BMC Medicine

RESEARCH ARTICLE

Open Access

New tuberculosis vaccines in India: modelling the potential health and economic impacts of adolescent/adult vaccination with M72/AS01$_E$ and BCG-revaccination

Rebecca A. Clark[1,2,3,4*], Chathika K. Weerasuriya[1,2,3], Allison Portnoy[5,6], Christinah Mukandavire[1,2,3], Matthew Quaife[1,2,3], Roel Bakker[1,2,3,7], Danny Scarponi[1,2,3], Rebecca C. Harris[1,2,3,8], Kirankumar Rade[9], Sanjay Kumar Mattoo[10], Dheeraj Tumu[9,10], Nicolas A. Menzies[5,11] and Richard G. White[1,2,3,4]

Abstract

Background India had an estimated 2.9 million tuberculosis cases and 506 thousand deaths in 2021. Novel vaccines effective in adolescents and adults could reduce this burden. M72/AS01$_E$ and BCG-revaccination have recently completed phase IIb trials and estimates of their population-level impact are needed. We estimated the potential health and economic impact of M72/AS01$_E$ and BCG-revaccination in India and investigated the impact of variation in vaccine characteristics and delivery strategies.

Methods We developed an age-stratified compartmental tuberculosis transmission model for India calibrated to country-specific epidemiology. We projected baseline epidemiology to 2050 assuming no-new-vaccine introduction, and M72/AS01$_E$ and BCG-revaccination scenarios over 2025–2050 exploring uncertainty in product characteristics (vaccine efficacy, mechanism of effect, infection status required for vaccine efficacy, duration of protection) and implementation (achieved vaccine coverage and ages targeted). We estimated reductions in tuberculosis cases and deaths by each scenario compared to the no-new-vaccine baseline, as well as costs and cost-effectiveness from health-system and societal perspectives.

Results M72/AS01$_E$ scenarios were predicted to avert 40% more tuberculosis cases and deaths by 2050 compared to BCG-revaccination scenarios. Cost-effectiveness ratios for M72/AS01$_E$ vaccines were around seven times higher than BCG-revaccination, but nearly all scenarios were cost-effective. The estimated average incremental cost was US$190 million for M72/AS01$_E$ and US$23 million for BCG-revaccination per year. Sources of uncertainty included whether M72/AS01$_E$ was efficacious in uninfected individuals at vaccination, and if BCG-revaccination could prevent disease.

Conclusions M72/AS01$_E$ and BCG-revaccination could be impactful and cost-effective in India. However, there is great uncertainty in impact, especially given the unknowns surrounding the mechanism of effect and infection status required for vaccine efficacy. Greater investment in vaccine development and delivery is needed to resolve these unknowns in vaccine product characteristics.

*Correspondence:
Rebecca A. Clark
Rebecca.Clark@lshtm.ac.uk
Full list of author information is available at the end of the article

Keywords Tuberculosis, Vaccines, Mathematical modelling, Health impact, Budget impact, Cost-effectiveness

Background

India has the largest global burden of tuberculosis. In 2021, there were an estimated 2.9 million cases and 506 thousand deaths—representing approximately 30% of the total globally [1]. The COVID-19 pandemic has negatively impacted tuberculosis prevention and care in India, with increases in the number of deaths per year seen for the first time since 2007 [1, 2]. Delays in diagnosis and treatment due to surveillance systems impacted by the pandemic (over 30% fewer notifications reported in 2021 than 2019) may lead to increases in the disease burden [1, 2].

Tuberculosis is a key focus for the Indian government. The National Strategic Plan to End Tuberculosis in India 2020–2025, developed by the National Tuberculosis Elimination Programme (NTEP), outlines ambitious goals for reducing *Mycobacterium tuberculosis* (*Mtb*) transmission, preventing tuberculosis disease, and addressing social determinants of health [3]. Despite the COVID-19 pandemic, the NTEP has made progress toward these goals, including expanding molecular diagnostics, implementing tuberculosis-COVID bidirectional screening, and expanding policy on preventive therapy to include all household contacts of people diagnosed with pulmonary tuberculosis [4].

The National Strategic Plan also calls for further development in tuberculosis vaccines, which has been a high priority for global organisations such as the World Health Organization (WHO). A recently completed WHO-commissioned study assessing the full value of tuberculosis vaccines made a strong case from the health and economic perspectives for continued investment [5–9], and previous work has demonstrated that novel vaccines or vaccination strategies will be needed to eliminate tuberculosis [10, 11].

Currently, sixteen candidates are in various phases throughout the vaccine pipeline, being trialled in a variety of ages and spanning prevention of disease, infection, and recurrence endpoints [12]. A phase IIb trial of M72/AS01$_E$ in adolescents and adults infected with *Mtb* demonstrated a prevention of disease efficacy of 49.7% (95% confidence interval: 2.1–74.2) after 3 years of follow-up [13]. However, M72/AS01$_E$ would need a supportive phase III trial for licensure, which is planned but likely to require years before results are available to inform policy.

Revaccination of uninfected adolescents with the Bacillus Calmette–Guérin (BCG) vaccine was assessed as a third parallel arm in a separate phase IIb trial and demonstrated an efficacy of 45.4% (6.4–68.1) against sustained infection [14], and an additional phase IIb confirmation trial is underway to verify this finding, with results expected mid-2024 [15]. The original Chingleput BCG vaccination trial reported efficacy of 27% (−8 to 50) against disease in children and no efficacy in adults [16]. A re-analysis of trial data restricted to participants with prior BCG vaccination and no tuberculosis disease at the time of vaccination showed a protective efficacy of 36% (11–54) against disease [17]. As BCG is already licensed, introducing BCG-revaccination may only require a policy change, which could happen quickly.

India is arguably the most important country for global tuberculosis elimination, and policy-makers require country-specific evidence of the anticipated health, cost, and budget impacts of specific vaccine candidates. As vaccines enter phase III trials, it is important to predict how variation in vaccine profile and implementation will affect the impact to maximise benefits and reduce delays between licensure and delivery. We estimated the potential health and economic impact of M72/AS01$_E$ and BCG-revaccination in India and investigated the impact of variation in vaccine characteristics and delivery strategies.

Methods

Data

We obtained demographic data for India from the United Nations Population Division with estimates for single ages and years from 1900 to 2100 [18]. Tuberculosis disease and infection prevalence estimates were derived from the National TB Prevalence Survey in India 2019–2021 [19]. Incidence, notifications, and mortality estimates were obtained from WHO [2].

Structure

We adapted previous models and developed a compartmental dynamic model of tuberculosis in India [5, 11, 20]. Our model was stratified by tuberculosis natural history and treatment, differences in access-to-care, vaccination, and age. We represented tuberculosis natural history by allowing for *Mtb* infection along a spectrum from uninfected to active clinical disease. We assumed a progressive loss of ability to reactivate following infection, with a monotonic decline in reactivation rates for subsequent latency compartments. Active disease was represented by both subclinical and clinical tuberculosis compartments to align with prevalence survey data [19]. Anti-tuberculosis treatment was assumed to begin in 1960 and increase following a sigmoid curve to 2020. Due to the

large contribution of private sector treatment in India, we incorporated differences in treatment mortality and completion probabilities between the public and private sectors. Full model structure and parameters are in Additional file 1 Sects. 1, 2 [5, 18, 21–37].

Calibration

The model was fit to 19 tuberculosis-related calibration targets: the incidence rate (all ages, children, and adults in 2000, 2020, and 2025), mortality rate (all ages in 2000, 2020, and 2025), notification rate (all ages, children, and adults in 2000 and 2020), disease prevalence (all ages, children, and adults in 2015 and 2021), infection prevalence (all ages in 2021), the proportion of incident cases with treatment history in 2020, the fraction of subclinical tuberculosis among active tuberculosis in 2020, and the prevalence ratio of active tuberculosis between access-to-care compartments in 2020 all assuming a uniform distribution between lower and upper bounds. We calibrated using the *hmer* R package [38] to perform history matching with emulation followed by ABC-MCMC until we obtained 1000 parameter sets fitting all targets (further information in Additional file 1 Sect. 3) [4, 38–52].

Scenarios

No-new-vaccine baselines

Assuming the quality and coverage of services remain constant post-2020, we used the calibrated model to project baseline epidemiology to 2050 (the *Status Quo* no-new-vaccine baseline). We assumed that neonatal BCG vaccination would not be discontinued during the period of our analysis and was not explicitly modelled as its effect is implicitly included in country burden estimates.

