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New tuberculosis vaccines: advances in clinical development and modelling

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Tuberculosis remains a major source of morbidity and mortality worldwide, with 10 million cases and 1.5 million deaths in 2018. Achieving 'End TB' prevention and care goals by 2035 will likely require a new tuberculosis vaccine. The tuberculosis vaccine development pipeline has seen encouraging progress; however, questions around their population impact and implementation remain. Mathematical modelling investigates these questions to inform vaccine development and deployment strategies. We provide an update on the current vaccine development pipeline, and a systematic literature review of mathematical modelling of the epidemiological impact of new tuberculosis vaccines. Fourteen prophylactic tuberculosis vaccine candidates are currently in clinical trials. Two candidates have shown promise in phase II proof-of-concept efficacy trials: M72/AS01$_E$ demonstrated 49.7% (95% CI; 2.1, 74.2) protection against tuberculosis disease, and BCG revaccination demonstrated 45.4% (95% CI; 6.4, 68.1) protection against sustained *Mycobacterium tuberculosis* infection. Since the last modelling review, new studies have investigated the epidemiological impact of differential vaccine characteristics, age targeting and spatial/risk group targeting. Critical research priorities for M72/AS01$_E$ include completing the currently in-design trial, powered to improve the precision of efficacy estimates, include uninfected populations and further assess safety and immunogenicity in HIV-infected people. For BCG revaccination, the priority is completing the ongoing confirmation of efficacy trial. Critical modelling gaps remain on the full value proposition of vaccines, comparisons with other interventions and more realistic implementation strategies. Using carefully designed trials and modelling, we must prepare for success, to ensure that new vaccines will be promptly received by those most in need.

Keywords: clinical trial, mathematical model, systematic review, tuberculosis, vaccine.

Introduction

Tuberculosis (TB) was the leading cause of death due to a single infectious pathogen worldwide in 2018, with an estimated 10 million new cases and approximately 1.5 million deaths [1]. Over two-thirds of cases are found amongst eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. Global TB control efforts are hindered by the emergent epidemic of drug-resistant tuberculosis. Approximately 500 000 cases of rifampicin-resistant tuberculosis (RR-TB) arose in 2018, of which 78% were multi-drug-resistant tuberculosis (MDR-TB).

The global community has set ambitious TB control and elimination targets. The World Health Organization (WHO) End TB Strategy defines milestones and targets for TB control by 2035, which aim to reduce TB deaths by 95% and incidence by 90% compared with 2015 [2]. Despite these goals, progress has been slow. TB incidence declined only 1.6% per year between 2000 and 2018, and TB deaths declined 11% between 2015 and 2018. To

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affirm its commitment to TB control, in 2019, the UN General Assembly issued a political declaration following the first-ever high-level meeting on TB, which included targets to mobilize at least USD 13 billion towards TB diagnosis, care and prevention by 2022, and at least USD 2 billion towards TB research.

The End TB Strategy recognizes that a lack of optimal tools to prevent TB, including a vaccine, is a key barrier for TB control, and calls for intensified research and innovation in this area. Encouragingly, the TB vaccine pipeline has recently seen rapid development. There are prophylactic vaccine candidates at all stages along the clinical development pathway [3,4], including three in phase I, eight in phase II and three in phase III, reflecting a diverse array of antigens and proposed mechanisms of vaccine effect. Two recent phase II efficacy trials have reported promising results. A trial of adolescent bacille Calmette–Guérin (BCG) revaccination in South Africa demonstrated 45.4% reduction in sustained *Mycobacterium tuberculosis* (Mtb) infection [5]. A trial of the new TB vaccine candidate M72/AS01$_E$ in adults reported 49.7% efficacy in preventing TB disease at 3 years of follow-up [6]. Given their likely integral role in TB elimination, we review the current state of clinical development of TB vaccines. In the following sections, we provide a general classification of TB vaccines and review the current candidates along the TB vaccine clinical development pathway. We summarize the mathematical modelling literature used to inform vaccine development, focusing on models that address the epidemiologic impact of new TB vaccines. Finally, we describe the future for TB vaccines in the effort towards TB elimination.

Classification of tuberculosis vaccines

Besides conventional characteristics such as the duration of protection and vaccine efficacy, we classify prophylactic TB vaccines along the two major qualitative axes: (a) the host infection status required for efficacy and (b) the mechanism of effect (Figure 1).

The host infection status required for efficacy is defined relative to the tuberculosis natural history state of the vaccine recipient in which the vaccine is effective. Vaccines effective only in individuals who are not infected by Mtb are referred to as 'preinfection' (PRI) vaccines (sometimes referred to as 'pre-exposure' vaccines). In contrast, vaccines effective in individuals who either have current latent infection or have recovered from disease (through treatment or through natural cure) are referred to as 'postinfection' (PSI) vaccines (sometimes referred to as 'postexposure' vaccines). Vaccines effective in uninfected, latent and recovered individuals are known as 'pre- and postinfection' vaccines (P&PI). Therapeutic vaccines, which modify disease in those with active tuberculosis, are not considered in this review.

We classify the mechanism of effect as the point along the progression from infection with Mtb to the development of active tuberculosis disease at which the vaccine exerts its effect. A prevention of infection (POI) vaccine reduces the probability of infection by Mtb. In contrast, the probability of infection is unaffected directly by a prevention of disease (POD) vaccine. POD vaccines act through one or more of (a) reducing the rate of progression to active disease following infection or reinfection with Mtb ('fast progression'); (b) reducing the rate of reactivation from latent infection to active disease; and/or (c) reducing the rate of relapse from recovered to active disease.

Candidates in clinical trials

The need for new TB vaccines and challenges in development

Infant BCG vaccination protects against severe extrapulmonary forms of TB in young children and is an important mainstay of national immunization programmes in TB endemic countries. However, BCG is contraindicated in HIV-positive individuals, an epidemiologically important population, due to an increased risk of disseminated BCGosis. Additionally, estimates of BCG efficacy against adolescent and adult pulmonary TB vary, ranging from an 'absence of clinically important benefit' in Malawi and India, to almost 80% protection in the UK and a North American Indigenous population [7–9]. Vaccines effective against pulmonary TB in adolescents and adults, but also in the elderly, and that are safe and effective in latently infected individuals and HIV-positive individuals are urgently needed.

The major impediment to new TB vaccine development is the lack of a correlate of protection, which necessitates large, long and expensive trials to demonstrate prophylactic efficacy against TB disease. The relatively low incidence of TB implies that adequately powered phase III trials will typically require at least 10 000 participants and cost in the

