Efficacy and safety of VPM1002 and Immuvac in preventing tuberculosis: phase 3 randomised clinical trial (PreVenTB trial)

Manjula Singh,[1] Sindhu Joshi,[2] Vikram Vohra,[3] Rohit Sarin,[3] Suchit Vasant Kamble,[4] Banurekha Velayutham,[5] Anant Mohan,[6] Urvashi B Singh,[6] Rakesh Kumar,[6] Sanghamitra Pati,[1,7] Manoranjan Pattnaik,[8] Prasanta Raghab Mohapatra,[9] Uma Shankar,[10] Somashekar Narasimhaiah,[10] Geeta Yadav,[11] Syed Hissar,[5] Rashmi Rodrigues,[12] Abhijit Vasantrao Kadam,[4] Paul Kumaran Paramasivam,[5] Sailaja Kambhampati,[13] Ariarathinam Newtonraj,[5] Natarajan Alangudi Palaniappan,[5] S Devarajulu Reddy,[5] Sourin Bhuniya,[9] Bijaya Kumar Mishra,[7] Ashwini Shete,[4] Luke Elizabeth Hanna,[5] Dipendra Kumar Mitra,[6] Samiran Panda,[1,4] Randeep Guleria,[6] Srikanth Tripathy,[5] Neelam Roy,[11] George D'Souza,[12] S K Tripathy,[10] Kiran Katoch,[1] Ravindra M Pandey,[1] Seema Sah,[1] Manisha Kashyap,[1] Vinay Telasey,[1] Meenakshi Bakshi,[1] Nitya Wadhwa,[14] Abdul Mabood Khan,[1] Raman R Gangakhedkar,[1] Rajni Rani[1]

For numbered affiliations see end of the article

Correspondence to: M Singh drmanjulasb@gmail.com; (ORCID 0000-0001-8656-3768)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;393:e085716 http://dx.doi.org/10.1136/bmj-2025-085716

Accepted: 01 March 2026

ABSTRACT

OBJECTIVE

To evaluate the safety and efficacy of VPM1002 and Immuvac in reducing the incidence of microbiologically confirmed tuberculosis (TB; pulmonary TB and extrapulmonary TB), development of latent TB infection, and immunogenicity.

DESIGN

Phase 3 randomised clinical trial (PreVenTB trial).

SETTING

18 sites across six states of India.

PARTICIPANTS

12 717 healthy household contacts (aged ≥6 years) of patients with a smear positive TB test.

INTERVENTIONS

Participants were randomly assigned in a 1:1:1 ratio (using block randomisation with variable sample size) to receive an intradermal injection of VPM1002, Immuvac, or placebo in both arms. After one month, a second dose was administered in one arm to 11 829 healthy participants.

OUTCOME MEASURES

The primary outcome was efficacy against confirmed TB (pulmonary TB and extrapulmonary TB) over 38 months of follow-up. Secondary outcomes were development of latent TB infection, adverse and serious adverse events, efficacy in predefined age groups, and immunogenicity. Exploratory outcomes were efficacy when considering tuberculin skin test status, and post hoc analyses of efficacy in participants aged 6-14 and according to body mass index.

RESULTS

252 and 227 participants developed microbiologically confirmed TB in modified intention-to-treat and per protocol groups, respectively. The per protocol analysis showed 65 (1.68%), 80 (2.09%), and 82 (2.13%) participants developed TB in the VPM1002, Immuvac, and placebo groups, respectively. Of these, 12 (0.31%), 16 (0.42%), and 24 (0.62%) developed extrapulmonary TB in the VPM1002, Immuvac, and placebo groups, respectively. In the per protocol analysis, VPM1002 showed vaccine efficacy of 21.4% (95% confidence interval (CI) −8.9% to 43.2%), 19.5% (−14.6% to 43.4%), and 50.4% (0.8% to 75.2%) against all TB, pulmonary TB, and extrapulmonary TB, respectively. Immuvac showed vaccine efficacy of 33.2% (−25.9% to 64.5%) against extrapulmonary TB. VPM1002 and Immuvac showed vaccine efficacy of 64.9% (−2% to 90.1%) and 66.3% (1.9% to 90.5%) against extrapulmonary TB in participants with tuberculin skin test positivity. Both vaccines were well tolerated with mild local reactions in about a third of participants. VPM1002 and Immuvac induced *Mycobacterium tuberculosis* specific polyfunctional CD4+ T cells. Post hoc analyses showed vaccine efficacy of 64.6% (95% CI 16.3% to 85.1%) against all forms of TB, 62.1% (3.0% to 85.2%) against pulmonary TB, and 77.6% (−3.7% to 95.2%) against extrapulmonary TB in participants aged 6-14 years in the VPM1002 group.

CONCLUSIONS

Both vaccines were safe but did not show any efficacy against all forms of microbiologically confirmed TB

WHAT IS ALREADY KNOWN ON THIS TOPIC

Extensive efforts have been made globally to develop new tuberculosis (TB) vaccines; a phase 2 trial with vaccine M72 showed efficacy of 49.7% against pulmonary TB in adults, and a phase 3 trial has started

VPM1002 vaccine has shown promising results in a phase 2 study

Immuvac has also shown immunoprophylactic potential in a large field based study

WHAT THIS STUDY ADDS

This multicentre, government funded, phase 3 trial evaluated two vaccines for efficacy against TB (pulmonary and extrapulmonary TB) in a single study, enrolling household contacts (aged ≥6 years) of patients with smear positive TB

Vaccine efficacy against microbiologically confirmed extrapulmonary TB (which poses diagnostic challenges and accounts for higher morbidity and mortality rates) was 50.4% for VPM1002

Because no licenced vaccine currently protects people >5 years old, this study included vulnerable household contacts ≥6 years old irrespective of comorbidities, reflecting a real world scenario (protective efficacy of both vaccines seen in children and adolescents against pulmonary and extrapulmonary TB)

or pulmonary TB. VPM1002 showed considerable efficacy against extrapulmonary TB. Both vaccines showed efficacy against extrapulmonary TB in participants who had a positive tuberculin skin test.

TRIAL REGISTRATION

Clinical Trials Registry India CTRI/2019/01/017026.

Introduction

Tuberculosis (TB) poses a major public health problem worldwide.[1] An estimated 10.8 million people were reported to have TB worldwide in 2023, with a 4.6% increase in incidence rate between 2020 and 2023.[2] India reported 2.55 million people with TB in 2024.[3] The efforts to achieve TB elimination by 2025 include early detection, treatment, and prevention of disease in the most vulnerable people. Although India has adopted TB preventive treatment, additional strategies like prophylactic vaccines are required. BCG is currently the only available licensed vaccine against TB that protects against extreme forms of TB in young children, but does not offer protection against pulmonary TB in adolescents and adults.[4 5] However, BCG revaccination did not reveal encouraging results even in school age children in Brazil[6] or in adolescents in Chingleput India.[7]

In the PreVenTB trial, we aimed to investigate the efficacy of two vaccines: VPM1002, a recombinant BCG vaccine, and Immuvac. We examined the safety and efficacy of these vaccines in preventing all forms of microbiologically confirmed TB: sputum positive pulmonary TB and microbiologically confirmed extrapulmonary TB in household contacts of people with newly diagnosed smear positive pulmonary TB. The rationale for choosing VPM1002 and Immuvac has been described in the published protocol.[8]

Methods

Study objectives

This trial was registered at Clinical Trials Registry India (CTRI/2019/01/017026;https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MjC0MTE=&Enc=&userName=). The primary objective of the study was to evaluate the efficacy of two vaccines, VPM1002 and Immuvac, in reducing the incidence of microbiologically confirmed TB (pulmonary TB and extrapulmonary TB). Other objectives were to examine the safety of the two vaccines in household contacts, the efficacy of the vaccines in preventing latent TB infection and immunogenicity in a subset of the population, their efficacy in preventing pulmonary TB and extrapulmonary TB in different age groups, and their efficacy in participants who were already infected with TB (ie, tuberculin skin test (TST) positive and negative).

This trial was a multicentre, double blind, randomised, placebo controlled trial undertaken at 18 sites in six states across India (Delhi, Maharashtra, Odisha, Karnataka, Tamil Nadu, and Telangana). Site specific block randomisation was used for enrolment (for details, see the PreVenTB trial protocol).[8] The 18 trial sites were selected because of their capacity to undertake the trial according to good clinical practice guidelines and the local prevalence of TB. Latent TB infection testing was performed in three states (Delhi, Chennai, and Hyderabad) using the TST (Span Diagnostics). Study participants were followed up for 38 months after their first vaccine dose. Immunogenicity was evaluated in a subgroup of participants in three states (Chennai, Delhi, and Pune). Initially 500 consecutively screened participants were recruited at baseline for immunogenicity and thereafter 150 consecutive participants were enrolled who received both doses of the vaccines and were tested at months 2 and 6 for immunological parameters. The trial was monitored by an external data safety monitoring board. The final analysis of primary and secondary outcomes was conducted after 38 months of follow-up, including immunological parameters and exploratory parameters.

Study design

This multicentre, randomised, double blind trial with placebo controlled design was undertaken at 18 sites in six states across India.[8] We used site specific block randomisation with variable block sizes.[8] The Clinical Development Services Agency, Department of Biotechnology, government of India, monitored the trial. The double blind codes remained with one of the data safety monitoring board members and were decoded on 28 August 2024 after presentation of the data under codes A, B, and C.

The trial was undertaken in accordance with good clinical practice guidelines and the Declaration of Helsinki. The trial was started after obtaining all the necessary statutory approvals from the respective institutional ethics committees and the Indian regulatory authority, Central Drugs Standard Control Organisation, and following the guidelines of the Indian Council of Medical Research. The trial was funded by the Indian Council of Medical Research. All the participants were recruited after written informed consent or assent was obtained. An independent data safety and monitoring committee reviewed the coded safety data during the trial and until the end of the study.

All participants and the study teams were unaware of the study groups. The first participant was enrolled and vaccinated on 15 July 2019 and the last participant on 31 December 2020. Participants were followed up for safety and efficacy according to the protocol until 38 months after the first vaccine dose was given or until they attended their last visit. Follow-up of all participants was completed by July 2024.