As an alternative future scenario, we calibrated a *Strengthened Current Interventions* no-new-vaccine baseline. This baseline assumed scale-up of non-vaccine tuberculosis interventions between 2021 and 2035 to meet the target of a 50% reduction in tuberculosis incidence in 2035 compared to the 2015 estimates. This scale-up was included in the model by introducing multipliers on the rate of progression to disease and in the force of infection equation.

Vaccine scenarios

Using the calibrated *Status Quo*no-new-vaccine model, we simulated Basecase scenarios over 2025–2050 for each product with characteristics informed a priori by clinical trial data and expert opinion [13, 14]. The Basecase M72/AS01$_E$ scenario assumed a 50% efficacy prevention of disease vaccine with 10-year protection, efficacious with any infection status aside from active disease at vaccination. We assumed the vaccine would be introduced in 2030 routinely to those aged 15 (reaching 80% coverage) and as a campaign for ages 16–34 (reaching 70% coverage), with a repeat campaign in 2040. Based on expert advice, the vaccine price was $2.50 per dose, assuming two doses per course.

The Basecase BCG-revaccination scenario assumed a 45% efficacy vaccine to prevent infection with 10-year protection, and efficacious without infection at time of vaccination. We assumed the vaccine would be introduced in 2025 routinely to those aged 10 (reaching 80% coverage) and as a campaign for ages 11–18 (reaching 80% coverage) with repeat campaigns in 2035 and 2045. Based on the average estimated BCG price from UNICEF [53], the vaccine price was set at US$0.17 per dose, assuming one dose per course.

Vaccine introduction costs for both vaccine products were assumed to be US$2.40 (95% uncertainty interval = 1.20–4.80) per individual in the targeted age group based on vaccine introduction support policy from Gavi, the Vaccine Alliance [54]. A further US$0.11 (0.06–0.22) supply costs and US$2.50 (1.00–5.00) delivery costs per dose were included [55], as well as US$0.94 (0.13–1.52) in patient and caregiver productivity losses per dose, to account for the time taken to receive vaccination [56, 57]. We assumed a 5% wastage rate.

Through consultation with vaccine and country-specific experts, we established specific M72/AS01$_E$ and BCG-revaccination *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios*. *Policy Scenarios* represented features of vaccination strategy under the control of decision-makers, which compared different age groups to target for vaccination. *Vaccine Characteristic and Coverage Scenarios* represented current uncertainties around vaccine performance and uptake, in which we varied unknowns in vaccine profile (such as efficacy, duration of protection, mechanism of effect) and achieved coverage, univariately from each Basecase scenario. We compared *Policy Scenarios* to identify the optimal implementation approach, and *Vaccine Characteristic and Coverage Scenarios* to quantify the impact of different sources of uncertainty (Table 1). Further details are provided in Additional file 1 Sect. 4 [13, 14, 58].

Outcomes

We estimated the cumulative number of tuberculosis cases and deaths averted between vaccine introduction and 2050 for each scenario compared to the predicted numbers in both no-new-vaccine baselines.

For each vaccine product, we conducted cost-effectiveness analyses for the *Policy Scenarios* indicated in Table 1, discounting both costs and health outcomes to 2025 (when vaccination began) at 3% per year as per guidelines [59]. We calculated the difference in total disability-adjusted life years (DALYs) from vaccine

Table 1 Assumed M72/AS01$_E$ and BCG-revaccination scenarios

	M72/AS01$_E$		BCG-revaccination	
Characteristic	**Basecase**	**Varied in univariate**	**Basecase**	**Varied in univariate**
Policy scenarios				
Age targeting	Routine age 15, campaign for ages 16–34	Older ages (campaign for ages 18–55) Elderly ages (routine age 60, campaign for ages 61 +)	Routine age 10, campaign for ages 11–18	Older ages (routine age 15, campaign for ages 16–34) Elderly ages (routine age 60, campaign for ages 61 +)
Vaccine characteristic and coverage scenarios				
Vaccine efficacy	50%	60% 70%	45%	70%
Duration of protection	10 years	5 years 15 years 20 years	10 years	5 years 15 years 20 years
Host infection status	AI	CI	NCI	AI
Mechanism of effect	Prevention of disease	Prevention of infection and disease	Prevention of infection	Prevention of infection and disease
Introduction year (years of any repeat campaigns)	2030 (2040)	2036 (2046)	2025 (2035, 2045)	2031 (2041)
Achieved vaccine coverage	Routine = 80%, campaign = 70%	Routine = 70%, campaign = 50% Routine = 90%, campaign = 90%	Routine and campaign = 80%	Routine and campaign = 70% Routine and campaign = 90%

Abbreviations: *AI* Any infection; *CI* Current infection; *NCI* No current infection

See Additional file 1 Sect. 4 for full details and references

introduction to 2050, using the disability weight for tuberculosis disease from the Global Burden of Disease 2019 study [60], and country- and age-specific life expectancy estimates from the United Nations Development Programme assuming no post-tuberculosis morbidity or mortality [61]. We calculated incremental cost-effectiveness ratios (ICERs) as the ratio of mean incremental costs to mean incremental benefits in DALYs averted, and 95% uncertainty intervals from the health-system perspective for each efficient strategy for the analytic period 2025–2050. Higher cost-effectiveness ratios indicate greater spending is needed to achieve health improvements, such that the intervention is less likely to be cost-effective. We measured cost-effectiveness by 2050 against three India-specific cost thresholds: 1 × gross domestic product (GDP) per capita (US$1,927.71) [57], and country-level opportunity cost thresholds defined by Ochalek et al. (country-level upper [US$363] and lower [US$264] bounds) [62].

To investigate how the consequences of vaccine introduction (versus no vaccination) changed based on the vaccine product characteristics, we examined the difference in ICERs for *Vaccine Characteristic and Coverage Scenarios* compared to the no-new-vaccine baseline assuming the vaccine was introduced using the delivery strategy from the most efficient *Policy Scenario* at the country-level lower bound.

We estimated the annual incremental costs of diagnosis, treatment, and vaccination for each scenario, as compared to the no-new-vaccine baseline in 2020 US dollars from health-system and societal perspectives. Further details are provided in Additional file 1 Sect. 5 [53–57, 59–69].

Results

The *Status Quo* baseline model fits all 19 calibration targets with at least 1000 parameter sets. Epidemiological projections from 2020 to 2050 are in Additional file 1 Sect. 7. The *Status Quo* baseline predicted 72.2 (63.3–79.7) million incident tuberculosis cases and 13.8 (12.9–15.2) million tuberculosis deaths between 2025 and 2050. Assuming current non-vaccine tuberculosis interventions would be strengthened such that the incidence rate in 2035 was 50% of the incidence rate in 2015, the *Strengthened Current Interventions* baseline predicted 36.0 (28.9–66.4) million incident cases and 7.6 (6.1–13.2) million deaths between 2025 and 2050.

With the *Status Quo* no-new-vaccine baseline, we found a 50% efficacy M72/AS01$_E$ prevention of disease vaccine, efficacious with any infection status, introduced in 2030 routinely to 15-year-olds and as a campaign for ages 16–34 (the Basecase M72/AS01$_E$ scenario), could avert approximately 12.7 (11.0–14.6) million cases and 2.0 (1.8–2.4) million deaths between 2030 and 2050 (Fig. 1). With a 70% efficacy vaccine, the number of averted cases and deaths by 2050 could be increased by

