Potential impact of tuberculosis vaccines in China, South Africa, and India

Authors:
Rebecca C. Harris,[1*] PhD (rebecca.harris@lshtm.ac.uk)

Tom Sumner,[1] PhD (tom.sumner@lshtm.ac.uk)

Gwenan M. Knight,[1]PhD (gwen.knight@lshtm.ac.uk)

Hui Zhang,[2] PhD (zhanghui@chinacdc.cn)

Richard G White,[1*] PhD (richard.white@lshtm.ac.uk)

Affiliations:

[1] TB Modelling Group, TB Centre and Centre for the Mathematical Modelling of Infectious Diseases, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

[2] Chinese Center for Disease Control and Prevention, Beijing 102206, China

*Corresponding author. Email: rebecca.harris@lshtm.ac.uk, richard.white@lshtm.ac.uk

Overline: TUBERCULOSIS

One-sentence summary: Tuberculosis vaccines should aim to protect infected populations against disease, but other vaccine types may be of use in high-transmission settings.

Abstract

More effective tuberculosis vaccines are needed to help reach the World Health Organization 2050 tuberculosis elimination goal. Insufficient evidence exists on the potential impact of future tuberculosis vaccines with varying characteristics and in different epidemiological settings. To inform vaccine development decision making, we modelled the impact of hypothetical tuberculosis vaccines in three high-burden countries. We calibrated *Mycobacterium tuberculosis (M.tb)* transmission models to age-stratified demographic and epidemiological data from China, South Africa, and India. We varied vaccine efficacy to prevent infection or disease, effective in persons *M.tb* uninfected or infected, and duration of protection. We modelled routine early-adolescent vaccination and 10-yearly mass campaigns from 2025 onwards. We estimated median percentage population-level tuberculosis incidence rate reduction (IRR) in 2050 compared to a no-new-vaccine scenario. In all settings, results suggested that vaccines preventing disease in *M.tb*-infected populations would have greatest impact by 2050 (10-year, 70% efficacy against disease, IRR 51%, 52% and 54% in China, South Africa and India, respectively). Vaccines preventing re-infection delivered lower potential impact (IRR 1%, 12%, 17%). Intermediate impact was predicted for vaccines effective only in uninfected populations, if preventing infection (IRR 21%, 37%, 50%), or disease (IRR 19%, 36%, 51%), with greater impact in higher transmission settings. Tuberculosis vaccines have the potential to deliver substantial population-level impact. For prioritising impact by 2050, vaccine development should focus on preventing disease in *M.tb*-infected populations. Preventing infection or disease in uninfected populations may be useful in higher transmission settings. As vaccine impact depended on epidemiology, different development strategies may be required.

Introduction

Tuberculosis (TB) is now the largest single-pathogen cause of global adult mortality.(*1*) The financial burden of TB is substantial; in 2018, US$10.4 billion was estimated to be required for global prevention, diagnosis, and treatment.(*2*) With more than 10 million incident cases of tuberculosis globally per year and a current average annual incidence rate decline of only 1.8%,(*1*) tools such as vaccines are urgently needed to accelerate progress towards the World Health Organization (WHO) 'End TB' and elimination goals.(*2*) New prophylactic tuberculosis vaccines will also be essential in preventing further development of multi-drug resistance.

There are currently 14 tuberculosis vaccine candidates in the clinical development pipeline, with the potential for diverse vaccine characteristics and indications.(*3*) Recent progress has been encouraging. The M72/AS01$_E$ phase IIB trial enrolling interferon-gamma release assay (IGRA)-positive adults demonstrated 49.7% (95%CI, 2.1 - 74.2) efficacy against bacteriologically-confirmed pulmonary disease over 3 years of follow up.(*4*) Adolescent revaccination with bacille Calmette-Guérin (BCG), the only licensed vaccine for TB, is also being re-examined following a placebo-controlled efficacy trial demonstrating 45.4% (6.4 - 68.1) efficacy against a secondary endpoint of sustained IGRA conversion as a measure of infection.(*5*) Results are expected soon from a late-phase *M. vaccae* study in China (NCT01979900). The field is hopeful that a new TB vaccine will be registered, or a new BCG indication provided, within the next decade.(*6*)

Target product profiles detailing minimum and ideal characteristics and indications for new vaccines help to guide strategic development. Mathematical modelling has informed age indications for TB vaccines, by demonstrating the greater and more rapid impact before 2050 of targeting adolescents and adults instead of infants in low and middle income countries,(*7*) and older adults in settings such as China.(*8*)

However, critical questions remain regarding the potential population-level impact of different vaccine characteristics, including in different epidemiological settings. In particular, although there is consensus in the literature that prevention of disease vaccines are likely to provide greater and more rapid impact than prevention of infection vaccines before 2050,(*9-11*) there is a lack of investigation of the relative impact of vaccines effective for the prevention of infection compared to the prevention of disease in adolescent/adult vaccination strategies, and no modelling has explored combinations of these characteristics.(*9*) Furthermore, the literature is divided as to whether greatest population-level impact would be delivered by vaccines with efficacy in *Mycobacterium tuberculosis (M.tb)*-infected populations versus uninfected populations,(*8, 9, 12-18*) and, as indicated in recent studies of the TB epidemic in China, Cambodia, and the US,(*8, 12*) how population-level impact may vary by age and setting.(*9*) Similarly, human immunodeficiency virus (HIV)-induced immunocompromise may lead to contraindication or reduced vaccine efficacy, but has not been explored in the modelling literature.(*9*) Vaccines currently in the clinical pipeline include studies recruiting either IGRA-positive (post-infection) or uninfected (pre-infection) populations, and endpoints measuring prevention of infection (as measured by IGRA) or prevention of disease. The current status of the pipeline and challenges in developing the most advanced candidates have been discussed in recent publications.(*3, 19*)

With recent positive efficacy results (*5, 20*) and more candidates in late-stage development,(*3*) there is an urgent need to understand the effect these vaccine and population differences could have on population-level impact, to inform the development of evidence-based target product profiles and clinical trial design. To meet this research need, we employed mathematical modelling to comprehensively explore the potential population-level impact of varying five key tuberculosis vaccine characteristics in China, South Africa, and India. In the light of recent positive efficacy results for BCG revaccination (*5*) and M72/AS01$_E$ (*4, 20*), we also report estimates of the population-level impact of vaccines with characteristics consistent with the phase IIB trial results.

Results

Modelling approach

In this study, we developed an age- and vaccination status-stratified compartmental deterministic *M.tb* transmission model (Figure 1B) to assess the population-level impact of these vaccines. The model was calibrated to age- (and HIV-) stratified TB epidemiological data in China (18 targets for calibration), South Africa (16 targets) and India (13 targets), representing 39% of global incident tuberculosis cases in 2017 and a diversity of epidemics.(*1*) The temporal evolution of population demographics in each country was reproduced through parameterisation with UN demographic data and projections. We incorporated country-specific epidemiologically important factors, including HIV co-infection and care in South Africa, private sector tuberculosis care in India, and historical temporal trends in tuberculosis detection and treatment and age-wise heterogenous social-mixing patterns in all three countries. Natural history parameter uncertainty was captured through multi-stage model calibration, initiated with random sampling and followed by approximate Bayesian computation Markov chain Monte Carlo with an adaptive acceptance criterion where required, to identify 1,000 parameter sets for each country. Calibration was achieved for all three countries (Figure 2A, figures S5-S16). Outcomes were estimated as the median and range from model runs with these 1,000-parameter sets.

We modelled the population-level impact of varying five key tuberculosis vaccine characteristics (Figure 1A): vaccine efficacy for prevention of infection (range 0-100%), vaccine efficacy for prevention of disease (0-100%), vaccine efficacy by host infection status (pre-, post-, or pre- and post-infection), vaccine safety and efficacy in HIV-positive populations (safe versus contraindicated, equal efficacy versus 20% reduction compared to HIV-negative populations), and duration of protection (2 years to lifelong). Vaccine implementation in China, South Africa and

India was modelled as delivered routinely to young adolescents and as 10-yearly mass campaigns to adults during 2025-2050. Vaccine efficacy was assumed to be 'degree/leaky', and duration of protection was 'exact'. In the main analysis, to align with global tuberculosis elimination goals,(*2*) impact was defined as the percentage incidence rate reduction in each vaccination scenario compared to the no new vaccine baseline in 2050, and cumulative cases averted 2025-2050.

