Chapter 12

How close are we to a new, effective tuberculosis vaccine? Recent advances in the field

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The most advanced of 14 candidate TB vaccines are expected to deliver licensure efficacy findings by 2028. Global TB vaccine advocacy and advance planning for country-level introduction will be critical to drive demand, funding, implementation and uptake. https://bit.ly/ERSM101

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Fourteen candidate TB vaccines are in clinical development, including eight in phase 2b–3 trials, although there is a paucity of new candidates advancing from preclinical testing. Live mycobacterial vaccines, including recombinant *Mycobacterium bovis* BCG and live-attenuated *Mycobacterium tuberculosis* candidates, are entering prevention of disease efficacy trials in infants and adolescents/adults. Several candidates are in nontraditional efficacy trials to prevent *M. tuberculosis* infection, treatment failure or recurrent disease. The most promising protein-subunit vaccine, M72/AS01$_E$, is expected to enter a large, multicountry, licensure trial in adolescents/adults, including PLHIV and those with/without prior *M. tuberculosis* sensitisation. Findings are expected by 2028. Efforts to discover immune correlates of vaccine-mediated protection are ongoing. Accelerated global TB vaccine advocacy, community sensitisation to reduce vaccine hesitancy, modelling of impact and development of the investment case, evidence considerations for policy and a framework for country-level introduction will be critical to drive demand, release funding and promote uptake of a new, effective TB vaccine.

Introduction

The world has had access to an old but effective TB vaccine for more than a century. Infant BCG vaccination partially protects against TB, especially the most severe extrapulmonary forms, including disseminated and meningitic disease, and mortality in young children [1]. It is for this reason that universal infant BCG vaccination is policy in 156 countries [2]. BCG efficacy wanes 10–15 years after infant vaccination and does not protect sufficiently against adolescent and adult pulmonary disease that drives *Mycobacterium tuberculosis* transmission and fuels the epidemic [3, 4].

We urgently need a new TB vaccine that is effective in adolescents and adults, including PLHIV [5]. WHO preferred product characteristics recommend such a vaccine should: 1) be protective in people with and without evidence of prior TBI at the time of vaccination; 2) prevent progression to TB disease following primary infection, re-infection and re-activation of latent infection; 3) and demonstrate protection for ⩾2 years after vaccination [6].

How can such a TB vaccine be achieved? A Global Roadmap for Research and Development of TB Vaccines, developed recently in consultation with global stakeholders, describes the short-, medium- and long-term priorities to accelerate TB vaccine development [7]. These priorities include greater diversity of immunological approaches to vaccine design and delivery, validated preclinical models, more efficient clinical trial designs, and greater understanding of demand for new cost-effective vaccines and integration into existing TB control programmes to stimulate vaccine production. Integral to acceleration of novel TB vaccine development will be the discovery of vaccine-induced immune correlates of protection using samples from recently completed efficacy trials. A reliable immune correlate of protection, ideally one that is generalisable across vaccine types, would allow estimation of the potential for protection against TB soon after vaccination, without waiting for completion of lengthy efficacy trials and clinical end-point accrual. Fundamentally, greater investment in TB vaccine research and development is needed.

How close are we to implementing a new TB vaccine strategy? This chapter discusses candidate TB vaccines designed for use in infant, adolescent and adult populations; for pre-exposure (IGRA-negative) and post-exposure (IGRA-positive) vaccination strategies; and for prevention of TBI, progression from infection to disease, or unfavourable treatment outcome.

Candidate TB vaccines in the clinical development pipeline

The WHO *Global Tuberculosis Report 2022* lists 14 candidate TB vaccines in the clinical development pipeline (table 1) [40]. The 2022 pipeline is dominated by candidates in phase 2b–3 trials, which raises the possibility of positive efficacy signals in the short term. However, it also flags the long-term risks of an empty upstream pipeline with few candidates advancing from preclinical testing, in the event that candidates in planned efficacy trials are not successful. It should also be noted that several of these efficacy trials are not traditional prevention of TB disease trials, but are being conducted for nontraditional prevention of TBI, prevention of recurrent disease or therapeutic indications, or in special populations. Such trials might not lead directly to licensure, or might support licensure only for very limited indications and/or populations.

Viral-vectored candidate vaccines

Three viral-vectored vaccines are in phase 1–2a trials.

Ad5Ag85A vaccine

Ad5Ag85A is a replication-deficient, adenovirus type 5 (Ad5) viral vector that expresses the mycobacterial antigen 85A (Ag85A). Animal studies have shown that Ad5Ag85A elicited a robust systemic antigen-specific T-cell response after intradermal injection but did not protect against TB in the lungs [41, 42]. However, when administered *via* the mucosa, a robust protective effect against *M. tuberculosis* lung challenge was observed [42]. Phase 1 trials have shown that Ad5Ag85A is well tolerated in both BCG-vaccinated and BCG-naïve adults, and Ad5Ag85A-induced T-cell responses were higher in BCG-vaccinated than in BCG-naïve individuals. As observed for HIV vaccine candidates based on Ad5 vectors [43], there is concern that vector-specific neutralising antibody responses in those with prior Ad5 infection may dampen the vaccine-induced immune response [8, 9].

