designed to target the adult population (aged 10 years and older). This vaccine functions by reducing the progression rate from latent tuberculosis infection to active disease, which represents the primary protective effect of TB vaccines in preventing the activation of the disease rather than preventing initial infection.

The vaccination coverage function incorporates realistic deployment dynamics, featuring a two-year rollout period that commences in 2026, followed by steady-state maintenance achieved through periodic revaccination every four years to address waning immunity (with a waning rate of 23.1% annually calculated using the half-life formula). Three vaccination scenarios were modelled: a baseline with 0% coverage, low coverage at 25%, and high coverage at 75%. The vaccine efficacy is set at 50%, based on current clinical trial data for tuberculosis vaccine candidates(34).

The mathematical implementation integrates the combined protective effect as  $\theta_1 \times (1 - \text{TPT effectiveness}) \times (1 - \text{vaccination protection})$ , ensuring that vaccination works synergistically with existing tuberculosis preventive therapy interventions. It also maintains biological plausibility through parameter bounds and smooth transition functions, which prevent unrealistic combinations during model execution.