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Population-level health and economic impacts of introducing Vaccae vaccination in China: a modelling study

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ABSTRACT

Introduction Given the ageing epidemic of tuberculosis (TB), China is facing an unprecedented opportunity provided by the first clinically approved next-generation TB vaccine Vaccae, which demonstrated 54.7% efficacy for preventing reactivation from latent infection in a phase III trial. We aim to assess the population-level health and economic impacts of introducing Vaccae vaccination to inform policy-makers.

Methods We evaluated a potential national Vaccae vaccination programme in China initiated in 2024, assuming 20 years of protection, 90% coverage and US$30/dose government contract price. An age-structured compartmental model was adapted to simulate three strategies: (1) no Vaccae; (2) mass vaccination among people aged 15–74 years and (3) targeted vaccination among older adults (60 years). Cost analyses were conducted from the healthcare sector perspective, discounted at 3%.

Results Considering postinfection efficacy, targeted vaccination modestly reduced TB burden (~20%), preventing cumulative 8.01 (95% CI 5.82 to 11.8) million TB cases and 0.20 (0.17 to 0.26) million deaths over 2024–2050, at incremental cost-effectiveness ratio of US$4387 (2218 to 10 085) per disability adjusted life year averted. The implementation would require a total budget of US$22.5 (17.6 to 43.4) billion. In contrast, mass vaccination had a larger bigger impact on the TB epidemic, but the overall costs remained high. Although both preinfection and postinfection vaccine efficacy type might have a maximum impact (>40% incidence rate reduction in 2050), it is important that the vaccine price does not exceed US$5/dose.

Conclusion Vaccae represents a robust and cost-effective choice for TB epidemic control in China. This study may facilitate the practice of evidence-based strategy plans for TB vaccination and reimbursement decision making.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Modelling studies for potential public health impact of next-generation tuberculosis (TB) vaccines are available but are limited to hypothetical vaccines or candidate vaccines under clinical trials.

⇒ Vaccae is the first clinically approved next-generation TB vaccine, for which the efficacy-effectiveness gap needs to be addressed.

WHAT THIS STUDY ADDS

⇒ We for the first time modelled the potential impact of a new TB vaccine that is available on the market and a vaccination programme that could be quickly implemented.

⇒ National targeted vaccination strategy towards older adults has been identified as a highly cost-effective epidemic control agent in China.

⇒ Mass vaccination strategy could be more effective, but reduction in vaccine price is necessary to ascertain a good economic return for the future vaccination programme.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may facilitate practice of evidence-based strategy plan for TB vaccination and reimbursement decision-making.

⇒ The framework may also provide valuable implications for TB control strategies in other countries.

INTRODUCTION

Globally, tuberculosis (TB) caused by *Mycobacterium tuberculosis* remains a major public health challenge. An estimated 10.6 million people developed active TB disease, with 1.4 million TB-related deaths in 2021. At least US$13 billion annually was required for worldwide TB prevention, diagnosis and treatment by 2022. India (28%), Indonesia (9.2%) and China (7.4%) are the top three countries with the most cases of TB in the world.[1] As the COVID-19 pandemic has aggravated the already suboptimal international TB response, new transformational tools such as vaccines are urgently needed to achieve the WHO 'end TB' goals.[2]

BCG, the most widely used TB vaccine in the world, was discovered in France in 1921.[3] Infant BCG vaccination is effective at preventing TB disease (pulmonary and extrapulmonary) in young children aged <5 years (efficacy 37%; 95% CI 19% to 51%).

It also has protection against TB-related death until 15 years after vaccination.[4] There are currently 16 TB vaccine candidates in the clinical development pipeline.[5] They include several different vaccine product profiles: (1) preinfection (PRI) or pre-exposure vaccines targeting infants, (2) postinfection (PSI) or post-exposure vaccines targeting adolescents and adults with latent TB infection (LTBI), (3) both preinfection and postinfection (P&PI) vaccines targeting all individuals except those who have active TB disease at time of vaccination and (4) therapeutic vaccines targeting active TB patients.[6] Vaccae, heat-killed *Mycobacterium* Vaccae (a non-TB mycobacteria closely related to *M. obuense*), is one of the next-generation candidates (ie, PSI efficacy type). The results from the phase III clinical trial showed that Vaccae was 54.7% efficacious in preventing pulmonary TB disease in tuberculin skin test (TST) confirmed latently infected persons (TST induration ≥15 mm) (online supplemental table S1 and S2). Strikingly, a century after the discovery of BCG, the China Food and Drug Administration granted approval to Vaccae in June 2021 for use in persons with LTBI (registered number of approval: S20010003; handling number: CXSS1800010; nmpa.gov.cn). The emphasis of the TB control approach might shift from treatment to prevention. As a new vaccine becomes available, questions remain regarding the potential public health impact of the vaccine and how to develop an optimal vaccination strategy. Deep interpretations of the efficacy trial results are warranted.

Most TB infections are asymptomatic and classified as LTBIs which serve as a reservoir for new disease and thereby perpetuate the disease cycle at a population level.[7] The risks of LTBI reactivation and TB-related death increase with age. With rapid ageing of the largest population in the world, China has a high disease burden of TB, among which LTBI reactivation accounts for nearly two thirds of total TB cases.[8] It is generally accepted that PSI or P&PI vaccines may provide more rapid and greater impact than PRI vaccines, especially in settings with reactivation-driven epidemics.[9] The approval of Vaccae provides an unprecedented opportunity for China.

In the last 10 years, the decline in diagnosed TB cases in China has plateaued.[1] Although TB elimination has long been a goal of the national TB plan, it is unclear whether and when this might be achieved and how declines in TB incidence can be accelerated. The vaccine may be a promising option for designing a novel vaccination strategy against TB in China. However, critical questions remain in planning and priority setting for vaccination strategies. There is currently no national TB vaccination programme for adolescents and adults in China. Self-paid Vaccae vaccination leads to extremely low vaccine uptake. Mathematical modelling incorporating transmission dynamics and intervention measures could help to guide strategy development. In this study, we intended to bridge the gap between the Vaccae efficacy trial and model-based impact evaluation. Our study may be timely to guide the design of nationwide TB control programmes and inform policy-making.

