Age-targeted tuberculosis vaccination in China and implications for vaccine development: a modelling study

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Summary

Background Tuberculosis is the leading single-pathogen cause of death worldwide, and China has the third largest number of cases worldwide. New tools, such as new vaccines, are needed to meet WHO tuberculosis goals. Tuberculosis vaccine development strategies mostly target infants or adolescents, but given China's ageing epidemic, vaccinating older people might be important. We modelled the potential impact of new tuberculosis vaccines in China targeting adolescents (15–19 years) or older adults (60–64 years) with varying vaccine characteristics to inform strategic vaccine development.

Methods A *Mycobacterium tuberculosis* transmission model was calibrated to age-stratified demographic and epidemiological data from China. Varying scenarios of vaccine implementation (age targeting [adolescents or older adults] and coverage [30% or 70%]) and characteristics (efficacy [40%, 60%, or 80%], duration of protection [10 years or 20 years], and host infection status required for efficacy [pre-infection, post-infection in latency, post-infection in latency or recovered, or pre-infection and post-infection]) were assessed. Primary outcomes were tuberculosis incidence and mortality rate reduction in 2050 in each vaccine scenario compared with the baseline (no new vaccine) scenario and cumulative number needed to vaccinate (NNV) per case or death averted, 2025–50.

Findings By 2050, results suggest that 74·5% (uncertainty interval [UI] 70·2–78·6) of incident tuberculosis cases in China would occur in people aged 65 years or older, and 75·1% (66·8–80·7) of all cases would be due to reactivation, rather than new infection. All vaccine profiles delivered to older adults had higher population-level impact (reduction of incidence and mortality rates) and lower NNV per case and per death averted than if delivered to adolescents. For an intermediate vaccine scenario of 60% efficacy, 10-year protection, and 70% coverage, the reduction of tuberculosis incidence rates with older adult vaccination was 1·9 times (UI 1·5–2·6) to 157·5 times (119·3–225·6) greater than with adolescent vaccination, and the NNV was 0·011 times (0·008–0·014) to 0·796 times (0·632–0·970) lower. Furthermore, with older adult vaccination, post-infection vaccines provided substantially greater mortality and incidence rate reductions than pre-infection vaccines.

Interpretation Adolescent-targeted tuberculosis vaccines, the focus of many development plans, would have only a small impact in ageing, reactivation-driven epidemics such as those in China. Instead, an efficacious post-infection vaccine delivered to older adults will be crucial to maximise population-level impact in this setting and would provide an important contribution towards achieving WHO goals. Older adults should be included in tuberculosis vaccine clinical development and implementation planning.

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Introduction

Despite progress in tuberculosis prevention and care during the past two decades,[1] China remains the third largest contributor to the global burden of new tuberculosis cases, accounting for 889 000 (761 000–1 030 000) new cases in 2017.[2] Increasing public-sector investment in tuberculosis care has contributed to the detection of 87% of cases and treatment success in 94% of cases.[1,2] Given the substantial achievements in the scale-up of existing tuberculosis care and prevention options, mathematical modelling suggests that gains possible from further investment in existing tools alone are unlikely to reach WHO tuberculosis goals for 2025 (50% incidence reduction *vs* 2015), 2035 (90% reduction *vs* 2015), and 2050 (elimination, defined as less than one case per million people per year) in China.[3–7] Innovative tools, such as new tuberculosis vaccines, will be essential for achieving these targets.[3–6]

There have been increasingly rapid advances in the development of new tuberculosis vaccines in the past few years, with 12 candidates in clinical trials, including four in phase 2B/3.[8] 2018 was an important year for tuberculosis vaccine development, with results from two new preclinical studies,[9] the late-stage H4 versus Bacillus Calmette–Guérin (BCG) revaccination[10] and M72/AS01$_E$ clinical trials,[11] and with results anticipated from the *Mycobacterium vaccae* trial (NCT01979900). Tuberculosis vaccine target product profiles outline the desired vaccine characteristics and recipient populations for new vaccines, and clinical development plans provide the pathway to achieving these

Research in context

Evidence before this study

We searched the tuberculosis vaccine epidemiological modelling literature up to July 19, 2017. We searched PubMed, Embase, and the WHO Global Health Library with the search terms ("models, theoretical"[mesh]) OR "mathematical model*") AND (TB OR tuberculosis OR "tuberculosis"[mesh]) AND (vaccin* OR immuniz* OR immunis* OR "tuberculosis vaccines"[mesh]). Previous studies suggest that targeting new vaccines to adolescents would have a greater impact than infant vaccination; however, no previous research has explored the potential impact of new tuberculosis vaccines targeting older adults. Only two modelling studies have explored the impact of new tuberculosis vaccines in China, one compared vaccination at birth to all-age mass vaccination and one was assumed mass vaccination. Results suggested that mass vaccination, particularly post infection, might be important for elimination in China. However, crucially, age specificity in demographic and epidemic dynamics in China has not been addressed in vaccine models.

Added value of this study

To the best of our knowledge, our research is the first to assess the potential effect of new tuberculosis vaccines targeting older adults (aged 60–64 years) and to compare this approach with adolescent vaccination, which is the age group that most vaccination strategies have focused on. This data-driven model is calibrated to age-stratified data from WHO and the UN population division, as well as empirical studies on tuberculosis demographics, prevalence, mortality, notification, and incidence, including temporal trends, and it incorporates empirical data on non-random age mixing. This study is the first to show that older adult vaccination with new tuberculosis vaccines is likely to be crucial to maximising impact in settings such as China and strengthens the conclusions from previous studies suggesting that vaccines effective post-infection will be needed in China.