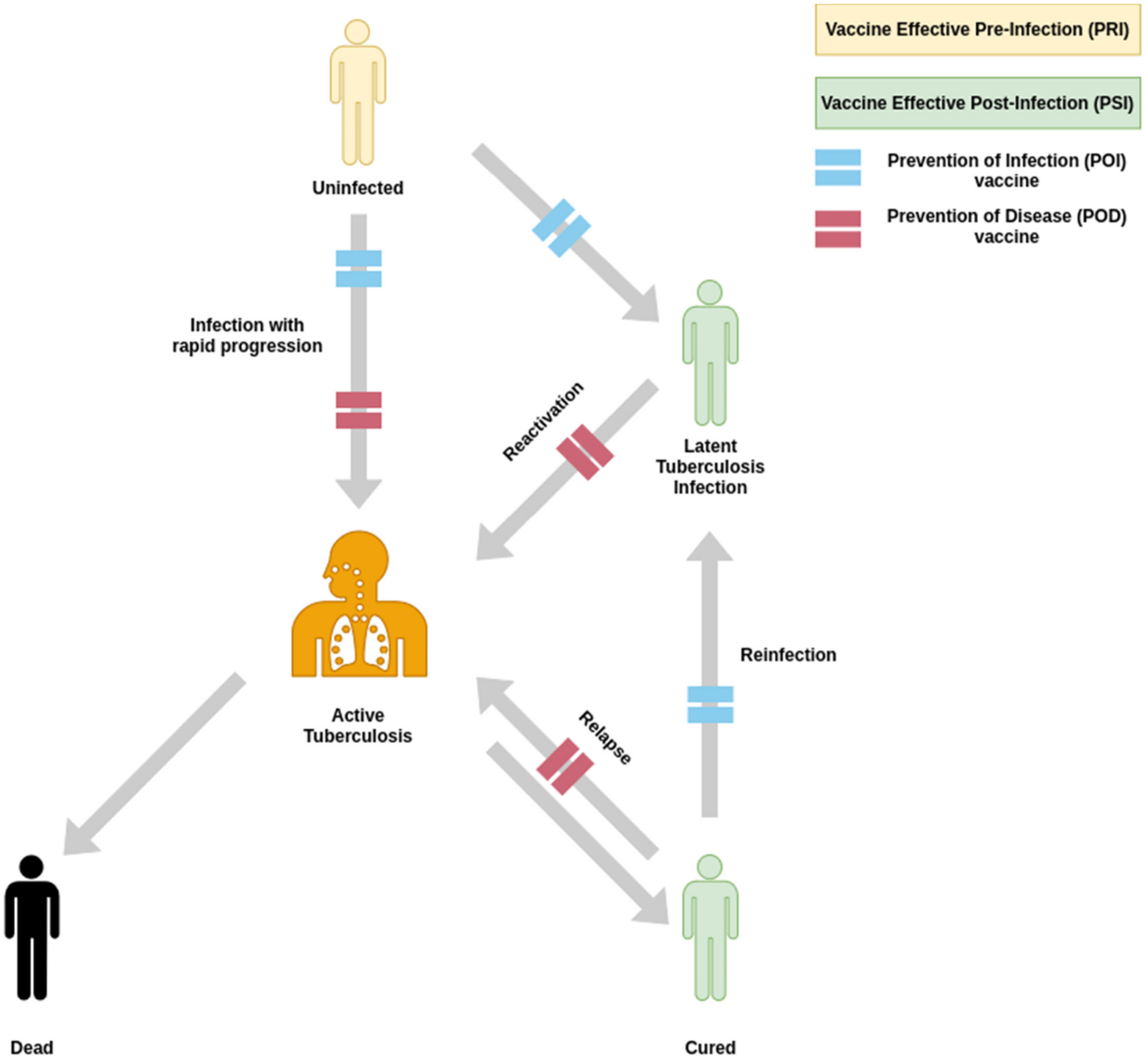

Fig. 1 *Tuberculosis vaccine mechanism of effect and host infection status required for efficacy. Mechanism of effect is indicated by double bars along natural history pathways. Host infection status required for efficacy is indicated by background colour.*

order of USD 100 million or more. Until a correlate of protection exists to allow immunobridging, efficacy trials may be necessary for extending registration to important populations other than those in the initial licensure trial, including HIV-positive populations, other age groups and other geographies. Short, inexpensive challenge studies are not yet an option in TB, as unlike malaria or influenza where quick, safe and effective treatments are available, TB treatment lasts at least 6 months and carries a risk of drug resistance.

Progress and innovation in clinical trials

Despite these challenges, the current TB vaccine candidate development pipeline is the strongest to date. Fourteen vaccine candidates (Figure 2) are in clinical development, including seven entering or

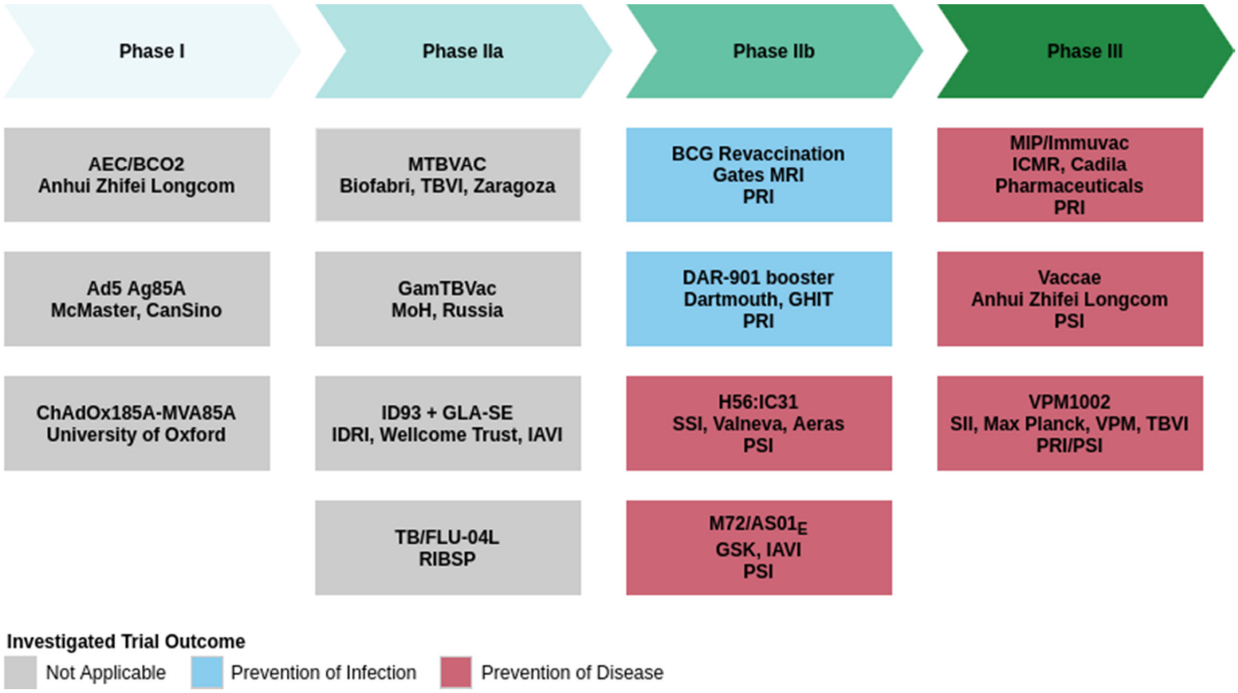

Fig. 2 *Classification of tuberculosis vaccines by trial phase, trial outcome (POI or POD) and population where vaccines were tested for efficacy (PSI, PRI or P&PI). The phase and trial outcome are based on the latest ongoing or completed clinical trials per candidate. POI and POD trial outcomes are only applicable to proof-of-concept or efficacy trials. H56:IC31 is under investigation for prevention of recurrent disease effect. VPM1002 is under investigation for both prevention of primary and recurrent disease effects. The host infection status required for efficacy reflects the various populations the candidate has been or is being trialled in for efficacy.*

already in proof-of-concept or full efficacy trials. The pipeline includes vaccines using viral vectors, live attenuated Mtb, inactivated whole cell and protein/adjuvant technologies.

Alongside the classical phase I/II/III trials, phase IIB (proof-of-concept) trials have been used to provide an initial assessment of efficacy for new TB vaccine candidates. These are valuable in stage-gating and de-risking the TB pipeline before the more substantive investment of a phase III trial. Studies in adults have historically focused on pulmonary disease as their outcome. Now, driven by the need for earlier indications of efficacy and de-risking of phase III investment, proof-of-concept trials may investigate infection or recurrence outcomes. Rates of infection and recurrence are greater than primary disease, so can help minimize trial size, as can recruiting other high-risk populations such as household contacts and healthcare workers. Furthermore, modelling has demonstrated the important contribution of reactivation and relapse to disease burden in many settings, leading to increased recognition of the need to protect postinfection (latently infected or recovered) populations [10–12]. Therefore, increasingly, studies either include or exclusively recruit postinfection populations.

We summarize the status of pipeline candidates in human trials and publicly available plans for upcoming trials.

Vaccine pipeline

Phase I

The early TB vaccine candidate pipeline is currently focused on new approaches to vaccine delivery (e.g. aerosolized, intranasal).

Two adenovirus-vectored candidates based on the mycobacterial antigen 85A are currently in separate phase I trials: Ad5-Ag85A [13] and ChAdOx185A-MVA85A prime-boost [14]. Both trials aim to investigate the safety and immunogenicity of aerosolized compared with intramuscular delivery

in BCG-vaccinated adults. The ongoing phase I trial for Ad5-Ag85A, developed by McMaster University, follows IGRA-negative adults for 24 weeks postadministration. The ongoing phase I trial for ChAdOx185A-MVA85A, developed at Oxford University, is following 39 IGRA-negative participants for 168 days and is expected to complete in late 2020. A phase IB/IIA trial for dose ranging and age de-escalation is ongoing in Uganda, with completion expected in 2022 [15], focusing on intramuscular administration.

AEC/BC02, developed by Anhui Zhifei Longcom, China, is a whole-cell freeze-dried Mtb vaccine delivered in six intramuscular doses. A nonrandomized open-label placebo-controlled phase I trial recruiting 135 adults (18–45 years old) with varying host infection status was completed in 2019, but results are unpublished at the time of writing [16].

Phase IIA

Four candidates have recently completed or are currently in phase IIA trials: TB/FLU-04L, GAMTBVac, MTBVAC and ID93 + GLA-SE.