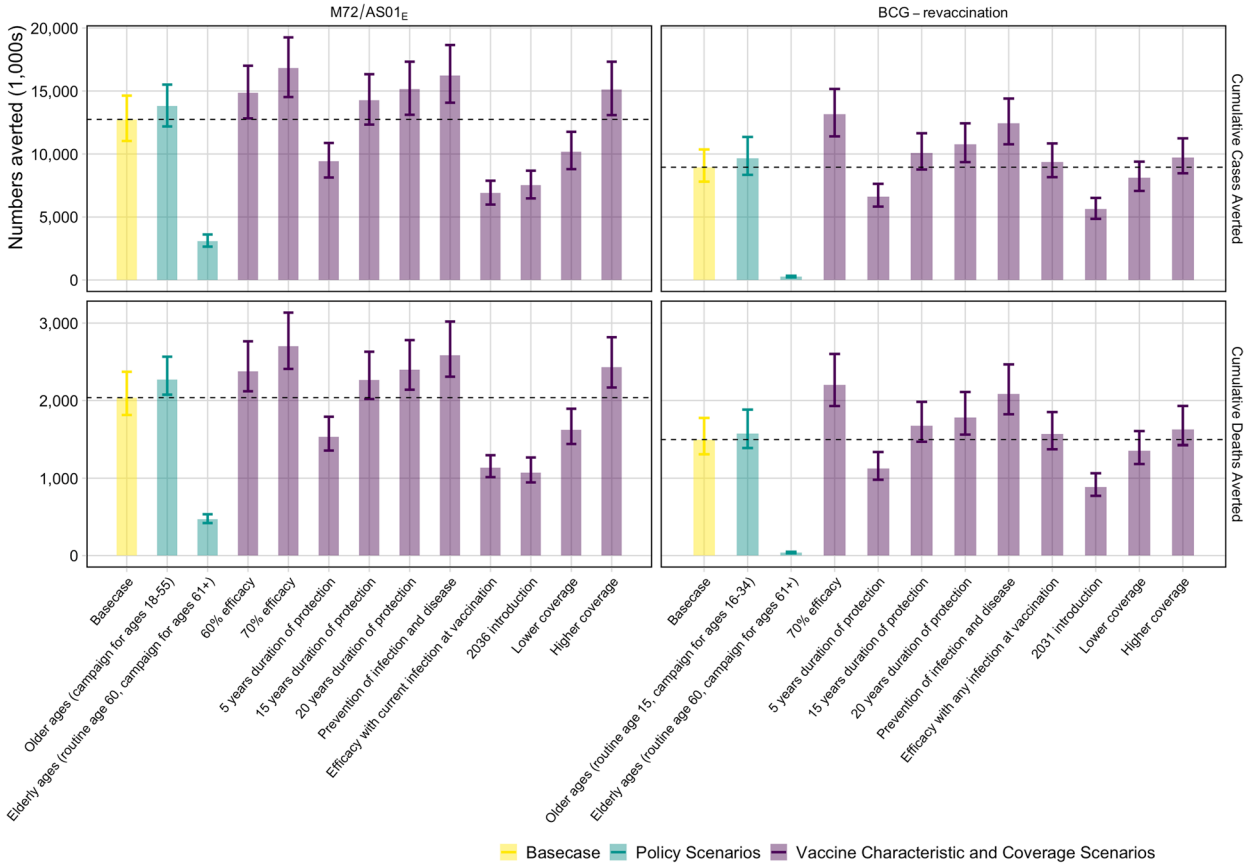

Fig. 1 Cumulative cases and deaths averted (in 1000 s) by 2050 from M72/AS01$_E$ and BCG-revaccination scenarios. The top of the bar is the median estimate of the number averted for each scenario compared to the estimated number predicted by 2050 with the *Status Quo* no-new-vaccine baseline with 95% uncertainty range. The horizontal line is the median value of the Basecase for each vaccine. The cases and deaths averted by each scenario are compared to 72.2 (63.3–79.7) million incident tuberculosis cases and 13.8 (12.9–15.2) million tuberculosis deaths predicted by the *Status Quo* baseline between 2025 and 2050

32–35% but delaying introduction of a vaccine until 2036 could lead to 5.2 million more cases and 968 thousand more deaths compared to the Basecase M72/AS01$_E$ scenario before 2050 (Fig. 1). If the vaccine was only efficacious with current infection at vaccination, 5.8 million fewer cases and 900 thousand fewer deaths could be averted compared to the Basecase M72/AS01$_E$ scenario.

A 45% efficacy prevention of infection BCG vaccine, efficacious in those with no current infection, introduced in 2025 as routine vaccination of 10-year-olds and a campaign for ages 11–18 (the Basecase BCG-revaccination scenario) could avert 9.0 (7.8–10.4) million cases and 1.5 (1.3–1.8) million deaths (Fig. 1). If the vaccine prevented infection and disease, 3.4 million more cases and 600 thousand more deaths could be averted by 2050 compared to the Basecase BCG-revaccination scenario. Fewer numbers could be averted compared to the Basecase BCG-revaccination scenario with reduced duration of protection, later introduction, lower coverage, or only delivering the vaccine to ages 60 years and older (Fig. 1).

Comparing the two products, even with a later introduction year for M72/AS01$_E$ scenarios, we found a higher health impact from M72/AS01$_E$ vaccines compared to BCG-revaccination. The Basecase M72/AS01$_E$ scenario was predicted to avert around 40% more tuberculosis cases and deaths before 2050 than the Basecase BCG-revaccination scenario.

With the *Strengthened Current Interventions* baseline, the Basecase M72/AS01$_E$ scenario could avert 3.0 (1.1–11.3) million tuberculosis cases and 0.51 (0.19–1.9) million tuberculosis deaths between 2025 and 2050, averting 8.3% of the median total cases and 6.7% of the median total deaths predicted to occur during the same period. The Basecase BCG-revaccination scenario could avert 1.9 (0.42–8.0) million cases and 0.34 (0.08–1.4) million deaths between 2025 and 2050, or 5.3% of the median total tuberculosis cases and 4.5% of the median total tuberculosis deaths predicted to occur during the same period. Health impact values for all scenarios of both vaccines are in Additional file 1 Sect. 8.

Table 2 Cost-effectiveness analysis for M72/AS01$_E$ and BCG-revaccination *Policy Scenarios*

Scenario	Total costs (USD, 1000 s)	Total DALYs (1000 s)	Total DALYs averted (1000 s)	Incremental cost (USD, 1000 s)	Incremental DALYs averted (1000 s)	Cost (USD) per DALY averted
M72/AS01$_E$ policy scenarios						
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Elderly ages (routine age 60, campaign for ages 61 +)	17,523,764	3,986,463	5257	–	–	*Weakly dominated*
Basecase (routine age 15, campaign for ages 16–34)	19,596,068	3,954,863	36,857	5,333,593	36,857	$145
Older ages (campaign for ages 18–55)	21,456,380	3,953,202	38,518	1,860,312	1661	$1120
BCG-revaccination policy scenarios						
No-new-vaccine	14,262,475	3,991,720	–	14,262,475	–	–
Basecase (routine age 10, campaign for ages 11–18)	14,918,037	3,962,629	29,091	655,526	29,091	$23
Older ages (routine age 15, campaign for ages 16–34)	15,819,567	3,961,671	30,049	901,530	958	$941
Elderly ages (routine age 60, campaign for ages 61 +)	15,922,705	3,991,270	450	–	–	*Strongly dominated*

Abbreviations: DALYs Disability-adjusted life years; *USD* United States dollars

Cost-effectiveness analysis is shown in Table 2 and Fig. 2 for the *Policy Scenarios* for each vaccine product. For M72/AS01$_E$, delivering the vaccine routinely to those age 60 and as a campaign for ages 61 + (Elderly Ages M72/AS01$_E$ scenario) was not efficient and removed from consideration. Scenarios delivering the vaccine routinely to age 15 and as a campaign for ages 16–34 (Basecase M72/AS01$_E$ scenario) and delivering the vaccine as a campaign for ages 18–55 (Older Ages M72/AS01$_E$ scenario) were considered efficient and displayed on the efficiency frontier in Fig. 2. The Basecase M72/AS01$_E$ scenario was optimal at both country-level thresholds (ICER = US$145 per DALY averted), and the Older Ages M72/AS01$_E$ scenario was optimal at 1 × GDP threshold (ICER = US$1,120 per DALY averted). The incremental cost of the Basecase M72/AS01$_E$ scenario was US$5.3 billion, with vaccination averting 36.9 million of the 4.0 billion DALYs predicted by the no-new-vaccine baseline between 2025 and 2050.