Implications of all the available evidence

Although adolescent vaccination might be a suitable global-level strategy, important differences in country-level epidemiology and demography might mean that adolescent-targeted tuberculosis vaccines have low impact in ageing, reactivation-driven tuberculosis epidemics such as that in China. In these settings, an efficacious post-infection vaccine delivered to older adults will be crucial to maximise population-level benefits. Older adults should be included in tuberculosis vaccine clinical development and implementation planning.

criteria. Mathematical modelling provides a systematic framework to explore the potential future impact of vaccine characteristics and implementation strategies to inform target product profile development. The impact achieved might vary by epidemiological and demographic setting,[12,13] therefore country-specific models are needed for appropriate vaccine selection and implementation planning, including age targeting. A phase 3 clinical trial of a prophylactic tuberculosis vaccine candidate has been conducted in China (NCT01979900) and therefore, modelling to clarify the potential benefit of new tuberculosis vaccines and different implementation strategies in China is urgently needed.

Traditional vaccine development pathways focused on infant vaccination; however, in the past few years, there has been a shift towards adolescents and adults,[14] supported by insights from mathematical modelling.[13,15] Yet populations aged 60 years and older remain neglected in tuberculosis vaccine development pathways, despite high tuberculosis disease burden in older age groups in several countries with different levels of socio-demographic development.[16] Given the dramatic and ongoing population ageing in China,[17] and higher prevalence of latent infection in older populations,[18] a shift in burden to older age groups could be expected.

According to a systematic review of modelling studies on tuberculosis vaccines, although vaccination of infants has been compared with adolescents or people of all ages, no model explores the potential impact of new tuberculosis vaccines for older age groups.[12] Dynamics of tuberculosis disease and demographics are intimately linked, and influence the effect of age-targeted interventions.[13] Only two studies have modelled new tuberculosis vaccines in China,[19,20] and neither accounted for age specificities in epidemiology or demographics. Furthermore, in these studies, vaccination was either at birth or all ages, and vaccine characteristics modelled were unclear or unrealistic (eg, 100% vaccine efficacy).[19,20] Although it did not explore vaccines, a modelling study in China showed that existing tuberculosis interventions alone would not be enough to reach WHO 2035 targets, whereas development of preventive therapy for adults aged 65 years or older could be transformational.[5] We aimed to estimate future trends in tuberculosis epidemiology and the impact of new tuberculosis vaccines in China with varying vaccination scenarios.

Methods

Study design

This prospective modelling study assessed the effect of varying implementation strategies (age targeting and coverage) and vaccine characteristics (efficacy, duration of protection, and host infection status required for efficacy) of new tuberculosis vaccines on the tuberculosis epidemic in China.

Model structure and calibration

An age-stratified population-level compartmental deterministic transmission model calibrated to China's tuberculosis epidemic was developed in R, based on the model developed by Knight and colleagues (appendix).[15] The model has five populations with different infection

See Online for appendix

states: uninfected, latent infection, bacteriologically positive active tuberculosis disease, bacteriologically negative active tuberculosis disease, and recovered from active tuberculosis disease. Transitions between states represent acquisition of infection; development of primary, reactivation, or relapse disease; effective detection and treatment; or natural cure (appendix). Neonates are assumed to be in the uninfected state at birth, all-cause mortality is in all states, and tuberculosis mortality is in active disease states. Uninfected, latent, and recovered states comprised both unvaccinated and vaccinated strata. Age was modelled in single years from 0 to 100. Age categories for vaccine implementation were adolescents (15–19 years) or older adults (60–64 years).

Main age categories for parameters were children (0–14 years), adolescents and adults (15–64 years), and people aged 65 years or older. We identified age-stratified natural history parameter prior ranges from available data (appendix). Data were unavailable for immunosenescence in people aged 65 years or older, but HIV has been proposed as a proxy.[21] Therefore, for parameters without available data for this age group, we assumed the lower bounds of the priors to be equal to HIV-negative populations and the upper bounds equal to mildly immunocompromised HIV-positive populations. When the HIV-positive and HIV-negative ranges overlapped, the upper bound of the prior for adults aged 65 years or older was equivalent to the upper bound of the HIV-positive parameter range. We captured temporal evolution of the age distribution of infection and disease historically and prospectively by calibration to age-stratified epidemiological and demographic data using age-specific natural history parameters and contact patterns. To provide a more gradual transition in reactivation, relapse, natural cure, and case detection parameters by age, we estimated parameters for people aged 55–64 years as the mean calibrated values of individuals aged 15–54 years and those aged 65 years or older. Heterogeneity in age-wise contact patterns was based on data from a study in southern China.[22] Treatment success was based on historical data, and assumed to plateau beyond 2011 because of the high success rates achieved (95%).[23] Case detection followed a generalised logistic function based on WHO 1990–2010 data.[23] BCG delivery was assumed to remain constant, so was not explicitly modelled.

We used a two-stage calibration process. The first stage was a manual calibration to UN 2010 and 2050 age-stratified demographic data and projections. The second stage used a method based on adaptive rejection approximate Bayesian computation (ABC)-Markov chain Monte Carlo (MCMC) using the *easyABC* package, modified to accept seed parameter values, to calibrate to historical epidemiological data (appendix).[24] To provide the temporal and age-stratified granularity required, we calibrated the model to 18 epidemiological data ranges: China's bacteriologically positive prevalence rates (ages ≥15, 15–29, 30–59, and ≥60 years) in 2000 and 2010,[1] 2010 notification rates (all-age and ages 0–14, 15–54, 55–64, and ≥65 years),[25] 2010 mortality rates (all-age and ages 0–14, 15–59, and ≥60 years),[26] and 2010 all-age incidence.[23] We first identified potential starting points for the MCMC chains from the 20 highest likelihood parameter sets from 1 million samples randomly selected from uniform priors, assuming the data were independently normally distributed. Because the underlying distributions of the data are unclear, in particular for the WHO-estimated incidence, we then used an ABC-based approach. We ran a series of ABC-MCMC chains seeding with acceptances from the previous chains and adapting the acceptance criterion iteratively from 13 datapoints to 18 datapoints until a full model fit to all 18 data ranges was achieved. Results and uncertainty intervals (UIs; defined as maximum and minimum values of outcomes from the 1000 model runs) were based on 1000 parameter sets randomly selected from the acceptances in the final set of ABC-MCMC runs.