TABLE 1 Candidate TB vaccines in clinical development

Vaccine	Antigen(s)	Developer(s)	Clinical trial[#]	First author [ref.]
Viral vectored				
Ad5Ag85A	Ag85A	McMaster University (Canada)	NCT02337270	Smaill [8], Jeyanathan [9]
ChAdOx1.85A	Ag85A	University of Oxford (UK)	NCT03681860	Wilkie [10], Folegatti [11]
TB/FLU-04L	Ag85A and ESAT-6	Research Institute of Biological Safety Problems (Kazakhstan)	NCT02501421	Buzitskaya [12]
Protein adjuvant				
H56:IC31	Ag85B, ESAT-6 and Rv2660c	Statens Serum Institut (Denmark), Valneva (France)	NCT03512249	Luabeya [13], Bekker [14], Suliman [15], Jenum [16]
ID93/GLA-SE	Rv1813, Rv2608, Rv3619 and Rv3620	Infectious Disease Research Institute (USA), National Institutes of Health (USA), Quratis (South Korea)	NCT03806699, NCT03806686	Penn-Nicholson [17], Day [18]
M72/AS01$_E$	Mtb32A and Mtb39A	Bill & Melinda Gates Medical Research Institute (USA), GlaxoSmithKline (UK)	NCT04556981	Day [19], Penn-Nicholson [20], Van Der Meeren [21], Tait [22]
GamTBvac	Ag85B, ESAT-6 and CFP-10	Gamaleya Federal Research Centre for Epidemiology and Microbiology (Russia)	NCT04975737	Vasina [23], Tkachuk [24]
AEC/BC02	Ag85B, ESAT-6 and CFP-10	Anhui Zhifei Longcom Biopharmaceutical (China)	NCT05284812	Chen [25]
Inactivated mycobacterial				
Immuvac	Whole-cell *M. indicus pranii*	National Institute of Immunology, Cadila Pharmaceuticals (India)	CTRI/2019/01/017206	Sharma [26], Mayosi [27], Steigler [28]
RUTI	Whole-cell *M. tuberculosis*	Archivel Farma (Spain)	NCT04919239, NCT05455112	Vilaplana [29], Nell [30]
DAR-901	Whole-cell *M. obuense*	Dartmouth College (USA)	NCT02712424	Von Reyn [31], Von Reyn [32], Munseri [33]
Live mycobacterial				
MTBVAC	Live, whole-cell *M. tuberculosis*	Biofabri (Spain)	NCT04975178	Spertini [34], Tameris [35]
VPM1002	Live, whole-cell *M. bovis* BCG (Prague strain)	Serum Institute of India (India)	NCT04351685, NCT03152903, CTRI/2019/01/017206	Loxton [36], Grode [37], Cotton [38]
BCG (revaccination)	*M. bovis* BCG, *M. tuberculosis* epitopes in RD regions absent	Bill & Melinda Gates Medical Research Institute (USA)	NCT04152161	Nemes [39]
mRNA				
BNT164a1/b1	Not in public domain	BioNTech (Germany)	NCT05537038, NCT05547464	NA

Ag85A/B: mycobacterial antigen 85A/B; ESAT-6: 6 kDa early secreted antigenic target; CFP-10: 10 kDa culture filtrate protein; RD: region of difference; *M. indicus pranii*: *Mycobacterium indicus pranii*; *M. tuberculosis*: *Mycobacterium tuberculosis*; *M. obuense*: *Mycobacterium obuense*; *M. bovis*: *Mycobacterium bovis*; NA: not applicable. [#]: current or most recent clinical trial according to ClinicalTrials.gov (NCT) or Clinical Trials Registry India (CTRI).

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ChAdOx1.85A

ChAdOx1.85A is a live-attenuated chimpanzee adenovirus (ChAd) viral vector that expresses Ag85A [10]. The potential advantage of the ChAd vector compared with vectors derived from commonly circulating human adenoviruses such as Ad5 is that humans are less likely to have had prior exposure, which can be associated with vector-specific neutralising antibodies that limit vaccine-induced immune responses [44]. Animal studies have shown that ChAdOx1.85A evokes both humoral and cell-mediated immune responses when administered either systemically or *via* the mucosa [45, 46]. Phase 1 trials have shown that ChAdOx1.85A is well tolerated and induces a strong humoral and cell-mediated immune response when administered *via* the nasal or sublingual route to humans [11, 47]. A phase 2a trial of ChAdOx1.85A dose escalation, followed by ChAdOx1.85A–MVA85A boost, with BCG revaccination as a comparator, has completed enrolment (ClinicalTrials.gov identifier NCT03681860). A previous phase 2b trial of MVA85A, a modified vaccinia Ankara expressing Ag85A, in BCG-vaccinated infants showed no efficacy for boost vaccination against TB.

TB/FLU-04L

TB/FLU-04L vaccine is a live-attenuated influenza virus strain, A/Puerto Rico/8/34 H1N1, that expresses the mycobacterial antigens Ag85A and ESAT-6 (6 kDa early secreted antigenic target), which have been shown to evoke strong cell-mediated immune responses [48]. TB/FLU-04L was shown to be immunogenic when administered *via* the nasal mucosa in animal studies, with a higher T-cell response when primed with BCG vaccine. A small phase 1 study was completed to assess the safety and immunogenicity of two doses of TB/FLU-04L in BCG-vaccinated, IGRA-negative adults (ClinicalTrials.gov identifier NCT02501421).

Protein adjuvant candidate vaccines

Five protein-subunit vaccines are in phase 2a–3 trials.

H56:IC31

H56:IC31 is a fusion protein consisting of three *M. tuberculosis* antigens, Ag85B, ESAT-6 and Rv2660c, formulated with a T-helper type 1 cell (Th1)-stimulating adjuvant, IC31 [49]. H56:IC31 was designed as both a preventive and a therapeutic vaccine. Three completed clinical trials investigated the safety and immunogenicity of H56:IC31 in adolescents and adults without *M. tuberculosis* sensitisation, and in *M. tuberculosis*-sensitised adults, defined by IGRA status. A total of 246 participants have been enrolled in all studies, of whom 158 were *M. tuberculosis* unsensitised, 49 were *M. tuberculosis* sensitised [13–15], and 39 were TB patients enrolled in Norway who were undergoing TB treatment [16]. These studies suggest that H56:IC31 is safe and immunogenic in BCG-primed individuals with or without *M. tuberculosis* sensitisation, as well as in individuals undergoing TB treatment. H56:IC31 is currently being evaluated in a phase 2b trial for efficacy in preventing TB recurrence (relapse or re-infection) in 831 HIV-negative patients who have been successfully treated for drug-susceptible TB (DS-TB) (ClinicalTrials.gov identifier NCT03512249). Follow-up was completed in March 2023 and the results, which may green-light expansion into larger preventive and/or therapeutic efficacy trials, are awaited.