METHODS

Model structure and calibration

We adapted an age-structured compartmental model originally developed to evaluate the effect of the WHO DOTS (chemotherapy delivered as directly observed treatment, short-course) strategy. The model was developed using R software populated with China-specific inputs and calibrated to epidemiological targets from surveillance data, with more details about the model reported in prior studies.[10 11] It simulated changes in demography and epidemiology from 1900 to 2050 for all population in China. We initiated the model with 1950 values in 1900, allowed to burn in during 1900–1950 to ensure adequate stabilisation of the *M. tuberculosis* transmission trend. Then all compartments in 1950 were rescaled by the same factor to match the estimate for 1950. Age was modelled from 0 to 100 years at 1-year intervals. The natural history of TB was composed of five states (compartments): uninfected (S), latently infected (L), infectious (ie, bacteriologically positive) active TB disease (I), noninfectious (ie, bacteriologically negative) active disease (NI) and recovered from active disease (R) (figure 1A). Newborns were assumed to be in the uninfected state. The initial prevalence rate of infectious cases was set as 2% in 1900. State transmission includes: (1) acquisition of infection; (2) development of active disease, reactivation or relapse; (3) case detection, successful treatment or spontaneous recovery and (4) TB mortality in active disease states, and all-cause mortality in all states (figure 1B, online supplemental tables S3–S6 and figure S1).

The model was calibrated for the 2000–2050 period. We employed an iterative, directed-search Nelder-Mead (NM) method (online supplemental table S7)[12] using the R package 'dfoptim' to calibrate the model to the observed epidemiological targets: (1) the population size estimates for 2000, 2020, 2035 and 2050 (online supplemental table S8); (2) microbiologically positive pulmonary TB prevalence rate for 2000 and 2010; (3) TB incidence rates for 2005, 2010, 2014 and 2018 and (4) TB mortality rates for 2010 (online supplemental table S9). The goodness of fit (GoF) metric, defined as the sum of the GoF of the individual calibration targets, served in the optimisation procedure to overcome the limitation of the NM method of reaching local optima and ensure the model's prediction accuracy. We used Latin hypercube sampling to draw multiple sets of parameter values from their predefined distributions as the simplexes. With each simplex seeded, the NM search algorithm was applied to produce one optimal set of input parameter values that locally minimised the overall GoF metric. Only the calibrated parameter sets that best minimise GoF were deemed acceptable. We repeated the same calibration step 1000 times with each simplex seeded and derived 100 best fitting parameter subsets.

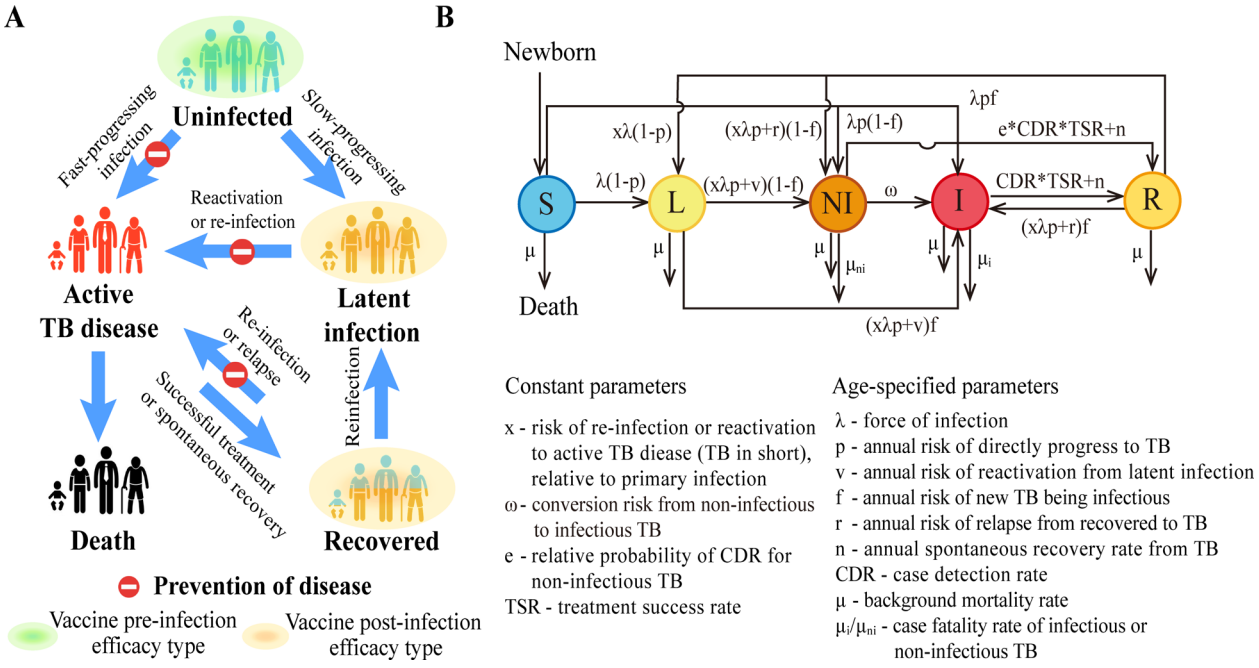

Figure 1 Vaccine characteristics and model structure. (A) Effect of TB vaccine on the natural history of *Mycobacterium tuberculosis* infection, preventing active TB disease (red) from individuals with or without a previous history of infection (PSI or PRI efficacy). (B) Age-structured compartmental model of *M. tuberculosis* infection, transmission and disease, consisting of S, L, NI, I and R states. I, infectious TB; L, latent infection; NI, non-infectious TB; PRI, preinfection; PSI, postinfection; R, recovered; S, susceptible; TB, tuberculosis.

The variables for BCG vaccination and DOTS programmes, including population coverage and treatment success rate, were assumed to remain stable. Therefore, the impacts of BCG and DOTS were intrinsic to the calibration data, although they were not explicitly modelled.