Study population

A total of 12 722 participants aged 6 years and older were randomised according to the inclusion and exclusion criteria. Of these, 12 717 participants received their first dose (VPM1002, Immuvac, or placebo) after written informed consent or assent was obtained between 15 July 2019 and 31 December

2020. Exclusion and inclusion criteria and study procedures have previously been published.[8] In brief, the participants included healthy household contacts of people with a positive smear test for TB, who were HIV negative or had stable chronic medical conditions, were not pregnant or lactating female contacts, did not have confirmed or suspected immunodeficient conditions, did not have a history of chronic renal failure or dialysis, silicosis, gastrectomy, jejunoileal bypass, solid organ transplantation, carcinoma and disorders of the liver, kidney, lung, heart, or nervous system, had no symptoms of TB or history of TB, and had a sputum sample (if produced) negative for *Mycobacterium tuberculosis* at baseline. A total of 11 829 participants of 12 717 enrolled received a second dose.

Sample size

The methods and sample size calculation have been described previously.[8] The sample size was determined considering the prevalence of TB in household contacts to be 2% over a period of three years and assuming that the individual vaccines would reduce the incidence by 50%. With 2.5% α error (significance level with adjustment for multiplicity (testing two hypotheses), ie, efficacy of each of VPM1002 and Immuvac compared with placebo), 90% power, and 10% dropout rate, the sample size was 3918 for each group, which was rounded off to 4000, and 12 000 in total. However, a total of 12 717 participants were enrolled in view of the covid-19 pandemic and considering that even if there was a higher than expected dropout rate owing to covid-19, we would still have enough numbers to draw conclusions.

Randomisation and enrolment

A total of 12 717 participants were enrolled and vaccinated (in 1:1:1 ratio) according to the randomisation schedule generated by an independent statistician. Block randomisation with variable sample sizes was generated with a sequence of random numbers for each enrolment site. Codes were kept in individually sealed opaque envelops. A randomisation series was allotted to each site in the state with randomisation codes. During the study, all procedures were conducted using the participants' unique code and all identifiers were removed. This confidential information remained with each site's principal investigator only.

Concealment and masking

To prevent bias in the results, a double blind design was followed. All participants and the research investigators involved in enrolment, assigning participants to groups, and follow-up were masked to the vaccine (or placebo) received. After the participants were found to be fit for vaccination, the randomisation number was assigned by the medical officer, which was then sent to the pharmacist. The site pharmacists were unmasked to treatment allocation and prepared the syringes for vaccination at the site pharmacy according to the randomisation number and the randomisation schedule. The syringes were labelled with only the visit number, randomisation number, and the arm (right or left) where each vaccine was to be administered. Reconstitution of the study vaccines was performed according to the relevant standard operating procedure on the morning of vaccine administration, immediately before dose administration. The vaccine doses were administered by the site staff nurse who was also masked to the study groups. A quality control person was assigned by the site investigator to ensure compliance with the vaccination.

Vaccination

For the first dose of VPM1002, 0.1 mL (2.8×10^5 colony forming units) was administered in one arm and 0.1 mL of placebo in the other arm. For the second dose, participants were given 0.1 mL of placebo in one arm after a month. Immuvac was administered in two divided doses in both arms; that is, 0.1 mL in each arm (0.2 mL, 1×10^9 bacilli) followed by the second dose of the vaccine (0.1 mL, 0.5×10^9 bacilli) administered in one arm after a month. In the placebo group, participants were given 0.1 mL of placebo in both arms for the first dose. For the second dose, participants were given 0.1 mL of placebo in one arm after a month (fig 1).[8]

The primary outcome was to evaluate the efficacy of VPM1002 and Immuvac in preventing microbiologically confirmed TB (pulmonary TB or extrapulmonary EPTB), pulmonary TB, and extrapulmonary TB compared with

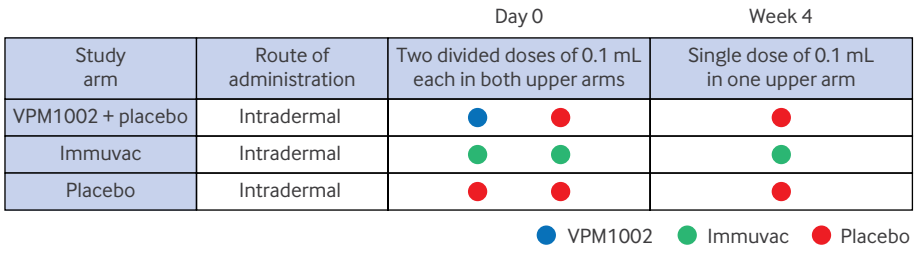

Fig 1 | Vaccine schedule. VPM1002: for first dose, 0.1 mL (2.8×10^5 colony forming units) of vaccine was administered in one arm and 0.1 mL of placebo in the other arm; for second dose (week 4), 0.1 mL of placebo was administered in one arm. Immuvac: for first dose, 0.1 mL of vaccine was administered in each arm (0.2 mL, 1×10^9 bacilli); for second dose (week 4), 0.1 mL (0.5×10^9 bacilli) of vaccine was given in one arm. Placebo: for first dose, 0.1 mL of placebo was administered in each arm; for second dose (week 4), 0.1 mL of placebo was given in one arm[8]

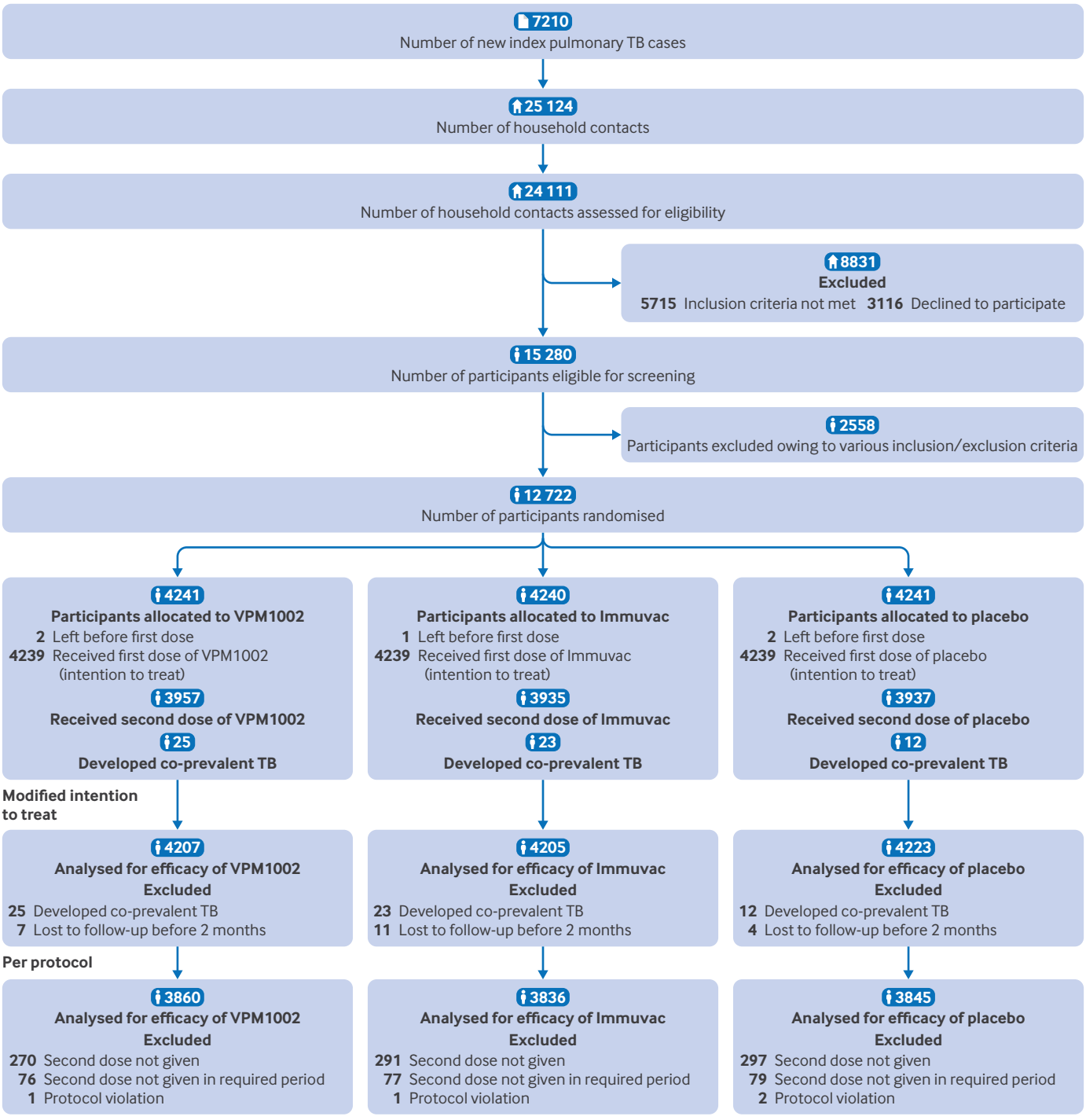

Fig 2 | CONSORT (consolidated standards of reporting trials) diagram showing participant numbers screened and enrolled for vaccine trial. Intention-to-treat analysis comprised randomised participants with at least one dose of vaccine or placebo. Modified intention-to-treat analysis included randomised participants with at least one dose and follow-up beyond two months (visit 6), excluding those with co-prevalent tuberculosis (TB). Per protocol analysis included participants from modified intention-to treat analysis, excluding those who did not receive second dose or did not receive it within required period

placebo. Secondary outcomes were safety, vaccine efficacy in preventing latent TB infection, preventing pulmonary TB or extrapulmonary TB in various age groups (6-18, 19-35, 36-60, and >60 years), efficacy in TST positive and negative household contacts, and immunogenicity of the vaccines.

All participants were followed up for 38 months after the first dose. Participants suspected of having TB were tested according to NTEP (national TB elimination programme) guidelines. Biological samples (sputum, gastric aspirate, or site specific fluid or sample in extrapulmonary TB) were collected for confirmation

of *M tuberculosis* according to NTEP guidelines. A TST was done on day 0 and repeated six months after vaccination in those who were negative on day 0 at three sites in Delhi, Tamil Nadu, and Hyderabad.[7]

Safety parameters

All solicited, unsolicited adverse events, and serious adverse events were recorded for all participants during the follow-up period.[7] The data safety monitoring board reviewed the coded safety data throughout the study.