Vaccine characteristics and implementation

We created 96 vaccine scenarios using combinations of two implementation characteristics (age targeting and coverage) and three vaccine characteristics (vaccine efficacy, host infection status required for efficacy, and duration of protection).

We explored two age-targeting scenarios: vaccination of adolescents (aged 15–19 years) and vaccination of older adults (60–64 years), implemented in 2025–50. In these scenarios, routine vaccination would be provided annually throughout this period to people aged 15 years or 60 years. Initial catch-up campaigns would be done in 2025–27 for people aged 16–19 years or 61–64 years.

We explored routine vaccine coverage of 30% and 70% of the target populations. Only people with active disease would be excluded from vaccination. We assumed annual coverage for catch-up campaigns to be a third of routine coverage. We assumed that there was no screening for latent infection before vaccination, but that each vaccine was only effective in the specified host infection status groups. Therefore, the proportion of people effectively immunised in a given year would be the product of coverage in hosts with the specified infection status and vaccine efficacy.

Vaccine efficacy was modelled as 40%, 60%, and 80% protective against development of tuberculosis disease (prevention of disease), based on expert opinion. Vaccination was modelled as all or nothing protection. We assessed vaccine protection with the following four host infection statuses: (1) uninfected individuals (pre-infection); (2) latently infected individuals (post-infection, latency only [PSI-L]): (3) individuals either latently infected or recovered from active disease (post-infection, latency and recovered [PSI-LR]): or (4) individuals either uninfected, latently infected, or recovered from active disease (pre-infection and post-infection [PPI]).

For the **UN Population Division World Population Prospects** see https://esa.un.org/unpd/wpp/Download/Standard/Population/

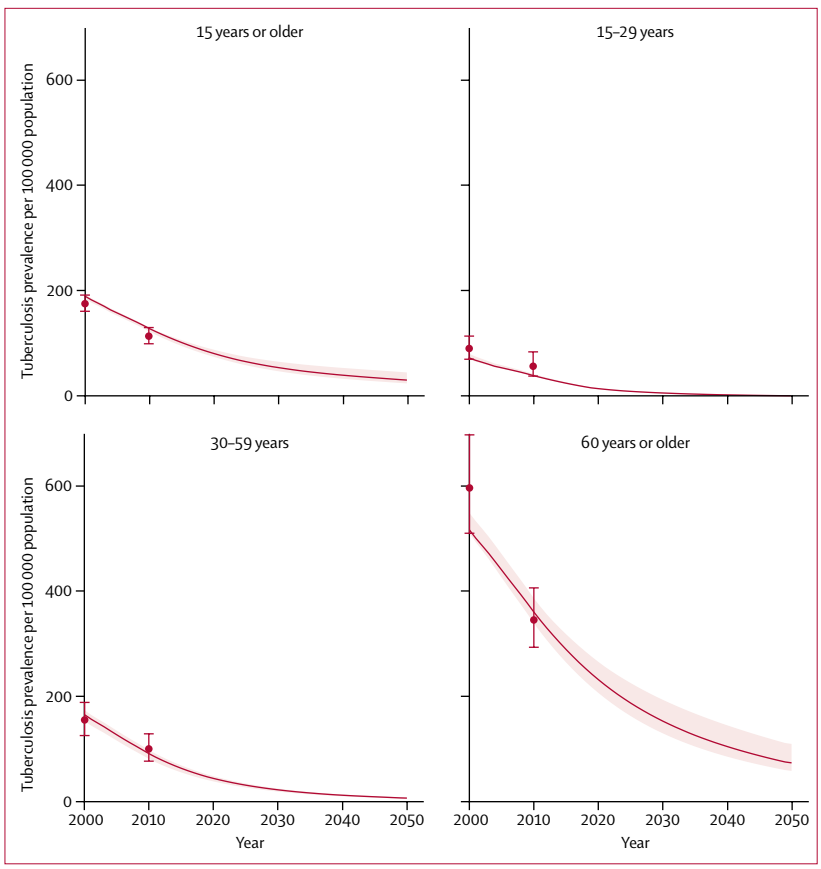


Figure 1: **Tuberculosis prevalence, 2000–50**
Modelled (lines and shading) and survey-based empirical data (points and vertical bars)[1] for microbiologically positive tuberculosis prevalence by age group. Shaded areas and vertical bars show uncertainty intervals. For calibration to other epidemiological and demographic calibration targets, see appendix.

The rate of vaccine waning was set so that the duration of vaccine protection was normally distributed with a mean of 10 years (SD 1) or 20 years (2). Modelled durations were based on expert opinion and the estimated duration of protection of neonatal BCG.[27] Waning returned the population to the equivalent unvaccinated state. To account for immunosenescence, an additional 2% annual waning was assumed for populations aged 65 years or older and was varied between 0% and 5% in sensitivity analyses.