Vaccination strategies and epidemiological outcomes

To reflect the real-world effectiveness of the Vaccae vaccine and recognise the changing evidence on TB vaccines with different mechanisms, we focused on two vaccine types: PSI (real-world efficacy type) and P&PI (hypothetical multi-stage efficacy type). A series of vaccination scenario cases were modelled using combinations of efficacy type, vaccination age and duration of protection (eg, 10 years and 20 years, assumed to wane instantly at the end of the protection, or lifelong). To identify the priority population for vaccination, we initially compared the epidemiological outcomes of vaccinating different age-cohorts, spaced at 15-year intervals from ages 15 years to 74 years (4 cohorts). Each routine vaccination scenario involved a 'catch-up' vaccination for certain age groups in the first year of implementation. Next, three main strategies were explored: (1) no new vaccine (status quo); (2) mass vaccination, delivered to all-age population (persons aged 15–74 years) with LTBI (PSI) or irrespective of infection status (P&PI), through campaigns (10 yearly, 20 yearly or once) and (3) targeted vaccination, annually delivered to the age group with the highest priority, using PSI or P&PI efficacy type, through routine vaccination. We assumed that Vaccae would be widely available in 2024. The TST with 77.2% sensitivity was applied to screen for LTBI.[13] We assumed that 100% of those screened as TST positive would accept the vaccine injection. We assumed a 90% vaccination coverage to be 90% here given China's strong immunisation programme and high national vaccination coverage (over 90%).[14]

In the latest phase III clinical trial (ClinicalTrials.gov number: NCT01979900), 29 of the 4698 participants in the Vaccae group, compared with 64 of 4730 in the placebo group, were detected with pulmonary TB (incidence, 0.328 vs 0.724 cases per 100 person-years). Herein, the vaccine efficacy was set as 54.7% (95% CI: 29.8% to 70.8%) (online supplemental table S2).

The epidemiological outcomes were calculated annually over 2024–2050 for all the scenario cases. Our primary outcome of interest was the cumulative number of TB cases or deaths averted over 27 years, compared with the 'no new vaccine' scenario (status quo). Secondary outcomes were a composite of incidence rate reduction (IRR), mortality rate reduction (MRR), cumulative number needed to vaccinate (NNV) per case or death averted, in comparison with the status quo.

Costs and cost-effectiveness analysis

Cost evaluation was conducted from the healthcare sector (direct medical costs) perspective, as well as societal (direct medical costs, direct nonmedical costs and indirect costs) in the online supplemental file. Unit cost estimates and assumptions are provided in online supplemental table S13. Costs were reported in US$ at the average exchange rate in 2021 (US$1 = ¥6.5). The

market price for Vaccae is US$62/dose (US$372 for a course of 6 doses). The government contract price was assumed to be US$30/dose (around 50% reduction), based on the experience of national strategic price negotiation for new medicine.[15] The costs of the vaccination programme were composed of vaccine price, delivery and administrative costs.

The model predicted the number of deaths due to TB by age, year and time spent with active TB disease. Based on the life expectancy (online supplemental table S14) and disability weights (0.375),[16] we estimated year of life lost (YLL) and year lived with disability (YLD), respectively. The disability-adjusted life year (DALY) is calculated by summing YLL and YLD.

We conducted three separate analyses for cost effectiveness. First, we calculated the incremental cost-effectiveness ratio (ICER), based on the 100 best-fit model runs. The cost-effectiveness threshold (CET) or willingness-to-pay (WTP) threshold was set at US$12 458 (China's national gross domestic product per capita (pGDP) in 2021) per DALY averted, as recommended by the WHO. The cost per case averted (CCA) and cost per death averted (CDA) were also estimated. Second, we ran threshold analysis to calculate the price at which each strategy is estimated to be 'cost effective' (CE). A larger range of vaccine profiles was explored: 30%–100% efficacy and a 5–25-year duration of protection. Third, we conducted sensitivity analyses, one-way deterministic sensitivity analysis as well as probabilistic sensitivity analysis (PSA), to explore the impact of parameter uncertainty.[17 18] Cost-effectiveness planes and cost-effectiveness acceptability curves were constructed through PSA. The lowest (Gansu province) to highest (Beijing) pGDP (US$6304–US$28 850) were set as the CE threshold range. Besides, we tested the robustness of results to also a lower threshold estimate (ie, 0.63 [0.47–0.88] × GDP per capita), based on a country-specific assessment of health opportunity costs.[19] Costs and DALYs were discounted at 3% per year.

Budget impact analysis

The most CE vaccination strategy would be investigated for the national vaccination budget in a 27-year period of 2024–2050. The number of required vaccines was estimated according to the targeted population, buffer stock and vaccine wastage rate. For the cumulative net cost of vaccination, the estimates included screening and vaccination costs incurred, and averted TB service costs and/or productivity loss, from healthcare sector or societal perspective.[20]

RESULTS

The model fitted overall and age-stratified demographic (online supplemental figure S2) and epidemiological data (prevalence, incidence and mortality rates in figure 2A–C and online supplemental figures S3-S5, respectively) in China. In our status quo projection, the general downward trend in incidence became flattened over 2020–2050, with an average annual decline rate of only 1.06% (figure 2B), which may be explained by the ageing and reactivation-driven epidemic of TB in the Chinese population (figure 2D). The model predicted that TB incidence was predominantly driven by reactivation/reinfection of latently infected individuals rather than new infection of susceptible individuals (figure 2E, online supplemental figure S6). TB burden gradually shifted to older adults. The proportion of older adults (≥60 years) among those incident TB cases nationally would steadily rise from 46.86% in 2020 to 80.51% in 2050, the year in which older adults would account for 38.8% of the Chinese population (online supplemental figure S7).

For PSI vaccination scenarios targeting adolescents (15 years), young adults (30 years), middle-aged adults (45 years) or older adults (60 years) assuming lifelong protection, the pairwise comparison found that the scenarios were statistically significantly different from one another for projected epidemiological outcomes. The modelled older adult vaccination had 13 193 TB cases (95% CI: 5902 to 22 708) and 332 TB-related deaths (178 to 436) averted per million vaccine doses, which were substantially higher than targeted vaccination scenarios toward the other three age groups (figure 2F, online supplemental table S10). There was also a distinct difference in ICERs across the cohorts assessed. Vaccinating 60-year olds had the lowest cost per DALY averted from both healthcare sector and societal perspectives (online supplemental tables S15 and S16).

The impact of targeted vacation for older adults on the TB epidemic was lower than that of mass vaccination, but high absolute numbers of cumulative cases and deaths could still be averted. With PSI efficacy and 20-year protection, it would prevent 8.01 million TB cases (5.82 to 11.8) and 0.20 million TB-related deaths (0.17 to 0.26) during the 2024–2050 time horizon (table 1). In 2050, the IRR and MRR compared with the status quo were 21.7% (19.9% to 23.2%) and 26.3% (24.1% to 27.6%), respectively (figure 2G, online supplemental table S11). In contrast, mass vaccination irrespective of infection status (P&PI efficacy) was considered to be the most effective strategy for lowering TB-related morbidity and mortality. With a 20-year protection setting, it could avert cumulative 32.7% (30.6% to 35.1%) and 32.0% (30.4% to 34.6%) of TB cases and deaths, respectively (table 1). In 2050, the IRR and MRR were 42.7% (37.8% to 53.6%) and 39.9% (37.5% to 44.5%), respectively (figure 2H, online supplemental table S11). In addition, most vaccine scenarios for older adults had a lower NNV per case and per death averted than those for all-age population. For example, assuming PSI efficacy and 20-year protection, the estimated NNV per case averted for targeted vaccination was 13 (8 to 29) (online supplemental table S12).