Baseline (no new vaccine) outcomes

Our model results suggest that, historically, recent transmission was the largest contributor to incident TB in all three settings (Figure 2B). A combination of reactivation and relapse TB were predicted to provide an increasing contribution over 2000-2050, due to scale up of TB control activities in all countries, plus the impact of the HIV epidemic in South Africa and rapid population ageing in China. Our results suggest a switch by 2025 to a predominately reactivation/relapse-driven epidemic in China, with India remaining predominately transmission-driven, and results for South Africa between those of India and China. We estimated the prevalence of latent *Mycobacterium tuberculosis* infection in 2015 at 16% (uncertainty range [UR]: 13-19%), 42% (26-60%) and 49% (34-59%) in China, South Africa and India, respectively. Although not calibrated, these estimates aligned with limited available data and existing modelling studies (table S10).

Vaccine impact scenarios

Our primary implementation strategy assumed routine vaccination of 9-year-olds, 10-yearly mass campaigns, and implementation from 2025. The greatest achievable impact delivered by vaccines with 100% efficacy for prevention of infection and disease, efficacious both pre- and post-infection and in HIV-positive populations, with 10 years duration of protection, was a 79% (UR: 77-81%) incidence rate reduction in 2050 in China, 84% (uncertainty range [UR]: 81-87%) in

South Africa, and 90% (UR: 87-94%) in India (Figure 3, top row, top right corner of each graph). Over 2025-50, this profile was estimated to avert 11.6 million (10.2-12.6m) cases and 0.3 million (0.1-0.5m) deaths in China, 4.3 million (2.5-7.0m) cases and 0.9 million (0.5-1.6m) deaths in South Africa, and 51.4 million (32.6-76.6m) cases and 4.3 million (2.5-8.4m) deaths in India (supplementary sections 8.2-8.3). Over 2025-50, this profile could potentially avert up to 67.3 million (45.3-96.2m) cases and 5.5 million (3.1-10.0m) deaths across these three countries.

Over the 2025-2035 timeframe of the WHO End TB strategy, this profile was estimated to avert 5.6 million (UR: 5.0-6.0m) cases in China, 1.8 million (UR: 1.2-2.9m) cases in South Africa, and 19.3 million (UR: 13.0-28.0m) cases in India. Additional results for 2035 are provided in supplementary section 8.4. If the vaccine was assumed to only protect against disease (that is, lacking protection against infection), impact was essentially unchanged (IRR 79% (77-81%), 84% (78-87%) and 90% (87-94%) in China, South Africa, and India, respectively) (Figure 3, top row, top left corner of each graph). In contrast, if the vaccine only protected against infection, and not disease, this resulted in an incidence rate reduction in 2050 of 28% (23-35%), 54% (42-65%) and 68% (59-80%), respectively (Figure 3, top row, bottom right corner of each graph).

A vaccine with 100% efficacy against both infection and disease, but which was only efficacious in uninfected populations (pre-infection), resulted in an incidence rate reduction of 27% (23-34%), 48% (39-58%) and 62% (54-76%) in China, South Africa, and India, respectively (Figure 3, middle row, top right corner of each graph). If, instead, the vaccine was only effective in post-infection populations, incidence rate reductions of 71% (70-71%), 72% (67-76%) and 73% (60-78%) were predicted (Figure 3, bottom row, top right corner of each graph).

Comparisons were also made for pre-infection versus post-infection vaccines effective either against infection or against disease. A vaccine effective only in uninfected populations (Figure 3) with 10-year protection and 70% efficacy for preventing infection reduced incidence rates by 21%

(17-26%), 37% (28-47%) and 50% (42-64%) in China, South Africa, and India, respectively; or for preventing disease reduced incidence rates by 19% (14-24%), 36% (24-47%), and 51% (42-65%), respectively. Equivalent vaccines effective only in populations already or previously infected with *M.tb* (Figure 3) with 70% efficacy for preventing disease would have greater impact (IRR 51% (50-51%), 52% (44-58%) and 54% (44-61%), respectively). We estimated a substantially lower impact of vaccines effective only in post-infection populations efficacious against infection (IRR 1% (1-2%), 12% (4-24%), and 17% (8-31%)).

We also explored differential vaccine efficacy by HIV status in South Africa (Figure 4). With a vaccine safe and equally effective in HIV-positive, -negative, and *M.tb*-infected and -uninfected populations (pre- and post-infection), an 84% (81-87%) incidence rate reduction was predicted with a 100% efficacy prevention of infection and disease vaccine with 10 year duration of protection. For a vaccine safe in HIV-positive populations, but with a 20% reduction relative to the efficacy in HIV-negative populations, the equivalent vaccine was estimated to produce an incidence rate reduction of 79% (72-84%) in 2050. However, when contraindicated in HIV-positive populations, impact in 2050 was further reduced, with incidence rate reduction estimated at 62% (44-74%) for an equivalent vaccine.

Impact was substantially affected by duration of protection (Figure 5). For a vaccine with 70% efficacy for prevention of infection and disease, effective pre- and post-infection, with 10-yearly mass campaigns, increasing duration of protection from 2 to 10 years increased incidence rate reduction in 2050 from 8% (6-10%) to 63% (60-66%) in China, 13% (8-20%) to 71% (66-78%) in South Africa, and 21% (16-30%) to 82% (77-89%) in India. Increasing mass vaccination campaign frequency from 10- to 5-yearly substantially increased impact for shorter duration vaccines (supplementary section 8.6).

Two phase IIB trials recently demonstrated positive efficacy results.(*5, 20*) An example profile based upon the BCG revaccination trial design and point-estimate efficacy results, and assuming 10 years duration of protection and revaccination effective only against infection, projected BCG revaccination would deliver an incidence rate reduction in 2050 of 16% (13-20%), 22% (16-32%) and 39% (32-53%) in China, South Africa, and India, respectively. If equivalent efficacy were observed against both infection and disease, incidence rate reductions of 21% (17-27%), 32% (23-44%) and 52% (44-67%) could be anticipated according to this model.

The likely duration of protection is unknown for M72/AS01$_E$, but with an indicative profile based upon the recent trial and the conservative estimate of 3-year protection, the vaccine was projected to reduce incidence rates by 4% (3-6%), 7% (1-11%) and 11% (8-15%) in China, South Africa and India, respectively. If 10-year protection were achieved, projected impact would increase to 37% (36-37%), 34% (25-42%) and 41% (32-46%), respectively.

Discussion

Our research explored the most comprehensive series of potential new TB vaccines to date, with thousands of profiles modelled, providing predicted vaccine impacts suitable for informing development. We explicitly explored the impact of prevention of infection and disease efficacies in combination and projected the impact in three settings (China, South Africa and India) based upon the recent M72/AS01$_E$ and BCG revaccination efficacy trial results. The models were calibrated to a large number of age-stratified epidemiological data points, and accounted for heterogeneous social mixing, HIV in South Africa, and private sector treatment in India.

In the three diverse epidemiological settings explored in this study, results suggest that vaccines preventing disease in populations already infected with *M.tb* would have most impact by 2050 (10-year 70% vaccine efficacy against disease, IRR 51% (50-51%), 52% (44-58%), and 54% (44-61%) in China, South Africa and India, respectively). Conversely, vaccines preventing re-infection in *M.tb* infected populations would deliver lower impact (IRR 1% (1-2%), 12% (4-24%) and 17% (8-31%)). Intermediate impact was predicted for vaccines effective only in uninfected populations, if preventing only infection (IRR 21% (17-26%), 37% (28-47%), and 50% (42-64%)), or for preventing only disease (IRR 19% (14-24%), 36% (24-47%), and 51% (42-65%)), with greater impact in settings experiencing more ongoing transmission over the modelled timeframe.

The potential epidemiological impact of BCG revaccination and the M72/AS01$_E$ vaccine were estimated based on recent efficacy trial results. The M72/AS01$_E$ candidate was the first new vaccine to demonstrate efficacy for prevention of disease,(*4*) and several other candidates are being tested for prevention of disease outcomes; therefore, there is hope that such a vaccine could be registered in the near future.