Immunogenicity of VPM1002 and Immuvac

The immunogenicity of VPM1002 and Immuvac to elicit *M tuberculosis* specific immune responses was evaluated in a subgroup of participants.[8] A total of 491 participants (169 in VPM1002 group, 162 in Immuvac group, and 160 in placebo group) were studied for immune responses against whole cell lysates of *M tuberculosis* at day 0, month 2, and month 6 after vaccination.

The peripheral blood mononuclear cells were stimulated using whole cell lysates of *M tuberculosis* along with costimulatory antibodies (anti-CD28 or anti-CD49d) and incubated for 24 hours in a humidified CO_2 incubator (37°C and 5% CO_2). After collection of supernatants for estimation of cytokines, monensin was added to the cells for intracellular cytokine staining. Percentages of CD3, CD4, and CD8 T cells expressing intracellular cytokines interferon (IFN)-γ, tumour necrosis factor (TNF)-α, and interleukin (IL)-2 were evaluated using flow cytometry. Amounts of IL-2, IFN-γ, TNF-α, IL-10, IL-2, IL-7, and IP-10 (interferon γ induced protein 10) were estimated in sera and supernatants obtained from the cultures using multiplex Luminex bead arrays.

Statistical analysis

Vaccine efficacy was calculated in intention-to-treat (ITT), modified intention-to-treat (mITT), and per protocol populations. The ITT analysis included all participants who received at least one vaccine dose or placebo. mITT analysis included all participants who received at least one vaccine dose or placebo, did not have co-prevalent TB[7] after vaccination, and completed a minimum of two months of follow-up after the first dose. Per protocol analysis included all participants from the mITT group who received both doses of the vaccine within the prescribed period of 30±7 days and no major protocol violations occurred that would potentially affect the vaccine efficacy.

Efficacy analysis in ITT, mITT, and per protocol cohorts was done for all participants with microbiologically confirmed TB (pulmonary TB or extrapulmonary TB), and for pulmonary TB and extrapulmonary TB separately as well. Subgroup analyses were also performed in the ITT, mITT, and per protocol groups. Post hoc analysis for younger age groups and analyses for exploratory endpoints were also conducted for the ITT, mITT, and per protocol groups.

STATA 14.2 software was used to determine vaccine efficacy using a Cox proportional hazards regression model (vaccine efficacy=1−hazard ratio×100), with 95% confidence interval (CI). Furthermore, 90% CIs were calculated as a post hoc analysis. When the numbers in any subgroup were five or less, Fisher's exact test was used and odds ratios (with CIs) were approximated by using Woolf's method with Haldane's correction to account for bias because of small numbers.[9-11] Immunological data were analysed using Graph-pad prism 8.0.2 software (San Diego, CA, USA). The χ^2 test was applied to compare variables such as responder rates for immunological parameters.

Patient and public involvement

Representatives from organisations supporting people affected by TB were engaged in the review of the study protocol. Their valuable suggestions about research design, conduct, and outcome measures were incorporated and their comments addressed.

Results

Trial population

Out of 12 722 randomised participants, 12 717 (4239 in each group) received at least one dose of VPM1002, Immuvac, or placebo and were included in the ITT analysis (fig 2, supplementary table S-2)[12]; 11 829 participants received a second dose. A total of 12 295 (96.68%) participants completed 38 months of follow-up, including those who received only one dose of the vaccine or placebo. The personal characteristics of participants in all three groups were similar (table 1). A total of 4207, 4205, and 4223 participants in the VPM1002, Immuvac, and placebo groups were included in the mITT analysis (table 2), and 3860, 3836, and 3845 were included in the per protocol analysis, respectively (fig 2).

Primary outcome: efficacy of VPM1002 and Immuvac against microbiologically confirmed TB

For the ITT analysis, the duration of follow-up (mean±standard deviation) was 36.14±6.05, 35.99±6.29, and 36.2±5.74 months for the VPM1002, Immuvac, and placebo groups, respectively. For the mITT analysis, the duration of follow up was 36.4±5.2, 36.3±5.5, and 36.3±5.3 months, respectively, and for the per protocol analysis, it was 36.5±5.01, 36.4±5.2, and 36.4±5.1 months, respectively (table 1).

Of the 12 717 participants in the ITT analysis, 275 developed microbiologically confirmed TB after vaccination—214 had pulmonary TB, 40 extrapulmonary TB, and 21 developed both pulmonary and extrapulmonary TB. The mITT analysis comprised 12 635 participants, of which 252 developed microbiologically confirmed TB—195 had pulmonary TB, 36 had extrapulmonary TB, and 21 participants had both pulmonary and extrapulmonary TB. In the per protocol analysis, 11 541 participants were analysed, of which 227 developed TB—175 had pulmonary TB, 33 had extrapulmonary TB, and 19 had both pulmonary and extrapulmonary TB. Therefore, for

Table 1 | Demographic characteristics of participants enrolled in study

Characteristics	VPM 1002 (n=4239)	Immuvac (n=4239)	Placebo (n=4239)
Sex			
Male	1997 (47.2)	1996 (47.1)	1930 (45.6)
Female	2242 (52.8)	2243 (52.9)	2309 (54.4)
Marital status			
Married	2013 (47.4)	1946 (45.9)	2019 (47.6)
Unmarried	2174 (51.3)	2247 (53.0)	2167 (51.2)
Other status	52 (1.3)	46 (1.1)	53 (1.2)
Age at enrolment (years)			
6-18	1525 (36.0)	1593 (37.5)	1536 (36.2)
19-35	1342 (31.6)	1326 (31.2)	1311 (31.0)
36-60	1246 (29.4)	1221 (29.0)	1286 (30.3)
>60	126 (3.0)	99 (2.3)	106 (2.5)
Weight (kg)			
Mean±SD	51.4±17.6	51.1±18.0	51.5±18.1
Median (IQR)	52 (40-63.3)	51.2 (39.3-63.5)	51.6 (39.5-64.1)
Height (cm)			
Mean±SD	153.1±14.7	152.8±15.1	152.8±14.9
Median (IQR)	154.3 (146.0-163.0)	154.1 (146.0-163.4)	154.2 (146.5-163.0)
Body mass index <18 in adults (n=1017, 8%)	346 (8.16)	338 (7.97)	333 (7.85)
Mean±SD	16.6±1.1	16.5±1.0	16.4±1.2
Median (IQR)	16.9 (16-17.4)	16.7 (15.9-17.3)	16.7 (15.8-17.4)
Body mass index >18 in adults (n=7447, 58.56%)	2512 (59.25)	2443 (57.63)	2492 (58.78)
Mean±SD	24.6±4.4	24.6±4.5	24.7±4.5
Median (IQR)	23.9 (21.2-27.2)	24 (21.1-27.2)	24 (21.2-27.4)
Children: normal weight (n=3531, 27.76%)	1140 (26.8)	1207 (28.4)	1184 (27.9)
Children: underweight (n=722, 5.67%)	241 (5.6)	251 (5.9)	230 (5.4)
Follow-up: ITT (n=12 717)			
Mean±SD	36.14±6.05	35.99±6.29	36.2±5.74
Median (IQR)	37.59 (37.4-37.79)	37.63 (37.36-37.79)	37.63 (37.4-37.79)
Follow-up: mITT (n=12 635)			
Mean±SD	36.4±5.2	36.3±5.5	36.3±5.3
Median (IQR)	37.6 (37.4-37.8)	37.6 (37.4-37.8)	37.6 (37.4-37.8)
Follow-up: per protocol (n=11 541)			
Mean ±SD	36.5±5.01	36.4±5.2	36.4±5.1
Median (IQR)	37.6 (37.4-37.8)	37.6 (37.4-37.8)	37.6 (37.4-37.8)
History of smoking or tobacco use			
Yes	779 (18.4)	750 (17.7)	751 (17.8)
No	3460 (81.6)	3489 (82.3)	3488 (82.2)
History of substance or alcohol misuse			
Yes	452 (10.6)	453 (10.7)	450 (10.6)
No	3787 (89.4)	3786 (89.3)	3789 (89.4)
Current smoking or tobacco use			
Yes	642(15.2)	594 (14.0)	613(14.4)
No	3597 (84.8)	3645 (86.0)	3626 (85.6)
Current substance misuse or alcohol consumption			
Yes	431 (10.2)	441 (10.4)	433 (10.3)
No	3808 (89.8)	3798 (89.6)	3806 (89.7)
Medical history			
Yes	1215 (28.6)	1146 (27.1)	1192 (28.1)
No	3024 (71.4)	3093 (72.9)	3047 (71.9)
Tuberculin skin test (n=8058)			
Positive	687 (25.6)	702 (26.2)	732 (27.3)
Negative	1994 (74.4)	1987 (73.8)	1956 (72.7)
Bacterial load of patients with TB with respect to enrolled participants			
Scanty	276 (6.5)	281 (6.6)	261 (6.2)
CBNAAT+	4 (0.1)	1 (0.2)	0
1+	1945 (46.0)	2039 (48.1)	1943 (45.8)
2+	876 (20.6)	834 (19.6)	878 (20.7)
3+ to 6+	1138 (26.8)	1085 (25.5)	1157 (27.3)

Data are numbers (%).
CBNAAT=cartridge based nucleic acid amplification test; IQR=interquartile range; SD=standard deviation; TB=tuberculosis.

the efficacy analysis of the vaccines against pulmonary TB and extrapulmonary TB, 21 participants in the ITT analysis, 21 in the mITT analysis, and 19 in the per protocol analysis were included in the counts for both pulmonary TB and extrapulmonary TB (supplementary table S-1).