TB/FLU-04L comprises a recombinant replication-deficient influenza virus A expressing mycobacterial antigen ESAT-6, developed by Research Institute of Influenza, St Petersburg [17]. A randomized open-label phase I trial of intranasal or sublingual vaccine administration in 36 IGRA-negative 18- to 50-year-olds has demonstrated safety and tolerability [18]. A phase IIA trial in IGRA-positive individuals is being implemented.

GAMTBVac, a subunit recombinant vaccine containing mycobacterial antigens 85A and ESAT-CFP10, developed by the Gamaleya Research Institute of Epidemiology and Microbiology, Russia, demonstrated safety and underwent dose selection in phase I. An ongoing phase IIA trial to assess safety and immunogenicity (measured as interferon-gamma response) in BCG-vaccinated IGRA-negative adults is expected to be completed in 2020 [19].

In a randomized, double-blind controlled phase IIA trial, MTBVAC (live attenuated *Mycobacterium tuberculosis*) was found to have a similar safety and reactogenicity profile to BCG in infants, and a specific and durable immune response up to one year [20,21]. Two further phase IB/IIA safety and immunogenicity and dose-finding trials are currently recruiting in South Africa, in infants [22] and in adults [23].

Ongoing or upcoming trials of ID93 + GLA-SE (a recombinant protein comprising four Mtb antigens, combined with adjuvant GLA-SE) span phases I to IIA. Safety and age de-escalation has been demonstrated in a South Korean BCG-vaccinated IGRA-negative adolescent phase I trial [24]. Phase IIA demonstrated safety and immunogenicity in 60 adults (aged 18–60 years) with a history of previous treatment for drug-sensitive tuberculosis [25]. A phase IIA trial of 107 BCG-vaccinated IGRA-negative South Korean healthcare workers is ongoing, with expected completion in 2020 [26]. A phase IIB study of 1000 BCG-vaccinated adolescents and adults in South Korea, China, Indonesia, the Philippines and Thailand is planned [4].

Phase IIB

There are four candidates that have recently completed or are currently undergoing phase IIB proof-of-concept efficacy trials: H56:IC31, DAR-901, BCG revaccination and M72/AS01$_E$.

H56:IC31, a fusion protein of mycobacterial antigens 85B, ESAT-6 and Rv2660c with IC31 adjuvant, is currently in a phase IIB trial expected to report in 2022. The study is recruiting 900 HIV-negative adults who have been successfully treated for drug-sensitive tuberculosis [27], with primary end-point of culture-positive recurrent TB disease within 12 months after a second vaccination.

Since the introduction of BCG, only a single new vaccine candidate, SRL-172 (an inactivated whole cell booster derived from non-tuberculous mycobacterium), has demonstrated safety and efficacy in a phase III trial. However, the agar based manufacturing process could not be scaled. A candidate from the same master cell bank, DAR-901, has since been adapted for broth-based production, and recently completed a phase IIb trial [28,29]. This study measured the prevention of Mtb infection in 667 BCG-vaccinated, HIV-negative and IGRA-negative Tanzanian adolescents. A three-dose series of DAR-901 was safe and well-tolerated, but did not show any differences in either primary (IGRA conversion) or secondary (sustained IGRA conversion) end-points [30]. [Correction added on 22 January 2021, after first online publication: this paragraph has been amended.]

Given that the historical literature suggests uncertain BCG efficacy for preventing disease in adults and adolescents, the use of BCG revaccination has been largely discontinued and remains

implemented in only nine countries. However, questions regarding the value of BCG revaccination to protect Mtb-uninfected individuals at high risk of Mtb infection have resurfaced following a three-arm randomized controlled trial recruiting IGRA-negative, neonatally BCG-vaccinated adolescents in South Africa, which compared the efficacy of the new H4:IC31 vaccine candidate or BCG revaccination against a placebo [5]. H4:IC31 did not meet the primary efficacy end-point for the prevention of infection (POI vaccine efficacy: 9.4%, $P = 0.63$), and development was discontinued. However, BCG revaccination did meet the secondary end-point of prevention of sustained infection compared with placebo. Efficacy, measured by sustained IGRA conversion for 6 months, was 45.4% (95% CI; 6.4, 68.1) [5]. As the trial was not primarily designed to study this end-point, a larger trial is required to further investigate this result. A BCG revaccination trial of 1800 BCG-vaccinated IGRA-negative children and adolescents (age 10–18) has been initiated in South Africa, with a primary outcome of prevention of sustained IGRA conversion at 3 and 6 months [31]. Results are anticipated in 2025. Further studies are likely to be needed to investigate whether sustained IGRA conversion translates into prevention of TB disease.

The M72/AS01$_E$ vaccine was the first protein-adjuvant vaccine to demonstrate efficacy against TB disease. The vaccine consists of the M72 antigen (recombinant fusion of Mtb32A and Mtb39A) and the liposome-based AS01$_E$ adjuvant. The phase IIB proof-of-concept randomized, double-blinded, placebo-controlled study enrolled 3575 IGRA-positive HIV-negative adults aged 18–50 years in Kenya, South Africa and Zambia. The primary outcome was bacteriological confirmation of pulmonary tuberculosis, in HIV-negative individuals and sampled before initiation of any treatment. According to this primary case definition, the interim analysis at two years of follow-up demonstrated a vaccine efficacy of 54% (95% CI; 2.9, 78.2). In the final analysis, protection was sustained through to three years of follow-up with overall vaccine efficacy of 49.7% (95% CI; 2.1, 74.2) [6]. Furthermore, a sensitivity analysis on this primary end-point applying a more stringent case definition requiring two bacteriologically positive tests indicated vaccine efficacy of 68.0% (95% CI; 25.1, 86.3). The study also demonstrated a good safety profile and highly persistent humoral and poly-positive cellular responses. The encouraging results of this vaccine and next steps in development were the subject of two World Health Organization consultations in 2019 [32,33]. Consensus was generated around other priority populations requiring further safety and/or efficacy data, including IGRA-negative populations, HIV-positive populations, age escalation (>50 years), age de-escalation, broader geography and pregnant women. Two pathways to registration were considered: a traditional multi-country phase III or single-country accelerated licensure based upon the existing phase IIB data. The accelerated pathway could theoretically achieve first licensure by 2022 but would likely be for a much-restricted indication (e.g. HIV-uninfected, LTBI-positive individuals in South Africa). This would likely lead to subsequent challenges generalizing to other countries, as conducting further placebo-controlled trials once there is no longer equipoise may be deemed unethical. The traditional pathway could ensure broader indication and generalizability but would likely delay initial registration by at least 4–5 years. In January 2020, M72/AS01$_E$ was licensed by GSK to the Gates Medical Research Institute (GMRI). Technology transfer to GMRI and development of a large safety study in people living with HIV and planning of the phase III trial are underway.

Phase III

Three candidates have recently completed or are currently undergoing phase III trials: *M.vaccae*, VPM1002 and Immunovac/MIP.

M.vaccae (a heat-killed preparation of *Mycobacterium vaccae*, developed by Anhui Zhifei Longcom) is already licensed as adjunctive immunotherapy for the treatment of active tuberculosis in China. A phase III efficacy trial of a six-dose regimen investigating prevention of disease in 10,000 individuals with LTBI has been completed [34], and publication of the results is anticipated.

VPM1002 (recombinant BCG modified to improve immunogenicity, developed by the Max Planck Institute of Infection Biology and licensed through Vakzine Projekt Management to Serum Institute of India) has demonstrated safety and immunogenicity in phase I [35]. In an open-label randomized phase IIA trial in Cape Town, VPM1002 has shown safety, tolerability and immunogenicity in 48 HIV-unexposed newborns [36]. A phase IIB in HIV-exposed newborns is ongoing [37]. A phase II/III trial to investigate prevention of recurrence in 2000 participants who have successfully completed treatment for drug-sensitive tuberculosis is underway in India and expected to complete in 2020 [38].

A 12 000-participant three-arm multi-centre randomized placebo-controlled phase III trial to assess the ability of VPM1002 or Immunovac/MIP (below) for preventing disease in household contacts of patients diagnosed with sputum-positive pulmonary TB is underway in India [39].

Immunovac/MIP (heat-killed *Mycobacterium indicus pranii*, a nonpathogenic nontuberculous mycobacterium, produced by Cadila Pharma) has been reported to demonstrate safety and efficacy as an adjunctive therapy for pulmonary TB [40,41], but to our knowledge is being investigated as a prophylactic TB vaccine for the first time.