All combinations of these characteristics and implementation strategies were explored. For reporting of some outcomes, an intermediate vaccination scenario was defined as 60% vaccine efficacy, 10-year protection, and 70% coverage. In primary analyses, vaccine characteristics were assumed unchanged by vaccination age, except immunosenescence in people aged 65 years or older. In sensitivity analyses, a high vaccination scenario vaccinating adolescents (aged 15–19 years) with 70% coverage, 80% efficacy, and 20 years of protection was compared with a low vaccination scenario vaccinating older adults (aged 60–64 years) with 30% coverage, 40% efficacy, and 10 years of protection.

Outcomes

We calculated epidemiological outcomes annually for 2000–50 in the baseline (no new vaccine) scenario. We calculated contribution by age group to annual incident cases as the proportion of total incident cases arising from a given age group. We annually estimated the proportion of incident disease due to new transmission versus reactivation. We estimated the population-attributable fraction (PAF) of each age group to annual *Mycobacterium tuberculosis* infections using methods described previously.[28] We estimated prevalence of latent infection by age for comparison to empirical data.[18]

Primary outcomes were the percentage tuberculosis incidence and mortality rate reduction in each vaccination scenario compared with the no new vaccine baseline in 2050. Secondary outcomes were cumulative number of tuberculosis cases or deaths averted in 2025–50 compared with baseline, and the cumulative number needed to vaccinate (NNV) per case or death averted in 2025–50. These outcomes were compared by age targeting and other vaccine characteristics.

Role of the funding source

The funder of the study was involved in development of the research question and commenting on the draft manuscript, but had no other role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and materials and had final responsibility for the decision to submit for publication.

Results

The model fitted overall and age-stratified data for demography and tuberculosis prevalence, notification, incidence, and mortality rates (figure 1; appendix). Modelled all-age infection prevalence was 15·7% (UI 12·8–18·7) in 2013, increasing almost linearly from 1·3% (1·0–1·6) in children aged 5–9 years to 37·0% (31·1–42·6) in people aged 70 years or older (appendix). Although not calibrated to these data, modelled age-stratified infection prevalence aligned closely with published QuantiFERON data.[18] At vaccine introduction, 2·2% (1·7–2·8) of people in the 15–19 years age group and 25·3% (20·5–30·2) of those in the 60–64 years age group were latently infected.

Between 2000 and 2050, a substantial shift was projected in the age distribution of incident tuberculosis cases, from 75·8% (UI 71·3–81·0) in adolescents and adults aged 15–64 years in 2000 to 74·5% (70·2–78·6) in those aged 65 years or older in 2050 (figure 2). A concurrent age shift occurred in the PAFs of new infections (figure 3; appendix). Between 2000 and 2050, the model predicted a transition from an epidemic driven by new infections to one driven by reactivation. Between 2000 and 2025, the estimated proportion of incident disease due to reactivation rose from 28·6% (UI 21·9–32·5) to 60·1% (51·1–64·9). By 2050, 75·1% (66·8–80·7) of all incident

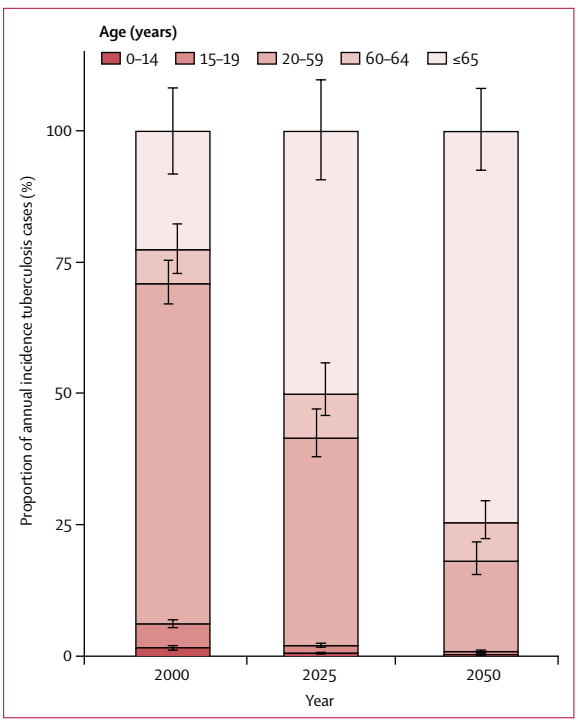


Figure 2: **Predicted percentage of incident tuberculosis cases by age and year, in the baseline scenario**
Vertical bars are uncertainty intervals in a given age group.

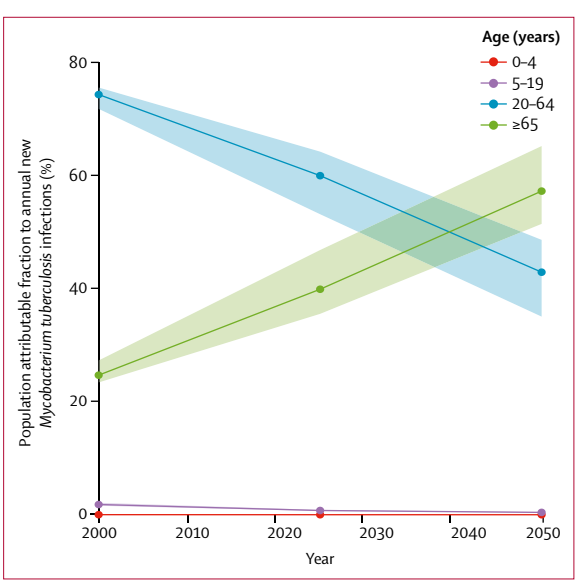


Figure 3: **Predicted population attributable fraction of each age group to new *Mycobacterium tuberculosis* infections by year, in the baseline scenario**
Lines are medians, shaded areas are uncertainty intervals.

disease cases were estimated to derive from reactivation (figure 4), although the proportion due to reactivation was lower in people aged 15–19 years (6·1%; UI 4·8–7·8) than in those aged 60–64 years (78·1%; 71·8–81·8; appendix).