For BCG-revaccination, delivering the vaccine routinely to those age 60 and as a campaign for ages 61 + (Elderly Ages BCG-revaccination scenario) was dominated by other strategies and removed from

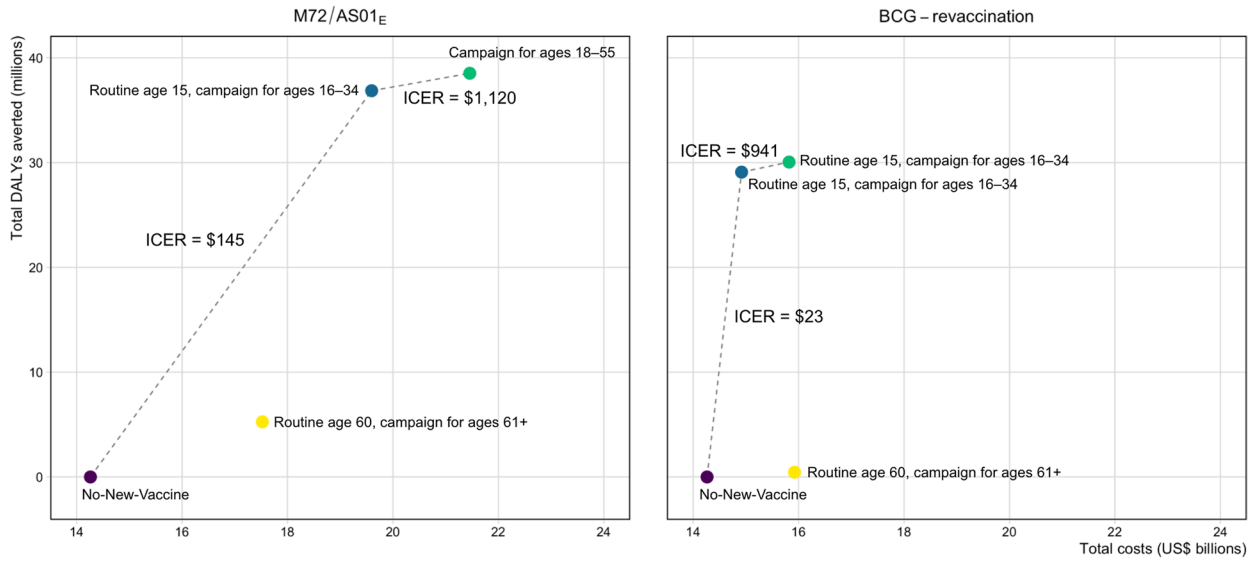

Fig. 2 Efficiency frontiers (discounted total costs [US$ billions] per disability-adjusted life year (DALY) averted) for *Policy Scenarios* for each vaccine product

consideration. Scenarios delivering the vaccine routinely to age 10 and as a campaign for ages 11–18 (Basecase BCG-revaccination scenario) and delivering the vaccine routinely to those aged 15 and as a campaign for ages 16–34 (Older Ages BCG-revaccination scenario) were considered efficient and displayed on the efficiency frontier in Fig. 2. The Basecase BCG-revaccination scenario (ICER = US$23 per DALY averted) was optimal at both country-level thresholds and the Older Ages BCG-revaccination scenario (ICER = US$941 per DALY averted) was optimal at 1xGDP threshold. The incremental cost of the Basecase BCG-revaccination scenario was US$656 million, and this strategy averted 29.1 million of the 4.0 billion DALYs predicted by the no-new-vaccine baseline between 2025–2050.

Figure 3 displays the ICERs for each *Vaccine Characteristic and Coverage Scenario* compared to the no-new-vaccine baseline for each vaccine product. For every M72/AS01$_E$ scenario shown in the figure, we assumed that the vaccine would be introduced routinely to those aged 15 and as a campaign to ages 16–34 (the most efficient strategy at the country-level lower bound from the cost-effectiveness analysis). Even with changes in the vaccine product characteristics, introducing an M72/AS01$_E$ vaccine would be cost-effective compared to not implementing a vaccine (Fig. 3). For every BCG-revaccination scenario, we assumed that the vaccine would be introduced routinely to those aged 10 and as a campaign to ages 11–18 (the most efficient strategy at the country-level lower bound from the cost-effectiveness analysis). Similarly, regardless of the resulting product characteristics, introducing BCG-revaccination to this age group would be cost-effective compared to not implementing a vaccine (Fig. 3).

From the health-system perspective, the annual average cost of vaccination in the Basecase M72/AS01$_E$ scenario was approximately US$251 (170–368) million between 2025 and 2050. The annual average cost-savings in treatment and diagnostics were US$60 (49–74) million over 2025–2050. The annual average cost of vaccination in the Basecase BCG-revaccination scenario was US$67 (29–122) million over 2025–2050. The annual average cost-savings in treatment and diagnostics were US$43 (35–55) million over 2025–2050. The average annual cost of vaccination in the Basecase M72/AS01$_E$ scenario was almost four times greater than the average annual cost of vaccination with the Basecase BCG-revaccination scenario. Accounting for cost-savings, the average annual incremental programme cost in the Basecase M72/AS01$_E$ scenario (US$190 million) was over eight times greater than the average annual incremental programme cost with the Basecase BCG-revaccination scenario (US$23 million).

Figure 4 demonstrates the distribution of costs and cost-savings per year from vaccine introduction to 2050

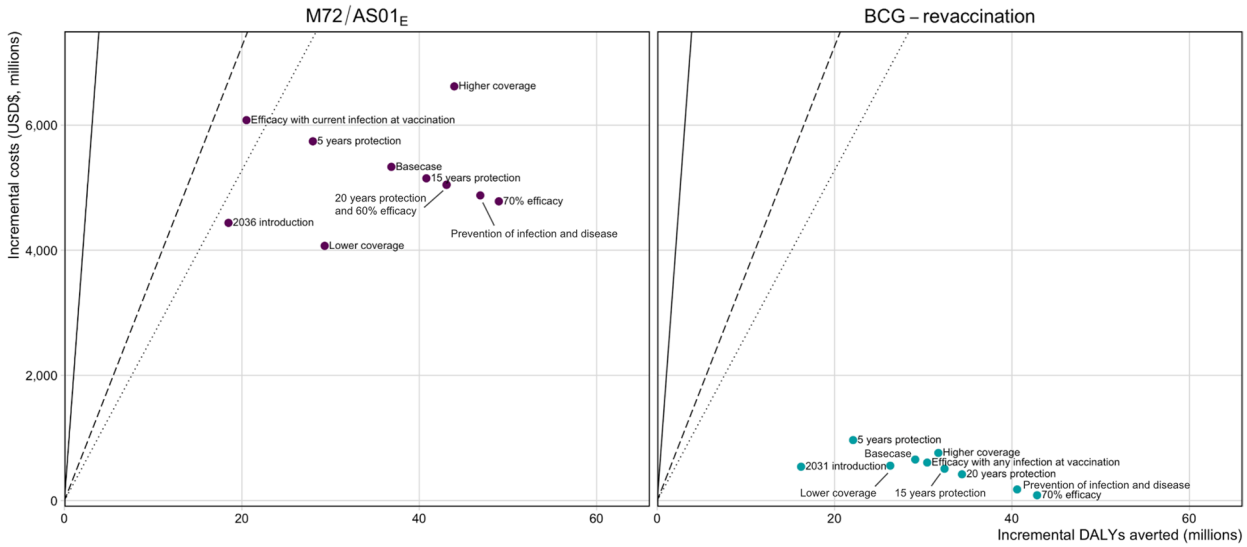

Fig. 3 Comparison of ICERs for *Vaccine Characteristic and Coverage Scenarios* compared to the *Status Quo* no-new-vaccine baseline for each vaccine product. The Basecase M72/AS01$_E$ scenario assumes a 50% efficacy POD vaccine efficacious with any infection status at the time of vaccination, with 10 years' duration of protection reaching 80% coverage for 15-year-olds and 70% coverage for those aged 16–34. Each M72/AS01$_E$ scenario is delivered routinely to those aged 15 and as a campaign for those aged 16–34. The Basecase BCG-revaccination scenario assumes a 45% efficacy POI vaccine efficacious with no current infection at the time of vaccination, with 10 years duration of protection and reaching 80% coverage. Each BCG-revaccination scenario is delivered routinely to those aged 10 and as a campaign for those aged 11–18. The scenarios on the figure are labelled with the difference in product characteristics for that scenario compared to the Basecase. The 20 years' protection and 60% efficacy scenarios for M72/AS01$_E$ overlap and appear as one point on the figure