The potential impact of COVID-19 on TB vaccine trials

The COVID-19 pandemic is likely to have implications for TB vaccine trials. First, trials are likely to be disrupted, halted or delayed, leading to lower recruitment, ability to conduct follow-up visits and altered participant care seeking behaviour. At the time of writing, the phase IIB BCG revaccination confirmatory trial is on hold. Other trials due to start may also be delayed.

Second, COVID-19 may affect TB incidence in study populations through two opposing influences: social distancing and reduced access to care [42,43]. If social distancing reduces Mtb transmission, this may reduce end-point accrual, particularly infection outcomes, and potentially disease outcomes. If access to TB care is reduced, transmission and severity could increase. Preliminary mathematical models suggest that increased social distancing may reduce TB incidence in some settings, with minimal impact on TB deaths, which were found to increase substantially with disruption to TB care [42]. Finally, it is unknown whether COVID-TB coinfection interacts to alter the rate or severity of TB cases.

Conversely, TB vaccine development may benefit from scientific developments due to COVID-19, and vice versa. Importantly, it may be possible to leverage clinical trial sites from COVID-19 site mapping initiatives, and technological developments for remote data collection and digital health monitoring may provide valuable tools to facilitate follow-up in future TB vaccine trials. Public and governmental perception of the value of vaccines has also increased during the pandemic, which may positively affect TB vaccine acceptance and funding.

Summary of pipeline

The current prophylactic TB vaccine pipeline is diverse, with candidates across all phases of trials. Recent positive phase II efficacy results have shifted focus towards adolescent and adult TB vaccines. Several phase III trials are planned, including investigating prevention of disease endpoints. TB vaccine trial design has also evolved, shifting from demonstrating prevention of disease in infants, towards more studies assessing prevention of infection, disease or recurrence in adolescents and adults, including in proof-of-concept studies to de-risk progression to phase III.

Mathematical modelling of tuberculosis vaccines

Other than for BCG, the real-world efficacy of the vaccine candidates discussed above has not yet been established. Questions around their likely population-level impact, targeting, delivery strategy and cost-effectiveness remain, which mathematical modelling aims to address by leveraging empirical data, expert input and scenario analyses.

In 2016, Harris et al [44] published a systematic review of the tuberculosis vaccine modelling literature evaluating the body of knowledge on the epidemiological impact of future TB vaccines. Here, we briefly summarize this systematic review and update the systematic searches to reflect the latest developments in TB vaccine modelling.

Systematically reviewed literature to date

The original systematic review identified 23 studies modelling the epidemiological impact of new TB vaccines [44]. These were summarized based on their proposed vaccine characteristics, implementation setting and epidemiological impacts.

The review found that most studies modelled prevention of disease (POD) or prevention of infection (POI) vaccines in a preinfection (PRI) population, or a POD vaccine in a postinfection (PSI) population. Whilst no clear consensus was achieved regarding the relative impact of vaccine types by host infection status required for efficacy, PSI vaccines appeared to have a generally greater and more rapid impact on the tuberculosis epidemic than PRI vaccines.

The modelling suggested targeting vaccination to all ages, or to adults/adolescents in place of, or in

addition to, neonatal vaccination could substantially increase vaccine impact. Most studies were set in Asia, or modelled Asia-like epidemics. Few studies were set in Africa or included TB-HIV coinfection.

The review highlighted several research gaps, including the lack of studies investigating differential effects of PRI versus PSI efficacy, age targeting of vaccines, impact of vaccines on drug-resistant tuberculosis, nonrandom mixing of individuals or impact of changing mixing patterns on vaccine impact.

Updated systematic literature review

Search methods

We systematically searched PubMed, Embase and the WHO Global Health Library for mathematical modelling studies reporting the epidemiologic impact of new human tuberculosis vaccines since 1 January 2016 using the same search terms as Harris et al [44]. Three-stage sifting was conducted independently by two reviewers (CKW and RAC). We included mathematical modelling studies estimating epidemiologic outcomes of TB vaccination. We excluded studies that modelled BCG vaccines with a single efficacy, studies that modelled the *in vitro* or immunological effects of vaccination, and reviews or commentaries that did not add new results or analysis. The full inclusion and exclusion criteria, search terms and flow diagram are presented in the supporting information.

Experts were also consulted to identify research aims and methods of unpublished work to identify where research gaps may be met by upcoming research.

We first describe the characteristics of the included studies by summarizing the principal modelling methods, vaccine characteristics and subgroups (including risk groups) included in the models. We then discuss and narratively synthesize the findings of these models, grouping the studies by comparison type. We employed the modelling study quality and risk-of-bias appraisal tool developed by Harris et al [44], assessing study design and reporting against 14 criteria, for a maximum score of 28 points.

Results

From 380 records identified through database searches, we identified seven published studies for inclusion. Through expert input, we also identified two unpublished studies and one study published after the search date. The modelled vaccine profiles and outcomes in the eight published papers are summarized in Table 1, and the research aims of the unpublished studies are briefly summarized.

Modelling methods. Seven of the eight included studies used compartmental difference or differential equation models [10,11,45–49], whilst one study implemented an individual-based model [50].

Vaccine characteristics. Vaccine efficacy of 40–80% was most frequently modelled [10,11,45–47,49,50]. Three studies modelled efficacy up to 100% [11,45,48]. Most studies varied vaccine efficacy in discrete intervals to undertake sensitivity analyses around assumptions of vaccine impact [10,11,45,49,50].

Vaccines were modelled as 'leaky' (also known as 'degree') vaccines, where all vaccine recipients receive protection proportional to the vaccine efficacy, in five studies [10,11,45,46,50]; two studies modelled vaccines assuming 'all-or-nothing' (also known as 'take') efficacy, where all successfully vaccinated individuals are completely protected [48,49]. We could not determine whether the vaccine was degree or take in one study [46].

Vaccines providing 10 years of protection were modelled in six studies [10,11,45,46,49,50]. Of these, three modelled durability of greater than 10 years, including up to 40 years [46] and lifelong [48]. One study modelled durations ranging from 2 years to lifelong [11]. One study [48] modelled only lifelong protection, and one study modelled an average vaccine half-life of five years [47]. Vaccine waning was modelled as exponential decay [47] or as 'exact' where all vaccine recipients lost protection at the end of the duration of protection [11].

The eight studies modelled a spectrum of host infection status required for efficacy and prevention of disease and/or infection effect. Two studies, one modelling a POI vaccine [48] and one modelling a POD [49] vaccine, did not specify the host infection status required for efficacy. In contrast, POD and POI effects were modelled in four [10,11,45,46] that assumed PRI efficacy, four studies that assumed PSI efficacy [10,11,45,50] and three that assumed P&PI efficacy [10,11,45]. Two studies modelled PSI efficacy with both POD

Table 1. *Summary of the new literature modelling the epidemiological impact of new TB vaccine impact* (n = 7)