In the per protocol analysis (table 2), 65 (1.68%) participants developed TB in the VPM1002 group

Table 2 | Vaccine efficacy of VPM1002 and Immuvac compared with placebo against microbiologically confirmed all tuberculosis (TB), pulmonary TB (PTB), and extrapulmonary TB (EPTB): per protocol and modified intention-to-treat (mITT) analysis

Analysis and type of TB	VPM1002 or Immuvac			Placebo			Absolute difference, relative difference (%)	Vaccine efficacy, % (90% CI)	P value; vaccine efficacy, % (95% CI)
	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)			
Per protocol: VPM1002 (n=3860) *v* placebo (n=3845)*									
All TB	65 (1.68)	11733.8	5.53 (4.51 to 6.79)	82 (2.13)	11647.9	7.03 (5.87 to 8.44)	0.45, 21.13	21.4 (−3.4 to 40.2)	0.14; 21.4 (−8.9 to 43.2)
PTB	56 (1.45)	11733.8	4.77 (3.83 to 5.94)	69 (1.79)	11647.9	5.92 (4.85 to 7.22)	0.34, 18.99	19.5 (−8.2 to 40.1)	0.22; 19.5 (−14.6 to 43.4)
EPTB	12 (0.31)	11733.8	1.02 (0.63 to 1.64)	24 (0.62)	11647.9	2.06 (1.47 to 2.88)	0.31, 50.0	50.4 (11.2 to 72.3)	0.04; 50.4 (0.8 to 75.2)
mITT: VPM1002 (n=4207) *v* placebo (n=4223)*									
All TB	73 (1.74)	12749.9	5.72 (4.72 to 6.94)	88 (2.08)	12766.9	6.89 (5.78 to 8.21)	0.34, 16.34	16.9 (−7.8 to 36)	0.24; 16.9 (−13.3 to 39.1)
PTB	63 (1.5)	12749.9	4.94 (4.01 to 6.07)	73 (1.73)	12766.9	5.71 (4.71 to 6.93)	0.23, 13.29	13.6 (−14.7 to 34.9)	0.39; 13.6 (−21.1 to 38.3)
EPTB	15 (0.36)	12749.9	1.17 (0.76 to 1.79)	26 (0.62)	12766.9	2.03 (1.47 to 2.81)	0.26, 41.94	42.3 (1.5 to 66.1)	0.09; 42.3 (−9.1 to 69.4)
Per protocol: Immuvac (n=3836) *v* placebo (n=3845)†									
All TB	80 (2.09)	11614.8	6.88 (5.73 to 8.27)	82 (2.13)	11647.9	7.03 (5.87 to 8.44)	0.04, 1.88	2.3 (−26.6 to 24.5)	0.88; 2.3 (−33.0 to 28.2)
PTB	69 (1.8)	11614.8	5.94 (4.87 to 7.24)	69 (1.79)	11647.9	5.92 (4.85 to 7.22)	−0.01, −0.56	0 (−32.6 to 24.3)	0.98; 0 (−39.9 to 28.2)
EPTB	16 (0.42)	11614.8	1.37 (0.91 to 2.07)	24 (0.62)	11647.9	2.06 (1.47 to 2.88)	0.2, 32.26	33.2 (−13.7 to 60.7)	0.21; 33.2 (−25.9 to 64.5)
mITT: Immuvac (n=4205) *v* placebo (n=4223)†									
All TB	91 (2.16)	12694.4	7.16 (6.03 to 8.51)	88 (2.08)	12766.9	6.89 (5.78 to 8.21)	−0.08, −3.84	−4 (−33.0 to 18.7)	0.79; −4 (−39.4 to 22.5)
PTB	80 (1.9)	12694.4	6.30 (5.24 to 7.57)	73 (1.73)	12766.9	5.71 (4.71 to 6.93)	−0.17, −9.82	−10.2 (−43.8 to 15.6)	0.54; −10.2 (−51.3 to 19.8)
EPTB	16 (0.38)	12694.4	1.26 (0.83 to 1.90)	26 (0.62)	12766.9	2.03 (1.47 to 2.81)	0.24, 38.71	38.1 (−4.4 to 63.3)	0.13; 38.1 (−15.4 to 66.8)

CI=confidence interval.
*Absolute difference: placebo−VPM1002. Vaccine efficacy of VPM1002.
†Absolute difference: placebo−Immuvac. Vaccine efficacy of Immuvac.

compared with 82 (2.13%) in the placebo group, giving a vaccine efficacy of 21.4% (95% CI −8.9% to 43.2%). Of these, 12 (0.31%) participants in the VPM1002 group developed extrapulmonary TB compared with 24 (0.62%) in the placebo group, therefore the vaccine efficacy of VPM1002 was 50.4% (95% CI 0.8 to 75.2) for extrapulmonary TB (incidence 1.02 (VPM1002) *v* 2.06 (placebo) per 1000 person years), reducing the incidence of extrapulmonary TB by 50%. The Kaplan-Meier plots in fig 3 (lower panel) show the effects of VPM1002 and Immuvac in providing protection against extrapulmonary TB.

Eighty three (1.96%) participants in the ITT analysis (table S-2) and 73 (1.74%) in the mITT analysis (table 2) developed microbiologically confirmed TB in the VPM1002 group compared with 89 (2.1%) and 88 (2.08%) in the placebo group, respectively, showing a vaccine efficacy of 7.7% (95% CI −24.6% to 31.6%) in the ITT analysis and 16.9% (−13.3% to 39.1%) in the mITT analysis. Of the 73 participants with confirmed TB in the VPM1002 group (mITT analysis), 63 (1.5%) developed pulmonary TB compared with 73 (1.73%) in the placebo group, showing a vaccine efficacy of 13.6% (95% CI −21.1% to 38.3%) against pulmonary TB. However, 15 (0.36%) participants developed extrapulmonary TB in the VPM1002 group compared with 26 (0.62%) in the placebo group, showing a vaccine efficacy of 42.3% (−9.1% to 69.4%) against extrapulmonary TB only (incidence 1.17 (VPM1002) *v* 2.03 (placebo) per 1000 person years).

The per protocol analysis of Immuvac revealed that 80 (2.09%) participants developed TB compared with 82 (2.13%) in the placebo group (table 2). Although Immuvac did not provide any protection for all TB and pulmonary TB, it gave a vaccine efficacy of 33.2% (95% CI −25.9% to 64.5%) against extrapulmonary TB. A total of 103 (2.43%) participants in the ITT analysis and 91 (2.16%) in the mITT analysis developed confirmed TB in the Immuvac group. In the mITT analysis, 80 (1.9%) developed pulmonary TB and 16 (0.38%) developed extrapulmonary TB (table 2, supplementary table S-2), with a vaccine efficacy of 38.1% (−15.4% to 66.8%) against extrapulmonary TB only (table 2).

Secondary outcomes

Efficacy in preventing latent TB infection

Of the 1994 participants in the VPM1002 group who were TST negative at baseline (supplementary tables S-3, S-4, S-5), 1681 (ITT), 1675 (mITT), and 1606 (per protocol) were tested again for TST at six months. Of these, 388 (23.08%), 386 (23.04%), and 360 (22.42%) tested positive, respectively. Of the 1987 participants in the Immuvac group who were TST negative at baseline, 1662 (ITT), 1652 (mITT), and 1581 (per protocol) were tested again for TST at six months. Of these, 334 (20.1%), 331 (20.04%), and 314 (19.86%) tested positive, respectively. In the placebo group, of the 1956 participants who were TST negative at baseline, 1648 (ITT), 1646 (mITT), and 1571 (per protocol) were tested again for TST at

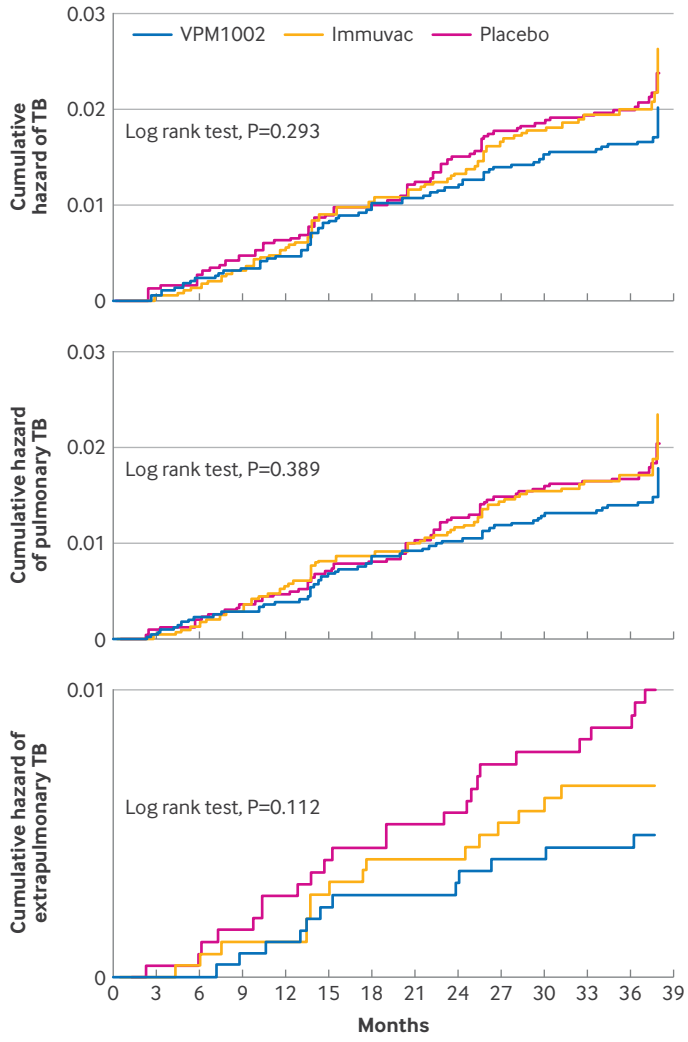

Fig 3 | Kaplan-Meier plots for cumulative hazard of tuberculosis (TB) over 38 months in participants who received VPM1002, Immuvac, or placebo. Upper panel: microbiologically confirmed pulmonary and extrapulmonary TB; middle panel: microbiologically confirmed pulmonary TB; lower panel: microbiologically confirmed extrapulmonary TB

six months. Of these, 335 (20.33%), 334 (20.29%), and 315 (20.05%) tested positive, respectively. The difference between the two vaccines and the placebo groups when considering the number of participants who converted from being TST negative at day 0 to TST positive at six months was not significant, indicating that the vaccines did not prevent infection.

Efficacy in participants who were TST positive and TST negative

We further checked the vaccine efficacy by considering latent TB infection status in the participants. In the per protocol analysis, 2447, 2456, and 2452 participants were tested for TST at baseline in the VPM1002, Immuvac, and placebo groups, respectively (table 3; ITT and mITT data are shown in supplementary tables S-6 and S-7). VPM1002 showed vaccine efficacy of 69.9% (95% CI −45.2% to 93.8%) against extrapulmonary TB (table 3, supplementary tables S-6, S-7) in participants who were TST positive. However, with Haldane's modification, a vaccine efficacy of 64.9% (−2.0 to 90.1) was observed for extrapulmonary TB. In participants who were TST negative, VPM1002 showed a vaccine efficacy of 36.8% (−8.1% to 63.1%) against all TB and 44.2% (−3.2% to 69.8%) against pulmonary TB.