ID93/GLA-SE or QTP101

ID93/GLA-SE vaccine is a recombinant protein comprising four *M. tuberculosis* antigens, Rv2608, Rv3620, Rv1813 and Rv3619, formulated with GLA-SE adjuvant, a Toll-like receptor 4 agonist in a stable oil-in-water emulsion. ID93/GLA-SE has been shown to be safe and immunogenic in HIV-negative individuals with or without *M. tuberculosis* sensitisation, defined by IGRA status, and in TB patients who have successfully completed treatment for

DS-TB [17, 18]. A US National Institutes of Health-funded phase 2b therapeutic trial of ID93/GLA-SE is planned, which will vaccinate 1500 DS-TB patients at progressively earlier time points during TB treatment to evaluate safety, immunogenicity and efficacy against TB-related unfavourable treatment outcomes. ID93/GLA-SE is also being co-developed in South-East Asia as QTP101, which has completed dose-defining trials of safety and immunogenicity in BCG-vaccinated adolescents (ClinicalTrials.gov identifier NCT03806699) and healthcare workers (ClinicalTrials.gov identifier NCT03806686). A phase 2b efficacy trial of QTP101 for prevention of TB disease in BCG-vaccinated adults is planned to start in 2023.

M72/AS01$_E$

M72/AS01$_E$ is a recombinant fusion protein derived from the antigens Mtb32A and Mtb39A, combined with the AS01$_E$ adjuvant. M72/AS01$_E$ appeared safe and immunogenic in phase 1–2a studies in adolescent and adult populations [19, 20], including *M. tuberculosis*-sensitised and -unsensitised individuals [20], but a trial of M72/AS01$_E$ among adult TB patients receiving treatment was previously discontinued due to unacceptable reactogenicity events [50]. The results of a phase 2b study of M72/AS01$_E$ reported the first positive efficacy signal for an adjuvanted protein-subunit TB vaccine and showed that *M. tuberculosis*-sensitised individuals were protected against progression to TB disease by vaccination [21]. The trial enrolled 3573 healthy, IGRA-positive, HIV-negative adults aged 18–50 years of age in South Africa, Kenya and Zambia, who were followed for symptomatic, microbiologically confirmed TB disease. Vaccine efficacy over 3 years of follow-up was 49.7% (95% CI 2.1–74.2%) [22]. A phase 3 licensure trial is now planned to confirm these exciting findings in a larger, more geographically diverse population, with a wider age range, to test efficacy against TB disease in IGRA-positive individuals. M72/AS01$_E$ vaccination of IGRA-negative adolescents and adults results in lower T-cell responses compared with IGRA-positive individuals [19, 20]. The planned phase 3 trial will include a subset of IGRA-negative individuals and will be powered to test efficacy against sustained IGRA conversion, but not against TB disease, in this group. The planned phase 3 trial will enrol an anticipated 26 000 adolescents and adults aged 15–44 years in multiple countries, selected in part on the basis of an ongoing epidemiological study of IGRA-positive prevalence at the different sites. PLHIV will be included, based on the results of a recently completed study of safety and immunogenicity of M72/AS01$_E$ vaccination in PLHIV who have been established on ART (ClinicalTrials.gov identifier NCT04556981).

GamTBvac

GamTBvac is a recombinant vaccine containing three *M. tuberculosis* antigens, Ag85A and an ESAT-6–CFP-10 (10 kDa culture filtrate protein) fusion protein, with a diethylaminoethyl-dextran and CpG-based adjuvant. A first-in-human trial in 60 IGRA-negative, previously BCG-vaccinated volunteers showed that GamTBvac had an acceptable safety profile and was well tolerated [23]. A subsequent phase 2a trial in 180 IGRA-negative, previously BCG-vaccinated Russian adults showed that GamTBvac induced antigen-specific humoral and cellular immune responses [24]. An ongoing phase 3 trial is recruiting 7180 previously BCG-vaccinated, IGRA- and TST-negative participants aged 18–45 years to receive placebo or two doses of GamTBvac (ClinicalTrials.gov identifier NCT04975737). The primary end-point is TB disease not associated with HIV. Given the low TB incidence expected in an IGRA-negative population, it remains to be seen whether the trial is adequately powered to estimate vaccine efficacy in a study of this size.

AEC/BC02

AEC/BC02 is a recombinant vaccine containing Ag85B and an ESAT-6–CFP-10 fusion protein, combined with a proprietary adjuvant, BC02A [25]. A phase 1b study evaluating the safety and

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immunogenicity of AEC/BC02 *versus* placebo in 30 IGRA- and TST-negative adult volunteers was completed recently (ClinicalTrials.gov identifier NCT04239313). A six-dose schedule of low and high doses of AEC/BC02 and adjuvant alone is currently being tested for safety, tolerability and immunogenicity in a phase 2 study in 200 skin test-positive adults (ClinicalTrials.gov identifier NCT05284812).

Inactivated mycobacterial vaccines

Three inactivated mycobacterial candidates are in phase 2b–3 trials.

Mycobacterium indicus pranii *or Immuvac*

Immuvac is a preparation that contains heat-killed *M. indicus pranii*, a nonpathogenic, nontuberculous mycobacterium closely related to *Mycobacterium avium* that was originally developed as an adjunctive leprosy treatment, but has been tested as an immunomodulator in TB patients [51]. Immuvac showed a small but statistically significant improvement in sputum culture conversion during treatment for PTB, compared with treatment alone, which was not associated with differences in rates of cure or relapse [26]. In a large therapeutic trial for TB pericarditis, a five-dose *M. indicus pranii* regimen had no significant benefit on the composite primary outcome of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis [27]. *M. indicus pranii* immunotherapy also did not significantly modulate frequencies of mycobacteria-specific T-cell responses in the blood [28]. A large phase 3 trial is currently under way that will compare the safety and efficacy of Immuvac or VPM1002 (see later) *versus* placebo for prevention of TB disease in children, adolescents and adults who are household contacts of recently diagnosed TB patients in India (Clinical Trials Registry India identifier CTRI/2019/01/017026).

RUTI

RUTI is comprised of purified fragments of *M. tuberculosis* bacilli that were cultured under stress conditions, delivered in liposomes, and was originally developed as an adjunctive immune modulator to shorten the duration of TB treatment [52]. RUTI was well tolerated, with dose-dependent local adverse reactions, and induced elevated IFN-γ-expressing T-cell responses to purified tuberculin protein in healthy volunteers [29]. A phase 2a trial in IGRA-positive and TST-positive individuals with and without HIV who were receiving isoniazid preventive therapy showed an acceptable safety profile, although nodules and abscesses were observed at the injection site [30]. RUTI administration also induced increases in purified tuberculin protein-specific IFN-γ-expressing cells in this trial. A study of the early bactericidal activity of RUTI in 44 DS-TB patients is ongoing (ClinicalTrials.gov identifier NCT05455112), as is a phase 2b trial of the therapeutic efficacy of RUTI, given as a single dose within 1 month of starting TB treatment, in 140 DS- or DR-TB patients (ClinicalTrials.gov identifier NCT04919239).