				Vaccine Characteristics											
Author and Year	Summary of Aims	Methods	Setting	Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized[+]	Duration of protection	Age targeting	Other targeting	Infection Status Targeting	Schedule	Time horizon	Outcomes
Shrestha et al. 2016 [49]	Epidemiological impact of spatially targeted vaccination	DE	Gujarat, India	P&PI	POD	60% (degree)	Routine: 80% Mass: 8%	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Untargeted	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 24%
						60% (degree)	Routine: 80% Mass: 80%	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: Similar to UTV
						60% (degree)	Routine: 80% Mass: 80% 1% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 25%
						60% (degree)	Routine: 80% Mass: 80% 3% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 28%
						60% (degree)	Routine: 80% Mass: 80% 5% mixing	14–18%	10 years	Routine: 10 yo Mass: ≥20 yo	Spatially targeted to 'incidence hotspots'	n/s	Routine: annual Mass: 10 yearly	20 years	IRR: 31%
Liu et al. 2017 [48]	Epidemiological impact of 'pulsed' mass vaccination strategy compared with neonatal vaccination	DE	China	PRI	POI	100% (take)	95%	95%[+]	L/L	Neo	-	Uninfected	Routine	18 years	Cannot achieve 2035 End TB goals
						100% (take)	Routine: 70–80% Mass: 10–40%	Routine: 70–80%[+] Mass: 10–40%[+]	L/L	Routine: Neo Mass: All	-	Uninfected	Routine: annual Mass: 3–6 yearly	18 years	Can achieve 2035 End TB goals with 70% neo and 25% 5-yearly mass coverage. Could be achieved sooner with more frequent campaigns or higher coverage.
Shrestha et al. 2017 [50]	Epidemiologic impact of targeting a mining community in South Africa	IBM	South Africa	P&PI	POD	60% (degree)	100% miners	60%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	ICA: 8090 (3750–13300) CAPVD: 0.374
						40% (degree)	100% miners	40%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	CAPVD: 0.276
						80% (degree)	100% miners	80%[+]	10 years	18–60 yo	Miners	All	Annual (routine)	20 years	CAPVD: 0.457
						60% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	ICA: 5,510 (2360–10000) CAPVD: 0.254
						40% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	CAPVD: 0.168
						80% (degree)	Equivalent vaccination in originating community	n/e	10 years	10–60 yo	All adults	All	Annual (routine)	20 years	CAPVD: 0.346
Fu et al. 2018 [46]	Effects of discontinuing BCG in an intermediate burden setting	DE	Taiwan	PRI	POI & POD	29% POD for EP (degree)	100% (assumed)	29%[+]	10 years	Neo	-	Uninfected	Annual (routine)	2018–2027	Discontinuing BCG results in 2.8 (2.3–3.2) additional TB cases
						22% POI; 54% POD for pulmonary TB; 54% POD for EP (degree)	n/s	n/e	10 years	Neo	-	Uninfected	Annual (routine)	2018–2027	Discontinuing BCG results in 82.9 (72.6–91.6) additional TB cases
Renardy and Kirschner 2019 [47]	Assessing the impact of age targeting a PRI vaccine and a PSI vaccine in endemic and nonendemic settings with a continuous age structure	PDE	Cambodia	PRI, PSI-L&R	POI (PRI vaccine) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI: 12–15 yo PSI: 50–70 yo	-	PRI vaccine: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized in 2075
				PRI, PRI (neo), PSI-L&R	POI (PRI vaccines) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI vaccines: Neo, 18–30 yo PSI-L&R Vaccine: 50–70 yo	-	PRI vaccines: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized in 2075, the second PRI vaccine acts as a booster to the neonatal BCG vaccination
			USA	PRI, PSI-L&R	POI (PRI vaccine) & POD (PSI-L&R vaccine)	*unclear* (degree)	80–99%	n/e	Vaccine half-life of 5 years	PRI: 22–30 yo PSI: 50–70 yo	-	PRI vaccine: susceptible PSI-L&R vaccine: latent	Annual (routine)	80 years	TB incidence minimized at all years evaluated (2035, 2050, 2075) if the PRI vaccine is targeted to ages 22–30 and the PSI-L&R vaccine is targeted to ages 50–70

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics								Infection Status Targeting	Schedule	Time horizon	Outcomes
				Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized[+]	Duration of protection	Age targeting	Other targeting				
Harris et al. 2019 [10]	Evaluating age targeting of TB vaccines in China	DE	China	PRI	POD	60% (take)	70%	42%[+]	10 years	Ado	-	Uninfected	Annual (routine) for 15yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 1.7% (1.4, 2.3), ICA (1000s): 248 (214, 292), NNVc: 1278 (1087, 1481)
					POD	60% (take)	70%	42%[+]	10 years	Older Adult	-	Uninfected	Annual (routine) for 60yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 3.3% (2.3, 5.3), ICA (1000s): 370 (287, 504), NNVc: 1022 (752, 1318)
				PSI - L	POD	60% (take)	70%	42%[+]	10 years	Ado	-	Latent	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 0.05% (0.04, 0.07), ICA (1000s): 8 (6, 11), NNVc: 40 065 (29 505, 52 492)
					POD	60% (take)	70%	42%[+]	10 years	Older Adult	-	Latent	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 6.1% (1.3, 8.7), ICA (1000s): 658 (131, 1081), NNVc: 574 (350, 2886)
				PSI - L&R	POD	60% (take)	70%	42%[+]	10 years	Ado	-	Latent, recovered	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 0.07% (0.05, 0.09), ICA (1000s): 12 (9, 16), NNVc: 26,831 (20 437, 34 840)
					POD	60% (take)	70%	42%[+]	10 years	Older Adult	-	Latent, recovered	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 10.8% (10.2, 11.2), ICA (1000s): 1295 (1037, 1469), NNVc: 292 (257, 365)
				P&PI	POD	60% (take)	70%	42%[+]	10 years	Ado	-	Uninfected, latent, recovered	Annual (routine) for 15 yo, 3-yr catch-up for 16–19 yo	25 years	IRR: 1.8% (1.5, 2.4), ICA (1000s): 259 (224, 304), NNVc: 1223 (1043, 1414)
					POD	60% (take)	70%	42%[+]	10 years	Older Adult	-	Uninfected, latent, recovered	Annual (routine) for 60 yo, 3-yr catch-up for 61–64 yo	25 years	IRR: 13.8% (12.9, 15.2), ICA (1000s): 1643 (1403, 1893), NNVc: 230 (199, 269)
Awad et al. 2020 [45]	Impact of targeting diabetic individuals with TB vaccines in India	DE	India	PRI	POD	60% reduction in fast progression (degree)	50%	30%[+]	10 years	n/s	All DM	Uninfected	Annual (routine)	30 years	2050 NNVc 38
						60% reduction in fast progression; + 50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	Uninfected	Annual (routine)	30 years	2050 NNVc 14
				PSI	POD	50% reduction in reactivation (degree)	50%	25%[+]	10 years	n/s	All DM	Latently Infected	Annual (routine)	30 years	2050 IRR 4.8% 2050 NNVc 105
						50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	Latently Infected	Annual (routine)	30 years	2050 NNVc 25
				P&PI	POD	60% reduction in fast progression; 50% reduction in reactivation in latents; 50% reduction in infectiousness (degree)	50%	n/e	L/L	n/s	All DM	All	Annual (routine)	30 years	2050 IRR 20.8% 2050 NNVc 17
Harries et al. 2020 [11]	Impact of vaccine characteristics focusing on POI/POD and duration in China, India,	DE	China	P&PI	POD&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 79% (77–81) ICA: 11.6 million (10.2–12.6), IDA: 0.3 million (0.1–0.5) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 51% [50–51]
				PRI	POD	70% (degree)	Routine: 80%	Routine: 80%	10 years	Routine: 9 yo	-		Routine: annual	26 years	2050 IRR: 19% [14–24]

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics: Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized*	Duration of protection	Age targeting	Other targeting	Infection Status Targeting	Schedule	Time horizon	Outcomes
	and South Africa						Mass: 70%	Mass: 70%		Mass: ≥10 yo		Uninfected, latent, recovered	Mass: 10 yearly		
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 1% (1–2)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 21% (17–26)
				PRI	POI or POI&D	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	BCG-like vaccine. 2050 IRR POI: 16% (13–20) 2050 IRR POI&D: 21% (17–27)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine. 2050 IRR 3-year duration: 4% (3–6) 2050 IRR 10-year duration: 37% (36–37)
			South Africa	P&PI	POI&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 84% (81–87) ICA: 4.3 million (2.5–7.0), IDA: 0.9 million (0.5–1.6) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 52% (44–58)
				PRI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 36% (24–47)
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 12% (4–24)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 37% (28–47)
				PRI	POI or POI&D	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	BCG-like, contraindicated in HIV-positive populations. 2050 IRR POI: 16% (13–20) 2050 IRR POI&D: 21% (17–27)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine. 2050 IRR 3-year duration: 7% (1–11) 2050 IRR 10-year duration: 34% (25–42)
			India	P&PI	POI&D	100% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	IRR: 90% (87–94) ICA: 51.4 million (32.6–76.6), IDA: 4.3 million (2.5–8.4) by 2050
				PSI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 54% (44–61)
				PRI	POD	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 51% (42–65)
				PSI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 17% (8–31)
				PRI	POI	70% (degree)	Routine: 80% Mass: 70%	Routine: 80% Mass: 70%	10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	2050 IRR: 50% (42–64)
				PRI		50% (degree)	Routine: 80%	Routine: 16%	10 years	Routine: 9 yo	-		Routine: annual	26 years	BCG-like vaccine.