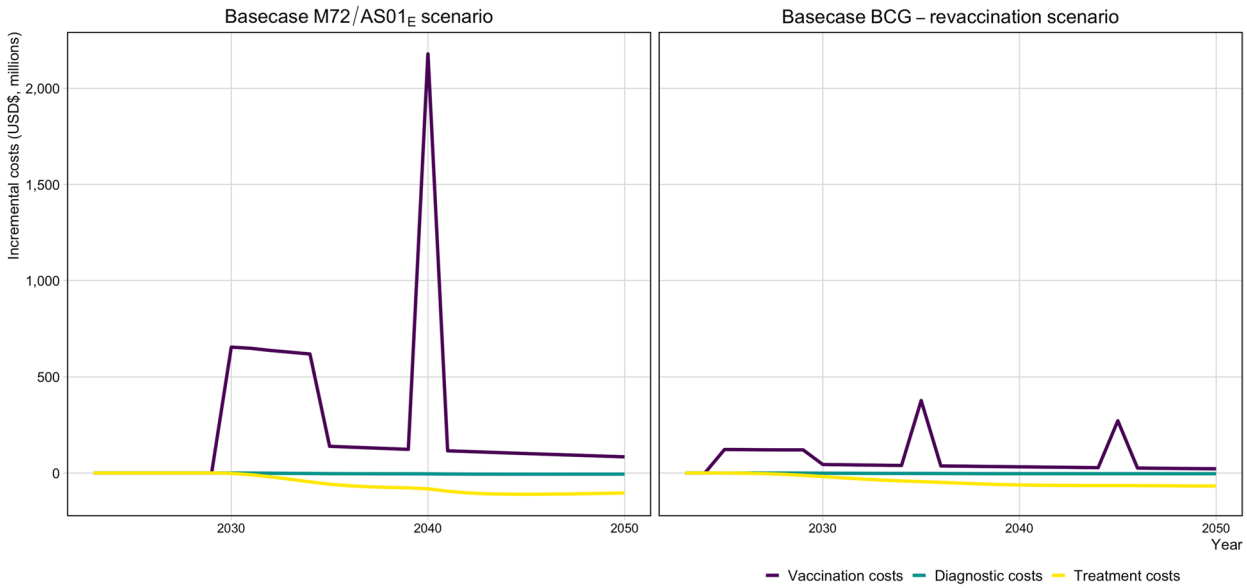

Fig. 4 Incremental costs by year until 2050 for the Basecase M72/AS01$_E$ and BCG-revaccination scenarios compared to the *Status Quo* no-new-vaccine baseline. USD$, United States dollars

for the Basecase scenarios for both vaccine products. During the initial 5-year scale-up to maximum achieved coverage, the average vaccination cost for the Basecase M72/AS01$_E$ scenario was US$638 million per year, compared to US$121 million per year for the Basecase BCG-revaccination scenario. The cost during the repeat campaign in 2040 for the Basecase M72/AS01$_E$ vaccine was US$2.2 billion, compared to US$377 million and US$272 million, respectively, for the two repeat campaigns in 2035 and 2045 for the Basecase BCG-revaccination scenario. Full economic results are in Additional file 1 Sect. 9.

Discussion

We found that M72/AS01$_E$ scenarios could avert approximately 12.7 (11.0–14.6) million cases and 2.0 (1.8–2.4) million deaths, and BCG-revaccination scenarios could avert approximately 9.0 (7.8–10.4) million cases and 1.5 (1.3–1.8) million deaths of the 72.2 (63.3–79.7) million cases and 13.8 (6.1–13.2) million deaths predicted by the *Status Quo* baseline between 2025 and 2050. Cost-effectiveness ratios for the Basecase M72/AS01$_E$ scenario were around seven times higher than that for the Basecase BCG-revaccination scenario, but regardless of the realised product characteristics, nearly all *Vaccine Characteristic and Coverage Scenarios* were cost-effective at the most conservative country-level threshold compared to the no-new-vaccine baseline. The average annual cost of M72/AS01$_E$ vaccination was four times greater than BCG-revaccination. Introducing the vaccine could lead to an annual incremental programme cost of US$190 million for M72/AS01$_E$ and US$23 million for BCG-revaccination, accounting for vaccination costs as well as savings in diagnostic and treatment costs.

Our modelling demonstrated a 40% greater health impact from M72/AS01$_E$ compared to BCG-revaccination. The difference in impact was due to assumptions made on vaccine characteristics and delivery. Based on clinical trial data and expert opinion, we assumed the Basecase M72/AS01$_E$vaccine would prevent disease and be efficacious in everyone without active disease at vaccination. In contrast, based on trial data [14, 70], we assumed the Basecase BCG-revaccination scenario would be efficacious only in people without infection at the time of vaccination, and would prevent infection. Therefore, M72/AS01$_E$would be effective in a larger proportion of the population compared to BCG-revaccination and have a more rapid impact on tuberculosis incidence. The effect of BCG-revaccination on disease will be delayed by the time between vaccination and infection in addition to the time from infection to disease. This is consistent with previous work showing more rapid impact on disease of a vaccine that prevents disease directly in those currently infected [11].

As demonstrated in the National Tuberculosis Prevalence Survey, the highest tuberculosis prevalence estimates are found in older adolescents and adults [19]. The Basecase scenario for M72/AS01$_E$ delivered the vaccine routinely to those aged 15 and as a campaign for ages 16–34, as opposed to the Basecase BCG-revaccination scenario which was targeted routinely to those aged 10

and a campaign for ages 11–18. As the M72/AS01$_E$ vaccine was targeted to an age group with a higher burden, we saw an increased impact on the burden.

We explored variation in decisions regarding delivery and the realised vaccine by evaluating *Policy Scenarios* and *Vaccine Characteristic and Coverage Scenarios* where we varied characteristics univariately from the Basecase for each vaccine product, and found all uncertainties had the anticipated direction of effect. Both M72/AS01$_E$ and BCG-revaccination were highly influenced by vaccine efficacy and duration of protection, with higher efficacies and longer durations of protection increasing health impact and cost-effectiveness. Key sources of uncertainty were whether M72/AS01$_E$ was efficacious without infection at vaccination, and if BCG-revaccination was also able to prevent disease in adults, both of which are key areas of research. Given the uncertainty surrounding prevention of disease efficacy from BCG-revaccination, any roll out of BCG to adolescents and adults should be rigorously evaluated with a prevention of disease outcome.

M72/AS01$_E$ scenarios were predicted to have higher vaccination costs per year compared to BCG-revaccination. The assumed M72/AS01$_E$ vaccine price per course of US$5.00 (two doses for US$2.50 each) was almost 30 times the US$0.17 price per course of BCG-revaccination, in addition to duplicated delivery and supply costs necessary to deliver two doses of M72/AS01$_E$ compared to one dose of BCG. These cost differences directly contribute to higher cost-effectiveness ratios and larger annual cost for M72/AS01$_E$. Our analyses demonstrated that both vaccines could be cost-effective, aligning with previous cost-effectiveness analyses of tuberculosis vaccines [6, 32]. While vaccination could have a substantial budget impact, costs could be partially offset with diagnostic and treatment savings.

Comparing the ICERs for *Vaccine Characteristic and Coverage Scenarios*, we see that even if the product characteristics change from the Basecase scenario for each vaccine product, the decision remains the same. Introducing M72/AS01$_E$ or BCG-revaccination would be a cost-effective intervention.

This work has limitations. We modelled the impact of specific M72/AS01$_E$ and BCG-revaccination scenarios with characteristics based on clinical trial data and consultation with vaccine and country-specific experts, but it will be many years before the actual characteristics are known. To capture some uncertainty, we univariately varied efficacy, duration of protection, whether the vaccine prevents only infection or disease or both, and who the vaccine would be efficacious in. The majority of scenarios continued to demonstrate large potential health impact and cost-effectiveness. We were not investigating the separate question of determining the range of plausible conditions that M72/AS01$_E$ would no longer be cost-effective or scenarios where BCG-revaccination would have a greater impact, which is an important area for future work to address.

The Basecase M72/AS01$_E$ scenario assumed efficacy with any infection status at vaccination, implying that the vaccine would work in both those who were infected with *Mtb* and those who were uninfected. While the Phase IIb trial of M72/AS01$_E$ only enrolled adults with a positive interferon-gamma release assay (IGRA) value, previous trials have indicated that an immune response is invoked in adolescents both with and without infection, and the phase III trial will enrol IGRA positive and negative individuals aged 15–44 years. Therefore, the expected initial indicated population is everyone within these ages, and thus we aligned our primary assumption for host infection status with this. We evaluated a scenario assuming only current infection at vaccination and determined that efficacy in those who are uninfected at the time of vaccination is important to maximise health impact and cost-effectiveness. Investigating whether M72/AS01$_E$ works in populations with any infection status is a key aspect for future research.

We modelled a small subset of age-targeted delivery scenarios, which may differ from the strategies India will choose. We evaluated alternatives informed by expert opinion and results from interviews with key decision-makers in India [58], but did not investigate targeting specific groups, such as healthcare workers, people completing tuberculosis treatment, or household contacts of people with tuberculosis, who could be at high risk of developing tuberculosis disease and may be prioritised for vaccination. This strategy has previously been suggested to have a high population-level impact per individual vaccinated [71–73 and greater than 45% for BCG-revaccination (aligning with the estimates of protection from the Phase IIb trials). However, the true vaccine efficacy is currently unknown, and if our assumptions were too optimistic, we may have overestimated the health and economic impacts.