Targeted vaccination with PSI efficacy was identified as the most CE strategy over the 2024–2050 time horizon. In a 20-year protection setting, it resulted in an ICER of US$4387 (2218 to 10 085) per DALY averted (table 1).

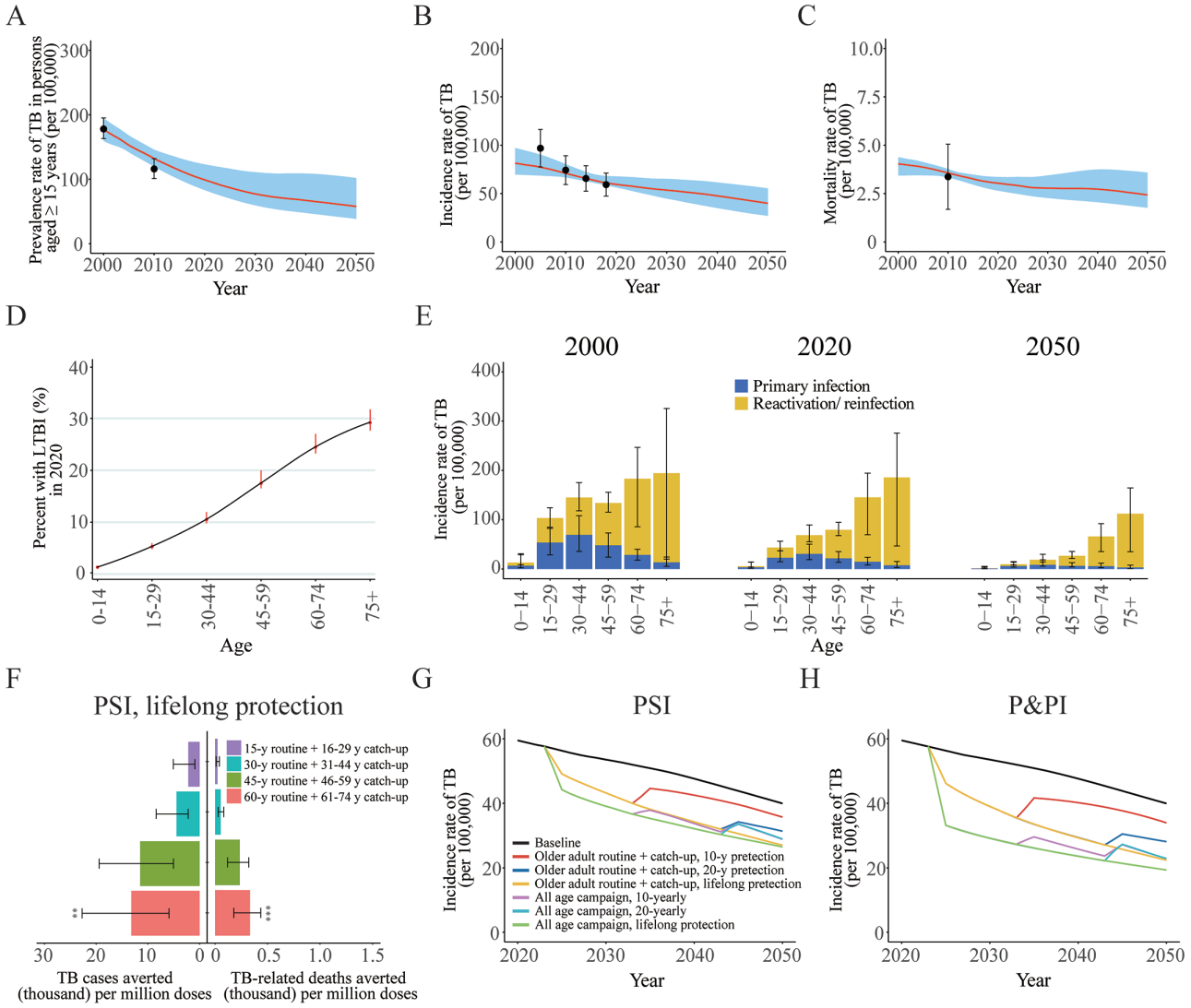

Figure 2 Modelling epidemiological impact of Vaccae vaccination in China. Model calibration for prevalence rate of microbiologically positive TB in persons aged ≥15 years (A), incidence rate (B) and mortality rate (C) of TB in the general population. (D) Estimated per cent of LTBI by age group in 2020. (E) Estimated incident rate of TB by age groups in 2000, 2020 and 2050. (F) Projected TB cases and deaths averted by targeted vaccination with Vaccae toward 15-year, 30-year, 45-year and 60-year population, with PSI efficacy and assumed lifelong protection. (G)–(H) Projected TB incidence over 2024–2050 for the 'no new vaccine' (black line) and vaccination scenarios (colour lines) for older adult or all age population, with PSI or both P&PI efficacy. Data are presented as median and 95% CI. TBI, latent TB infection; P&PI, preinfection and postinfection; PSI, postinfection; TB, tuberculosis.

The CCA and CDA were 2022 (915 to 5279) and US$83 733 (49 337 to 173 388), respectively (online supplemental table S17). In contrast, mass vaccination led to an ICER of US$7315 (4259 to 15 860) compared with the status quo but an ICER of US$21 450 (12 797 to 42 019) compared with the next best strategy (table 1). When productivity loss was included (societal perspective), the ICER of mass vaccination with PSI efficacy would become close to 1 × GDP per capita when compared with targeted vaccination (online supplemental table S18). Vaccination with hypothetical P&PI efficacy might both have a maximum impact, but costs remained high. Due to the high price and low coverage, vaccination with Vaccae provided through the private market would be more costly and less CE (online supplemental tables S19 and S20). The cost-effectiveness findings did not change if the time horizon was extended to 2100 (online supplemental tables S21 and S22). In addition, for a lower CET (0.63×GDP per capita), targeted vaccination with PSI vaccine remained the most CE (online supplemental tables S23 and S24).