Table 1 (*Continued*)

Author and Year	Summary of Aims	Methods	Setting	Vaccine Characteristics								Infection Status Targeting	Schedule	Time horizon	Outcomes
				Host infection status	Effect type	Efficacy (take or degree)	Coverage	Proportion immunized[a]	Duration of protection	Age targeting	Other targeting				
					POI or POI&D		Mass: 70%	Mass: 14%		Mass: ≥10 yo		Uninfected, latent, recovered	Mass: 10 yearly		2050 IRR POI: 39% (32–53) 2050 IRR POI&D: 52% (44–67)
				PSI	POD	50% (degree)	Routine: 80% Mass: 70%	Routine: 16% Mass: 14%	3 years or 10 years	Routine: 9 yo Mass: ≥10 yo	-	Uninfected, latent, recovered	Routine: annual Mass: 10 yearly	26 years	M72-like vaccine: 2050 IRR 3-year duration: 11% (8–15) 2050 IRR 10-year duration: 41% (32–46)

Ado, adolescent; BCG, bacillus Calmette–Guérin; CAPVD, Cases Averted Per Vaccine Dose; DE, deterministic/ dynamic/ difference/ differential equation; DM, diabetes mellitus; EP, extrapulmonary tuberculosis; IBM, individual-based model; ICA, incident cases averted; IDA, incident deaths averted; intro, introduced; IRR, incidence rate ratio; L/L, lifelong; n/e, not estimated; n/s, not stated; neo, neonatal; NNVc, number needed to vaccinate to prevent one TB case; P&PI, pre- and postinfection; PDE; partial differential equation; POI, prevention of infection; POI&D, prevention of infection and disease; PRI, preinfection; PSI, postinfection; PSI-L, postinfection: effective in latent infection; PSI-L&R, postinfection: effective in latent and resolved infection; STV, spatially targeted vaccination; TB, tuberculosis; UR, uncertainty range; UTV, untargeted vaccination; yo, year olds; yr, year. [+]Calculated as (coverage × efficacy) where possible.

and POI effects [11,47] and three studies modelled PRI efficacy with both POD and POI effects [11,46,47].

Vaccine deployment, setting, population and risk groups. Eight studies implemented country-level models, two of which were set in multiple countries [11,47]. Three modelled Mtb transmission in China [10,11,48], three in India [11,45,49] and two in South Africa [11,50]. One study compared a high-income country with low Mtb transmission (the United States) against a lower-middle-income country with high levels of Mtb transmission (Cambodia) [47]. Only one study, which investigated spatial targeting, modelled at a subnational level (in the Indian state of Gujarat) [49].

All models were age-structured. Two models stratified their populations by HIV status [11,50]. Both studies modelled an increased risk of TB disease progression and reactivation in people living with HIV, represented antiretroviral therapy (which reduced the impact of HIV on TB progression) and included HIV-specific mortality rates. Shrestha et al. also included age- and sex-specific risk of HIV acquisition and increased risk of TB incidence with decreasing CD4 + cell count. Both studies assumed that new TB vaccines were effective in HIV-positive populations, but one [11] further varied vaccine safety and efficacy in HIV-positive populations. In this study, vaccine protection in HIV-positive individuals was modelled at three levels: equal to HIV negative, 20% relative reduction in protection than HIV negative and contraindicated (not administered).

A single study, set in India, included a diabetes mellitus (DM) stratum [45]. DM was modelled as influencing TB natural history and treatment outcomes, and the DM burden was calibrated to age- and time-specific trends. Vaccination was targeted solely to individuals with DM to assess the population impact of targeting interventions to this risk group. This study did not investigate differential vaccine efficacy by DM status.

Heterogeneous mixing was implemented in four studies [10,11,49,50]. Two studies implemented age-specific contact matrices based on empirical data for China [10,11], and one for South Africa [11]. One study [49] investigated targeting new TB vaccines to high incidence spatial 'hotspots', compared with random untargeted community vaccination. This population-based model implemented

homogeneous mixing within hotspot and non-hotspot populations, but differential mixing between them. Differential inter-population mixing was modelled by varying the fraction of the per capita hazard of Mtb infection generated in each population, which results in Mtb transmission to members of the alternate population. One further study [50] developed an individual-based model of Mtb transmission in miners and their original labour sending communities. This model investigated the impact of targeted vaccination amongst miners in comparison with random vaccination of their originating communities. Miners were assumed to travel to and stay at the mine whilst employed, where they only mix with other miners; on returning to their original communities, they mix with nonminers.

Epidemiologic impact of future new TB vaccines. Seven studies modelled new, hypothetical vaccines [10,11,45,47–50], one of which also included modelling of the potential impact of adolescent BCG revaccination [11]. One study [46] modelled the impact of discontinuing BCG vaccination, with BCG vaccine efficacy varied during scenario analysis. These eight studies, along with their respective modelled vaccine profiles, are summarized in Table 1.

Age-based vaccine targeting—Three studies compared the impact of targeting vaccine delivery by age [10,47,48].

Harris et al [10] investigated the relative impact of targeting adolescents for vaccination compared with older adults in China. Delivery to adolescents was modelled as routine annual vaccination, with 70% coverage of 15-year-olds, beginning in 2025 with an initial catch-up campaign to 16- to 19-year-olds. For older adults, routine vaccination was delivered to 60-year-olds with a catch-up campaign delivered to 61- to 64-year-olds. Due to the low-transmission, high-relapse and reactivation-driven TB epidemic in China, the study found that older adult targeting of vaccination resulted in greater TB incidence rate reduction and lower number needed to vaccinate per case averted than adolescent targeting across all modelled vaccine characteristics.

Liu et al [48] found that routine neonatal vaccination with a high efficacy (100%) vaccine delivered with 95% coverage from 2018 to onwards in China failed to achieve the 'End TB' incidence rate reduction goal by 2035. In contrast, End TB goals were achieved with a mixed targeting strategy, with routine annual neonatal vaccination with 70% coverage, combined with 5-yearly pulsed mass vaccine campaigns applied to all ages with 25% coverage. Decreased inter-pulse intervals and increased mass campaign coverage were predicted to achieve the End TB goals sooner, with 80% neonatal coverage combined with 30% 3-yearly mass campaign coverage from 2018 accomplishing the goals by 2030.

Renardy and Kirschner [47] compared the effect of delivering PRI-POI and PSI-POD vaccines, simultaneously, with two distinct age groups in a high transmission (Cambodia) and low transmission (the United States) setting. They found that TB incidence in 2075 was minimized in the United States through PRI-POI vaccination of adolescents (aged 12–15) and PSI-POD vaccination of adults (aged 50–70). In contrast, in Cambodia, the optimal age group for PRI-POI vaccination increased to age 22–30. Further, in the low transmission setting, the age group targeted for PSI-POD vaccination was a greater determinant of vaccine impact than the age group targeted for PRI-POI vaccination. The latter effect was attributed to a lower rate of primary Mtb infection in the low transmission setting. The study also found that including high coverage routine PRI-POI neonatal vaccination in a high transmission setting potentially reduced TB incidence in 2075 further and shifted the optimal age for adolescent PRI-POI vaccination upwards (to 18- to 30-year-olds).

Host infection status required for efficacy and mechanism of effect—Three studies directly compared vaccines profiles with varying host infection status required for efficacy. One of these studies also compared the relative impact of POI versus POD vaccines.

In the Awad et al [45] model, PRI-POD, PSI-POD and P&PI-POD vaccines were administered to individuals with diabetes mellitus (DM) in India with 50% coverage. The outcome of interest was the number of individuals who needed to receive vaccination to avert a single TB case (NNVc). This study assumed that a PRI vaccine was only administered to DM individuals without TB, whereas a PSI vaccine was only delivered to DM individuals with latent TB. PRI-POD vaccination of populations with DM (conferring lifelong duration of protection, with 60% protection against fast progression following infection, 50% reduction in reactivation

from latent TB and a 50% reduction in infectiousness) was found to result in an NNVc of 14 by 2050. In contrast, PSI-POD vaccination of populations with DM (conferring lifelong duration of protection, 50% reduction in reactivation from latent TB and 60% reduction in infectiousness) was predicted to achieve an NNVc of 25. Finally, simultaneous PRI-POD and PSI-POD vaccination of populations with DM was predicted to achieve an NNVc of 17. Despite lower overall impact, PSI vaccination had a faster epidemiologic impact.

The study of age-targeted vaccination in China by Harris et al [10] modelled POD vaccines and directly compared PRI-POD, PSI-POD, P&PI-POD and a further subtype of PSI vaccination only effective in reducing reactivation from latent TB infection (PSI-L-POD). The study found P&PI-POD, PSI-POD, PSI-L-POD and PRI-POD vaccination of older adults achieved TB incidence rate reductions in 2050 of 13.8% (uncertainty range: 12.915.2), 10.8% (UR: 10.2–11.2), 6.1% (UR: 1.3–8.7%) and 3.3% (UR: 2.3–5.3), respectively. For adolescent vaccination, P&PI-POD and PRI-POD vaccination led to incidence rate reductions in 2050 of 1.8% (UR: 1.5–2.4) and 1.7% (UR: 1.4–2.3), respectively. Adolescent PSI-POD and PSI-L-POD vaccination had a comparatively small impact, leading to incidence rate reductions of 0.07% (UR: 0.05–0.09) and 0.05% (UR: 0.04–0.07), respectively. As above, these findings likely represent a TB epidemic dominated by relapse-driven disease in the elderly population, with a smaller contribution by primary Mtb infection of younger age groups.