DAR-901

DAR-901 is a broth-grown, heat-inactivated, whole-cell mycobacterial vaccine made from *Mycobacterium obuense.* The agar-grown precursor of DAR-901, SRL172, although not scalable, is notable for providing the only positive efficacy signal of any TB vaccine among PLHIV [31]. In the DAR-DAR trial, a five-dose regimen of SRL172 did not offer statistically significant protection against the primary end-point, disseminated TB; however, the rate of culture-confirmed TB was reduced by 39% (hazard ratio 0.61, 95% CI 0.39–0.96). DAR-901 appeared to be safe and moderately immunogenic in a subsequent phase 1 trial in adults with and without HIV infection [32], and although it was safe and immunogenic in a phase 2b trial among *M. tuberculosis*-unsensitised adolescents (ClinicalTrials.gov identifier NCT02712424),

it did not protect against initial or sustained IGRA conversion [33]. DAR-901 is no longer being developed as a TB vaccine (C.F. von Reyn, personal communication), but remains in clinical development as a candidate vaccine against nontuberculous mycobacterial disease.

Live-attenuated mycobacterial vaccines

Three live mycobacterial vaccines are in phase 2b–3 trials.

MTBVAC

MTBVAC is a live-attenuated mycobacterial vaccine derived from a clinical isolate of *M. tuberculosis* lineage 4, which was rendered nonvirulent by the deletion of two independent genes, encoding PhoP and FadD26 [53, 54]. PhoP is a transcription factor that regulates expression of >2% of *M. tuberculosis* genes, most of which are implicated in virulence. FadD26 is required for the biosynthesis and export of phthiocerol dimycocerosates, a major virulence-associated cell-wall lipid of *M. tuberculosis*. MTBVAC contains the genes present in the *M. bovis* BCG vaccine, except for *phoP* and *fadD26*, plus the RD1 (region of difference 1) genes originally deleted from *M. bovis* [53]. MTBVAC was safe in animal models, including SCID (severe combined immunodeficient) mice, and was more immunogenic, with improved protection against TB, than BCG [54]. Phase 1–2 trials of MTBVAC in newborn infants and adults have shown acceptable safety and immunogenicity [34, 35], and larger dose-defining trials have recently been completed (ClinicalTrials.gov identifiers NCT02933281 and NCT03536117). A large, multicentre phase 3 trial of MTBVAC, in approximately 7000 newborns (HIV unexposed, and HIV exposed and uninfected) recently started in Madagascar, Senegal and South Africa (ClinicalTrials.gov identifier NCT04975178). Participants will be followed for TB disease for up to 72 months. An efficacy trial of MTBVAC is also planned for adolescents and adults. As MTBVAC is a live vaccine like BCG with potential to cause disease in immunocompromised individuals, a study of the safety of MTBVAC in PLHIV on ART will be required to establish whether this population at increased risk for TB can be included in a future licensure trial.

VPM1002

VPM1002 is a recombinant, urease C-deficient, listeriolysin-expressing BCG vaccine derived from the BCG Prague strain, thus lacking both RD1 and RD2 regions. Completed phase 1 and 2 trials have demonstrated the safety and immunogenicity of VPM1002 in infants and adults [36, 37]. VPM1002 appeared less reactogenic, with lower rates of injection site ulceration, abscess and scarring, but was also less immunogenic than BCG in a recent phase 2 trial among infants [38]. Three efficacy trials of VPM1002 are currently being conducted in parallel, in different populations. First, a phase 3 infant trial has now fully enrolled 6940 newborns (HIV unexposed, and HIV exposed and uninfected) in Gabon, Kenya, South Africa, Tanzania and Uganda, to assess the safety and efficacy of VPM1002 in comparison with BCG in the prevention of TBI, defined by IGRA-positive conversion (ClinicalTrials.gov identifier NCT04351685); secondary end-points include TB disease, occurring through at least 36 months of follow-up. Second, a prevention of disease trial among close contacts of TB patients in India has enrolled 12 721 HIV-uninfected household contacts >6 years of age, and will test the efficacy and safety of VPM1002 or *M. indicus pranii*/Immuvac *versus* placebo for prevention of incident TB disease over 3 years of follow-up (Clinical Trials Registry India identifier CTRI/2019/01/017026). Third, a phase 2b trial in India to assess the efficacy of VPM1002 for prevention of recurrent TB in 2000 HIV-uninfected, adult TB patients who have been successfully treated and cured of active TB is expected to complete in 2023 (ClinicalTrials.gov identifier NCT03152903). A phase 1–2 trial is planned to evaluate the safety and immunogenicity of VPM1002 and BCG revaccination in pre-adolescents with and without HIV, and with and without *M. tuberculosis* sensitisation, who have previously received the BCG vaccine at birth (ClinicalTrials.gov identifier NCT05539989).