Phase IIB studies assessing prevention of infection endpoints are increasingly common in TB vaccine development to de-risk development, reduce cost, and potentially serve as a stand-alone

indication.(*5*) However, there has been insufficient modelling research exploring the population-level impact of a prevention of infection indication.(*9*) Our results suggested that vaccines to prevent disease would have greater impact in all three countries by 2050 than vaccines aimed at preventing infection. That said, the relative impact of efficacy for prevention of infection versus disease varied substantially by setting, with the greatest differential seen in China and the smallest in India, due to the relative contribution of transmission to the incident epidemic. Therefore, although phase III studies should prioritise prevention of disease endpoints, prevention of infection endpoints may also be of value in higher transmission settings such as India and South Africa. Therefore, prevention of infection endpoints could be used in phase IIB studies to de-risk late-stage development, and potentially as stand-alone registration studies.

Phase II trials vary in their recruitment of latently infected or uninfected populations.(*5, 20*) In this modelling study, prevention of infection and disease vaccines effective post-infection delivered a similar incidence rate reduction in all three settings, whereas the impact of vaccines effective in pre-infection populations varied by setting, with the greatest impact in India and lowest in China. Pre- versus post-infection efficacy must be considered in combination with the vaccine's efficacy for prevention of infection versus disease. If efficacious only against disease, post-infection vaccines were still projected to provide the greatest impact in all three settings. Whereas if efficacious only against infection, post-infection vaccines would provide lower population-level impact in all but the highest transmission settings, and would be out-performed by pre-infection vaccines. The degree of ongoing transmission in each setting was a key driver of these relative impacts, and therefore generalisability to other settings will require consideration of the degree and trends of transmission.

Evidence from paediatric studies suggests that BCG efficacy may be reduced when vaccinated post-infection (*21*). Therefore, we consider the assumption in our modelling study of efficacy only pre-infection as appropriate. For the M72/AS01$_E$ vaccine, immunological data are indicative of a

similar magnitude of CD4+ T cell responses in both pre- and post-infection populations, though functionally distinct CD8+ T-cells populations have been observed.(*22*) No correlate of protection exists, but if M72/AS01$_E$ does have pre-infection efficacy our modelled impact estimates from efficacy only post-infection will underestimate the possible future impact of the vaccine.

HIV co-infection may affect vaccine safety or efficacy,(*23-25*) but the population-level impact of such characteristics has not previously been explored.(*9*) Our results suggest that in South Africa, a relative 20% reduction in efficacy in HIV-positive populations would minimally affected impact, whereas contraindication could substantially reduce impact. In high HIV prevalence settings, trials exploring safety and efficacy in HIV-positive populations will be imperative for predicting impact.

Most clinical trials do not extend beyond 2-3 years, yet many previous TB vaccine modelling studies have assumed up to lifelong protection.(*9*) In this study, we explored durations of protection as short as 2 years. Our results from shorter durations of protection (2 and 3 years) are indicative of what could be expected if no extrapolation is made beyond the usual 2-3 year clinical trials. However, it should be noted that results suggested substantial additional impact of longer durations of protection, so extending the duration of follow up to explore efficacies over longer durations would be informative for predicting impact. We also explored mass campaign frequency of 5- or 10-years, and substantially higher impact was predicted with the more frequent mass campaigns.

With routine vaccination of 9-year-olds and 10-yearly mass campaigns of adolescents/adults, the most effective vaccine profile that we modelled averted 67.3 million (45.3-96.2m) cases and 5.5 million (3.1-10.0m) deaths across the three countries over 2025-2050. This would be a substantial health benefit, and an important contribution towards End TB and elimination goals.(*1*)

Previous research has not been informative on the relative impact of vaccines effective for the prevention of infection compared to the prevention of disease in adolescent/adult vaccination

strategies.(*9-11*) Previous studies modelled routine neonatal vaccination combined with either a one-off adult mass campaign or continuous vaccination of uninfected populations, and found that prevention of disease vaccines provided greater impact than prevention of infection vaccines.(*10, 11*) However, there was limited comparability of implementation of the different vaccines and unreported duration of protection in one of these studies,(*11*) and unreported efficacy and duration of protection in the other.(*10*) Our study clearly defined and reported vaccine characteristics, and modelled routine young adolescent vaccination plus 10-yearly adult mass campaigns, which is relevant for the current development priority of adolescent/adult vaccination. Our model projected that protection against disease provided greater impact than protection against infection for adolescent/adult-targeted vaccination strategies over the 2050 time horizon, and added quantitative information on how the relative impact of prevention of infection versus disease may vary in these three epidemiologically distinct settings.

Previous literature exploring pre- versus post-infection vaccines was divided as to which would provide greatest impact.(*8, 9, 12-18*) We recently proposed two likely reasons for the differences in impact in previous modelling studies - the assumed proportion with latent infection (which determines the number effectively vaccinated), and the assumed proportion of disease from recent infection versus reactivation (*9*). We demonstrated these were plausible hypotheses by reproducing the model from one published study, but the other modelling studies were not reported in enough detail to be reproduceable (*9*). A key advantage of this current work was that we were able to control or account for a number of factors that differed across the published modelling studies, such as such as model structure, natural history parameterisation, latent TB prevalence, proportion of disease due to reactivation, and vaccine implementation differences. We were therefore able to explore these aspects in a controlled systematic way and in contrasting epidemiological settings, with direct implications for vaccine development decision making. In so doing, we showed that greater impact may be expected from post-infection vaccines that prevent

disease in all three settings before 2050, but that pre-infection vaccines that prevent infection or disease may still have useful impact, particularly in higher transmission settings.

Our results should be interpreted in the context of certain limitations. We assumed future case detection and treatment success rates would plateau post-2016, but if substantial future investment were to occur, South Africa and India results could become more reactivation-driven, like China. Unknowns in the trajectory of the HIV epidemic in South Africa include whether antiretroviral therapy targets will be met. Future change in the burden of unmodelled co-morbidities such as diabetes may alter the projected trends in TB burden and the absolute numbers of cases averted, but they are less likely to influence the relative impact of new vaccines. We assumed neonatal BCG coverage would not change in the future, as even with the introduction of a new adolescent/adult vaccine, protection of infants with BCG would still be required. Changes in BCG coverage in the future would influence the projected trends in TB burden and the absolute numbers of cases averted; relative impact may be less influenced. There are many implementation unknowns, but the simulated rapid vaccine introduction and mass vaccination may be practically infeasible. As such, our results should be primarily used to inform the relative impacts between vaccine characteristics in different epidemiological settings. We modelled vaccines as “leaky”, a method which tends to deliver more conservative estimates of vaccine impact than the alternative “all-or-nothing” approach.(*26*) Vaccine efficacy upon repeated boosting with the same vaccine has not been examined in clinical trials. Modelled time horizons are important, as the relative impact of pre-infection vaccines may increase over longer horizons. Vaccine protection from infection was assumed not to be correlated with likelihood of progression to disease, but if a correlation existed between efficacy and non-progression, efficacy against infection may not impact the burden of disease. This is raised as a potential limitation, but will only be known from clinical trials measuring both outcomes longitudinally. We employed a model structure common to around half of modelling studies in the literature,(*27*) but as the

understanding of TB natural history develops, projections could be updated to reflect these changes. The scenarios presented are simplified representations of the China, South Africa, and India epidemics, though some generalisation to other settings may be possible.

This research has implications for vaccine developers and policy makers. Prevention of disease trial outcomes should be prioritised, however, in South Africa, India, and other settings with high ongoing transmission, prevention of infection outcomes could be considered. For recruitment, our models indicate that post-infection populations are important, and in higher transmission settings inclusion of pre-infection populations should be considered. HIV-positive populations should be included in development plans where possible (ideally for efficacy, but as a minimum for safety and immunogenicity) and trial follow-up should be continued beyond 2 years (for example in an immunological sub-cohort). If vaccines have low efficacy or short duration of protection, the feasibility, efficacy, and cost effectiveness of more frequent mass campaigns should be explored.

If the efficacy signals are confirmed in phase III studies, both BCG revaccination and M72/AS01$_E$ could deliver substantial population-level impact in these settings. For BCG revaccination, confirmation of the prevention of infection signal and exploration of prevention of disease efficacy will be important for estimating the value proposition. For M72/AS01$_E$, duration of protection is currently an important unknown; long term follow-up will be essential. In South Africa, to maximise population-level impact, and to ensure an important risk group can be protected, registration in both HIV-negative and HIV-positive populations would be important.