In the baseline scenario, the all-age tuberculosis disease incidence rate was projected to decline from

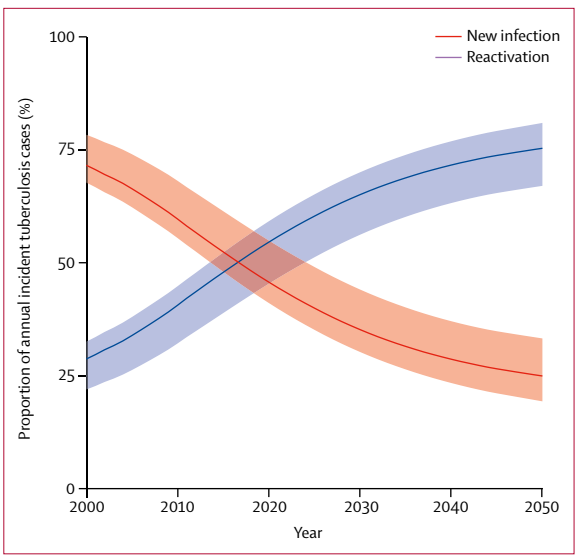


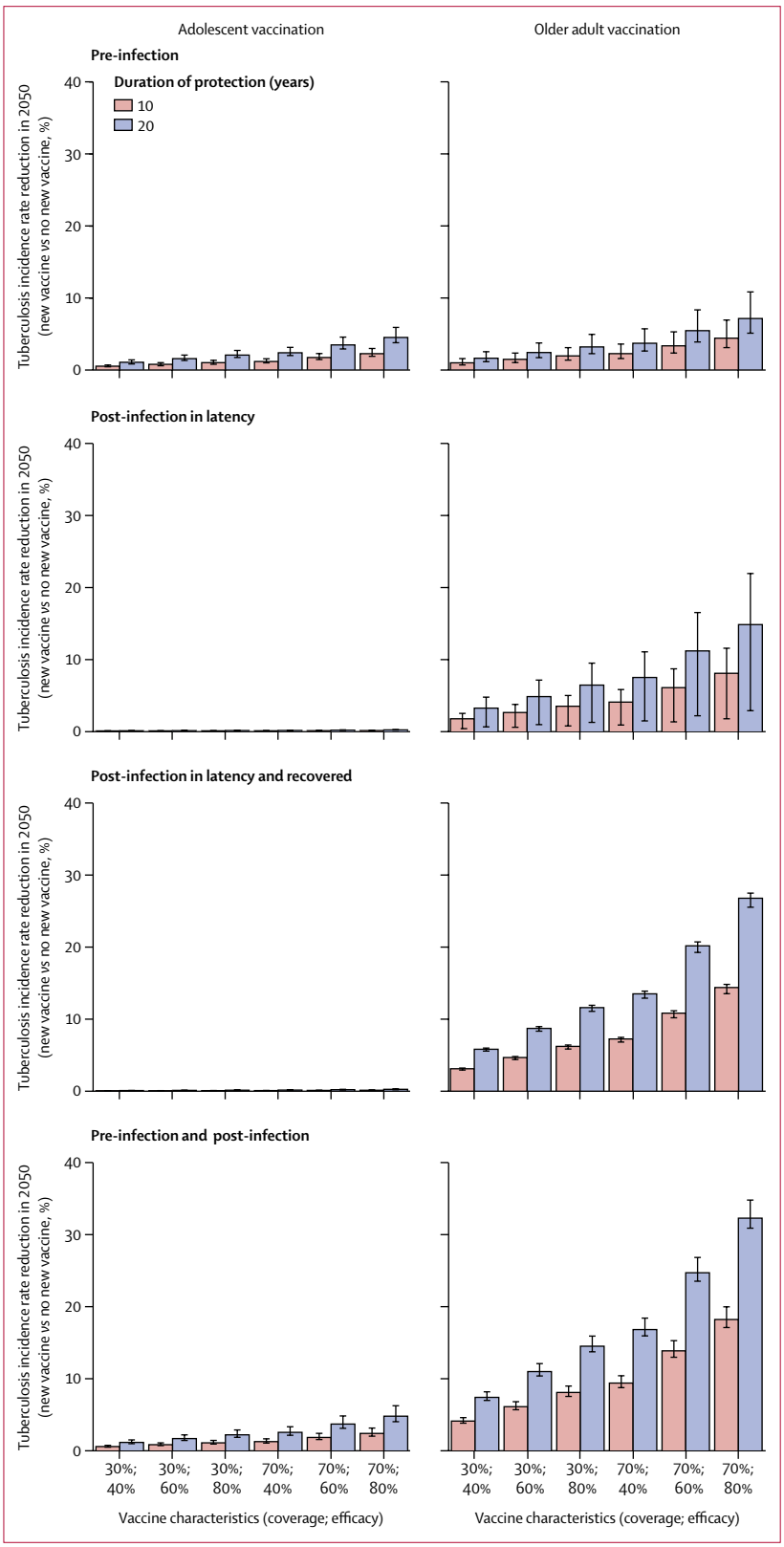
Figure 4: **Predicted proportion of all annual incident disease cases due to new infections and reactivation by year in the baseline scenario**
Lines are medians, shaded areas are uncertainty intervals.