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BCG revaccination

Randomised controlled trials of primary BCG vaccination have shown wide variability in efficacy results in both younger and older age groups, but overall, despite limited efficacy against all forms of TB in older children, adults and previously *M. tuberculosis*-sensitised individuals, BCG appears to offer protection against severe and disseminated TB in infants and young children, especially *M. tuberculosis*-unsensitised individuals [55]. Two large randomised controlled trials of BCG revaccination showed no efficacy against TB disease in adolescents and adults of unknown IGRA or TST status [56, 57]. However, case–control studies suggest that primary BCG vaccination may protect against childhood IGRA conversion [58], and subanalyses of randomised controlled trials are consistent with low-to-moderate efficacy against TB disease in younger children with no or lower rates of *M. tuberculosis* sensitisation [59, 60]. A recent trial of BCG revaccination and H4:IC31 vaccination *versus* placebo in 989 IGRA-negative South African adolescents showed no significant efficacy against conversion to IGRA positivity. However, BCG revaccination was associated with 45.4% efficacy (95% CI 6.4–68.1%) based on a secondary end-point of sustained IGRA conversion over 6 months, compared with placebo [39]. Sustained IGRA conversion may reflect established TBI. A follow-on trial of BCG revaccination is being conducted to confirm these findings in a larger study population of 1800 IGRA-negative adolescents, with sustained IGRA conversion as the primary end-point, in a population of a wider age range (10–18 years), at multiple sites in South Africa, and with longer follow-up of up to 48 months (ClinicalTrials.gov identifier NCT04152161). The results of the primary event-driven analysis, expected at the end of 2023, will inform modelling projections of the potential impact of BCG revaccination on rates of TBI and TB disease. A very large, and possibly unaffordable, prevention of disease efficacy trial would be necessary to quantify the contribution of prevention of TBI to a reduction in TB disease incidence in an IGRA-negative population. These considerations will be critical for national health departments to estimate the cost-effectiveness of a BCG revaccination programme for TB control in adolescents and young adults.

mRNA candidate vaccines

BNT164a1/b1

The most recent entrants to the TB vaccine development pipeline, two variants of an mRNA TB vaccine candidate based on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine backbone from BioNTech (BNT164a1 and BNT164b1), recently started a first-in-human trial in Germany (ClinicalTrials.gov identifier NCT05537038), with a second trial (ClinicalTrials.gov identifier NCT05547464) to follow in South Africa.

Immune correlates of protection against TB

Interactions between *M. tuberculosis* and its human host are complex, and host defence includes several immune cell subsets and effector mechanisms [61]. Likewise, TB vaccines stimulate a variety of immune responses by multiple subsets of myeloid and lymphoid cells (T- and/or B-cells) [61]. However, it is unclear which immune subsets or responses correlate with protection against TB. Animal models and human studies suggest that $CD4^+$ T-cells, in particular IFN-γ-expressing Th1 cells, are the cornerstone of immunity against *M. tuberculosis* [62]. Accordingly, most viral-vectored and subunit vaccine candidates were designed to specifically induce Th1 immune responses. However, a phase 2b trial of the candidate vaccine MVA85A [63], and studies that aimed to identify correlates of TB risk [64–66], have shown that frequencies of Th1 responses were not associated with TB outcome. Recent preclinical (in animal models) and observational studies point to possible contributing roles of antigen-specific Th1 and Th17 cells, antigen-specific $CD8^+$ T-cells, humoral and "trained" innate cell

responses for control of *M. tuberculosis* [67–69]. Identification of immune correlates of vaccine-mediated protection (CoP) that are necessary and sufficient for protective immunity would enable rational design of new candidate TB vaccines tailored to induce such protective responses. Features of immune responses that correlate with protection may not necessarily be mechanistically causal. However, if they are easy to quantify and good predictors of vaccine efficacy, such CoP responses could be measured soon after vaccination, circumventing the need to accrue clinical TB disease end-points during long periods of follow-up. This advance could significantly accelerate clinical development of candidate vaccines. Once validated, CoPs may even contribute evidence towards licensure of new products, or extension to new populations for licensed vaccines, through "immunobridging": measurement of immune responses as efficacy end-points, rather than clinical outcomes such as IGRA conversion or TB disease [70]. Several study designs enable identification of CoPs, but the gold standard relies on samples collected from placebo-controlled, randomised clinical trials with partial vaccine efficacy to allow analysis of vaccine responses in protected and unprotected individuals [71].

Two recently completed phase 2b clinical trials offer the first opportunity to discover human CoPs. As discussed earlier, adolescent BCG revaccination afforded partial protection against sustained IGRA conversion [39], while M72/AS01$_E$ vaccination induced partial protection against PTB in IGRA-positive adults [22]. Samples collected from participants in these trials are being studied by two international collaborative research programmes to discover CoPs against sustained IGRA conversion or TB disease. State-of-the-art technologies and an integrated statistical approach are being applied to test prespecified hypotheses and identify features of protective immune responses against *M. tuberculosis* [72]. To reach their full potential and transform TB vaccine research, candidate CoPs will require independent validation, which may be possible by leveraging the ongoing larger BCG revaccination trial (ClinicalTrials.gov identifier NCT04152161) and the planned phase 3 trial of M72/AS01$_E$, should these trials confirm vaccine efficacy. To be acceptable for immunobridging and licensure studies, CoPs also need to be measurable by validated and relatively simple laboratory assays [71]. Importantly, CoPs may well be specific to different vaccines and clinical outcomes. The studies outlined above will provide a first glimpse into whether common CoPs are induced by a live-attenuated mycobacterial and a protein-subunit vaccine, and whether immune responses associated with protection against TBI and TB disease have any common features. Determining whether such CoPs extend to other vaccine candidates and other clinical outcomes, such as recurrent TB, will require detection of efficacy signals in ongoing phase 2b–3 trials and biobanking of appropriate samples from protected and unprotected participants.

Discussion

We have shown that the pipeline of new TB vaccine candidates, although including diverse viral-vectored, protein-subunit, live and inactivated mycobacterial and now mRNA platforms, is shallow [40]. The presence of several candidates in, or about to enter, phase 2b–3 trials raises the possibility of new efficacy signals, but the paucity of new candidates moving from preclinical studies into phase 1–2a trials raises concern about sustainability of the pipeline if current efficacy trials do not demonstrate sufficient protection. It is also evident that the TB vaccine field has not swiftly capitalised on recent successes, such as the positive efficacy signal for M72/AS01$_E$ against progression from TBI to TB disease in IGRA-positive adults [21, 22], whether due to lack of funder risk appetite, or failure to understand the drivers of global and country-level demand for new TB vaccines. These deficiencies are being addressed actively, through development of a consensus research and development roadmap [7], evaluation of full value and the investment case for new TB vaccines [73], development of evidence considerations for policy [74], and development of a global framework for countries to achieve

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rapid introduction of new TB vaccines for adults and adolescents. Nevertheless, a phase 3 licensure trial of M72/AS01$_E$ will probably start almost 5 years after completion of the successful phase 2b trial, with results not expected until 2028. Positive new developments of the last decade include the entry of eight new candidates into clinical trials, including, most recently, two mRNA vaccine candidates (ClinicalTrials.gov identifier NCT05547464). Another protein-subunit vaccine, H107e/CAF10b, is also poised to enter clinical development in 2023 [47]. It is notable that two live mycobacterial vaccines, MTBVAC and VPM1002, have progressed steadily through safety and immunogenicity studies in infants and adults and have entered efficacy trials. Demonstration of vaccine safety in PLHIV who are established on ART and are virally suppressed are important given the increased risk of TB among PLHIV, who should ideally be included in future licensure trials of these live vaccines [5]. It is also highlighted that MTBVAC and the several new candidates that include either CFP-10 or ESAT-6 antigen are expected to result in vaccine-induced IGRA positivity and complicate testing for *M. tuberculosis* sensitisation. Clearly, if such a vaccine proves to be effective, development of an IGRA or other diagnostic platform based on alternative antigens would be beneficial for diagnosis of post-vaccination TB exposure.