The threshold analysis estimated the maximum price for the vaccine at which it would be CE with different efficacies and durations of protection (figure 3A–D). Generally, the median threshold prices below which the vaccination would be deemed CE were higher for PSI vaccine profiles than for P&PI vaccine profiles. For older adult vaccination with PSI vaccine, it had a 'CE price' of US$78.7/dose (37.2 to 122.5) at 54.7% efficacy and 20-year duration, reflecting the high treatment

Table 1 Epidemiological and economic impacts of introducing fully government-funded national Vaccae vaccination in China over 2024–2050.

Strategy	TB cases (million)		TB-related deaths (million)		Cost (US$ million)	DALY (million)		
No Vaccae (status quo)	45.59 (34.20 to 74.18)		1.02 (0.87 to 1.27)		40 352 (30 942 to 64 094)	24.5 (20.7 to 32.6)		
	TB cases averted		**TB-related deaths averted**		**Incremental cost (US$ million)**	**DALY averted* (million)**	**ICER (US$ per DALY averted)**	
	n (million)	**%**	**n (million)**	**%**			**vs status quo**	**vs next best strategy†**
Vaccae with 10-year protection								
PSI, older adult (60-year routine + 61–74-year catch-up)	5.30 (3.97 to 7.93)	11.7 (9.4 to 12.9)	0.13 (0.11 to 0.17)	13.0 (11.9 to 14.0)	18 305 (12 172 to 39 281)	2.79 (2.32 to 3.67)	6723 (3829 to 14 098)	6724 (3831 to 14 099)
P&PI, older adult (60-year routine + 61–74-year catch-up)	7.61 (5.72 to 11.3)	16.6 (14.0 to 18.7)	0.19 (0.15 to 0.26)	18.3 (17.0 to 20.7)	123 403 (120 282 to 125 036)	4.01 (3.32 to 5.41)	30 797 (22 387 to 37 671)	90 458 (50 443 to 116 174)
PSI, all age (15–74 years and 10-yearly campaigns)	9.21 (7.03 to 13.8)	20.1 (17.8 to 21.4)	0.21 (0.17 to 0.27)	20.3 (19.0 to 21.6)	52 908 (37 527 to 113 380)	4.46 (3.81 to 5.96)	11 815 (7506 to 24 567)	20 135 (13 367 to 40 165)
P&PI, all age ((15–74 years and 10-yearly campaigns)	14.2 (11.1 to 22.2)	31.1 (29.2 to 33.6)	0.30 (0.25 to 0.41)	30.0 (28.3 to 32.5)	538 652 (532 094 to 541 311)	7.05 (6.01 to 9.63)	76 430 (55 350 to 89 932)	118 681 (84 464 to 146 564)
Vaccae with 20-year protection								
PSI, older adult (60-year routine + 61–74-year catch-up)	8.01 (5.82 to 11.8)	17.7 (13.4 to 20.0)	0.20 (0.17 to 0.26)	20.0 (18.1 to 21.6)	16 715 (9539 to 37 704)	3.83 (3.16 to 5.04)	4387 (2217 to 10 085)	4387 (2218 to 10 085)
PSI, all age (15–74 years and 20-yearly campaigns)	9.74 (7.40 to 14.4)	21.2 (18.4 to 22.6)	0.22 (0.18 to 0.28)	21.8 (20.2 to 23.1)	33 663 (22 432 to 74 632)	4.63 (3.91 to 6.10)	7315 (4259 to 15 860)	21 450 (12 797 to 42 019)
P&PI, older adult (60-year routine + 61–74-year catch-up)	11.3 (8.28 to 16.5)	24.7 (19.9 to 27.5)	0.28 (0.23 to 0.38)	27.8 (25.7 to 30.3)	120 883 (116 642 to 123 262)	5.42 (4.44 to 7.05)	22 205 (16 616 to 27 715)	69 036 (40 418 to 86 908)
P&PI, all age (15–74 years and 20-yearly campaigns)	14.9 (11.7 to 23.0)	32.7 (30.6 to 35.1)	0.32 (0.27 to 0.43)	32.0 (30.4 to 34.6)	355 192 (348 620 to 357 923)	7.29 (6.22 to 9.87)	48 746 (35 414 to 57 384)	96 300 (65 229 to 118 322)
Vaccae with lifelong protection								
PSI, older adult (60-year routine + 61–74-year catch-up)	8.35 (6.05 to 12.2)	18.4 (13.9 to 20.9)	0.21 (0.17 to 0.27)	20.8 (18.8 to 22.5)	16 556 (9263 to 37 547)	3.91 (3.23 to 5.17)	4234 (2097 to 9833)	4235 (2098 to 9834)
PSI, all age (15–74 years and 1 campaign)	10.2 (7.68 to 14.9)	22.0 (18.9 to 23.6)	0.23 (0.19 to 0.30)	22.8 (21.1 to 24.2)	23 204 (14 279 to 53 276)	4.76 (3.99 to 6.22)	4933 (2644 to 11 071)	8788 (4675 to 17 409)
P&PI, older adult (60-year routine + 61–74-year catch-up)	11.7 (8.58 to 17.2)	25.7 (20.6 to 28.6)	0.29 (0.24 to 0.39)	28.8 (26.6 to 31.5)	120 639 (116 258 to 123 078)	5.55 (4.53 to 7.20)	21 667 (16 207 to 27 089)	129 082 (62 193 to 276 707)
P&PI, all age (15–74 years and 1 campaign)	15.6 (12.1 to 23.9)	33.9 (31.6 to 36.5)	0.34 (0.29 to 0.45)	33.4 (31.7 to 36.2)	231 423 (224 826 to 234 259)	7.45 (6.34 to 10.1)	31 091 (22 428 to 36 845)	75 854 (47 425 to 96 178)

Data are presented as median and 95% CI.
*Strategies were in ascending order of effectiveness.
†WTP was set at 1 × nationalpGDP (US$12 458).
DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio, was calculated from healthcare sector perspective, with government contract price of US$30/dose, and costs and effectiveness discounted with 3% per year; pGDP, gross domestic product per capita; TB, tuberculosis; WTP, willingness to pay.