In sum, upcoming TB vaccines have the potential to deliver substantial impact in China, South Africa, and India. For prioritising impact by 2050, vaccine development strategy should focus on preventing disease in populations already *M.tb* infected. Vaccines that prevent infection or disease in *M.tb*-uninfected populations may also be useful in high transmission settings. As we

found that vaccine impact was dependent on epidemiology, different vaccine development strategies may be required.

Materials and Methods

Study design

To inform decision making in TB vaccine development and trial design, we estimated the population-level impact of varying the characteristics of tuberculosis vaccines (both hypothetical, and real vaccines in late-stage development). We conducted a broad exploration of five core vaccine characteristics, which would be anticipated to include the known characteristics of vaccines currently in the pipeline, as well as currently-unknown characteristics, and hypothetical future vaccines.

The impact of these vaccines was explored using a mathematical dynamic transmission model calibrated to age-stratified demographics and epidemiology in China, South Africa and India. We developed an age-stratified population-level compartmental deterministic transmission model in *R*. The model was calibrated to the TB epidemics in China, South Africa, and India. These three high-burden countries account for 39% of global TB incident cases, and represent a diversity of epidemics.(*1*) A summary follows; full details are available in the supplementary materials.

Model structure and parameterisation

We assumed that the underlying TB natural history was consistent across all three countries. The model included five TB natural history infection or disease states: uninfected, latent infection, bacteriologically-positive active disease, bacteriologically-negative active disease, and recovered from disease (Figure 1B). Transitions between the states represented (re-)infection, development of primary, reactivation or relapse disease, and successful detection and treatment or natural cure of disease. The model was stratified by age and new TB vaccination status. In South Africa, TB natural history states were stratified by HIV infection status. For parsimony, HIV stratification was

not included for India and China, as HIV coinfection in patients with TB was low (<5%).(*1, 28*) All three countries included country-specific age mixing patterns.

Age- and HIV-stratified natural history parameter prior ranges, based upon available data, are summarised in tables S1 and S2. Heterogeneous age-wise social contact patterns were parameterized using data for China and South Africa,(*29, 30*) and estimated for India.(*31-33*)

TB case detection rates and treatment success were parameterised using WHO data by country between approximately 1994 and 2016.(*34*) To minimise short-term reporting fluctuations, case detection was assumed to follow a generalised logistic function and treatment success employed a 3-point moving average. TB control improved substantially during the period for which data were available, and was assumed to remain constant outside the available data time period at the value of the nearest time point. Due to the size and differential quality of care in the private sector in India,(*35*) treatment success parameters were adjusted. In South Africa, antiretroviral therapy reduced TB progression parameters.(*36-38*) Antiretroviral therapy coverage in HIV-positive populations was parameterised using historical data up to 2016, then assumed to scale linearly to 90% by 2022. Neonatal BCG vaccine coverage was assumed to remain constant, and so was not explicitly modelled.

Calibration targets and methods

A previously-calibrated demographic model was employed for China.(*8*) For South Africa and India, population demographics were reproduced by parameterisation with UN population division birth and probability of death data.(*32*) Burn-in from 1900 allowed for appropriate levels of latent *M.tb* prevalence due to historical infection. Empirical age-wise HIV prevalence trends in South

Africa were achieved by parameterising with age- and year-specific HIV incidence and acquired immune deficiency syndrome (AIDS)-related mortality.(*36, 38, 39*)

Models for all three countries were calibrated separately to country-level age-stratified TB disease prevalence, incidence, mortality and notification rate data, and HIV data for South Africa, where available. This comprised 18 epidemiological calibration targets for China, 16 for South Africa, and 13 for India. A multi-stage model calibration method was used, starting with random sampling and then approximate Bayesian computation Markov chain Monte Carlo, with an adaptive acceptance criterion where required.(*40*) Median outcome estimates and uncertainty ranges (URs) were estimated from 1,000 calibrated parameter sets for each country. A previously-calibrated epidemiological model was employed for China.(*8*) Details of the data sources, and calibration method are in the supplementary materials. Visualisation of the model calibration to the epidemiological data can be found in Figure 2A and figures S5-S17.

Vaccine characteristics and implementation

We introduced new TB vaccines into the model in 2025 with immediate scale up. In all three countries, 80% coverage of annual routine vaccination of 9-year-olds was assumed (based upon likely co-administration with the HPV vaccine),(*41, 42*) plus mass campaigns with 70% coverage of 10-year-olds and above,(*43*) with a frequency of the duration of protection or 10 years, whichever was longer. Routine vaccination age assumed co-administration with the Human Papilloma Virus vaccine as part of the school-based vaccination platform.(*44*) Mass campaigns ensured vaccination covered the peak age of infection and disease in each setting and over time, with coverage based upon Menafrivac campaigns.(*43*) Populations of vaccination age without active disease were eligible for vaccination.

Five vaccine characteristics were varied (Figure 1A): vaccine efficacy for prevention of infection, vaccine efficacy for prevention of disease, vaccine efficacy by host infection status, vaccine safety and efficacy in HIV-positive populations, and duration of protection. Ranges for vaccine efficacy and duration were broad, to allow exploration of both in-development and hypothetical vaccines. Scenarios for host infection status for efficacy, outcomes prevented, and HIV-positive safety/efficacy were based upon possible or demonstrated characteristics of pipeline vaccines. Vaccine efficacies for prevention of infection and prevention of disease were varied from 0-100% in 10% intervals, independently and in combination. Efficacy was assumed to be 'degree/leaky', meaning efficacy was implemented as a reduction in natural history parameters.(*26*) For South Africa, vaccination of HIV-positive populations was assumed to be either safe or contraindicated, and efficacy assumed to be equivalent or reduced by 20% relative to HIV-negative populations.(*24, 25*) Although we did not explicitly model drug-resistant TB, vaccine efficacy was assumed to be unaffected by resistance status, due to the different mechanistic pathways of drugs and vaccines. Testing *M.tb* infection status before vaccination was considered programmatically unlikely, therefore vaccine was delivered regardless of infection status, but was assumed to be either effective or not effective by host infection status. The host infection statuses in which the vaccine was assumed to be effective were susceptible, latently infected and recovered populations for vaccines effective both pre- and post-infection, only susceptible populations for pre-infection vaccines, or only latently infected and recovered populations for post-infection vaccines. Duration of protection, assumed to be 'exact',(*7*) was explored for 2, 3, 5, 7, 10, 15, 20, 25 years or lifelong protection.

All possible combinations of the above vaccine characteristics were explored, leading to 3,267 combinations of characteristics in both India and China, and 13,068 combinations in South Africa due to the additional variation in safety and efficacy in HIV-positive populations.

Two phase IIB clinical trials published positive efficacy results in 2018,(*5, 20*) and therefore we highlighted combinations of vaccine characteristics reflective of the trial results from the modelled scenarios. BCG revaccination was assumed to be a pre-infection vaccine, with 50% efficacy either for prevention of infection or prevention of infection and disease, 10 years duration of protection, and contraindicated in HIV-positive populations (due to risk of BCGosis).(*5, 23*) If HIV infection happened after BCG vaccination, we assumed a 20% relative reduction in protection compared to HIV-negative populations due to immunocompromise.(*5, 23*) The M72-AS01$_E$ vaccine was assumed to be a post-infection vaccine, with 50% efficacy for prevention of disease, 20% relative efficacy reduction in HIV-positive populations, and 3 or 10 years duration of protection.(*4, 20, 45*) The above profiles are intended as illustrative for both vaccines, based upon results from recent studies and an approximation of likely characteristics. Efficacy was approximated from the point estimate in recent trials,(*4, 5*) prevention of infection versus disease was based upon recent trials or assumed.(*4, 5*) Pre-/post-infection was based upon the enrolment population in recent trials.(*4, 5*) Assumptions regarding safety in HIV-positive individuals were based upon existing studies, and efficacy in HIV-positive individuals was assumed based upon immunology and experience from other vaccines (*24, 25*). Duration of protection was either based upon available data or assumed.(*46*)

Scenario analyses

Natural history parameter uncertainty was represented in the uncertainty ranges estimated from 1,000 calibrated parameter sets for each country. Scenario analyses were conducted reducing the minimum interval of mass campaigns to 5-yearly, and reporting outcomes in 2035.