Critical knowledge gaps remain. Approximately three-quarters of the global population are not *M. tuberculosis* sensitised [75], and we know that risk of progression to TB disease is greatest in the 2 years immediately after TBI [76]. In the absence of known exposure–infection events, vaccinating young, IGRA-negative adolescents before they become infected with *M. tuberculosis* would seem logical. It is unclear whether current candidate vaccines are immunogenic or protective in this population. The large size and long duration of TB disease efficacy trials necessary to test this hypothesis in IGRA-negative populations would be a considerable disincentive. However, modelling projections suggest that effective vaccination of IGRA-positive populations alone would still have a major impact on the reduction in TB incidence and mortality [77]. Another challenge for design of future efficacy trials, which currently focus on protection against symptomatic disease, is demonstration of protection against subclinical TB, which formed more than half of all bacteriologically confirmed PTB in a recent South African prevalence survey [78]. It remains to be seen whether an asymptomatic, subclinical TB end-point, presumably reflecting early disease, would represent a higher bar to demonstration of vaccine efficacy than symptomatic, clinical TB.

In summary, ongoing and imminent prevention of disease efficacy trials in infant and adolescent/adult populations will soon report results of proof-of-concept prevention of infection, prevention of recurrence and therapeutic efficacy studies that may accelerate entry of vaccine candidates into new licensure trials. However, the best-case scenario for even the most promising candidates is that they deliver licensure efficacy trial results by 2028. It is critical that this time is not wasted. Initiatives such as the investment case for new TB vaccines, development of evidence considerations for policy, and development of a global framework for country-level introduction will be critical in driving demand and securing the funding necessary for implementation. The final key component is the need for renewed focus on TB vaccine advocacy and community sensitisation to address vaccine hesitancy, so that when the world finally gets a new, effective TB vaccine, those most in need of protection are well informed and willing to receive it.

References

1 Colditz GA, Berkey CS, Mosteller F, *et al.* The efficacy of bacillus Calmette–Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics* 1995; 96: 29–35.

2 Lancione S, Alvarez JV, Alsdurf H, *et al.* Tracking changes in national BCG vaccination policies and practices using the BCG World Atlas. *BMJ Glob Health* 2022; 7: e007462.

3 Abubakar I, Pimpin L, Ariti C, *et al.* Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guerin vaccination against tuberculosis. *Health Technol Assess* 2013; 17: 1–372.
4 Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? *Int J Tuberc Lung Dis* 1998; 2: 200–207.
5 Miner MD, Hatherill M, Mave V, *et al.* Developing tuberculosis vaccines for people with HIV: consensus statements from an international expert panel. *Lancet HIV* 2022; 9: e791–e800.
6 WHO. WHO Preferred Product Characteristics for New Tuberculosis Vaccines. Geneva, WHO, 2018.
7 Cobelens F, Suri RK, Helinski M, *et al.* Accelerating research and development of new vaccines against tuberculosis: a global roadmap. *Lancet Infect Dis* 2022; 22: e108–e120.
8 Smaill F, Jeyanathan M, Smieja M, *et al.* A human type 5 adenovirus-based tuberculosis vaccine induces robust T cell responses in humans despite preexisting anti-adenovirus immunity. *Sci Transl Med* 2013; 5: 205ra134.
9 Jeyanathan M, Damjanovic D, Yao Y, *et al.* Induction of an immune-protective T-cell repertoire with diverse genetic coverage by a novel viral-vectored tuberculosis vaccine in humans. *J Infect Dis* 2016; 214: 1996–2005.
10 Wilkie M, Satti I, Minhinnick A, *et al.* A phase I trial evaluating the safety and immunogenicity of a candidate tuberculosis vaccination regimen, ChAdOx1 85A prime – MVA85A boost in healthy UK adults. *Vaccine* 2020; 38: 779–789.
11 Folegatti PM, Jenkin D, Morris S, *et al.* Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: standardized template with key considerations for a risk/benefit assessment. *Vaccine* 2022; 40: 5248–5262.
12 Buzitskaya Z, Stosman K, Khairullin B, *et al.* A new intranasal influenza vector-based vaccine TB/FLU-04L against tuberculosis: preclinical safety studies. *Drug Res (Stuttg)* 2022; 72: 255–258.
13 Luabeya AK, Kagina BM, Tameris MD, *et al.* First-in-human trial of the post-exposure tuberculosis vaccine H56:IC31 in *Mycobacterium tuberculosis* infected and non-infected healthy adults. *Vaccine* 2015; 33: 4130–4140.
14 Bekker LG, Dintwe O, Fiore-Gartland A, *et al.* A phase 1b randomized study of the safety and immunological responses to vaccination with H4:IC31, H56:IC31, and BCG revaccination in *Mycobacterium tuberculosis*-uninfected adolescents in Cape Town, South Africa. *EClinicalMedicine* 2020; 21: 100313.
15 Suliman S, Luabeya AKK, Geldenhuys H, *et al.* Dose optimization of H56:IC31 vaccine for tuberculosis-endemic populations. A double-blind, placebo-controlled, dose-selection trial. *Am J Respir Crit Care Med* 2019; 199: 220–231.
16 Jenum S, Tonby K, Rueegg CS, *et al.* A phase I/II randomized trial of H56:IC31 vaccination and adjunctive cyclooxygenase-2-inhibitor treatment in tuberculosis patients. *Nat Commun* 2021; 12: 6774.
17 Penn-Nicholson A, Tameris M, Smit E, *et al.* Safety and immunogenicity of the novel tuberculosis vaccine ID93 + GLA-SE in BCG-vaccinated healthy adults in South Africa: a randomised, double-blind, placebo-controlled phase 1 trial. *Lancet Respir Med* 2018; 6: 287–298.
18 Day TA, Penn-Nicholson A, Luabeya AKK, *et al.* Safety and immunogenicity of the adjunct therapeutic vaccine ID93 + GLA-SE in adults who have completed treatment for tuberculosis: a randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet Respir Med* 2021; 9: 373–386.
19 Day CL, Tameris M, Mansoor N, *et al.* Induction and regulation of T-cell immunity by the novel tuberculosis vaccine M72/AS01 in South African adults. *Am J Respir Crit Care Med* 2013; 188: 492–502.
20 Penn-Nicholson A, Geldenhuys H, Burny W, *et al.* Safety and immunogenicity of candidate vaccine M72/AS01E in adolescents in a TB endemic setting. *Vaccine* 2015; 33: 4025–4034.
21 van der Meeren O, Hatherill M, Nduba V, *et al.* Phase 2b controlled trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med* 2018; 379: 1621–1634.
22 Tait DR, Hatherill M, van der Meeren O, *et al.* Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med* 2019; 381: 2429–2439.
23 Vasina DV, Kleymenov DA, Manuylov VA, *et al.* First-in-human trials of GamTBvac, a recombinant subunit tuberculosis vaccine candidate: safety and immunogenicity assessment. *Vaccines (Basel)* 2019; 7: 166.
24 Tkachuk AP, Bykonia EN, Popova LI, *et al.* Safety and immunogenicity of the GamTBvac, the recombinant subunit tuberculosis vaccine candidate: a phase II, multi-center, double-blind, randomized, placebo-controlled study. *Vaccines (Basel)* 2020; 8: 652.
25 Chen L, Xu M, Wang ZY, *et al.* The development and preliminary evaluation of a new *Mycobacterium tuberculosis* vaccine comprising Ag85b, HspX and CFP-10:ESAT-6 fusion protein with CpG DNA and aluminum hydroxide adjuvants. *FEMS Immunol Med Microbiol* 2010; 59: 42–52.
26 Sharma SK, Katoch K, Sarin R, *et al.* Efficacy and safety of *Mycobacterium indicus pranii* as an adjunct therapy in Category II pulmonary tuberculosis in a randomized trial. *Sci Rep* 2017; 7: 3354.
27 Mayosi BM, Ntsekhe M, Bosch J, *et al.* Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med* 2014; 371: 1121–1130.