The burden of tuberculosis varies widely across India. From the recent National Tuberculosis Prevalence Survey, the prevalence per 100,000 population of pulmonary tuberculosis among adults ranged from 115 (47–184) in Kerala to 534 (365–704) in Delhi [19]. Optimal delivery strategies may vary by state, given the vast differences in age composition, population size, and tuberculosis burden. Modelling specific regions to investigate the generalisability of national predictions is an important area of future research.

We ran cost-effectiveness analysis for each product on the age-targeting *Policy Scenarios*. We selected the

Basecase vaccine profile characteristics for each vaccine product as it incorporates the primary assumptions from experts in the field on the likely vaccine product characteristics, but we did not run cost-effective analysis for the age-targeting strategies with other vaccine characteristics.

Our work is a modelling exercise, and limitations associated with mathematical models apply. We developed our tuberculosis natural history structure incorporating recent advances in knowledge regarding the clinical course of disease, such as subclinical tuberculosis and a latency structure with a progressive loss in the ability to reactivate. If our assumptions around these novel aspects, particularly around interactions with vaccines, are incorrect, we may have over- or underestimated the impact. While we used the best available data to inform calibration targets and natural history parameters, we were limited by what was available. We ensured that the modelled trends aligned with the most recent estimates of tuberculosis burden, as vaccines are not anticipated to be introduced until at least 2025. However, with only one estimate of whole-country disease prevalence and one estimate of whole-county infection prevalence in India, we were restricted with what we could infer about these measures over time, which highlights the need for more regularly collected data on disease prevalence and infection. We made decisions on natural history parameter ranges based on the most recent literature available, but this still resulted in wide prior ranges for some parameters. Further data collection into these areas would improve model estimates.

We projected the no-new-vaccine baseline as *Status Quo*, where we assume that the rate and quality of services remained constant from 2020 onwards, and the resulting trends in burden from 2020–2050 follows a slight decline. Given the commitment of the Indian government to improvements in tuberculosis care, prevention, and ending the tuberculosis epidemic, our model could be overestimating the burden of tuberculosis. Therefore, our health and economic impacts may be overestimated. We ran a sensitivity analysis for the Basecase scenario for each vaccine product using the *Strengthened Current Interventions* no-new-vaccine baseline. We found that vaccines would still have a positive health impact and would be cost-effective even if the incidence rate was declining faster than assumed in our primary scenario. We demonstrated that vaccines could also be an impactful and cost-effective investment for the Indian government if future tuberculosis burden is much lower.

The results from this study could be used to inform policy-makers considering novel tuberculosis vaccine introduction. We have demonstrated that both BCG-revaccination and M72/AS01$_E$ could have a positive health impact and would be cost-effective if delivered, given our current assumptions. We evaluated uncertainty surrounding vaccine characteristics and found that even if characteristics were changed, we would still see positive health impact and cost-effectiveness.

The decision for how to take these results forward to country-level introduction lies with the policy-maker, and how they are able to allocate their available budget. While we made some comparisons between products, the results of our study assume a reality where only one vaccine product is introduced. However, it is likely that both vaccine products could be introduced into the population, and the resulting health benefit could be increased. BCG is already licensed and recommended by the WHO for infants, and therefore BCG-revaccination of older adolescents and adults could be introduced earlier than M72/AS01$_E$ through a policy change. Resources may need to be spent on epidemiological studies investigating population characteristics, such as the infection prevalence, to determine where a vaccine effective in those who are uninfected will have the most impact. M72/AS01$_E$ is still a vaccine candidate and forward progression depends on results from the phase III trial which has yet to start. More uncertainty surrounding costs and product characteristics exists, but overall M72/AS01$_E$ predicted an increased health impact compared to BCG-revaccination.

Conclusions

We propose it is inadvisable to focus solely on one or two vaccine candidates to address the tuberculosis burden. While promising results have been seen from recent trials, it will be years before we can verify these characteristics, and therefore, we need a wide selection of options for the greatest likelihood of mitigating tuberculosis burden. We need to continue investment in all candidates currently in the pipeline, and support the development of new candidates, to increase the probability of success.

Our modelling suggests that M72/AS01$_E$ and BCG-revaccination may substantially reduce the tuberculosis burden in India over future decades and would be cost-effective regardless of the assumed product characteristics. We informed vaccine characteristics using clinical trial data but found variability in the vaccine profile as a crucial source of uncertainty. We cannot solely rely on M72/AS01$_E$ and BCG-revaccination in case the realised characteristics differ considerably from expectations. Investment in multiple vaccine developments and delivery should be increased to raise the probability of success.

Abbreviations

BCG	Bacillus Calmette–Guérin
DALY	Disability-adjusted life years
ICER	Incremental cost-effectiveness ratio
Mtb	Mycobacterium tuberculosis
NTEP	National Tuberculosis Elimination Programme
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-02992-7.

Additional file 1. The model structure, parameterisation, calibration, and simulation is described in detail, and additional epidemiological and economic results are provided. **Figure S1.1**--Tuberculosis natural history model structure. **Figure S3.1**--The estimated impact of the COVID-19 pandemic on tuberculosis incidence and mortality. **Figure S3.2**--Contribution of the private sector to reported case notifications. **Figure S4.1**--Vaccine structure for a NCI vaccine. **Figure S4.2**--Vaccine structure for a CI vaccine. **Figure S4.3**--Vaccine structure for an AI vaccine (protection does not build). **Figure S4.4**--Vaccine structure for an AI vaccine (protection builds). **Figure S7.1**--Tuberculosis incidence, disease prevalence, case notification and mortality rate trends. **Figure S7.2**--Tuberculosis infection prevalence, proportion retreated, access-to-care ratio and ratio of subclinical tuberculosis to total tuberculosis trends. **Figure S7.3**--Tuberculosis incidence and mortality rate trends. **Figure S7.4**--Tuberculosis disease and infection prevalence trends. **Figure S7.5**--Tuberculosis case notification and proportion retreated trends. **Figure S7.6**--Access-to-care ratio and the ratio of subclinical tuberculosis to all active tuberculosis trends. **Figure S7.7**--Posterior distributions for the 19 parameters varied during calibration. **Figure S7.8**--Tuberculosis incidence rate for the *Strengthened Current Interventions* baseline. **Figure S8.1**--Incidence and mortality rate reductions in 2050 for M72/AS01$_E$ scenarios. **Figure S8.2**--Cumulative tuberculosis cases, treatments, and deaths averted for M72/AS01$_E$ scenarios. **Figure S8.3**--Incidence and mortality rate reductions in 2050 for the BCG-revaccination scenarios. **Figure S8.4**--Cumulative tuberculosis cases, treatments, and deaths averted for BCG-revaccination scenarios. **Figure S9.1**--Efficiency frontiers for M72/AS01$_E$ *Policy Scenarios*. **Figure S9.2**--Comparison of ICERs for M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios*. **Figure S9.3**--Basecase M72/AS01$_E$ scenario incremental discounted costs by year. **Figure S9.4**--Efficiency frontiers for BCG-revaccination *Policy Scenarios*. **Figure S9.5**--Comparison of ICERs for BCG-revaccination *Vaccine Characteristic and Coverage Scenarios*. **Figure S9.6**--Basecase BCG-revaccination scenario incremental discounted costs by year. **Figure S9.7**--Cost-effectiveness planes for the M72/AS01$_E$ and BCG-revaccination Basecase scenarios with the *Strengthened Current interventions* baseline. **Table S2.1**--India national model parameter values and sources. **Table S2.2**--How age varying parameters are operationalized. **Table S2.3**--Calculating treatment outcome parameter values for adults and children. **Table S2.4**--Calculation of treatment outcomes for India by year. **Table S3.1**--India national model calibration targets. **Table S3.2**--Incidence and mortality rate targets for all ages for 2025. **Table S3.3**--Number of incident tuberculosis cases by year in India. **Table S3.4--**The fraction of tuberculosis treatment notifications in India from the private sector and overall. **Table S3.5**--The WHO reported and adjusted tuberculosis case notification targets for India. **Table S4.1**--M72/AS01$_E$ and BCG-revaccination scenarios evaluated in the analysis. **Table S4.2**--Increase in protection for the number of vaccine courses. **Table S5.1**--Tuberculosis testing, diagnostic, and vaccination related cost inputs. **Table S8.1**--Health impact results for M72/AS01$_E$ scenarios. **Table S8.2**--Health impact results for BCG-revaccination scenarios. **Table S9.1**--Cost-effectiveness analysis for M72/AS01E *Policy Scenarios*. **Table S9.2**--Incremental DALYs averted, incremental costs averted, and ICERs from health-system and societal perspectives for M72/AS01$_E$ *Vaccine Characteristic and Coverage Scenarios*. **Table S9.3**--Total costs for the M72/AS01$_E$ scenarios from the health-system perspective. **Table S9.4**--Total costs for the M72/AS01$_E$ scenarios from the societal perspective. **Table S9.5**--Cost-effectiveness analysis for BCG-revaccination *Policy Scenarios*. **Table S9.6**--Incremental DALYs averted, incremental costs averted, and ICERs from health-system and societal perspectives for BCG-revaccination *Vaccine Characteristic and Coverage Scenarios*. **Table S9.7**--Total costs for the BCG-revaccination scenarios from the health-system perspective. **Table S9.8**--Total costs for the BCG-revaccination scenarios from the societal perspective.