56·2 per 100 000 population per year (UI 51·4–60·0) in 2025 to 33·7 per 100 000 population per year (27·6–38·8) in 2050, and the mortality rate from 2·0 per 100 000 population per year (1·2–3·4) in 2025 to 1·1 per 100 000 population per year (0·6–2·2) in 2050 (appendix).

All vaccine profiles explored provided a greater population-level reduction of tuberculosis incidence rate when delivered to older adults than to adolescents (figure 5). With the intermediate vaccine profile, vaccination of older adults aged 60–64 years reduced the population-level incidence by 1·9 times (UI 1·5–2·6) in the pre-infection vaccination scenario up to 157·5 times (119·3–225·6) in the post-infection (PSI-LR) vaccination scenario compared with equivalent vaccination of adolescents aged 15–19 years (table). For the same intermediate profiles, the estimated median cumulative NNVs per case averted in 2025–50 for older adult vaccination were 0·011 times (0·008–0·014) to 0·796 times (0·632–0·970) the NNV estimates for adolescent vaccination.

The relative impact of pre-infection versus post-infection vaccines varied by age at vaccination (figure 5). With older adult vaccination, the predicted reductions in tuberculosis incidence and mortality rates were smallest in vaccines given pre-infection, followed by the PSI-L, PSI-LR, and then PPI vaccines (figure 5; appendix). With vaccination of older adults, post-infection vaccines had smaller NNVs than corresponding pre-infection vaccine scenarios (appendix). For adolescent vaccination, the greatest reduction in incidence rate was with the PPI vaccine scenario, as with the older adult group; however, the pre-infection vaccine scenario had a greater impact than both of the post-infection vaccine scenarios (PSI-L and PSI-LR).

The ratio of the tuberculosis incidence rate reductions with older adult vaccination to the reduction with



adolescent vaccination was smallest in the pre-infection vaccine scenario (1·9 [UI 1·5–2·6] with the intermediate vaccine profile), and greatest with the PSI-LR vaccine scenario (157·5 [119·3–225·6] with the intermediate vaccine profile).

Post-infection vaccine protection in both latent and recovered populations provided markedly greater reductions in incidence and mortality rates than protection only in latency (figure 5; appendix). This was especially important in older adult populations, where PSI-L vaccines provided a 44% (UI 20–89%) smaller incidence rate reduction than PSI-LR vaccines (figure 5).

As expected, increased vaccine efficacy, duration of protection or coverage led to greater incidence rate reductions (figure 5). The cumulative NNV per case or death averted declined with increasing vaccine efficacy and duration of protection, because additional benefit was gained without delivery of additional vaccines (appendix). Although raising coverage substantially increased numbers of cases averted, many more vaccine doses were required, so cumulative NNV increased slightly at higher coverages.

Of the vaccine profiles and implementation strategies explored, the most effective was the PPI vaccine with 80% vaccine efficacy, 20-year protection, and 70% coverage (figure 5). Delivered to older adults, this vaccine scenario averted 3·0 million (UI 2·5–3·5) cases during 2025–50, whereas when delivered to adolescents only, 502 000 (431 000–591 000) cases were averted (appendix). The lowest-impact vaccines averted as few as 2000 cases (UI 2000–3000; the PSI-L scenario with 30% coverage, 40% efficacy, and 10-year duration delivered to adolescents) during 2025–50.

We did a sensitivity analysis comparing high coverage (70%), efficacy (80%), and duration of protection (20 years) in adolescents versus low coverage (30%), efficacy (40%), and duration (10 years) in older adults. The two post-infection vaccine scenarios still averted more cases when targeting older adults than when targeting adolescents, whereas the pre-infection scenario averted more cases with adolescent vaccination than older adult vaccination. The PPI vaccine averted similar numbers of cases when targeting older adults (489 000 [UI 418 000–566 000]) to when targeting adolescents (502 000 [431 000–591 000]), but older adult vaccination still led to a lower NNV per case averted (332 [286–387]) than adolescents (632 [537–737]; appendix).

Figure 5: **Predicted population-level impact of vaccine scenarios on tuberculosis incidence rate in 2050 compared with the no new vaccine scenario**

Vaccination was implemented in 2025–50. Adolescent vaccination was delivered routinely to people aged 15 years during 2025–50, with a 3-year catch-up campaign in people aged 16–19 years in 2025–27. Older adult vaccination was delivered to people aged 60 years, with a 3-year catch-up campaign in people aged 61–64 years in 2025–27.

Immunosenescent waning assumptions had minimal effect on the primary outcome. Increasing annual immunosenescent waning from 2% to 5% reduced the intermediate vaccine incidence rate reduction from 13·8% to 12·9%. Conversely, assuming no immunosenescence increased this estimate to 14·4%.

Discussion

In 2025–50, all vaccine profiles explored in China provided higher population-level impact on incidence and mortality rates and lower cumulative NNV per case or death averted when delivered to older adults (60–64 years) than adolescents (15–19 years). By 2050, the no new vaccine baseline results suggest that about 75·1% of incident tuberculosis cases would be due to reactivation of existing infections rather than new infections, and 74·5% of incident cases would occur in people aged 65 years or older. Vaccination of older adults with post-infection vaccines provided much greater reductions in tuberculosis incidence and mortality rates than pre-infection vaccines. Adolescent vaccination provided only a small benefit in terms of these outcomes. Thus, the inclusion of older adults in clinical trials will be imperative for vaccine development strategy in China and similar settings.

In the no new vaccine baseline scenario, transition from a transmission-driven epidemic mostly in adolescents and adults aged 15–64 years to a reactivation-driven epidemic mostly in people aged 65 years and older was predicted to occur before a new vaccine is likely to be launched, because of population ageing and reduced transmission resulting from improved tuberculosis diagnosis, care, and prevention.