Statistical analysis

In the baseline (‘no new vaccine’) scenarios, the proportion of incident TB disease due to new transmission versus reactivation/relapse, and the prevalence of latent *Mycobacterium tuberculosis* infection, were estimated annually for 2000-2050. Primary outcomes of the vaccination scenarios were the median percentage incidence rate reduction in each vaccination scenario compared to the no new vaccine baseline in 2050, and the median cumulative number of TB cases averted 2025-2050 compared to baseline. Outcomes were estimated as the median and range from model runs with the 1,000 calibrated parameter sets for each country.

References and notes

1. World Health Organization. (World Health Organization, Geneva, Switzerland, 2018), vol. 2018.
2. Stop TB Partnership. (2015), vol. 2018.
3. L. Schrager, R. Harris, J. Vekemans, Research and development of new tuberculosis vaccines: a review [version 1; referees: awaiting peer review]. *F1000Research* **7**, (2018).
4. D. R. Tait, M. Hatherill, O. Van Der Meeren, A. M. Ginsberg, E. Van Brakel, B. Salaun, T. J. Scriba, E. J. Akite, H. M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T. G. Evans, P. Gillard, E. Hellström, J. C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T. G. Pascal, M. Tameris, F. Thienemann, R. J. Wilkinson, F. Roman, Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *New England Journal of Medicine*, (2019).
5. E. Nemes, H. Geldenhuys, V. Rozot, K. T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W. A. Hanekom, S. G. Self, L.-G. Bekker, R. Ryall, S. Gurunathan, C. A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R. D. Ellis, B. Landry, D. A. Hokey, R. Hopkins, A. M. Ginsberg, T. J. Scriba, M. Hatherill, Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. *New England Journal of Medicine* **379**, 138-149 (2018).
6. B. R. Bloom, New Promise for Vaccines against Tuberculosis. *New England Journal of Medicine* **379**, 1672-1674 (2018).
7. G. M. Knight, U. K. Griffiths, T. Sumner, Y. V. Laurence, A. Gheorghe, A. Vassall, P. Glaziou, R. G. White, Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proc Natl Acad Sci U S A* **111**, 15520-15525 (2014).
8. R. C. Harris, T. Sumner, G. M. Knight, T. Evans, V. Cardenas, C. Chen, R. G. White, Age-targeted tuberculosis vaccination in China and implications for vaccine development: a modelling study. *The Lancet Global Health* **7**, e209-e218 (2019).
9. R. C. Harris, T. Sumner, G. M. Knight, R. G. White, Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines. *Hum Vaccin Immunother* **12**, 2813-2832 (2016).
10. C. Dye, Z. Fengzeng, S. Scheele, B. Williams, Evaluating the impact of tuberculosis control: Number of deaths prevented by short-course chemotherapy in China. *International journal of epidemiology* **29**, 558-564 (2000).
11. C. J. Murray, J. A. Salomon, Modeling the impact of global tuberculosis control strategies. *Proc Natl Acad Sci U S A* **95**, 13881-13886 (1998).
12. M. Renardy, D. E. Kirschner, Evaluating vaccination strategies for tuberculosis in endemic and non-endemic settings. *J Theor Biol* **469**, 1-11 (2019).
13. L. J. Abu-Raddad, L. Sabatelli, J. T. Achterberg, J. D. Sugimoto, I. M. Longini, C. Dye, M. E. Halloran, Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences* **106**, 13980-13985 (2009).
14. C. Dye, B. G. Williams, Eliminating human tuberculosis in the twenty-first century. *Journal of the Royal Society, Interface / the Royal Society* **5**, 653-662 (2008).
15. C. Dye, P. Glaziou, K. Floyd, M. Raviglione, Prospects for tuberculosis elimination. *Annu Rev Public Health* **34**, 271-286 (2013).
16. D. Young, C. Dye, The development and impact of tuberculosis vaccines. *Cell* **124**, 683-687 (2006).
17. T. Lietman, S. M. Blower, Potential Impact of Tuberculosis Vaccines as Epidemic Control Agents. *Clinical Infectious Diseases* **30**, S316-S322 (2000).
18. E. Ziv, C. L. Daley, S. Blower, Potential public health impact of new tuberculosis vaccines. *Emerg Infect Dis* **10**, 1529-1535 (2004).

19. R. G. White, W. A. Hanekom, J. Vekemans, R. C. Harris, The way forward for tuberculosis vaccines. *The Lancet. Respiratory medicine* **7**, 204-206 (2019).
20. O. Van Der Meeren, M. Hatherill, V. Nduba, R. J. Wilkinson, M. Muyoyeta, E. Van Brakel, H. M. Ayles, G. Henostroza, F. Thienemann, T. J. Scriba, A. Diacon, G. L. Blatner, M. A. Demoitie, M. Tameris, M. Malahleha, J. C. Innes, E. Hellstrom, N. Martinson, T. Singh, E. J. Akite, A. Khatoon Azam, A. Bollaerts, A. M. Ginsberg, T. G. Evans, P. Gillard, D. R. Tait, Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *N Engl J Med*, (2018).
21. P. Mangtani, I. Abubakar, C. Ariti, R. Beynon, L. Pimpin, P. E. M. Fine, L. C. Rodrigues, P. G. Smith, M. Lipman, P. F. Whiting, J. A. Sterne, Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. *Clinical Infectious Diseases* **58**, 470-480 (2014).
22. C. L. Day, M. Tameris, N. Mansoor, M. van Rooyen, M. de Kock, H. Geldenhuys, M. Erasmus, L. Makhethe, E. J. Hughes, S. Gelderbloem, A. Bollaerts, P. Bourguignon, J. Cohen, M. A. Demoitie, P. Mettens, P. Moris, J. C. Sadoff, A. Hawkridge, G. D. Hussey, H. Mahomed, O. Ofori-Anyinam, W. A. Hanekom, Induction and regulation of T-cell immunity by the novel tuberculosis vaccine M72/AS01 in South African adults. *American journal of respiratory and critical care medicine* **188**, 492-502 (2013).
23. E. Nemes, T. J. Scriba, M. Hatherill, Prospects for a vaccine to prevent HIV-related tuberculosis. *Current opinion in HIV and AIDS* **13**, 522-527 (2018).
24. N. F. Crum-Cianflone, M. R. Wallace, Vaccination in HIV-infected adults. *AIDS patient care and STDs* **28**, 397-410 (2014).
25. L. A. Nicolini, D. R. Giacobbe, A. Di Biagio, C. Viscoli, Insights on common vaccinations in HIV-infection: efficacy and safety. *Journal of preventive medicine and hygiene* **56**, E28-32 (2015).
26. R. Ragonnet, J. M. Trauer, J. T. Denholm, N. L. Geard, M. Hellard, E. S. McBryde, Vaccination Programs for Endemic Infections: Modelling Real versus Apparent Impacts of Vaccine and Infection Characteristics. *Scientific reports* **5**, 15468 (2015).
27. N. A. Menzies, E. Wolf, D. Connors, M. Bellerose, A. N. Sbarra, T. Cohen, A. N. Hill, R. Yaesoubi, K. Galer, P. J. White, I. Abubakar, J. A. Salomon, Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. *Lancet Infect Dis* **18**, e228-e238 (2018).
28. UNAIDS. (2018), vol. 2018.
29. J. M. Read, J. Lessler, S. Riley, S. Wang, L. J. Tan, K. O. Kwok, Y. Guan, C. Q. Jiang, D. A. T. Cummings, Social mixing patterns in rural and urban areas of southern China. *Proceedings of the Royal Society B: Biological Sciences* **281**, (2014).
30. S. P. Johnstone-Robertson, D. Mark, C. Morrow, K. Middelkoop, M. Chiswell, L. D. Aquino, L. G. Bekker, R. Wood, Social mixing patterns within a South African township community: implications for respiratory disease transmission and control. *American journal of epidemiology* **174**, 1246-1255 (2011).
31. J. Mossong, N. Hens, M. Jit, P. Beutels, K. Auranen, R. Mikolajczyk, M. Massari, S. Salmaso, G. S. Tomba, J. Wallinga, J. Heijne, M. Sadkowska-Todys, M. Rosinska, W. J. Edmunds, Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS medicine* **5**, e74 (2008).
32. United Nations Department of Economic and Social Affairs Population Division. (2017).
33. S. Funk. (2017), vol. 2017.
34. World Health Organization. (http://www.who.int/tb/country/data/download/en/, 2017), vol. 2017.
35. S. Satyanarayana, S. A. Nair, S. S. Chadha, R. Shivashankar, G. Sharma, S. Yadav, S. Mohanty, V. Kamineni, N. C. Wilson, A. D. Harries, P. K. Dewan, From Where Are