Additional file 2. The CHEERS checklist for the study.

Acknowledgements

We thank the Bill & Melinda Gates Foundation for providing funding (INV-001754) to undertake this research.

Authors' contributions

Conception: RCH, RGW, NAM, CKW. Data acquisition and preparation: RAC, AP, CM, MQ, CKW. Data analysis: RAC, RGW, CM, CKW, RB. Interpretation of results: RAC, RGW, CKW, AP, NAM, CM. Manuscript drafting and revisions: RAC, RGW, AP, NAM, CKW, MQ, DT, KR, CM, RB, SKM, RCH, DS. All authors had the opportunity to access and verify the data and were responsible for the decision to submit the manuscript for publication. All authors read and approved the final manuscript.

Authors' Twitter handles

Rebecca A Clark: @ra_clark18
Chathika K Weerasuriya: @cweerasuriya
Allison Portnoy: @AllisonPortnoy
Christinah Mukandavire: @cmukandavire
Matthew Quaife: @matthew_quaife
Danny Scarponi: @DannyScarponi
Rebecca C Harris: @RebeccaCHarris
Kirankumar Rade: @drkiranrade
Sanjay Kumar Mattoo: @Sanjay_kamttoo
Dheeraj Tumu: @dheedoc
Nicolas A Menzies: @NickMenzies2
Richard G White: @richardwhite321

Funding

We thank the Bill & Melinda Gates Foundation for providing funding (INV-001754) to undertake this research. The funder was involved in the development of the research question and study design, but had no role in the collection, analysis, and interpretation of the data, or writing of the report.

Availability of data and materials

Epidemiologic data used are available from the *World Health Organization Global TB Report CSV files to download* (https://www.who.int/teams/global-tuberculosis-programme/data) and summarised in Additional file 1. Population estimates and projections are available from the *United Nations Department of Economic and Social Affairs World Population Prospects 2019* (https://population.un.org/wpp/Download/Standard/Population/). Analytic code will be made available at https://doi.org/10.5281/zenodo.6421372 immediately following publication indefinitely for anyone who wishes to access the data for any purpose.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

RCH reports employment by Sanofi Pasteur, unrelated to tuberculosis and outside the submitted work. NAM received consulting fees from The Global Fund to Fight AIDS, Tuberculosis and Malaria, and the WHO, and reports funding to their institution from the US Centers for Disease Control and Prevention, the Bill & Melinda Gates Foundation, NIH, and US Council of State and Territorial Epidemiologists. RGW is also funded for other work by the Wellcome Trust (218261/Z/19/Z), NIH (1R01AI147321-01), EDCTP (RIA208D-2505B), UK MRC (CCF 17–7779 via SET Bloomsbury), ESRC (ES/P008011/1), BMGF (OPP1084276, OPP1135288 & INV-001754), and the WHO. All other authors declare no conflicts of interest.

Author details

[1]TB Modelling Group and TB Centre, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. [2]Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK. [3]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. [4]Vaccine Centre, London School of Hygiene and Tropical Medicine, London, UK. [5]Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, USA. [6]Department of Global Health, Boston University School of Public Health, Boston, USA. [7]KNCV Tuberculosis Foundation, The Hague, Netherlands. [8]Sanofi Pasteur, Singapore, Singapore. [9]World Health Organization, New Delhi, India.

[10]Central TB Division, NTEP, MoHFW Govt of India, New Delhi, India. [11]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA.

Received: 24 February 2023 Accepted: 20 July 2023
Published online: 04 August 2023

References

1. World Health Organization. Global Tuberculosis Report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
2. World Health Organization. Tuberculosis data. 2022. https://www.who.int/teams/global-tuberculosis-programme/data. Accessed 13 Dec 2022.
3. National Tuberculosis Elimination Programme. National Strategic Plan to End Tuberculosis in India 2020–2025. New Delhi: Ministry of Health with Family Welfare; 2020.
4. Central TB Division, Ministry of Health and Family Welfare, Government of India. Report 2022. New Delhi: Ministry of Health with Family Welfare; 2022.
5. Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study. Lancet Glob Health. 2023;11(4):E546–55.
6. Portnoy A, Clark RA, Quaife M, et al. The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modeling study. PLOS Med. 2023;20: e1004155.
7. Portnoy A, Clark RA, Weerasuriya CK, et al. The potential impact of novel tuberculosis vaccines on health equity and financial protection in low- and middle-income countries. BMJ Glob Health. 2023;8: e012466.
8. Portnoy A, Arcand J-L, Clark RA, et al. The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries. PLOS Med. 2023;20(7): e1004252.
9. World Health Organization. An investment case for new tuberculosis vaccines. Geneva: World Health Organization; 2022. (Licence: CC BY-NC-SA 3.0 IGO).
10. Weerasuriya CK, Clark RA, White RG, Harris RC. New tuberculosis vaccines: advances in clinical development and modelling. J Intern Med. 2020;288:661–81.
11. Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. Sci Transl Med. 2020;12(564):eaax4607.
12. The Stop TB Partnership Working Group on New TB Vaccines. TB Vaccine Pipeline. Work. Group New TB Vaccines. 2022. https://newtbvaccines.org/tb-vaccine-pipeline/. Accessed 13 Dec 2022.
13. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. N Engl J Med. 2019;381:2429–39.
14. Nemes E, Geldenhuys H, Rozot V, et al. Prevention of M. tuberculosis Infection with H4:1C31 Vaccine or BCG Revaccination. N Engl J Med. 2018;379:138–49.
15. Bill & Melinda Gates Medical Research Institute. A randomized, placebo controlled, observer-blind, phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination in healthy adolescents for the prevention of sustained infection with Mycobacterium tuberculosis. Clinicaltrials.gov, 2021. https://clinicaltrials.gov/ct2/show/NCT04152161. Accessed 8 Dec 2022.
16. Tuberculosis Research Centre (ICMR), Chennai. Fifteen year follow up of trial of BCG vaccines in south India for tuberculosis prevention. Indian J Med Res. 1999;110:56–69.
17. Velayutham B, Thiruvengadam K, Kumaran PP, et al. Revisiting the Chingleput BCG vaccination trial for the impact of BCG revaccination on the incidence of tuberculosis disease. Indian J Med Res. 2023;157(2&3):152–9.
18. United Nations, Department of Economic and Social Affairs, Population Division. World Population Projections [2019 Revision]. 2019. https://population.un.org/wpp/Download/Standard/Population/. Accessed 2 Nov 2022.
19. Indian Council of Medical Research (ICMR). National TB prevalence survey India 2019–2021. New Delhi: Indian Council of Medicine Research; 2022.
20. Knight GM, Griffiths UK, Sumner T, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. Proc Natl Acad Sci. 2014;111:15520–5.
21. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS ONE. 2011;6(4): e17601.
22. Quaife M, Houben RMGJ, Allwood B, et al. Post-tuberculosis mortality and morbidity: valuing the hidden epidemic. Lancet Respir Med. 2020;8(4):332–3.
23. Prem K, van Zandvoort K, Klepac P, et al. Projecting contact matrices in 177 geographical regions: an update and comparison with empirical data for the COVID-19 era. PLOS Comput Biol. 2021;17(7): e1009098.
24. World Health Organization. WHO TB burden estimates. CSV files to download. 2022. https://www.who.int/tb/country/data/download/en/. Accessed 2 Nov 2022.
25. World Health Organization. Case Notifications. CSV files to download. 2022. https://www.who.int/tb/country/data/download/en/ Accessed 2 Nov 2022.
26. Emery JC, Dodd PJ, Banu S, et al. Estimating the contribution of subclinical tuberculosis disease to transmission—an individual patient data analysis from prevalence surveys. medRxiv 2022. https://doi.org/10.1101/2022.06.09.22276188 (preprint).
27. Emery JC, Richards AS, Dale KD, et al. Self-clearance of Mycobacterium tuberculosis infection: implications for lifetime risk and population at-risk of tuberculosis disease. Proc Biol Sci. 1943;2021(288):20201635.
28. Abu-Raddad L, Sabatelli L, Achterberg JT, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci U S A. 2009;106(33):13980–5.
29. Dye C, Williams BG. Eliminating human tuberculosis in the twenty-first century. J R Soc Interface. 2008;5(23):653–62.
30. Marx FM, Dunbar R, Enarson DA, et al. The temporal dynamics of relapse and reinfection tuberculosis after successful treatment: a retrospective cohort study. Clin Infect Dis. 2014;58(12):1676–83.
31. Gomes MGM, Franco AO, Gomes MC, Medley GF. The reinfection threshold promotes variability in tuberculosis epidemiology and vaccine efficacy. Proc R Soc B Biol Sci. 2004;271(1539):617–23.
32. Dangisso MH, Woldesemayat EM, Datiko DG, Lindtjørn B. Long-term outcome of smear-positive tuberculosis patients after initiation and completion of treatment: a ten-year retrospective cohort study. PLoS ONE. 2018;13(3): e0193396.
33. Sutherland I, Svandová E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. Tubercle. 1982;63(4):255–68.
34. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect. 1997;119(2):183–201.
35. Gabriela M, Gomes M, Rodrigues P, Hilker FM, et al. Implications of partial immunity on the prospects for tuberculosis control by post-exposure interventions. J Theor Biol. 2007;248(4):608–17.
36. Rajagopalan S. Tuberculosis and aging: a global health problem. Clin Infect Dis Off Publ Infect Dis Soc Am. 2001;33(7):1034–9.
37. World Health Organization. Global Tuberculosis Report 2020. Geneva: World Health Organization; 2020.
38. Iskauskas A. hmer: history matching and emulation package. 2022. https://cran.r-project.org/web/packages/hmer/index.html. Accessed 2 Nov 2022.
39. Andrianakis I, Vernon I, McCreesh N, et al. History matching of a complex epidemiological model of human immunodeficiency virus transmission by using variance emulation. J R Stat Soc Ser C Appl Stat. 2017;66(4):717–40.
40. Andrianakis I, Vernon IR, McCreesh N, et al. Bayesian history matching of complex infectious disease models using emulation: a tutorial and a case study on HIV in Uganda. PLOS Comput Biol. 2015;11(1): e1003968.
41. Goldstein M. Bayes Linear Analysis for Complex Physical Systems Modeled by Computer Simulators. In: Dienstfrey AM, Boisvert RF (Hrsg) Uncertainty quantification in scientific computing. 10th IFIP WG 2.5 Working Conference, WoCoUQ 2011, Boulder, CO, USA, 1–4 Aug 2011, Revised selected papers, Bd 377. Berlin:: Springer; 2012. p. 78–94.
42. Williamson D, Goldstein M, Allison L, et al. History matching for exploring and reducing climate model parameter space using observations and a large perturbed physics ensemble. Clim Dyn. 2013;41:1703–29.