 https://doi.org/10.1183/2312508X.10024922

28 Steigler P, Chhiba M, Francis V, *et al.* T cell responses to *Mycobacterium indicus pranii* immunotherapy and adjunctive glucocorticoid therapy in tuberculous pericarditis. *Vaccine X* 2022; 11: 100177.
29 Vilaplana C, Montane E, Pinto S, *et al.* Double-blind, randomized, placebo-controlled phase I clinical trial of the therapeutical antituberculous vaccine RUTI. *Vaccine* 2010; 28: 1106–1116.
30 Nell AS, d'Lom E, Bouic P, *et al.* Safety, tolerability, and immunogenicity of the novel antituberculous vaccine RUTI: randomized, placebo-controlled phase II clinical trial in patients with latent tuberculosis infection. *PLoS One* 2014; 9: e89612.
31 von Reyn CF, Mtei L, Arbeit RD, *et al.* Prevention of tuberculosis in Bacille Calmette–Guerin-primed, HIV-infected adults boosted with an inactivated whole-cell mycobacterial vaccine. *AIDS* 2010; 24: 675–685.
32 von Reyn CF, Lahey T, Arbeit RD, *et al.* Safety and immunogenicity of an inactivated whole cell tuberculosis vaccine booster in adults primed with BCG: a randomized, controlled trial of DAR-901. *PLoS One* 2017; 12: e0175215.
33 Munseri P, Said J, Amour M, *et al.* DAR-901 vaccine for the prevention of infection with *Mycobacterium tuberculosis* among BCG-immunized adolescents in Tanzania: a randomized controlled, double-blind phase 2b trial. *Vaccine* 2020; 38: 7239–7245.
34 Spertini F, Audran R, Chakour R, *et al.* Safety of human immunisation with a live-attenuated *Mycobacterium tuberculosis* vaccine: a randomised, double-blind, controlled phase I trial. *Lancet Respir Med* 2015; 3: 953–962.
35 Tameris M, Mearns H, Penn-Nicholson A, *et al.* Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC *versus* BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial. *Lancet Respir Med* 2019; 7: 757–770.
36 Loxton AG, Knaul JK, Grode L, *et al.* Safety and immunogenicity of the recombinant *Mycobacterium bovis* BCG vaccine VPM1002 in HIV-unexposed newborn infants in South Africa. *Clin Vaccine Immunol* 2017; 24: 1472–1483.
37 Grode L, Ganoza CA, Brohm C, *et al.* Safety and immunogenicity of the recombinant BCG vaccine VPM1002 in a phase 1 open-label randomized clinical trial. *Vaccine* 2013; 31: 1340–1348.
38 Cotton MF, Madhi SA, Luabeya AK, *et al.* Safety and immunogenicity of VPM1002 *versus* BCG in South African newborn babies: a randomised, phase 2 non-inferiority double-blind controlled trial. *Lancet Infect Dis* 2022; 22: 1472–1483.
39 Nemes E, Geldenhuys H, Rozot V, *et al.* Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med* 2018; 379: 138–149.
40 WHO. Global Tuberculosis Report 2022. Geneva, WHO, 2022.
41 Wang J, Thorson L, Stokes RW, *et al.* Single mucosal, but not parenteral, immunization with recombinant adenoviral-based vaccine provides potent protection from pulmonary tuberculosis. *J Immunol* 2004; 173: 6357–6365.
42 Xing Z, McFarland CT, Sallenave J-M, *et al.* Intranasal mucosal boosting with an adenovirus-vectored vaccine markedly enhances the protection of BCG-primed guinea pigs against pulmonary tuberculosis. *PLoS One* 2009; 4: e5856.
43 Barouch DH, Kik SV, Weverling GJ, *et al.* International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. *Vaccine* 2011; 29: 5203–5209.
44 Folegatti PM, Ewer KJ, Aley PK, *et al.* Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; 396: 467–478.
45 Saramago S, Magalhães J, Pinheiro M. Tuberculosis vaccines: an update of recent and ongoing clinical trials. *Appl Sci* 2021; 11: 9250.
46 Khoshnood S, Heidary M, Haeili M, *et al.* Novel vaccine candidates against *Mycobacterium tuberculosis*. *Int J Biol Macromol* 2018; 120: 180–188.
47 Woodworth JS, Clemmensen HS, Battey H, *et al.* A *Mycobacterium tuberculosis*-specific subunit vaccine that provides synergistic immunity upon co-administration with Bacillus Calmette–Guerin. *Nat Commun* 2021; 12: 6658.
48 Brandt L, Elhay M, Rosenkrands I, *et al.* ESAT-6 subunit vaccination against *Mycobacterium tuberculosis*. *Infect Immun* 2000; 68: 791–795.
49 Kochenderfer JN, Chien CD, Simpson JL, *et al.* Synergism between CpG-containing oligodeoxynucleotides and IL-2 causes dramatic enhancement of vaccine-elicited $CD8^+$ T cell responses. *J Immunol* 2006; 177: 8860–8873.
50 Gillard P, Yang PC, Danilovits M, *et al.* Safety and immunogenicity of the M72/AS01E candidate tuberculosis vaccine in adults with tuberculosis: a phase II randomised study. *Tuberculosis (Edinb)* 2016; 100: 118–127.
51 Patel N, Deshpande MM, Shah M. Effect of an immunomodulator containing mycobacterium w on sputum conversion in pulmonary tuberculosis. *J Indian Med Assoc* 2002; 100: 191–193.
52 Cardona PJ. RUTI: a new chance to shorten the treatment of latent tuberculosis infection. *Tuberculosis (Edinb)* 2006; 86: 273–289.