Even though immunosenescence did reduce the impact of older adult vaccination, targeting older adults consistently provided greater impact than targeting adolescents with equivalent vaccine scenarios. Although the larger size of the older adult population required more vaccines than adolescent campaigns with equivalent percentage coverage, the NNV per case averted was lower, often considerably, for older adult than for adolescent vaccination, suggesting that cost-effectiveness calculations might also support older adult vaccination strategies. Even if lower coverage was assumed for older adult campaigns (30%) than school-based adolescent campaigns (70%), PPI vaccines targeting older adults would still be likely to provide at least equivalent, if not greater, impact than adolescent vaccination.

The relative impact of pre-infection versus post-infection vaccines on tuberculosis incidence and mortality rates varied between adolescent and older adult populations. Vaccination of older adults achieved higher population-level impact with post-infection vaccines, whereas greater impact was achieved by pre-infection vaccines targeting adolescents. This finding is explained by the substantially higher prevalence of latent infection in older adults. Pre-infection vaccines provided similarly

	Incidence rate reduction, 2050		Mortality rate reduction, 2050		Cases averted, 2025–50		Deaths averted, 2025–50		NNV per case averted		NNV per death averted	
	Percentage (UI)	Ratio (UI)	Percentage (UI)	Ratio (UI)	Number, thousands (UI)	Ratio (UI)	Number, thousands (UI)	Ratio (UI)	Number (UI)	Ratio (UI)	Number (UI)	Ratio (UI)
Pre-infection												
Adolescent	1·7 (1·4–2·3)	..	0·9 (0·5–1·4)	..	248 (214–292)	..	3 (2–5)	..	1278 (1087–1481)	..	101 379 (77 813–144 867)	..
Older adult	3·3 (2·3–5·3)	1·9 (1·5–2·6)	3·5 (2·6–5·3)	4·0 (2·2–7·7)	370 (287–504)	1·4 (1·2–1·9)	9 (5–21)	3·3 (1·9–7·2)	1022 (752–1318)	0·796 (0·632–0·970)	44 613 (36 654–51 666)	0·360 (0·166–0·627)
Post-infection latency only												
Adolescent	0·05 (0·04–0·07)	..	0·02 (0·01–0·04)	..	8 (6–11)	..	0·09 (0·05–0·20)	..	40 065 (29 505–52 492)	..	2 623 571 (2 094 819–4 317 445)	..
Older adult	6·1 (1·3–8·7)	120·1 (26·4–215·5)	6·4 (1·3–9·4)	229·7 (42·8–593·3)	658 (131–1081)	82·2 (18·0–155·2)	16 (2–45)	170·6 (30·1–497·0)	574 (350–2886)	0·015 (0·008–0·066)	31 324 (25 609–55 197)	0·007 (0·002–0·040)
Post-infection in latency or recovered from active disease												
Adolescent	0·07 (0·05–0·09)	..	0·04 (0·02–0·06)	..	12 (9–16)	..	0·14 (0·07–0·29)	..	26 831 (20 437–34 840)	..	1 383 557 (1 285 122–2 556 696)	..
Older adult	10·8 (10·2–11·2)	157·5 (119·3–225·6)	11·7 (11·0–12·1)	312·6 (186·5–584·8)	1295 (1037–1469)	109·7 (83·8–154·6)	33 (16–65)	253·8 (140·3–550·8)	292 (257–365)	0·011 (0·008–0·014)	13 164 (10 132–14 590)	0·005 (0·002–0·009)
Pre-infection and post-infection												
Adolescent	1·8 (1·5–2·4)	..	0·9 (0·5–1·4)	..	259 (224–304)	..	3 (2–5)	..	1223 (1043–1414)	..	94 346 (73 535–137 392)	..
Older adult	13·8 (12·9–15·2)	7·7 (6·4–8·8)	14·9 (14·2–16·0)	16·1 (10·4–0·3)	1643 (1403–1893)	6·3 (5·1–7·3)	42 (22–81)	14·0 (9·0–31·9)	230 (199–269)	0·188 (0·164–0·233)	10 292 (8048–11 534)	0·085 (0·038–0·133)

Intermediate vaccine profile is 60% vaccine efficacy, 10 years protection, and 70% coverage. Adolescents are people aged 15–19 years and older adults are those aged 60–64 years. Ratios are older adult:adolescent. NNV=number needed to vaccinate. UI=uncertainty interval.

Table: **Predicted population-level impact on tuberculosis outcomes of the intermediate vaccine profile, by host infection status required for efficacy and age targeting**

low population-level impact whether vaccinating adolescents or older adults. Post-infection vaccines delivered to older adults will be central to achieving the greatest possible impact. However, post-infection vaccines would have negligible impact if delivered to adolescents. Post-infection vaccines that are effective in both latent and recovered populations provided greater impact than those effective in latency only, particularly when delivered to older adults, indicating that vaccines that are also effective against relapse after recovery from active disease could have important additional value. The vaccine that is effective both pre-infection and post-infection provided the greatest impact when delivered to both age groups, and would be the ideal candidate for development, but at a minimum, a post-infection vaccine suitable for older adult vaccination should be developed for tuberculosis prevention in China if the highest population-level impact before 2050 is the primary goal.