43. Iskauskas A, Vernon I, Goldstein M, et al. Emulation and history matching using the hmer package. arXiv 2023. http://arxiv.org/abs/2209.05265 (preprint)
44. Jabot F, Faure T, Dumoulin N. EasyABC: performing efficient approximate Bayesian computation sampling schemes using R. O'Hara RB, ed. Methods Ecol Evol. 2013;4(7):684–7.
45. Roberts GO, Rosenthal JS. Examples of Adaptive MCMC. J Comput Graph Stat. 2009;18(2):349–67.
46. World Health Organization. WHO TB incidence estimates disaggregated by age group, sex and risk factor. CSV files to download. 2022. https://www.who.int/tb/country/data/download/en/. Accessed 2 Nov 2022.
47. World Health Organization. Global Tuberculosis Report 2021. Geneva: World Health Organization; 2021.
48. Pandey S, Chadha VK, Laxminarayan R, Arinaminpathy N. Estimating tuberculosis incidence from primary survey data: a mathematical modeling approach. Int J Tuberc Lung Dis. 2017;21(4):366–74.
49. Mandal S, Chadha VK, Laxminarayan R, Arinaminpathy N. Counting the lives saved by DOTS in India: a model-based approach. BMC Med. 2017;15(1):47.
50. Singh SK, Kashyap GC, Puri P. Potential effect of household environment on prevalence of tuberculosis in India: evidence from the recent round of a cross-sectional survey. BMC Pulm Med. 2018;18(1):66.
51. Frascella B, Richards AS, Sossen B, et al. Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. Clin Infect Dis. 2021;73(3):e830–41.
52. Shewade HD, Gupta V, Satyanarayana S, et al. Are we missing 'previously treated' smear-positive pulmonary tuberculosis under programme settings in India? A cross-sectional study. F1000Res. 2019;8:338.
53. UNICEF. Bacillus Calmette–Guérin (BCG) vaccine price data. 2021. https://www.unicef.org/supply/documents/bacillus-calmettegu%C3%A9rin-bcg-vaccine-price-data. Accessed 13 Dec 2022.
54. Gavi The Vaccine Alliance. GAVI Alliance Vaccine Introduction Grant and Operational Support for Campaigns Policy Version No. 1.0. Geneva: Gavi, The Vaccine Alliance; 2013. https://www.gavi.org. Accessed 12 July 2018.
55. UNICEF. Costs of Vaccinating a Child. Published 2020. https://immunizationeconomics.org/recent-activity/2021/6/15/standard-costs-of-vaccinating-a-child. Accessed 20 Jan 2021.
56. Prosser LA, O'Brien MA, Molinari NAM, et al. Non-traditional settings for influenza vaccination of adults. Pharmacoeconomics. 2008;26:163–78.
57. The World Bank. World Bank. World development indicators. 2020. https://data.worldbank.org/. Accessed 12 Apr 2022.
58. Pelzer PT, Seeley J, Sun FY, et al. Potential implementation strategies, acceptability, and feasibility of new and repurposed TB vaccines. PLOS Glob Public Health. 2022;2: e0000076.
59. Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. Value Health. 2016;19:921–8.
60. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204–22.
61. United Nations Development Programme. Human Development Report: Life Expectancy by Country. United Nations, 2020 https://hdr.undp.org/data-center. Accessed 13 June 2022.
62. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. BMJ Glob Health. 2018;3: e000964.
63. Vassall A, van Kampen S, Sohn H, et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLOS Med. 2011;8(11): e1001120.
64. Muniyandi M, Lavanya J, Karikalan N, et al. Estimating TB diagnostic costs incurred under the National Tuberculosis Elimination Programme: a costing study from Tamil Nadu. South India Int Health. 2021;13(6):536–44.
65. Chatterjee S, Toshniwal MN, Bhide P, et al. Costs of TB services in India. Int J Tuberc Lung Dis. 2021;25(12):1013–8.
66. Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother. 2017;72(4):1243–52.
67. Sinha P, Carwile M, Bhargava A, et al. How much do Indians pay for tuberculosis treatment? A cost analysis. Public Health Action. 2020;10(3):110–7.
68. Sarin R, Vohra V, Singla N, Thomas B, Krishnan R, Muniyandi M. Identifying costs contributing to catastrophic expenditure among TB patients registered under RNTCP in Delhi metro city in India. Indian J Tuberc. 2019;66(1):150–7.
69. Chandra A, Kumar R, Kant S, Parthasarathy R, Krishnan A. Direct and indirect patient costs of tuberculosis care in India. Trop Med Int Health. 2020;25(7):803–12.
70. Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis. 2014;58:470–80.
71. Awad SF, Critchley JA, Abu-Raddad LJ. Epidemiological impact of targeted interventions for people with diabetes mellitus on tuberculosis transmission in India: modelling based predictions. Epidemics. 2020;30: 100381.
72. Weerasuriya CK, Harris RC, McQuaid CF, et al. The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China. BMC Med. 2021;19:60.
73. Shrestha S, Chihota V, White RG, Grant AD, Churchyard GJ, Dowdy DW. Impact of targeted tuberculosis vaccination among a mining population in South Africa: a model-based study. Am J Epidemiol. 2017;186:1362–9.

Publisher's Note