53 Arbues A, Aguilo JI, Gonzalo-Asensio J, *et al.* Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated *M. tuberculosis*-based vaccine to enter clinical trials. *Vaccine* 2013; 31: 4867–4873.
54 Martin C, Marinova D, Aguilo N, *et al.* MTBVAC, a live TB vaccine poised to initiate efficacy trials 100 years after BCG. *Vaccine* 2021; 39: 7277–7285.
55 Mangtani P, Abubakar I, Ariti C, *et al.* Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; 58: 470–480.
56 Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996; 348: 17–24.
57 Rodrigues LC, Pereira SM, Cunha SS, *et al.* Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet* 2005; 366: 1290–1295.
58 Roy A, Eisenhut M, Harris RJ, *et al.* Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ* 2014; 349: g4643.
59 Barreto ML, Pereira SM, Pilger D, *et al.* Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: second report of the BCG-REVAC cluster-randomised trial. *Vaccine* 2011; 29: 4875–4877.
60 Glynn JR, Fielding K, Mzembe T, *et al.* BCG re-vaccination in Malawi: 30-year follow-up of a large, randomised, double-blind, placebo-controlled trial. *Lancet Glob Health* 2021; 9: e1451–e1459.
61 Larsen SE, Williams BD, Rais M, *et al.* It takes a village: the multifaceted immune response to *Mycobacterium tuberculosis* infection and vaccine-induced immunity. *Front Immunol* 2022; 13: 840225.
62 Morgan J, Muskat K, Tippalagama R, *et al.* Classical CD4 T cells as the cornerstone of antimycobacterial immunity. *Immunol Rev* 2021; 301: 10–29.
63 Tameris MD, Hatherill M, Landry BS, *et al.* Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet* 2013; 381: 1021–1028.
64 Kagina BM, Abel B, Scriba TJ, *et al.* Specific T cell frequency and cytokine expression profile do not correlate with protection against tuberculosis after bacillus Calmette–Guerin vaccination of newborns. *Am J Respir Crit Care Med* 2010; 182: 1073–1079.
65 Fletcher HA, Filali-Mouhim A, Nemes E, *et al.* Human newborn bacille Calmette–Guerin vaccination and risk of tuberculosis disease: a case–control study. *BMC Med* 2016; 14: 76.
66 Fletcher HA, Snowden MA, Landry B, *et al.* T-cell activation is an immune correlate of risk in BCG vaccinated infants. *Nat Commun* 2016; 7: 11290.
67 Flynn JL, Chan J. Immune cell interactions in tuberculosis. *Cell* 2022; 185: 4682–4702.
68 Khader SA, Divangahi M, Hanekom W, *et al.* Targeting innate immunity for tuberculosis vaccination. *J Clin Invest* 2019; 129: 3482–3491.
69 Darrah PA, Zeppa JJ, Wang C, *et al.* Airway T cells are a correlate of i.v. Bacille Calmette–Guerin-mediated protection against tuberculosis in rhesus macaques. *Cell Host Microbe* 2023; 31: 962–977.e8.
70 Plotkin SA, Gilbert PB. Nomenclature for immune correlates of protection after vaccination. *Clin Infect Dis* 2012; 54: 1615–1617.
71 WHO. Correlates of Vaccine-induced Protection: Methods and Implications. Geneva, WHO, 2013.
72 Nemes E, Fiore-Gartland A, Boggiano C, *et al.* The quest for vaccine-induced immune correlates of protection against tuberculosis. *Vaccine Insights* 2022; 1: 165–181.
73 WHO. An Investment Case for New Tuberculosis Vaccines. Geneva, WHO, 2022.
74 WHO. WHO Evidence Considerations for Vaccine Policy Development. Geneva, WHO, 2022.
75 Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; 13: e1002152.
76 Abubakar I, Drobniewski F, Southern J, *et al.* Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis* 2018; 18: 1077–1087.
77 Harris RC, Sumner T, Knight GM, *et al.* Potential impact of tuberculosis vaccines in China, South Africa, and India. *Sci Transl Med* 2020; 12: eaax4607.
78 Moyo S, Ismail F, van der Walt M, *et al.* Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: a multistage, cluster-based, cross-sectional survey. *Lancet Infect Dis* 2022; 22: 1172–1180.

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