Tuberculosis Patients Accessing Treatment in India? Results from a Cross-Sectional Community Based Survey of 30 Districts. *PloS one* **6**, e24160 (2011).
36. J. Stover, T. Brown, R. Puckett, W. Peerapatanapokin, Updates to the Spectrum/Estimations and Projections Package model for estimating trends and current values for key HIV indicators. *AIDS (London, England)* **31 Suppl 1**, S5-s11 (2017).
37. SANAC. (South Africa, 2017), vol. 2018.
38. J. Stover, P. Johnson, B. Zaba, M. Zwahlen, F. Dabis, R. E. Ekpini, The Spectrum projection package: improvements in estimating mortality, ART needs, PMTCT impact and uncertainty bounds. *Sexually transmitted infections* **84 Suppl 1**, i24-i30 (2008).
39. UNAIDS. (2017), vol. 2018.
40. A. Gelman, K. Shirley, in *Handbook of Markov Chain Monte Carlo,* S. Brooks, A. Gelman, G. L. Jones, X. Meng, Eds. (CRC Press, 2011), chap. Chapter 6: Inference from Simulations and Monitoring Convergence.
41. HPV information centre. (2016).
42. UNESCO Institute for Statistics. (2016), vol. 2017.
43. M. Harouna Djingarey. (2014), vol. 2016.
44. WHO, Human papillomavirus vaccines: WHO position paper, October 2014. *WHO Weekly Epidemiological Report* **89**, 465-492 (2014).
45. N. Kumarasamy, S. Poongulali, F. E. Beulah, E. J. Akite, L. N. Ayuk, A. Bollaerts, M. A. Demoitie, E. Jongert, O. Ofori-Anyinam, O. Van Der Meeren, Long-term safety and immunogenicity of the M72/AS01E candidate tuberculosis vaccine in HIV-positive and -negative Indian adults: Results from a phase II randomized controlled trial. *Medicine (Baltimore)* **97**, e13120 (2018).
46. I. Abubakar, L. Pimpin, C. Ariti, R. Beynon, P. Mangtani, J. A. Sterne, P. E. Fine, P. G. Smith, M. Lipman, D. Elliman, J. M. Watson, L. N. Drumright, P. F. Whiting, E. Vynnycky, L. C. Rodrigues, Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health technology assessment (Winchester, England)* **17**, 1-372, v-vi (2013).
47. R Core Team. (R Foundation for Statistical Computing, Vienna, Austria, 2014).
48. World Health Organization. (Geneva, Switzerland, 2017), vol. 2017
49. D. Schenzle, An age-structured model of pre- and post-vaccination measles transmission. *IMA J Math Appl Med Biol* **1**, 169-191 (1984).
50. S. Rajagopalan, Tuberculosis and aging: a global health problem. *Clin Infect Dis* **33**, 1034-1039 (2001).
51. Richard Aspinall*,* R. Harris, Ed. (2015).
52. L. Aaron, D. Saadoun, I. Calatroni, O. Launay, N. Mémain, V. Vincent, G. Marchal, B. Dupont, O. Bouchaud, D. Valeyre, O. Lortholary, Tuberculosis in HIV-infected patients: a comprehensive review. *Clinical Microbiology and Infection* **10**, 388-398 (2004).
53. G. Di Perri, M. Cruciani, M. C. Danzi, R. Luzzati, G. De Checchi, M. Malena, S. Pizzighella, R. Mazzi, M. Solbiati, E. Concia, et al., Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet (London, England)* **2**, 1502-1504 (1989).
54. C. L. Daley, P. M. Small, G. F. Schecter, G. K. Schoolnik, R. A. McAdam, W. R. Jacobs, Jr., P. C. Hopewell, An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* **326**, 231-235 (1992).
55. E. Vynnycky, P. E. Fine, The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and infection* **119**, 183-201 (1997).
56. I. Sutherland, E. Svandova, S. Radhakrishna, 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* **63**, 255-268 (1982).
57. K. Styblo, Epidemiology of Tuberculosis. Selected papers (Royal Netherlands Tuberculosis Association, The Hague (the Netherlands)). (1991).
58. E. Vynnycky, An Investigation of the Transmission Dynamics of M. tuberculosis. (University of London). (1996).
59. P. A. Selwyn, D. Hartel, V. A. Lewis, E. E. Schoenbaum, S. H. Vermund, R. S. Klein, A. T. Walker, G. H. Friedland, A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* **320**, 545-550 (1989).
60. F. Vazquez, R. White, R. Harris, A systematic review and meta-analysis of the effect of HIV status on the incidence of tuberculosis disease among individuals with latent Mycobacterium tuberculosis infection. (In preparation).
61. P. J. Dodd, A. J. Prendergast, C. Beecroft, B. Kampmann, J. A. Seddon, The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. *Thorax* **72**, 559-575 (2017).
62. A. B. Suthar, S. D. Lawn, J. del Amo, H. Getahun, C. Dye, D. Sculier, T. R. Sterling, R. E. Chaisson, B. G. Williams, A. D. Harries, R. M. Granich, Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS medicine* **9**, e1001270 (2012).
63. P. Cao, W. W. Li, A. R. Morris, P. D. Horrocks, C. Q. Yuan, Y. Yang, Investigation of the antibiofilm capacity of peptide-modified stainless steel. *Royal Society open science* **5**, 172165 (2018).
64. J. Stover, P. Johnson, T. Hallett, M. Marston, R. Becquet, I. M. Timaeus, The Spectrum projection package: improvements in estimating incidence by age and sex, mother-to-child transmission, HIV progression in children and double orphans. *Sexually transmitted infections* **86 Suppl 2**, ii16-21 (2010).
65. Sutherland I, "The ten-year incidence of clinical tuberculosis following “conversion” in 2550 individuals aged 14 to 19 years.," *TSRU Conference report* (KNCV, The Hague, The Netherlands, 1968).
66. S. H. Ferebee, Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibliotheca tuberculosea* **26**, 28-106 (1970).
67. G. W. Comstock, Epidemiology of tuberculosis. *Am Rev Respir Dis* **125**, 8-15 (1982).
68. M. G. M. Gabriela, P. Rodrigues, F. M. Hilker, N. B. Mantilla-Beniers, M. Muehlen, A. Cristina Paulo, G. F. Medley, Implications of partial immunity on the prospects for tuberculosis control by post-exposure interventions. *Journal of theoretical biology* **248**, 608-617 (2007).
69. B. M. Murphy, B. H. Singer, S. Anderson, D. Kirschner, Comparing epidemic tuberculosis in demographically distinct heterogeneous populations. *Mathematical biosciences* **180**, 161-185 (2002).
70. E. W. Tiemersma, M. J. van der Werf, M. W. Borgdorff, B. G. Williams, N. J. Nagelkerke, Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PloS one* **6**, e17601 (2011).
71. A. Odone, S. Amadasi, R. G. White, T. Cohen, A. D. Grant, R. M. Houben, The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *PloS one* **9**, e112017 (2014).
72. E. L. Corbett, C. J. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Raviglione, C. Dye, The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Archives of internal medicine* **163**, 1009-1021 (2003).
73. Y. D. Mukadi, D. Maher, A. Harries, Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS (London, England)* **15**, 143-152 (2001).