The vaccine efficacy of Immuvac was 44.3% (95% CI −16.2% to 73.4%) against all TB, 43.1% (−28.8% to 74.9%) against pulmonary TB, and 71.1% (−39.3% to 93.9%) against extrapulmonary TB in participants who were TST positive (table 3, supplementary tables S-6, S-7). However, with Haldane's modification, the vaccine efficacy for extrapulmonary TB reduced to 66.3% (1.9% to 90.5%).

Of those who became TST positive at six months, 6 (1.67%) in the VPM1002 group, 8 (2.55%) in the Immuvac group, and 16 (5.08%) in the placebo group developed TB during the follow-up period of 38 months (table 4, supplementary tables S-8, S-9). The VPM1002 group showed a vaccine efficacy of 68.4% (95% CI 19.2% to 87.7%) against all TB (5.41 *v* 17.12 per 1000 year follow-up in VPM1002 and placebo groups, respectively), 66.4% (−7.2% to 89.5%) against pulmonary TB (3.61 *v* 10.7 per 1000 year follow-up, respectively), and 78.9% (0.4% to 95.6%) against extrapulmonary TB (1.8 *v* 8.56 per 1000 year follow-up, respectively) in those who converted to being TST positive after six months.

Immuvac showed a vaccine efficacy of 50.7% (95% CI −15.4% to 78.9%) against all TB (8.46 *v* 17.12 per 1000 year follow-up in Immuvac and placebo groups, respectively), 40.9% (−62.8% to 78.5%) against pulmonary TB (6.35 *v* 10.7 per 1000 year follow-up, respectively), and 62.9% (−39.8% to 90.2%) against extrapulmonary TB (3.17 *v* 8.56 per 1000 year follow-up , respectively).

Efficacy in preventing pulmonary and extrapulmonary TB in prespecified age groups

An analysis was performed of vaccine efficacy 38 months after the first dose was administered in the ITT (supplementary table S-10), mITT (supplementary table S-11), and per protocol (table 5) groups by considering prespecified age groups (6-18, 19-35, 36-60, and >60 years).

For VPM1002, the per protocol analysis showed that in participants aged 6-18 years, the vaccine efficacy was 24.9% (95% CI −19.8% to 52.9%) against all forms of TB, 31% (−15.0% to 58.6%) against pulmonary TB, and 33.9% (−61.8% to 73.0%) against extrapulmonary TB (table 5). In the 19-35 year age group, the vaccine efficacy was 27.3% (−34.0% to 60.6%) against all forms of TB, 29.5% (−34.2% to 63.0%) against pulmonary TB, and 27.3% (−225.2% to 83.8%) against extrapulmonary TB. In those aged 36-60 years, the vaccine efficacy against extrapulmonary TB was 85.2% (−20.6% to 98.2%) and 79.5% (27.2% to 96.2%) when Woolf's method with Haldane's modification was applied (to avoid bias because the number in one group was less than five).

Table 3 | Vaccine efficacy of VPM1002 and Immuvac against microbiologically confirmed all tuberculosis (TB), pulmonary (PTB), and extrapulmonary TB (EPTB) considering tuberculin skin test (TST) status (ie, latent TB infection): per protocol analysis

	VPM1002 or Immuvac			Placebo					
TST status at baseline and type of TB	No (%) of participants who developed TB	Person years of Follow-up	Rate per 1000 person years (90% CI)	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	Absolute difference, relative difference (%)	Vaccine efficacy, % (90% CI)	P value; vaccine efficacy, % (95% CI)
VPM1002 (n=3860) *v* placebo (n=3845)*									
Positive for TST at baseline	632 (25.8)	—	—	671 (27.4)	—	—	—	—	
All TB	21 (3.32)	1897.3	11.06 (7.73 to 15.84)	20 (2.98)	2001.5	9.99 (6.91 to 14.43)	−0.34, −11.4	−10.2 (−84.2 to 34.1)	0.75; −10.2 (−103.3 to 40.3)
PTB	20 (3.16)	1897.3	10.54 (7.29 to 15.22)	16 (2.38)	2001.5	7.99 (5.29 to 12.06)	−0.78, −32.8	−31.0 (−127.5 to 24.6)	0.42; −31.0 (−152.9 to 32.1)
EPTB	2 (0.32)	1897.3	1.05 (0.32 to 3.37)	7 (1.04)	2001.5	3.49 (1.87 to 6.51)	0.72, 69.23	69.9 (−12.8 to 92.0); 64.9 (11.5 to 87.8)‡	0.13; 69.9 (−45.2 to 93.8); 64.9 (−2 to 90.1)‡
Negative for TST at baseline	1815 (74.2)	—	—	1781 (72.6)	—	—	—	—	—
All TB	22 (1.2)	5542.9	3.96 (2.79 to 5.63)	34 (1.91)	5415.0	6.27 (4.73 to 8.32)	0.71, 37.17	36.8 (0.08 to 59.7)	0.09; 36.8 (−8.1 to 63.1)
PTB	16 (0.88)	5542.9	2.88 (1.91 to 4.35)	28 (1.57)	5415.0	5.17 (3.78 to 7.05)	0.69, 43.95	44.2 (6.5 to 66.7)	0.06; 44.2 (−3.2 to 69.8)
EPTB	8 (0.44)	5542.9	1.44 (0.80 to 2.58)	9 (0.51)	5415.0	1.66 (0.96 to 2.87)	0.07, 13.73	13.2 (−93.1 to 61.0)	0.77; 13.2 (−125.1 to 66.5)
Immuvac (n=3836) *v* placebo (n=3845)†									
Positive for TST at baseline	657 (26.8)	—	—	671 (27.4)	—	—	—	—	—
All TB	11 (1.67)	1975.4	5.56 (3.39 to 9.14)	20 (2.98)	2001.5	9.99 (6.91 to 14.43)	1.31, 43.96	44.3 (−3.2 to 69.6)	0.11; 44.3 (−16.2 to 73.4)
PTB	9 (1.37)	1975.4	4.55 (2.63 to 7.88)	16 (2.38)	2001.5	7.99 (5.29 to 12.06)	1.01, 42.44	43.1 (−13 to 71.3)	0.17; 43.1 (−28.8 to 74.9)
EPTB	2 (0.3)	1975.4	1.01 (0.31 to 3.23)	7 (1.04)	2001.5	3.49 (1.87 to 6.51)	0.74, 71.15	71.1 (−8.2 to 92.3); 66.3 (14.9 to 88.3)‡	0.12; 71.1 (−39.3 to 93.9); 66.3 (1.9 to 90.5)‡
Negative for TST at baseline	1799 (73.2)	—	—	1781 (72.6)	—	—	—	—	—
All TB	37 (2.06)	5443.7	6.79 (5.18 to 8.90)	34 (1.91)	5415.0	6.27 (4.73 to 8.32)	−0.15, −7.85	−8.1 (−59.8 to 26.9)	0.74; −8.1 (−72.2 to 32.2)
PTB	32 (1.78)	5443.7	5.87 (4.39 to 7.86)	28 (1.57)	5415.0	5.17 (3.78 to 7.05)	−0.21, −13.38	−13.5 (−73.8 to 25.8)	0.62; −13.5 (−88.6 to 31.7)
EPTB	7 (0.39)	5443.7	1.28 (0.69 to 2.39)	9 (0.51)	5415.0	1.66 (0.96 to 2.87)	0.12, 23.53	22.7 (−77.1 to 66.3)	0.61; 22.7 (−107.6 to 71.2)

Participants checked for TST at baseline: VPM1002, n=2447 (63.4%); Immuvac, n=2456 (64.02%); placebo, n=2452 (63.8%). CI= confidence interval.
*Absolute difference: placebo–VPM1002. Vaccine efficacy of VPM1002.
†Absolute difference: placebo–Immuvac. Vaccine efficacy of Immuvac.
‡Additional analysis done (per protocol) when n<5 for any variable. Vaccine efficacy derived from odds ratio (OR), calculated using Woolf 's method with Haldane's modification: vaccine efficacy=1–OR×100.

Table 4 | Vaccine efficacy against microbiologically confirmed all tuberculosis (TB), pulmonary TB (PTB), and extrapulmonary TB (PTB) in participants who were initially tuberculin skin test (TST) negative and converted to TST positivity at six months: per protocol analysis

TST positive at 6 months and type of TB	VPM1002 or Immuvac			Placebo			Absolute difference, relative difference (%)	Vaccine efficacy, % (90% CI)	P value; vaccine efficacy, % (95% CI)
	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)			
VPM1002 (n=360, 22.42%) *v* placebo (n=315, 20.05%)*									
All TB	6 (1.67)	1107.2	5.41 (2.76 to 10.60)	16 (5.08)	934.3	17.12 (11.35 to 25.83)	3.41, 67.13	68.4 (30.5 to 85.6)	0.01; 68.4 (19.2 to 87.7)
PTB	4 (1.11)	1107.2	3.61 (1.58 to 8.22)	10 (3.17)	934.3	10.70 (6.36 to18.0)	2.06, 64.98	66.4 (11 to 87.3); 63.3 (24.9 to 83.1)‡	0.06; 66.4 (−7.2 to 89.5); 63.3 (15.6 to 85.3)‡
EPTB	2 (0.56)	1107.2	1.80 (0.56 to 5.77)	8 (2.54)	934.3	8.56 (4.78 to 15.31)	1.98, 77.95	78.9 (22.3 to 94.3); 74.8 (37.5 to 91.2)‡	0.05; 78.9 (0.4 to 95.6); 74.8 (28.2 to 92.8)‡
Immuvac (n=314, 19.86%) *v* placebo (n=315, 20.05%)†									
All TB	8 (2.55)	944.7	8.46 (4.73 to 15.14)	16 (5.08)	934.3	17.12 (11.35 to 25.83)	2.53, 49.8	50.7 (0 to 75.8)	0.10; 50.7 (−15.4 to 78.9)
PTB	6 (1.91)	944.7	6.35 (3.24 to 12.42)	10 (3.17)	934.3	10.70 (6.36 to18.0)	1.26, 39.75	40.9 (−38.3 to 74.7)	0.31; 40.9 (−62.8 to 78.5)
EPTB	3 (0.96)	944.7	3.17 (1.22 to 8.20)	8 (2.54)	934.3	8.56 (4.78 to 15.31)	1.58, 62.2	62.9 (−13 to 87.9); 59.4 (8.6 to 83.3)‡	0.14; 62.9 (−39.8 to 90.2); 59.4 (−4 to 85.9)‡

CI=confidence interval.
*Absolute difference: placebo−VPM1002. Vaccine efficacy of VPM1002.
†Absolute difference: placebo−Immuvac. Vaccine efficacy of Immuvac.
‡Additional analysis done (per protocol) when n<5 for any variable. Vaccine efficacy derived from odds ratio (OR), calculated using Woolf 's method with Haldane's modification: vaccine efficacy=1−OR×100.