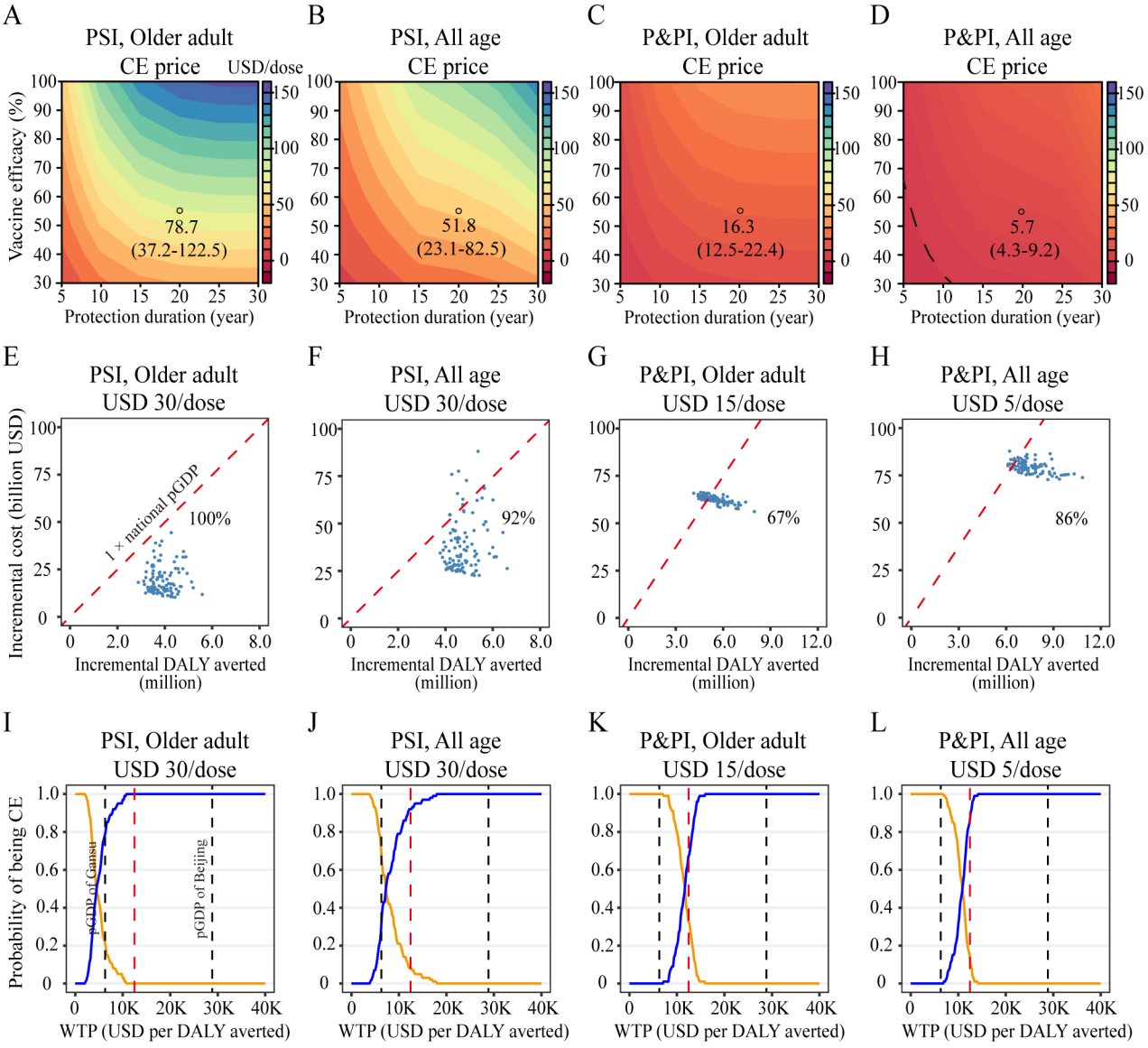

Figure 3 Cost-effectiveness analyses of Vaccae vaccination in China. (A)–(D) Contour plots showing the CE vaccine prices that lead to an average incremental cost per DALY equal to 1 × GDP per capita for specified vaccine efficacy and protection duration settings. The values below the dashed black line (D) denote that no price would be CE. (E)–(H) Cost-effectiveness planes for vaccination strategies. (I)–(L) Cost-effectiveness acceptability curves. CE, cost-effective; DALY, disability-adjusted life year; GDP, gross domestic product per capita; PSI, postinfection; WTP willingness to pay; P&PI, both preinfection and postinfection.

costs averted (figure 3A). For all-age vaccination with PSI vaccine, it would be CE at a price of US$51.8 (23.1 to 82.5) (figure 3B). Although all-age vaccination with hypothetical P&PI vaccine might have a maximum impact (>40% IRR in 2050, online supplemental table S11), the vaccine cannot exceed US$5/dose to be CE (CE price: 5.7 (4.3 to 9.2)) (figure 3D). In one-way sensitivity analyses, changing input parameters with upper and lower limits showed that the vaccine price, efficacy and protection duration were the key inputs in the economic model (online supplemental table S8). In PSA (figure 3E, F1 and J), PSI vaccine profiles at price of US$30/dose were likely to be CE from the healthcare sector perspective (92%–100% probability of cost effectiveness). However, P&PI vaccine profiles would only be CE (67%–86% probability of cost effectiveness) at lower prices (figure 3G, H, K and L). Results of cost-effectiveness analyses from the societal perspective are presented in online supplemental figures S9 and S10. Furthermore, at a lower CET (0.63×GDP per capita), PSI vaccine remained CE from the healthcare sector perspective with 58%–91% probability at price of US$30/dose, but either from the healthcare sector or society perspective, P&PI vaccine need to reduce vaccine prices further to maintain previous probability (online supplemental figures S11 and S12).

The models tracked the Chinese population eligible for vaccination from 2024 to 2050. Deploying Vaccae with 90% coverage among older adults with LTBI, a total of 104.34 (78.58 to 211.06) million older adults were predicted to receive the vaccine. The programme would

lead to a total vaccination budget of US$27.34 (21.11 to 53.13) billion (US$22.55 billion after discounting (17.55 to 43.36)). Most programme costs are concentrated in the first year of vaccination: over US$10 billion in 2024. It would generate a total net cost of US$16.72 (9.54 to 37.70) billion over the 27-year period, from the healthcare sector perspective. The annual expenditure by the national vaccination programme and medical costs averted are also shown in table 2. Accounting for savings on productivity loss averted from the societal perspective, the net cost of the vaccination programme among older adults would be US$10.99 billion (2.92 to 32.10) (online supplemental table 28). Budget impact analyses were performed under various scenarios to explore plausible futures of new TB vaccines (online supplemental tables S25-S37).