In a separate study, Harris et al [11] directly compared the effect of all combinations of P&PI, PSI and PRI against POI, POD and prevention of infection and disease (POI&D) across China, South Africa and India, with the latter reflecting epidemics with greater levels of transmission. Vaccines with a POD effect were found to have the greatest impact overall. A 10-year, 70% efficacy PSI-POD vaccine delivered routinely to 9-year-olds, with 10-yearly campaigns to those aged 10 and above, was predicted to achieve incidence rate reductions of 51% (UR: 50–51), 52% (44–58) and 54% (44–61) in China, South Africa and India, respectively. In contrast, PSI-POI vaccination (vaccines which protect against reinfection) achieved the smallest incidence rate reduction, leading to 1% (1–2), 12% (4–24) and 17% (8–31) in China, South Africa and India, respectively. The impact of PRI-POI and PSI-POI vaccines was intermediate and comparable to one another. In South Africa, a 100% efficacy, 10-year P&PI-POI&D vaccine with equal efficacy between HIV-positive and HIV-negative populations was predicted to achieve incidence rate reductions of 84% (81–87%), falling to 79% (72–84%) and 62% (44–74%) with a relative efficacy reduction of 20% compared with HIV-negative populations or contraindicated in HIV-positive individuals, respectively.

Non-age risk group targeting—Two studies compared targeting subpopulations (not based on age) against untargeted mass vaccination.

Shrestha et al [50] compared the impact of targeting members of a mining population with untargeted vaccination of the originating labour sending community. Mine-targeted vaccination averted 1.46 (95% range: 1.13–1.91) times more TB cases than community vaccination. The greater impact of mine targeting was correlated with the proportion of incident TB occurring amongst adult men (all miners were adult men in this model). Similarly, the study found that the proportion of adult men in the original labour sending community was inversely related to the impact of mine targeting. The study concluded that occupational targeting may be most effective where a substantial demographic gradient of TB incidence with a concurrent demographic gradient by occupation exists.

In a separate study, Shrestha et al [49] compared vaccinating high incidence spatial 'hotspots' of TB with spatially untargeted vaccination in Gujarat, India. With no mixing of individuals between hotspots and the general population, targeting either population led to comparable incidence rate reductions (approximately 24% compared with no vaccine). Vaccination of hotspots with increasing levels of inter-population mixing was predicted to lead to progressively higher vaccine impact. Spatially targeted vaccination was predicted to be more impactful as the relative size of TB incidence in hotspots relative to the general population was increased.

Health economic analyses—Fu et al [46] modelled the cost implications of discontinuing the national BCG programme in an intermediate burden setting (Taiwan), varying BCG efficacy against pulmonary and extrapulmonary TB and accounting for decreased BCG-related side effects and increased

TB incidence. This study found BCG discontinuation to be cost-saving over all scenarios of vaccine efficacy; the incremental cost of TB treatment because of increased burden was small compared with reduced costs of BCG vaccination.

Modelled time frame—The WHO/Stop TB global targets aim to reduce TB incidence rates to 10 cases per 100 000 population per year by 2035, and 'eliminate' TB by 2050 (<1 case per million population). Liu et al [48] presented results suggesting 2035 goals could be met, but assumed vaccine introduction in 2018 and required relatively frequent mass campaigns in addition to neonatal vaccination. Five studies modelled time horizons until at least 2050 [10,11,45–47]. Four of these studies [10,11,45,47] projected that the scenarios of novel vaccines and implementation modelled may not achieve 2035 nor 2050 goals in the countries modelled (Cambodia, South Africa, India and China), but would likely provide an important contribution towards reduction in incidence and cases averted. One study [46] presented outcomes not aligned with 'End TB goals'. Two studies specified their models in relative time, rather than calendar time, so could not be compared with WHO goals [49,50].

Modelling studies in relation to the vaccine pipeline. Only one study [46] modelled a currently in-use vaccine (BCG). As the remaining published studies modelled hypothetical vaccines, their results cannot be directly mapped to the possible epidemiologic impact of late-stage vaccine pipeline candidates. Moreover, not all candidates in the late-stage pipeline have been assessed across comparable populations and implementation scenarios to those in the modelling studies. However, there are broad overlaps between the known (or under-investigation) host infection status required for efficacy and mechanism of effect pipeline vaccine candidates and vaccines investigated in the modelling studies (Table 2), with one study explicitly modelling vaccines with M72/AS01$_E$ and BCG revaccination-like characteristics [11]

M72/AS01$_E$, VPM1002, Vaccae, MIP/Immunovac and H56:IC31 have been investigated or are under investigation for POD effect in PSI populations (Fig 2). Correspondingly, studies by Harris et al [10,11], Awad et al [45], Shrestha et al [49,50] and Renardy and Kirschner [47] have modelled the possible impact of vaccines with PSI-POD effect. VPM1002 is planned to be investigated for PRI-POD efficacy, modelled by Fu et al [46], Harris et al [11] and Awad et al [45]. Finally, PRI-POI effect has been investigated for BCG revaccination and DAR-901 and modelled most closely by Fu et al [46], Renardy and Kirschner [47], Harris et al [11] and Liu et al [48]. Finally, two unpublished studies (below) are expected to directly model epidemiologic impact and cost-effectiveness of M72/AS01$_E$ or M72/AS01$_E$-like vaccination [51,52].

Quality appraisal. We found study quality scores ranging from 11 to 26 out of 28, with a median score of 23 points (Table S4). The major quality gap was in model validation: only 1 of 8 studies [45] was validated.

Unpublished studies. We describe two unpublished studies presented as conference abstracts, identified through expert consultation. The first study was an age-structured dynamic transmission model, which investigates the impact and cost-effectiveness of routine adolescent M72/AS01$_E$ vaccination in India and South Africa [51]. This study includes stratification by HIV status in South Africa. The second study was an age-, drug resistance- and treatment history-stratified dynamic transmission model, which models PRI, PSI and P&PI vaccines with POD effect in India and China, reporting vaccine impact on drug-resistant tuberculosis and cost-effectiveness [52]. Both studies explore outcomes over the 2050 time frame.

Discussion

Since the last systematic review of the epidemiologic impact of TB vaccine modelling literature in 2016 [44], new studies have investigated the differential impact of PRI versus PSI vaccines, combinations of POI and POD effect, and age and risk group targeting of vaccination. Whereas in the previous review, the reason for the polarization of outcomes for PRI versus PSI vaccines was unclear, the new studies reviewed here suggested that PSI versus PRI impact may be driven by the level of Mtb transmission in the modelled epidemiologic setting. Where disease incidence is driven more by reactivation or relapse rather than new infections with fast progression to disease, PSI vaccines were predicted to have greater impact. This differential impact for PRI versus PSI vaccines in recurrence-driven settings like China becomes greater when vaccines are age-targeted: PSI vaccines were most impactful when delivered to older populations.

Similarly, when both PRI and PSI vaccines were deployed simultaneously, to adolescents and older adults, respectively, the age group to which PSI vaccines were targeted was the major determinant of overall vaccine impact in a low transmission environment (the United States). In contrast, in a high transmission environment (Cambodia), the major determinant was the age group to which PRI vaccine was targeted. In the previous review, no models had explicitly explored targeting of vaccination of older adults or the elderly, an evidence gap that has now begun to be addressed in the literature. Finally, evidence for the value of all-age mass campaigns as a supplement to continuous routine neonatal vaccination has also been strengthened.

Seven of eight studies modelled vaccines that included POD effect [10,11,45–47,49,50], whereas only two studies modelled a vaccine with only POI effect [11,48]. One study [11] directly compared POI versus POD vaccination. This study found that PSI-POD vaccination would be likely to have a substantially larger epidemiologic impact than PRI-POD vaccination over the 2050 time frame, but that PRI-POI and PSI-POI vaccination would likely lead to intermediate impact, so POD vaccines would provide greatest impact over the 2050 time frame if effective in PSI populations. Finally, modelling studies have begun to reflect the latest developments in the vaccine development pipeline, now explicitly representing M72/AS01$_E$- and BCG revaccination-like characteristics.

New developments include studies that investigated vaccine targeting to individuals with diabetes mellitus [45], targeting by occupation [50] and targeting to spatial hotspots [49]. These results suggested that targeting of risk groups may contribute to efficiently reducing overall burden, through a lower number of people needed to vaccinate per TB case averted. It is noted that risk group targeting has been studied only in narrow contexts and the generalizability of these findings across epidemiologic settings is unknown. Moreover, other epidemiologically important risk groups, for example malnourished populations [53], may need evaluation depending on context.