For Immuvac, in the 6-18 year age group, the vaccine efficacy was 16.8% (95% CI −34.5% to 48.6%) against pulmonary TB and 19.7% (−86.0% to 65.3%) against extrapulmonary TB. For extrapulmonary TB, in participants aged 19-35 years, the vaccine efficacy was 26.0% (−230.7% to 83.5%), and in those aged 36-60 years, the vaccine efficacy was 69.8% (−45.4% to 93.8%) and 62% (−10.4% to 89.2%; 90% CI 4.3% to 86.8%) when Woolf's method with Haldane's modification was applied (to avoid bias because the number in one group was less than five; table 5).[9 10]

Immunogenicity of VPM1002 and Immuvac

We studied the responder rate, that is, the proportion of participants in the vaccine and placebo groups who showed a positive recall response to whole cell lysates of *M tuberculosis*. A responder was defined as someone who had a detectable recall T cell response—at least 0.02% cells above unstimulated control—after stimulation with whole cell lysates. A total of 458 (93.3%) participants showed a CD3 IFN-γ response at screening—95.3% in the VPM1002 group, 91.4% in the Immuvac group, and 93.1% in the placebo group (supplementary table S-12). Considerably higher numbers of participants in the Immuvac group showed CD3 IFN-γ (98.1%) and CD3 TNF-α (95.1%) responses than in the placebo group (91.9% and 88.8%, respectively) at two months.

Median frequencies of the CD4 and CD8 T cells expressing single cytokines IFN-γ, TNF-α, or IL-2 showed wide interquartile ranges and did not show significant differences in the vaccine groups compared with placebo (data not shown). However, frequencies of *M tuberculosis* specific polyfunctional CD4 T cells expressing IFN-γ and IL-2, IL-2 and TNF-α (fig 4, upper panel) increased significantly in the VPM1002 group compared with the placebo group at two months. CD4 T cells expressing all three cytokines (ie, IFN-γ, IL-2, and TNF-α) increased significantly at six months in the VPM1002 group compared with placebo. The Immuvac group showed significantly higher frequencies of polyfunctional CD4 T cells expressing IFN-γ and TNF-α compared with the placebo group at six months (fig 4, lower panel). Polyfunctional CD8 T cells did not show any significant differences (data not shown). The differences observed in the numbers of cytokines secreted in the supernatants of whole cell lysate stimulated peripheral blood mononuclear cells and sera of patients at day 0, two months, and six months between the vaccines and placebo were not significant (data not shown).

Safety of VPM1002 and Immuvac

Both the vaccines were safe. After the first dose, solicited self-healing local reactions at the site of injection were observed in one arm of about a third of participants vaccinated with VPM1002, and in both arms of about a third of those vaccinated with Immuvac. After the second dose, about the same proportion had a reaction in one arm only in the Immuvac group. These proportions were considerably higher than in the placebo group, as expected (supplementary table S-13).

Serious adverse events were observed in less than 10% of the vaccinated population in each group. A total of 887 serious adverse events were observed in 760 participants, with 251 (5.9%) participants in the VPM1002 group, 264 (6.2%) in the Immuvac group, and 245 (5.7%) in the placebo group throughout the follow-up period (supplementary tables S-14, S-15). Sixty-eight participants had several events: 29 (0.68%) in the VPM1002 group, 20 (0.47%) in the Immuvac group, and 19 (0.44%) in the placebo group; however, none were related to the vaccines. There were 109 deaths in total (41 (0.96%) in the VPM1002 group, 33 (0.78%) in the Immuvac group, and 35 (0.83%) in the placebo group). None of the serious adverse events and deaths were related to the vaccines (supplementary tables S-14, S-15, S-16).

Table 5 | Subgroup analysis: distribution by age of microbiologically confirmed all tuberculosis (TB), pulmonary TB (PTB), and extrapulmonary TB (EPTB) in VPM1002 and Immuvac groups compared with placebo: per protocol analysis

	VPM1002 or Immuvac			Placebo					
Age (years) and type of TB	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	Absolute difference, relative difference (%)	Vaccine efficacy, % (90% CI)	P value; vaccine efficacy, % (95% CI)
VPM1002 (n=3860) *v* placebo (n=3845)*									
Age 6-18	1407 (36.45)	—	—	1414 (36.78)	—	—	—	—	—
All TB	31 (2.2)	4291.9	7.22 (5.37 to 9.70)	41 (2.9)	4264.3	9.61 (7.43 to 12.43)	0.7, 24.14	24.9 (−11.2 to 49.2)	0.23;24.9 (−19.8 to 52.9)
PTB	25 (1.78)	4291.9	5.82 (4.19 to 8.09)	36 (2.55)	4264.3	8.44 (6.41 to 11.10)	0.77, 30.2	31 (−6.0 to 55.0)	0.15; 31 (−15.0 to 58.6)
EPTB	8 (0.57)	4291.9	1.86 (1.04 to 3.33)	12 (0.85)	4264.3	2.81 (1.75 to 4.52)	0.28, 32.9	33.9 (−40.1 to 68.8)	0.36; 33.9 (−61.8 to 73.0)
Age 19-35	1202 (31.14)	—	—	1168 (30.38)	—	—	—	—	—
All TB	18 (1.5)	3638.7	4.94 (3.35 to 7.28)	24 (2.05)	3531.3	6.79 (4.85 to 9.50)	0.55, 26.83	27.3 (−21.4 to 56.5)	0.30; 27.3 (−34.0 to 60.6)
PTB	16 (1.33)	3638.7	4.39 (2.91 to 6.63)	22 (1.88)	3531.3	6.22 (4.38 to 8.84)	0.55, 29.26	29.5 (−21.0 to 59.0)	0.28; 29.5 (−34.2 to 63.0)
EPTB	3 (0.25)	3638.7	0.82 (0.31 to 2.13)	4 (0.34)	3531.3	1.13 (0.49 to 2.57)	0.09, 26.47	27.3 (−155.6 to 79.3); 24.5 (−94.5 to 71.6)‡	0.67; 27.3 (−225.2 to 83.8); 24.5 (−128.3 to 76.2)‡
Age 36-60	1131 (29.3)	—	—	1169 (30.4)	—	—	—	—	—
All TB	12 (1.06)	3440.9	3.48 (2.16 to 5.60)	14 (1.2)	3567.3	3.92 (2.52 to 6.09)	0.14, 11.67	11.1 (−69.9 to 53.5)	0.76; 11.1 (−92.3 to 58.9)
PTB	11 (0.97)	3440.9	3.19 (1.94 to 5.24)	8 (0.68)	3567.3	2.24 (1.25 to 4.01)	−0.14, −4.39	−42.6 (−206.3 to 33.6)	0.44; −42.6 (−254.6 to 42.7)
EPTB	1 (0.09)	3440.9	0.29 (0.05 to 1.50)	7 (0.6)	3567.3	1.96 (1.05 to 3.65)	0.51, 85.0	85.2 (13.9 to 97.5); 79.5 (37.8-95.0)‡	0.07; 85.2 (−20.6 to 98.2); 79.5 (27.2 to 96.2)‡
Age >60	120 (3.11)	—	—	94 (2.44)	—	—	—	—	—
All TB	4 (3.33)	362.2	11.04 (4.85 to 25.13)	3 (3.19)	285.0	10.52 (4.07 to 27.20)	−0.14, −4.39	−3.8 (−264.9 to 70.5); 0 (−172.7 to 61.5)‡	0.96; −3.8 (−364.2 to 76.8); 0 (−225.0 to 67.3)‡
PTB	4 (3.33)	362.2	11.04 (4.85 to 25.13)	3 (3.19)	285.0	10.52 (4.07 to 27.20)	−0.14, −4.39	−3.7 (−264.3 to 70.5); 0 (−172.7 to 61.5)‡	0.96; −3.7 (−363.5 to 76.8); 0 (−225.0 to 67.3)‡
EPTB	0	362.2	—-	1 (1.06)	285.0	3.50 (0.67 to 18.17)	1.06, 100	—	—
Immuvac (n=3836) *v* placebo (n=3845)†									
Age 6-18	1463 (38.14)	—	—	1414 (36.78)	—	—	—	—	—
All TB	37 (2.53)	4419.3	8.37 (6.38 to 10.97)	41 (2.9)	4264.3	9.61 (7.43 to 12.43)	0.37, 12.76	12.9 (−26.6 to 40.0)	0.54; 12.9 (−35.9 to 44.1)
PTB	31 (2.12)	4419.3	7.01 (5.22 to 9.42)	36 (2.55)	4264.3	8.44 (6.41 to 11.10)	0.43, 16.86	16.8 (−24.5 to 44.4)	0.45; 16.8 (−34.5 to 48.6)
EPTB	10 (0.68)	4419.3	2.26 (1.34 to 3.80)	12 (0.85)	4264.3	2.81 (1.75 to 4.52)	0.17, 20.0	19.7 (−62.5 to 60.3)	0.61; 19.7 (−86.0 to 65.3)
Age 19-35	1177 (30.68)	—	—	1168 (30.38)	—	—	—	—	—
All TB	27 (2.29)	3573	7.55 (5.50 to 10.37)	24 (2.05)	3531.3	6.79 (4.85 to 9.50)	−0.24, −11.7	−11.0 (−76.2 to 30.0)	0.70; −11.0 (−92.5 to 35.9)
PTB	25 (2.12)	3573	6.99 (5.03 to 9.72)	22 (1.88)	3531.3	6.22 (4.38 to 8.84)	−0.24, −12.77	−12.2 (−81.4 to 30.7)	0.69; −12.2 (−99.0 to 36.8)
EPTB	3 (0.25)	3573	0.83 (0.32 to 2.17)	4 (0.34)	3531.3	1.13 (0.49 to 2.57)	0.09, 26.47	26.0 (−160.0 to 79.0); 22.9 (−98.5 to 71.0)‡	0.69; 26.0 (−230.7 to 83.5); 22.9 (−133.1 to 75.7)‡
Age 36-60	1107 (28.85)	—	—	1169 (30.4)	—	—	—	—	—
All TB	15 (1.36)	3366.3	4.45 (2.91 to 6.81)	14 (1.2)	3567.3	3.92 (2.52 to 6.09)	−0.16, −13.33	−13.3 (−108.8 to 38.5)	0.73; −13.3 (−134.8 to 45.3)
PTB	13 (1.17)	3366.3	3.86 (2.44 to 6.09)	8 (0.68)	3567.3	2.24 (1.25 to 4.01)	−0.49, −72.06	−71.9 (−260.0 to 17.9)	0.22; −71.9 (−314.8 to 28.8)
EPTB	2 (0.18)	3366.3	0.59 (0.18 to 1.90)	7 (0.6)	3567.3	1.96 (1.05 to 3.65)	0.42, 70.0	69.8 (−12.9 to 92.0); 62.0 (4.3 to 86.8)‡	0.13; 69.8 (−45.4 to 93.8); 62.0 (−10.4 to 89.2)‡
Age >60	89 (2.32)	—	—	94 (2.44)	—	—	—	—	—
All TB	1 (1.12)	256.1	3.90 (0.75 to 20.22)	3 (3.19)	285.0	10.52 (4.07 to 27.20)	2.07, 64.89	63.0 (−147.9 to 94.5); 55.7 (−62.4 to 90.3)‡	0.39; 63 (−256.7 to 96.2); 55.7 (−98.2 to 92.8)‡
PTB	0	—	—	3 (3.19)	285.0	10.52 (4.07 to 27.20)	3.19, 100	85.4 (7.5 to 99.4)‡	85.4 (−15.9 to 99.7)‡
EPTB	1 (1.12)	256.1	3.90 (0.75 to 20.22)	1 (1.06)	285.0	3.50 (0.67 to 18.17)	−0.06, −5.66	−14.4 (−1071 to 88.9); −5.3 (−491.2 to 81.2)‡	0.92; −14.4 (−1730 to 92.9); −5.3 (−699 to 86.1)‡