Although herpes zoster vaccine trials provide proof of concept for achieving robust efficacy and immunogenicity in older age groups,[29] efficacy or duration of protection could conceivably be compromised with age. Our results show that for post-infection vaccines or PPI vaccines, older adult vaccination would be recommended even with substantially lower efficacy, duration, and coverage than observed in adolescents. Therefore, clinical trial data to support vaccine registration in older populations will be vital. For pre-infection-only vaccines, the preference for vaccinating older adults would be diminished or negated if vaccine characteristics and coverage were substantially worse in older adults than in adolescents. Therefore, age-stratified estimates of efficacy from clinical trials in pre-infection populations will be important for designing impact-maximising implementation strategies. All of these sensitivity analysis results further strengthen our recommendation that older adults should be included in clinical trials.

With the vaccine profiles and delivery strategies explored, up to a 32% reduction in tuberculosis incidence rates could be achieved in 2050, which would be a substantial contribution towards WHO 2050 goals. Even greater benefits could be achieved with less-conservative delivery strategies (eg, one-off mass vaccination to all adults) or if higher efficacy or duration of protection were achieved. Our model shows that an appropriately designed and delivered new tuberculosis vaccine could substantially contribute to tuberculosis prevention in China.

This study had several limitations. Data were scarce for tuberculosis natural history parameters for people aged 65 years or older. We represented this uncertainty in the calibration process by sampling from wide parameter priors in this age group, combining HIV-negative and HIV-positive adult ranges. Future secular changes in excluded risk factors might affect the projected baseline trends and absolute changes in incidence and mortality rates, but the projected relative impact would be expected to be robust to these changes. Given population ageing, the assumption that the contact matrix remained constant throughout the study period might provide conservative effect estimates. The probable under-reporting of the number of contacts in the study informing the contact matrix was accounted for by a scaling factor; however, this might not have completely accounted for under-reporting. HIV co-infection was not modelled because estimates suggest that less than 1% of patients with tuberculosis in China are co-infected with HIV.[2,30] Urbanisation, migrants, and gender might affect tuberculosis transmission and vaccine coverage, and might be important to consider in vaccine targeting, but were beyond the scope of our research question. The vaccine was assumed to provide all or nothing protection, but the alternative leaky assumption could reduce effect estimates.[31]

Because of high treatment success and case detection during calibration years, these were assumed to plateau after the calibration period. Potential future policy changes are challenging to predict, but if improvements in care measures (eg, mass active case finding) were achieved, or better diagnostics or treatments introduced, the impact achieved by vaccines could potentially be reduced. However, this would not affect conclusions with respect to age targeting, unless such an intervention varied in effectiveness by age. Preventive therapy for people aged 65 years or older was not included as a future intervention in this study, but comparison of the relative impact and cost-effectiveness of vaccines versus preventive therapy in this age group could provide an interesting avenue for future research.

Outcomes were assessed up to 2050 to align with the WHO 2050 elimination goal, so results are specific to 2025–50. Full benefit of vaccines delivered before 2050 would extend beyond 2050, therefore relative vaccine impact might change over longer time periods.[12] Better vaccines (eg, lifelong protection) or coverage could improve impact,[19] but were not considered likely scenarios by experts. Heterogeneity within the adult population could affect efficacy; variable efficacy by infection status was explored here, but when more is understood about a candidate's mechanism of action, future studies could examine other population heterogeneity. Infant vaccination could be explored, but the impact would be very low over this time period given the decreasing force of infection in China.[13,15] To answer the research question, we deliberately restricted mass campaigns to narrow age ranges (15–19 years and 60–64 years). If a new efficacious vaccine became available, broader campaigns could be implemented to increase overall benefits but would not affect our overall conclusions.

The results of this study are specific to the tuberculosis epidemic and demographics in China, but they might also be relevant to other countries with ageing populations and improvements in tuberculosis control leading to reactivation-driven epidemics.

This study is the first to assess the potential impact of new tuberculosis vaccines targeting older adults and to provide a comparison with adolescent vaccination, which has been a strategic focus over the past 5–10 years.[14] Our analysis required age-specific model parameterisation and calibration, and is the first China tuberculosis model to calibrate age-stratified mortality and notification rates and include data-informed non-random mixing by age. Our results are consistent with the conclusions of the study by Dye and colleagues[19] regarding the importance of post-infection vaccines in China, but provide a crucial clarification: that population-level impact with such vaccines might be contingent on delivery to older age groups. These results build on the study by Huynh and colleagues,[5] which showed the importance of controlling reactivation disease in people aged 65 years or older. Our results extend previous studies that suggested that adolescent and adult campaigns would have a greater benefit than infant vaccination,[13,15,20] and we develop the argument further by showing that in an epidemic in an ageing population, the greatest benefit could be achieved by targeting older adults, potentially minimising the resources required per case averted.

Adolescent-targeted vaccines, the focus of development strategy for the past 5–10 years, would have only a small impact in ageing, reactivation-driven tuberculosis epidemics such as that in China. In these settings, an efficacious post-infection vaccine delivered to older adults will be crucial to maximise population-level impact and would provide a necessary contribution towards achieving the WHO 2050 tuberculosis goals. In conclusion, older adults should be included in tuberculosis vaccine clinical development and implementation planning.

Contributors

All authors developed the research question. RCH, RGW, TS, and GMK developed the research method. RCH, TS, and GMK developed the mathematical model. RCH, RGW, and TS contributed to interpretation of the model. RCH wrote the manuscript. All authors reviewed manuscript drafts and approved the final manuscript.

Declaration of interests

RCH provided consultancy to GlaxoSmithKline vaccines, ending in 2015 and outside the scope of the submitted work. TE and VC were employed at the tuberculosis vaccine development organisation Aeras (Rockville, MD, USA), and CC was employed at Aeras Asia (Beijing, China) during the period when this work was completed. All other authors declare no competing interests.

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