74. M. Lindhart, The statistics of pulmonary tuberculosis in denmark 1925-1934: A statistical investigation on the occurrence of pulmonary tuberculosis in the period 1925-1934, worked out on the basis of the danish national health service file of notified cases and of deaths. *Journal of the American Medical Association* **113**, 2447-2447 (1939).
75. P. Nunn, R. Brindle, L. Carpenter, J. Odhiambo, K. Wasunna, R. Newnham, W. Githui, S. Gathua, M. Omwega, K. McAdam, Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality. *Am Rev Respir Dis* **146**, 849-854 (1992).
76. D. W. Mulder, A. J. Nunn, A. Kamali, J. Nakiyingi, H. U. Wagner, J. F. Kengeya-Kayondo, Two-year HIV-1-associated mortality in a Ugandan rural population. *Lancet (London, England)* **343**, 1021-1023 (1994).
77. K. Styblo, in *Recent Advances in Respiratory Medicine,* D. C. Flenley, T. L. Petty, Eds. (Churchill, London, 1986), vol. 4, pp. 77-108.
78. S. Grzybowski, D. Enarson, [Results in pulmonary tuberculosis patients under various treatment program conditions]. *Bulletin of the International Union against Tuberculosis* **53**, 70-75 (1978).
79. R. M. Houben, J. R. Glynn, S. Mboma, T. Mzemba, N. J. Mwaungulu, L. Mwaungulu, M. Mwenibabu, J. Mpunga, N. French, A. C. Crampin, The impact of HIV and ART on recurrent tuberculosis in a sub-Saharan setting. *AIDS (London, England)* **26**, 2233-2239 (2012).
80. Y. F. van der Heijden, F. Karim, T. Chinappa, G. Mufamadi, L. Zako, B. E. Shepherd, F. Maruri, M. Y. S. Moosa, T. R. Sterling, A. S. Pym, Older age at first tuberculosis diagnosis is associated with tuberculosis recurrence in HIV-negative persons. *The International Journal of Tuberculosis and Lung Disease* **22**, 871-877 (2018).
81. M. H. Dangisso, E. M. Woldesemayat, D. G. Datiko, B. Lindtjorn, Long-term outcome of smear-positive tuberculosis patients after initiation and completion of treatment: A ten-year retrospective cohort study. *PloS one* **13**, e0193396 (2018).
82. P. J. Dodd, C. Looker, I. D. Plumb, V. Bond, A. Schaap, K. Shanaube, M. Muyoyeta, E. Vynnycky, P. Godfrey-Faussett, E. L. Corbett, N. Beyers, H. Ayles, R. G. White, Age- and Sex-Specific Social Contact Patterns and Incidence of Mycobacterium tuberculosis Infection. *American journal of epidemiology* **183**, 156-166 (2016).
83. M. Baguelin, S. Flasche, A. Camacho, N. Demiris, E. Miller, W. J. Edmunds, Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study. *PLoS medicine* **10**, e1001527 (2013).
84. WHO. (http://www.who.int/tb/country/data/download/en/, 2015).
85. WHO. (http://www.who.int/tb/country/data/download/en/, 2015), vol. 2016.
86. T. Kufa, T. Mabuto, E. Muchiri, S. Charalambous, D. Rosillon, G. Churchyard, R. C. Harris, Incidence of HIV-Associated Tuberculosis among Individuals Taking Combination Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PloS one* **9**, e111209 (2014).
87. S. S. Lal, M. Uplekar, I. Katz, K. Lonnroth, R. Komatsu, H. M. Yesudian Dias, R. Atun, Global Fund financing of public-private mix approaches for delivery of tuberculosis care. *Trop Med Int Health* **16**, 685-692 (2011).
88. P. Bhatter, A. Chatterjee, N. Mistry, The dragon and the tiger: realties in the control of tuberculosis. *Interdisciplinary perspectives on infectious diseases* **2012**, 625459-625459 (2012).
89. R. M. Houben, N. A. Menzies, T. Sumner, G. H. Huynh, N. Arinaminpathy, J. D. Goldhaber-Fiebert, H. H. Lin, C. Y. Wu, S. Mandal, S. Pandey, S. C. Suen, E. Bendavid, A. S. Azman, D. W. Dowdy, N. Bacaer, A. S. Rhines, M. W. Feldman, A. Handel, C. C. Whalen, S. T. Chang, B. G. Wagner, P. A. Eckhoff, J. M. Trauer, J. T. Denholm, E. S. McBryde, T. Cohen, J. A. Salomon, C. Pretorius, M. Lalli, J. W. Eaton, D. Boccia, M.

Hosseini, G. B. Gomez, S. Sahu, C. Daniels, L. Ditiu, D. P. Chin, L. Wang, V. K. Chadha, K. Rade, P. Dewan, P. Hippner, S. Charalambous, A. D. Grant, G. Churchyard, Y. Pillay, L. D. Mametja, M. E. Kimerling, A. Vassall, R. G. White, Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *The Lancet. Global health* **4**, e806-e815 (2016).
90. L. Wang, H. Zhang, Y. Ruan, D. P. Chin, Y. Xia, S. Cheng, M. Chen, Y. Zhao, S. Jiang, X. Du, G. He, J. Li, S. Wang, W. Chen, C. Xu, F. Huang, X. Liu, Y. Wang, Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. *The Lancet* **383**, 2057-2064 (2014).
91. WHO. (2013).
92. H. Zhang, F. Huang, W. Chen, X. Du, M. G. Zhou, J. Hu, L. X. Wang, Estimates of tuberculosis mortality rates in China using the disease surveillance point system, 2004-2010. *Biomed Environ Sci* **25**, 483-488 (2012).
93. W. B. Wang, Q. Zhao, Z. A. Yuan, W. L. Jiang, M. L. Liu, B. Xu, Deaths of tuberculosis patients in urban China: a retrospective cohort study. *The International Journal of Tuberculosis and Lung Disease* **17**, 493-498 (2013).
94. G. Yang, C. Rao, J. Ma, L. Wang, X. Wan, G. Dubrovsky, A. D. Lopez, Validation of verbal autopsy procedures for adult deaths in China. *International journal of epidemiology* **35**, 741-748 (2006).
95. J. Cheng, L. Wang, H. Zhang, Y. Xia, Diagnostic Value of Symptom Screening for Pulmonary Tuberculosis in China. *PloS one* **10**, e0127725 (2015).
96. H. Lin, L. Wang, H. Zhang, Y. Ruan, D. P. Chin, C. Dye, Tuberculosis control in China: use of modelling to develop targets and policies. *Bulletin of the World Health Organization* **93**, 790-798 (2015).
97. World Health Organization. (Geneva, Switzerland, 2016), vol. 2017
98. S. Pandey, V. K. Chadha, R. Laxminarayan, N. Arinaminpathy, Estimating tuberculosis incidence from primary survey data: a mathematical modeling approach. *The International Journal of Tuberculosis and Lung Disease* **21**, 366-374 (2017).
99. P. J. Dodd, E. Gardiner, R. Coghlan, J. A. Seddon, Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *The Lancet Global Health* **2**, e453-e459 (2014).
100. S. Mandal, V. K. Chadha, R. Laxminarayan, N. Arinaminpathy, Counting the lives saved by DOTS in India: a model-based approach. *BMC medicine* **15**, 47 (2017).
101. P. Marjoram, J. Molitor, V. Plagnol, S. Tavare, Markov chain Monte Carlo without likelihoods. *Proc Natl Acad Sci U S A* **100**, 15324-15328 (2003).
102. F. Jabot, T. Faure, N. Dumoulin, C. Albert, Adapted by Funk S and Knight G. (2014).
103. Advisory Committee on Vaccines & Immunization Practices. (2017), vol. 2017.
104. P.-H. Lambert*,* W. Haneknom, Ed. (2016).
105. HPV information centre. (2016), vol. 2016.
106. Stakeholders from Aeras; BMGF, TBVI, and WHO. (2016).
107. G. Widmeyer*,* W. Hannekom, Ed. (2016).
108. S. Wu, P. Yang, H. Li, C. Ma, Y. Zhang, Q. Wang, Influenza vaccination coverage rates among adults before and after the 2009 influenza pandemic and the reasons for non-vaccination in Beijing, China: a cross-sectional study. *BMC Public Health* **13**, 636 (2013).
109. Y. Zheng, P. Yang, S. Wu, C. Ma, H. Seale, C. R. MacIntyre, Q. Wang, A cross-sectional study of factors associated with uptake of vaccination against influenza among older residents in the postpandemic season in Beijing, China. *BMJ Open* **3**, (2013).
110. B. R. Das, G. Kakoti, H. Bahety, N. Das, A. H. Medhi, Adult Japanese Encephalitis mass vaccination campaign: A rapid convenience assessment. *International Journal of Current Research and Academic Review* **2**, 30-36 (2014).