CI=confidence interval.
*Absolute difference: placebo–VPM1002. Vaccine efficacy of VPM1002.
†Absolute difference: placebo–Immuvac. Vaccine efficacy of Immuvac.
‡Additional analysis done (per protocol) when n<5 for any variable. Vaccine efficacy derived from odds ratio (OR), calculated using Woolf 's method with Haldane's modification: vaccine efficacy=1−OR×100.

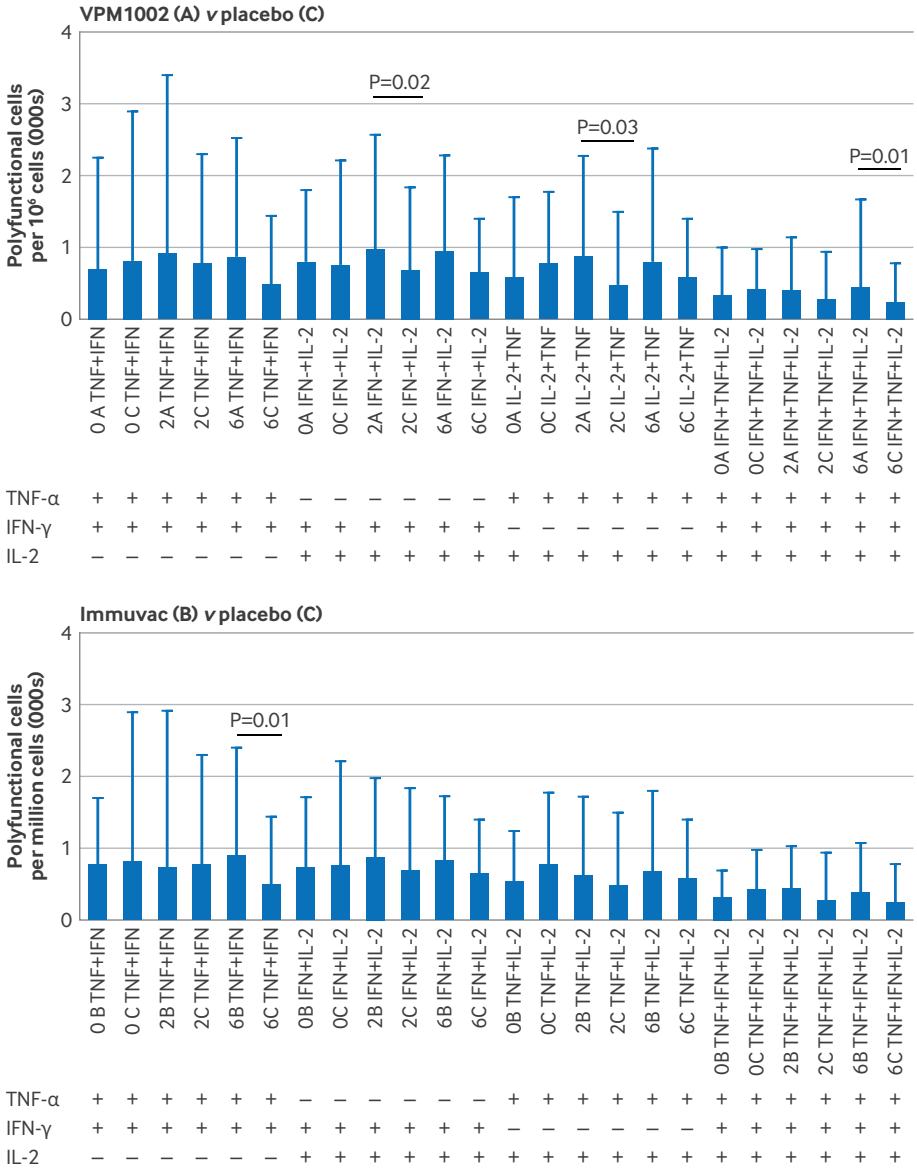

Fig 4 | Bar graphs showing medians with interquartile ranges of polyfunctional CD4 T cells simultaneously expressing IFN-γ and TNF-α (No of cells per million CD4 T cells), IFN-γ and IL-2, IL-2 and TNF-α, and all three cytokines IFN-γ, TNF-α, and IL-2 in peripheral blood mononuclear cells stimulated with whole cell lysates of *Mycobacterium tuberculosis* in participants administered VPM1002, Immuvac, and placebo. Upper panel: polyfunctional CD4 T cells in VPM1002 group compared with placebo. CD4 T cells expressing IFN-γ+IL-2 and IL-2+TNF-α were significantly higher in numbers in VPM1002 group at two months after vaccination than placebo. CD4 T cells expressing all three cytokines were significantly increased in VPM1002 group six months after vaccination compared with placebo. Lower panel: polyfunctional CD4 T cells in Immuvac group compared with placebo. CD4 T cells expressing IFN-γ and TNF-α were significantly enhanced at six months in Immuvac group compared with placebo. Although CD4 T cells expressing all three cytokines were increased in Immuvac group, the difference was not statistically significant. 0A, 2A, 6A represent day 0, two months, and six months after vaccination with VPM1002; 0B, 2B, 6B represent day 0, two months, and six months after vaccination with Immuvac; 0C, 2C, 6C represent day 0, two months, and six months after placebo. IFN, interferon; IL, interleukin; TNF, tumour necrosis factor

Post hoc analysis in younger age groups

Because BCG has been shown to protect children <5 years old,[13] we performed a post hoc analysis of age groups 6 to <10 years and 6 to <14 years for the ITT (supplementary table S-17), mITT (supplementary table S-18), and per protocol (table 6) groups. VPM1002 showed a vaccine efficacy of 78.9% (95% CI −81.8% to 97.6%) and 71.2% (−9.6% to 94.9%; 90% CI 7.5% to 93.2%) when Haldane's modification was applied in the age group 6 to <10 years against all TB (0.86 *v* 4.06 per 1000 person years in VPM1002 and placebo groups, respectively), and 78.9% (−81.2% to 97.6%) against extrapulmonary TB (0.86 *v* 4.06 per 1000 person years in VPM1002 and placebo groups, respectively). Immuvac showed a vaccine efficacy of 61.6% (−98.3% to 92.6%) against all TB (1.56 *v*

Table 6 | Post hoc analysis: distribution by age of microbiologically confirmed tuberculosis (TB), pulmonary TB (PTB), and extrapulmonary TB (EPTB) in VPM1002 and Immuvac groups compared with placebo in participants aged 6 to <14 years: per protocol analysis