DISCUSSION

For the ageing, reactivation-driven TB epidemic in China, new TB vaccine is a promising intervention for TB control. Policy-makers are facing challenges and we hope our analysis can help optimise future policy. As in this study, we demonstrate that: targeted vaccination strategy towards older adults would be a highly CE epidemic control agent in China; mass vaccination strategy could be more effective but costs remained high; and reduction in vaccine price is necessary to ascertain a good economic return for the future vaccination programme.

Our study is not the first economic evaluation of TB vaccination in China.[21 22] We searched articles in PubMed, up to 1 April 2023, with the terms ('TB' OR 'tuberculosis' (mesh)) AND (vaccin* OR immuniz* OR immunis* OR 'tuberculosis vaccines' (mesh)) AND ('mathematical model*' OR 'models, theoretical' (mesh)) AND ('cost-effectiveness' OR 'costs and cost analysis' (mesh)). Our search yielded more than twenty articles. The literature suggested that potential TB vaccines might be effective but differences in strategies and CET varied greatly across countries.[23] To the best of our knowledge, this is the first study to investigate the value of a new TB vaccine that is available on the market and a vaccination programme that could be quickly implemented. A large strength of our findings is the consistency throughout the multiple scenario analyses performed. Indeed, we found that targeted vaccination of older adults was consistently robust and CE in the study under each scenario. In addition, we simultaneously compared TB vaccinees in all stages through the adolescent to older adult life course. These calculations illustrated the significance of the age-specific strategy. The budgetary feasibility of vaccination programmes has also been considered for the prospective application of this vaccine in the context of China.

The adolescent strategy aimed to vaccinate 15-year olds in whom TB incidence was increasing while infant BCG vaccination became ineffective.[4] A previous modelling study suggested that PSI vaccines would have a negligible impact if delivered to adolescents in China, as the TB incidence reduction with older adult vaccination was 157.5 (119.3 to 225.6) times greater than that with adolescent vaccination.[11] Our projected outcomes are consistent with their estimates regarding the TB incidence reduction, as well as the downstream economic interpretation. In contrast, a study modelled that adolescent vaccination of M72/AS01$_E$ (also a PSI vaccine type) in South Africa could be CE.[18] This may be explained by the epidemiological differences between the two countries, such as high LTBI prevalence among adolescents and HIV syndemic in South Africa.[24 25] The contribution of incident TB cases from people living with HIV (PLHIV) in China was only 2%,[1] and, therefore, including HIV coinfection in the model is unlikely to affect our conclusions. This study is timely to guide vaccination decisions, as well as design in phase IV trials among high-risk populations.

Aside from vaccines, there is another option for LTBI: TB preventive treatment (TPT, chemoprophylaxis with rifamycin-based preferred regimens).[26] Community-based active case finding (ACF, usually among high-risk populations such as close contacts of patients with TB, healthcare workers (HCWs), PLHIV, etc) is essential for early identification of new cases of active TB,[27] as well as for ruling out active TB before providing TPT. A modelling study indicated that the 2035 target of the 'end TB' goal might be achieved in China if (1) nationwide ACF (in the particular study, ACF denotes active screening and finding LTBIs among the 'entire population') and TPT were completed within 5 years; (2) ACF and TPT were completed in high incidence areas within 2 years and (3) TPT completed among the older adults within 2 years.[21] However, the administration of chemoprophylaxis to the whole LTBI population carries critical ethical challenges. Individuals receiving TPT bear the risk of adverse effects such as severe or even fatal drug-induced hepatitis.[28] Unfortunately, TPT coverage is low even in HCWs in China.[29] In addition, potent new diagnostic tools, such as *M. tuberculosis* culturing and Xpert MTB/RIF tests, are limited to major hospitals.[30] According to our study, vaccination with Vaccae is insufficient to control the disease to meet the WHO's goals. The combined effects of vaccination and ACF could provide an interesting topic for future research.

Vaccine price and/or payment mechanism are important factors for TB vaccination programme scale-up. Currently, Vaccae is classified as a category II vaccine and provided through the private market at a high out-of-pocket price (US$62/dose), resulting in low vaccine coverage across the country. Inclusion of a vaccine into the government-funded vaccination programme and reducing out-of-pocket costs will improve vaccination coverage. China's basic public health services, including the expansion of government-funded vaccination programmes, are currently undergoing reforms. For example, many provinces have established fully government-funded seasonal influenza vaccination programmes in older adults, covered by medical or social insurance reimbursement systems.[31]

Table 2 Budget impact of introducing Vaccae vaccination programme among older adults in China during 2024–2050