111. L. Gao, W. Lu, L. Bai, X. Wang, J. Xu, A. Catanzaro, V. Cardenas, X. Li, Y. Yang, J. Du, H. Sui, Y. Xia, M. Li, B. Feng, Z. Li, H. Xin, R. Zhao, J. Liu, S. Pan, F. Shen, J. He, S. Yang, H. Si, Y. Wang, Z. Xu, Y. Tan, T. Chen, W. Xu, H. Peng, Z. Wang, T. Zhu, F. Zhou, H. Liu, Y. Zhao, S. Cheng, Q. Jin, L.-N. s. team, Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study. *Lancet Infect Dis* **15**, 310-319 (2015).
112. R. M. G. J. Houben, P. J. Dodd, The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS medicine* **13**, e1002152 (2016).
113. Institute for Health Metrics and Evaluation (IHME). (IHME, University of Washington, Seattle, WA, 2016), vol. 2018.
114. L. Lebina, P. M. Abraham, M. Milovanovic, K. Motlhaoleng, R. E. Chaisson, M. Rakgokong, J. Golub, E. Variava, N. A. Martinson, Latent tuberculous infection in schoolchildren and contact tracing in Matlosana, North West Province, South Africa. *Int J Tuberc Lung Dis* **19**, 1290-1292 (2015).
115. S. den Boon, S. Verver, B. J. Marais, D. A. Enarson, C. J. Lombard, E. D. Bateman, E. Irusen, A. Jithoo, R. P. Gie, M. W. Borgdorff, N. Beyers, Association between passive smoking and infection with Mycobacterium tuberculosis in children. *Pediatrics* **119**, 734-739 (2007).
116. K. Shanaube, C. Sismanidis, H. Ayles, N. Beyers, A. Schaap, K.-A. Lawrence, A. Barker, P. Godfrey-Faussett, Annual Risk of Tuberculous Infection Using Different Methods in Communities with a High Prevalence of TB and HIV in Zambia and South Africa. *PloS one* **4**, e7749 (2009).
117. R. Wood, S. Johnstone-Robertson, P. Uys, J. Hargrove, K. Middelkoop, S. D. Lawn, L. G. Bekker, Tuberculosis transmission to young children in a South African community: Modeling household and community infection risks. *Clinical Infectious Diseases* **51**, 401-408 (2010).
118. F. E. Kritzinger, S. den Boon, S. Verver, D. A. Enarson, C. J. Lombard, M. W. Borgdorff, R. P. Gie, N. Beyers, No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa. *Trop Med Int Health* **14**, 136-142 (2009).
119. H. Mahomed, T. Hawkridge, S. Verver, L. Geiter, M. Hatherill, D. A. Abrahams, R. Ehrlich, W. A. Hanekom, G. D. Hussey, Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. *Int J Tuberc Lung Dis* **15**, 331-336 (2011).
120. J. R. Ncayiyana, J. Bassett, N. West, D. Westreich, E. Musenge, M. Emch, A. Pettifor, C. F. Hanrahan, S. R. Schwartz, I. Sanne, A. van Rie, Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. *BMC infectious diseases* **16**, 661 (2016).
121. R. M. G. J. Houben, D. W. Dowdy, A. Vassall, T. Cohen, M. P. Nicol, R. M. Granich, J. E. Shea, P. Eckhoff, C. Dye, M. E. Kimerling, R. G. White, How can mathematical models advance tuberculosis control in high HIV prevalence settings? *International Journal of Tuberculosis and Lung Disease* **18**, 509-514+i (2014).
122. T. Mahmood. (2016), vol. 2018.
123. Chinese Center for Disease Control and Prevention China National Tuberculosis Prevalence Survey 2000. (2000).
124. V. K. Chadha, R. Sarin, P. Narang, K. R. John, K. K. Chopra, R. Jitendra, D. K. Mendiratta, V. Vohra, A. N. Shashidhara, G. Muniraj, P. G. Gopi, P. Kumar, Trends in the annual risk of tuberculous infection in India. *Int J Tuberc Lung Dis* **17**, 312-319 (2013).
125. S. Nasreen, M. Shokoohi, M. S. Malvankar-Mehta, Prevalence of Latent Tuberculosis among Health Care Workers in High Burden Countries: A Systematic Review and Meta-Analysis. *PloS one* **11**, e0164034 (2016).

Supplementary Materials

Acknowledgements

We would like to sincerely thank Willem Hanekom (Bill and Melinda Gates Foundation) for input in to design of the research question, and feedback on various versions of this work. We are very grateful to Johan Vekemans and Birgitte Giersing (WHO), Ann Ginsberg, Danny Casimiro, and Jacqui Shea (Aeras), Bernard Fritzell, Nick Drager and Frank Verrek (TBVI), and Helen Fletcher (LSHTM) for guidancein the development of this work. We also gratefully acknowledge Chathika Weerasuriya (LSHTM) for preparation of the India contact matrix, and Anne Kasmar (BMGF) for collation of data to inform assumptions regarding vaccine efficacy in HIV-positive populations.

Funding

This research was funded by the Bill and Melinda Gates Foundation (grant number: OPP1160830). The funder (Bill and Melinda Gates Foundation) contributed to the development of the research question, stakeholder discussions on the approach, and provided feedback on early versions of this work. RCH was funded by the Bill and Melinda Gates Foundation (OPP1160830) and the UK Medical Research Council (MRC) under the LSHTM MRC vaccines scholarship program. RGW was funded by the UK MRC and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement that is also part of the EDCTP2 programme supported by the European Union (MR/P002404/1), the Bill and Melinda Gates Foundation (TB Modelling and Analysis Consortium: OPP1084276/OPP1135288, CORTIS: OPP1137034/OPP1151915, Vaccines: OPP1160830) and UNITAID (4214-LSHTM-Sept15; PO 8477-0-600).

Author contributions

RCH, TS and RGW conceptualised the research, were responsible for funding acquisition and developed the methodology. RCH and RGW managed project administration, TS and RGW provided supervision. All authors contributed to data curation. RCH and TS conducted the formal analysis, with validation by RGW. Study investigation, modelling, visualisation, writing of original draft were conducted by RCH. All authors reviewed, edited and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests. After manuscript submission, RCH began employment at Sanofi-Pasteur, but on work unrelated to the subject of this research.

Data and materials availability

All data associated with this study are available in the main text or the supplementary materials.

Figure headings

Figure 1: Vaccine characteristics and model structure. A) Effect on the natural history of TB disease by vaccines that help prevent infection (purple) or disease (red) and in populations pre-infection (green) or post-infection (yellow). B) Mathematical model of *M.tuberculosis* transmission and TB disease natural history, consisting of unvaccinated (top left) and vaccinated (bottom left) states. Symbols are defined in the supplement.

Figure 2: Model epidemiological fit

A) Model epidemiological fit to country-level incidence rate data, stratified by age (overall, black; children, red; adults, blue) and HIV status (overall, black; HIV-positive, orange) where available. Black circles and vertical bars represent data and ranges; solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note y axes scale differences. B) Proportion of new infections/transmission (red) versus reactivation/relapse (black) disease in China, South Africa, and India. Lines are median estimates, and shaded areas represent the modelled uncertainty range. All other model calibration plots can be found in the online supplement.

Figure 3: Vaccine impact by prevention of infection and prevention of disease efficacy.

Incidence rate reduction in 2050 by country from a vaccine with 10 years duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (P&PI, top row), pre-infection populations (PRI, centre row) or post-infection populations (PSI, bottom row), assumed safe and efficacious in HIV-positive populations, delivered from 2025 as routine vaccination of 9-year-olds and as 10-yearly mass campaigns in China, South Africa, and India.

Figure 4: Vaccine impact varying safety and efficacy in HIV-positive populations.

Incidence rate reduction in South Africa in 2050 for vaccines assuming varying safety and efficacy in HIV-positive populations: Safe and equally effective in HIV-positive populations (left panel); safe, with 20% reduction in efficacy compared to HIV-negative populations (centre panel); and contraindicated in HIV-positive populations (right panel). Vaccine assumed efficacious in pre- and post-infection populations (P&PI), with duration of protection of 10 years, 10-yearly mass campaigns, and routine vaccination of 9-year-olds.

Figure 5: Vaccine impact varying duration of protection

Projected incidence rate reductions in 2050 by duration of protection for pre- and post-infection (P&PI) prevention of infection and disease (POI&D) vaccines with 10-yearly mass campaigns in China, South Africa, and India.