Significant research gaps persist. The only study to investigate the impact of vaccination on drug-resistant TB [52] remains unpublished. No new studies investigated how vaccine impact might interact with nonvaccine interventions such as preventive therapy for latent Mtb infection, novel diagnostic technologies or changes to national TB policy, including active case finding strategies. Few studies implemented heterogeneous mixing other than between age groups (e.g. between miners and nonminers, between a hotspot population and nonhotspot populations). No studies assessed how changing patterns of social contact in the general population over time might affect TB vaccine impact. Whilst we identified three new model settings (Taiwan, Cambodia and the United States), the remaining studies remained focused on China, India and South Africa. Studies in other high-burden countries, including Indonesia, the Philippines, Pakistan, Nigeria or Bangladesh that collectively account for 28% of global TB burden, were lacking [1]. Moreover, only one study investigated a subnational setting. As implementation-related questions arise, subnational models will be needed for large, heterogeneous countries. In the previous review, HIV stratification was only present in four studies and was identified as an important research gap for exploring vaccine impact. Of two new studies that included people living with HIV, one investigated differential vaccine safety and efficacy by HIV status. In South Africa, where HIV prevalence is high, contraindication in HIV-positive populations was found to substantially reduce the overall epidemiologic impact of TB vaccination. However, neither study investigated HIV-related targeting. Whilst incremental progress has been made, the impact of TB vaccines on TB-HIV coinfection remains underexplored. One unpublished study including HIV stratification investigating vaccine cost-effectiveness in a high-HIV-burden setting may contribute towards addressing this research need [51].

Previous modelling literature found new TB vaccines to be an overwhelmingly cost-effective intervention. New economic analyses were limited to questions around BCG, and gaps remain for assessing the full potential value of new TB vaccines and for estimating the value of reducing uncertainties around estimates of vaccine impact. Studies have not explored differential costs of differential routes of administration or dose regimens. Finally, the range of vaccine implementation strategies was limited, with no exploration of country-specific delivery strategies grounded in local capacity, strategic objectives or costs. However, cost-effectiveness analyses of new TB vaccines are underway with publication anticipated.

The key strength of this review is the conduct of independent search, filtration, data extraction and quality appraisal by two authors. Analysis of study results was limited by lack of access to underlying data, leading to crude estimates of outcomes such as proportion immunized (if these data were not reported). We found that the median quality of new TB modelling studies was slightly higher than in the previous review, possibly reflecting continuing maturation of TB vaccine modelling as a field.

Our findings, taken together with the results from the systematic review by Harris et al [44] in 2016, suggest a growing consensus amongst TB vaccine models. Overall, Mtb transmission is driven by pulmonary disease amongst adults, with a relatively larger contribution from younger adults in high transmission settings, for example Cambodia, or the elderly in high reactivation settings, for example China. Effective vaccines targeted towards these higher burden populations are likely to achieve a greater and more rapid epidemiologic impact than vaccines targeted towards neonates. As such, routine or period mass campaigns of adolescents and/or adults may be required if End TB targets are to be met. However, the specific characteristics of any new vaccine, and epidemiology within the population to which it is being introduced, must be factored into targeting and deployment strategies. If multiple vaccine candidates with differing characteristics (e.g. PRI vs PSI efficacy) are successfully developed, mixed vaccination strategies targeting differing groups may be appropriate depending on the specific epidemiology of the target setting. Previous work has found adult and adolescent tuberculosis vaccination to likely be overwhelmingly cost-effective. Whilst no further cost-effectiveness analyses have been published, the epidemiological evidence now suggests that targeting to (context-specific) risk groups may be more efficient in terms of number needed to vaccinate per case averted. The cost-effectiveness of such targeting strategies must be explored to inform optimal implementation strategies. Evidence for the impact of vaccines on other cost drivers, such as drug-resistant tuberculosis, needs further exploration and is upcoming. Overall, the implementation aspects of TB vaccine delivery remain underexplored. As there is little precedent for large-scale adolescent and adult vaccination in the order likely required for TB control, and as

Table 2. *Overlap between known or under-investigation host status required for efficacy and mechanism of effect in late-stage vaccines and vaccines in modelling studies*

Investigated for efficacy in:	BCG revaccination PRI-POI	DAR-901 PRI-POI	H56:IC31 PSI-POD	M72/AS01E PSI-POD	MIP/ mmunovac PSI-POD	Vaccae PSI-POD	VPM1002 PRI-POD PSI-POD
Shrestha et al. [49]			a	a	a	a	a
Liu et al. [46]	a	a					
Shrestha et al. [50]			a	a	a	a	a
Fu et al. [46]	a	a					a
Renardy and Kirschner [47]	a	a	a	a	a	a	a
Harris et al. [10]			a	a	a	a	a
Awad et al. [45]			a	a	a	a	a
Harris et al. [11]	a	a	a	a	a	a	a
Harris et al. (unpublished) [51]			a	a	a	a	a
Weerasuriya et al. (unpublished) [52]			a	a	a	a	a

[a]Indicates that a vaccine candidate (column) had characteristics overlapping with a vaccine profile investigated in a modelling study (row). Overlap in vaccine efficacy and duration of protection are not shown.

candidates progress towards licensure, such studies will become increasingly important to inform decision-making.

Concluding remarks and future directions

We have identified critical priorities for M72/AS01$_E$ and BCG revaccination, for other late-stage candidates, for modelling and for the field as a whole.

A larger confirmatory M72/AS01$_E$ trial, currently in-design, should be powered to improve the precision of efficacy estimates, include uninfected populations and further assess safety and immunogenicity in HIV-infected people. Further investigations will need to explore protection in other high-risk groups and the duration of vaccine protection. Results from multiple geographical settings may be required to generalize findings. Investments are needed not only for the next phase of clinical trials, but also to ensure sustainable and affordable supply of vaccine antigens and adjuvant. Preparatory work on licensure and policy pathways, equitable access and delivery should be initiated early to allow rapid implementation, should phase III trial results be positive.

For BCG revaccination, the priority is completing the ongoing confirmation of efficacy trial to estimate vaccine efficacy with more precision, as the original confidence intervals were wide [5]. Further trials are likely to be needed to explore efficacy against disease. Even if confirmed, obstacles to BCG delivery would include its current contraindication for people living with HIV. Support for other candidates should continue in case BCG revaccination or M72/AS01$_E$ do not succeed, and to ensure a pipeline of next-generation vaccines.

Samples from the two recent efficacy trials [5,6] are being examined to identify mechanisms and correlates of protection, which should lead to a better understanding of protective immunity against TB. This, in turn, should guide future vaccine discovery and accelerate the clinical testing of candidates. Trials incorporating other important risk groups, such as the elderly, patients with diabetes or pregnant women, will become important as candidates advance towards the end of the development pipeline.

Tuberculosis vaccine modelling has produced useful new insights over the past four years, by exploring the differential impact of vaccine characteristics, age targeting, spatial or risk group targeting and accounting for drug-resistant TB. Future models should generate evidence on the full value proposition of TB vaccines including comparison with other interventions, more realistic implementation strategies including vaccine targeting, and estimating the value of information to reduce uncertainties about BCG revaccination and M72/AS01$_E$ impact.

The TB vaccine field needs to progress strategically. An increase and diversification of resources is required because currently available funding for TB vaccines [54] is insufficient. Allocation of these resources should include the discovery and development of early pipeline candidates and increasing clinical trial capacity.

Finally, we must prepare now for the prompt and equitable implementation of a successful new vaccine, so that the benefits are felt quickly by people most in need.

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Conflict of interests

RCH reports employment by Sanofi Pasteur, unrelated to TB and outside the submitted work. All other authors have nothing to disclose.

Author contributions

CKW, RGW and RCH conceived the review. CKW and RAC undertook the modelling literature search, review and data extraction. CKW analysed

the results of the literature review. RAC and RCH identified and extracted clinical pipeline data. CKW led writing of the first draft of the article, with contributions from all authors. All authors approved the final draft.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Research question PICOS framework.

Table S2. Search terms used in literature review.

Table S3. Risk of bias tool for assessment of epidemiological modelling studies.

Table S4.PRISMA 2009 Checklist.

Table S5. Results of Quality Appraisal.

Box S1. Inclusion and Exclusion Criteria for Literature Search.

Figure S1.A flowchart of the literature screening for the updated search.