Year	Screened population* (million)	Vaccinated population (million)	Vaccination programme budget† (US$ million)	Direct medical costs averted (US$ million)	Net cost‡ (US$ million)
Undiscounted					
2024	216.46 (216.18 to 216.63)	40.15 (31.77 to 75.75)	10 303 (8277 to 18 906)	12.9 (9.03 to 19.0)	10 291 (8265 to 18 896)
2025	22.12 (22.09 to 22.13)	3.49 (2.67 to 6.90)	906 (707 to 1729)	62.0 (44.0 to 91.7)	846 (627 to 1677)
2026	21.73 (21.71 to 21.74)	3.35 (2.55 to 6.67)	870 (677 to 1673)	107 (76.9 to 160)	768 (538 to 1582)
2027	20.65 (20.63 to 20.66)	3.11 (2.36 to 6.24)	808 (627 to 1565)	150 (108 to 223)	668 (433 to 1436)
2028	23.88 (23.86 to 23.89)	3.51 (2.65 to 7.09)	914 (706 to 1780)	191 (138 to 284)	733 (459 to 1616)
2029	23.62 (23.60 to 23.63)	3.39 (2.55 to 6.90)	884 (680 to 1732)	231 (165 to 342)	659 (381 to 1533)
2030	24.36 (24.33 to 24.37)	3.41 (2.55 to 6.99)	892 (684 to 1756)	267 (192 to 396)	630 (335 to 1524)
2031	23.27 (23.25 to 23.28)	3.18 (2.37 to 6.56)	834 (637 to 1649)	300 (216 to 446)	538 (240 to 1386)
2032	22.59 (22.57 to 22.60)	3.02 (2.23 to 6.25)	791 (602 to 1573)	331 (240 to 491)	465 (164 to 1281)
2033	22.08 (22.06 to 22.09)	2.88 (2.12 to 5.99)	756 (574 to 1509)	360 (262 to 533)	398 (101 to 1191)
2034	20.75 (20.74 to 20.76)	2.64 (1.94 to 5.52)	694 (525 to 1392)	388 (282 to 570)	301 (19 to 1049)
2035	18.79 (18.77 to 18.80)	2.33 (1.70 to 4.90)	614 (463 to 1236)	412 (300 to 605)	205 (–76 to 870)
2036	18.07 (18.06 to 18.08)	2.18 (1.59 to 4.61)	577 (434 to 1165)	433 (315 to 635)	147 (–133 to 779)
2037	16.84 (16.83 to 16.85)	1.98 (1.44 to 4.21)	524 (393 to 1064)	452 (329 to 661)	74 (–198 to 660)
2038	16.91 (16.90 to 16.92)	1.93 (1.40 to 4.13)	514 (384 to 1045)	469 (341 to 684)	49 (–228 to 626)
2039	17.89 (17.88 to 17.90)	1.99 (1.43 to 4.27)	530 (395 to 1082)	483 (350 to 703)	52 (–234 to 650)
2040	18.58 (18.57 to 18.59)	2.00 (1.44 to 4.33)	535 (399 to 1099)	495 (358 to 719)	49 (–243 to 656)
2041	19.43 (19.42 to 19.44)	2.03 (1.46 to 4.42)	544 (406 to 1123)	504 (364 to 732)	51 (–246 to 671)
2042	21.04 (21.03 to 21.05)	2.13 (1.53 to 4.67)	573 (427 to 1188)	511 (369 to 741)	75 (–231 to 730)
2043	18.76 (18.75 to 18.77)	1.84 (1.32 to 4.06)	497 (370 to 1034)	515 (371 to 748)	–16 (–294 to 571)
2044	19.78 (19.77 to 19.79)	1.88 (1.34 to 4.17)	509 (378 to 1063)	510 (365 to 742)	5 (–276 to 603)
2045	20.86 (20.85 to 20.87)	1.92 (1.36 to 4.28)	521 (387 to 1093)	485 (348 to 710)	48 (–232 to 650)
2046	22.55 (22.53 to 22.56)	2.00 (1.42 to 4.50)	546 (406 to 1151)	463 (332 to 683)	99 (–182 to 722)
2047	23.87 (23.85 to 23.88)	2.05 (1.45 to 4.64)	561 (416 to 1186)	444 (319 to 659)	131 (–145 to 771)
2048	22.87 (22.86 to 22.88)	1.89 (1.34 to 4.32)	521 (386 to 1106)	428 (306 to 638)	109 (–151 to 703)
2049	23.60 (23.59 to 23.61)	1.89 (1.33 to 4.32)	521 (386 to 1110)	413 (295 to 618)	125 (–129 to 718)
2050	24.54 (24.52 to 24.54)	1.89 (1.33 to 4.36)	525 (388 to 1121)	398 (284 to 600)	142 (–107 to 740)
Total	765.87 (765.14, 766.24)	104.34 (78.58 to 211.06)	27 340 (21 113 to 53 132)	9808 (7128 to 14 396)	18 181 (8716 to 44 293)
Discounted at 3% per year					

Continued

Table 2 Continued

Year	Screened population* (million)	Vaccinated population (million)	Vaccination programme budget† (US$ million)	Direct medical costs averted (US$ million)	Net cost‡ (US$ million)
Total	765.87 (765.14 to 766.24)	104.34 (78.58 to 211.06)	22 545 (17 550 to 43 359)	6301 (4580 to 9254)	16 715 (9539 to 37 704)

Data are presented as median and 95% CI.
*Screening population: 60-year routine and 61–74-year catch-up in 2024.
†Vaccination programme budget = screening cost + vaccine cost (US$30/dose, 6 doses per course, plus 5% buffer stock and 15% vaccine wastage) + delivery and administrative cost.
‡Net cost (healthcare sector perspective) = vaccination programme budget – direct medical costs averted.

Several cities have diverse payment mechanisms for expanding HPV vaccination, including partial coverage by governmental subsidy or partial incorporation in basic medical insurance.[32] The experience from other vaccines provides a reference for the future development of TB vaccination programmes in China. In addition, vaccine price is a key determinant of cost effectiveness. Policy-makers in China should negotiate with pharmaceutical companies to secure a good price through bulk purchasing contracts.

Our study shows that if the status quo strategy is maintained, the TB burden in China will decline but cannot reach the goals of the WHO, which is to reduce the incidence rate of TB by 80% and 90% in 2030 and 2035, respectively, compared with 2015, and by less than one case per million individuals per year in 2050.[2] According to the simulation results, implementing government-funded national Vaccae vaccination among older Chinese adults can generate good health and economic value, and can remarkably shorten the gap between our expectation and China's 'end TB' goals.[33] It would facilitate the strategy plan for TB vaccination and reimbursement decision making for China. The framework may also prove valuable for the identification of suitable vaccination strategies for other countries.

Admittedly, our study has several limitations. First, our model considered the entire country as a single population. As a huge country, China has substantial heterogeneities of TB across different regions. Using fixed values for some parameters may not be appropriate. Because of a lack of adequate epidemiological data for calibration, it is difficult to construct models to accurately fit the province-specific settings. Second, the model does not account for sex differences, immunosenescence, drug-resistance, imperfect test specificity of screening, vaccine acceptance and compliance. These issues are beyond the scope of this research and may be opportunities for future research. Third, the vaccine was assumed to provide 'all-or-nothing' protection, yet the alternative 'degree/leaky' (efficacy was implemented as a reduction in natural history) assumption might reduce effect estimates.[9] Monitoring real-world vaccine effectiveness and its durability is essential. Our model may be adapted as more information emerges. Last but not least, although we have performed extensive uncertainty and sensitivity analyses, there may still be other factors influencing of vaccination impacts that we did not measure. For example, unpredictable future population policies in China might cause significant variations in future fertility rates and age structures.

In summary, government-funded national Vaccae vaccination represents a CE choice from the Chinese state perspective. Policy-makers in China should prioritise the elderly and, where possible, secure affordable prices. Developing or adopting vaccines with better characteristics and comprehensive prevention and control measures would be the focus for future TB vaccination promotion.

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