	VPM1002 or Immuvac			Placebo					
Age (years) and type of TB	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	No (%) of participants who developed TB	Person years of follow-up	Rate per 1000 person years (90% CI)	Absolute difference, relative difference (%)	Vaccine efficacy, % (90% CI)	P value; vaccine efficacy, % (95% CI)
VPM1002 (n=3860) *v* placebo (n=3845)*									
Age 6 to <10	375 (9.72)	—	—	400 (19.4)	—	—	—	—	—
All TB	1 (0.27)	1162.7	0.86 (0.16 to 4.45)	5 (1.25)	1229.6	4.06 (1.94 to 8.48)	0.98, 78.4	78.9 (−28.2 to 96.6); 71.2 (7.5 to 93.2)‡	0.15; 78.9 (−81.8 to 97.6); 71.2 (−9.6 to 94.9)‡
PTB	1 (0.27)	1162.7	0.86 (0.16 to 4.45)	2 (0.5)	1229.6	1.62 (0.50 to 5.20)	0.23, 46.0	47.3 (−295.4 to 93.0); 36.1 (−162.4 to 86.8)‡	0.60; 47.3 (−481.6 to 95.3); 36.2 (−229.4 to 90.2‡
EPTB	1 (0.27)	1162.7	0.86 (1.16 to 4.45)	5 (1.25)	1229.6	4.06 (1.94 to 8.48)	0.98, 78.4	78.9 (−28.3 to 96.6); 71.2 (7.5 to 93.2)‡	0.15; 78.9 (−81.2 to 97.6); 71.2 (−9.6 to 94.9)‡
Age 6 to <14	816 (21.14)	—	—	841 (21.87)	—	—	—	—	—
All TB	7 (0.86)	2519.2	2.77 (1.49 to 5.17)	20 (2.38)	2552.1	7.83 (5.42 to 11.32)	1.52, 63.87	64.6 (27.1 to 82.8)	0.01; 64.6 (16.3 to 85.1)
PTB	6 (0.74)	2519.2	2.38 (1.21 to 4.66)	16 (1.9)	2552.1	6.26 (4.15 to 9.45)	1.16, 61.05	62.1 (16.6 to 82.7)	0.04; 62.1 (3.0 to 85.2)
EPTB	2 (0.25)	2519.2	0.79 (0.24 to 2.54)	9 (1.07)	2552.1	3.52 (2.03 to 6.10)	0.82, 76.64	77.6 (19.0 to 93.9); 73.2 (34.8 to 90.5)‡	0.05; 77.6 (−3.7 to 95.2); 73.2 (25.3 to 92.2)‡
Immuvac (n=3836) *v* placebo (n=3845)†									
Age 6 to <10	417 (10.87)	—	—	400 (10.4)	—	—	—	—	—
All TB	2 (0.48)	1278.8	1.56 (0.48 to 5.0)	5 (1.25)	1229.6	4.06 (1.94 to 8.48)	0.77, 61.6	61.6 (−52.4 to 90.3); 56.8 (−16.1 to 85.6)‡	0.25; 61.6 (−98.3 to 92.6); 56.8 (−35.6 to 88.3)‡
PTB	2 (0.48)	1278.8	1.56 (0.48 to 5.0)	2 (0.5)	1229.6	1.62 (0.50 to 5.20)	0.02, 4.0	3.9 (−398.0 to 81.5); 4.1 (−236.4 to 72.7)‡	0.96; 3.9 (−582.4 to 86.5); 4.1 (−318.4 to 78.1)‡
EPTB	1 (0.24)	1278.8	0.78 (0.15 to 4.05)	5 (1.25)	1229.6	4.06 (1.94 to 8.48)	1.01, 80.8	80.8 (−16.6 to 96.9); 74.2 (16.9 to 93.9)‡	0.13; 80.8 (−64.7 to 97.8); 74.2 (1.5 to 95.4)‡
Age 6 to <14	931 (24.27)	—	—	841 (21.87)	—	—	—	—	
All TB	14 (1.5)	2839.7	4.92 (3.17 to 7.65)	20 (2.38)	2552.1	7.83 (5.42 to 11.32)	0.88, 36.97	37.0 (−11.8 to 64.5)	0.18; 37.0 (−24.8 to 68.2)
PTB	11 (1.18)	2839.7	3.87 (2.35 to 6.36)	16 (1.9)	2552.1	6.26 (4.15 to 9.45)	0.72, 37.9	38.0 (−18.1 to 67.5)	0.22; 38 (−33.6 to 71.3)
EPTB	6 (0.64)	2839.7	2.11 (1.07 to 4.13)	9 (1.07)	2552.1	3.52 (2.03 to 6.10)	0.43, 40.19	40.2 (−42.3 to 74.9)	0.33; 40.2 (−68.0 to 78.8)

CI=confidence interval.
*Absolute difference: placebo–VPM1002. Vaccine efficacy of VPM1002.
†Absolute difference: placebo–Immuvac. Vaccine efficacy of Immuvac.
‡Additional analysis done (per protocol) when n<5 for any variable. Vaccine efficacy derived from odds ratio (OR), calculated using Woolf 's method with Haldane's modification: vaccine efficacy=1−OR×100.

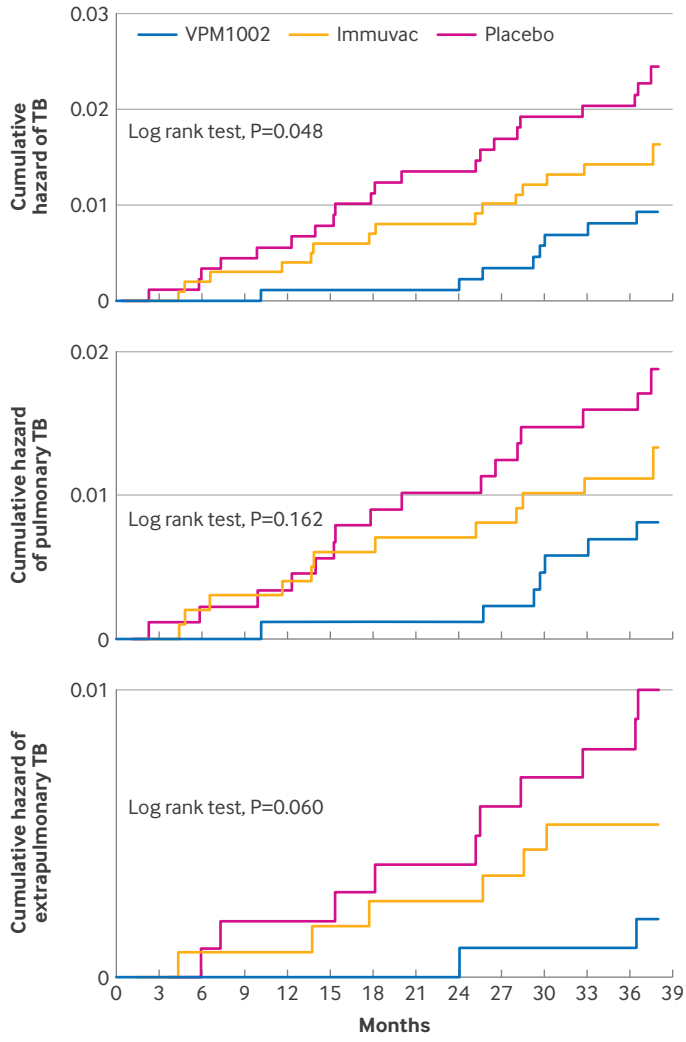

Fig 5 | Kaplan-Meier plots for cumulative hazard of microbiologically confirmed tuberculosis (TB) over 38 months in participants aged 6 to <14 years who received VPM1002, Immuvac, or placebo. Upper panel: microbiologically confirmed pulmonary and extrapulmonary TB; middle panel: microbiologically confirmed pulmonary TB; lower panel: microbiologically confirmed extrapulmonary TB

4.06 per 1000 years in Immuvac group and placebo groups, respectively) and 80.8% (−64.7% to 97.8%) and 74.2% (1.5% to 95.4%; 90% CI 16.9% to 93.9%) against extrapulmonary TB in the age group 6 to <10 years when Haldane's modification was applied (0.78 *v* 4.06 per 1000 years in Immuvac and placebo groups, respectively; table 6, supplementary tables S-17, S-18).

In the age group 6 to <14 years, VPM1002 showed a vaccine efficacy of 64.6% (95% CI 16.3% to 85.1%) against all TB (2.77 *v* 7.83 per 1000 person years in VPM1002 and placebo groups, respectively), a vaccine efficacy of 62.1% (3.0% to 85.2%) against pulmonary TB (2.38 *v* 6.26 per 1000 person years in VPM1002 and placebo groups, respectively), and 77.6% (−3.7% to 95.2%) and 73.2% (25.3% to 92.2%; 90% CI 34.8% to 90.5%) against extrapulmonary TB when Haldane's modification was applied (0.79 *v* 3.52 per 1000 person years in VPM1002 and placebo groups, respectively). Immuvac showed a vaccine efficacy of 37% (−24.8% to 68.2%) against all TB (4.92 *v* 7.83 per 1000 person years in Immuvac and placebo groups, respectively), 38% (−33.6% to 71.3%) against pulmonary TB (3.87 *v* 6.26 per 1000 person years in Immuvac and placebo groups, respectively), and 40.2% (−68.0% to 78.8%) against extrapulmonary TB (2.11 *v* 3.52 per 1000 person years in VPM1002 and placebo groups, respectively; table 6, supplementary tables S-17, S-18). Kaplan-Meier curves for TB (log rank test P=0.048), pulmonary TB (P=0.162), and extrapulmonary TB (P=0.06) clearly show the cumulative occurrence of the disease was more pronounced in the placebo group compared with the vaccine groups (fig 5).

Post hoc analysis considering body mass index

For adult participants (>18 years), body mass index ≥18 and <18 were considered (supplementary tables S-19, S-20, S-21). For participants <18 years, classification of normal weight or underweight was done based on the weight for age.[13] In the per protocol analysis, the vaccine efficacy for VPM1002 in participants with a body mass index ≥18 was 64.1% (95% CI −13.0% to 88.6%; 90% CI 6.0% to 86.3%) and 61.7% (13.8% to 84.4%; 90% CI 23.1% to 82.0%) against extrapulmonary TB when Haldane's modification was applied (supplementary table S-21). For Immuvac, the vaccine efficacy was 53.5% (−33.8% to 83.9%) and 51.3% (−4.2% to 78.6%; 90% CI 6.5% to 75.7%) against extrapulmonary TB only when Haldane's modification was applied. However, neither VPM1002 nor Immuvac provided any protection against any form of TB in participants with body mass index <18 (supplementary table S-21).

In children <18 years, who were in the normal weight range,[14] VPM1002 showed a vaccine efficacy of 45.1% (95% CI 5.4% to 68.2%) against all forms of TB, 56.9% (19.4% to 77.0%) against pulmonary TB and 39.2% (−67.3% to 77.9%) against extrapulmonary TB. Immuvac showed a vaccine efficacy of 31.6% (−12.9% to 58.6%) against all forms of TB, 38% (−7.1% to 64.2%) against pulmonary TB and 22.4% (−96.8% to 69.4%) against extrapulmonary TB. Neither VPM1002 nor Immuvac provided any protection to children who were underweight (supplementary table S-21).

We further evaluated vaccine efficacy in participants by considering other covariates like gender (tables S-22, S23, S-24), BCG vaccination status (supplementary tables S-25, S-26, S-27), diabetes (supplementary tables S-28, S-29, S-30), and smoking status (supplementary tables S-31, S-32, S-33) at baseline.

In the per protocol cohort, VPM1002 showed a vaccine efficacy of 42.8% (95% CI −36.5% to 76.0%) against extrapulmonary TB in participants who had a BCG scar (supplementary table S-27). However, in those without a BCG scar, the vaccine efficacy for extrapulmonary TB was 61.0% (−24% to 87.8%) and 58.4% (4.9% to 83.3%; 90% CI 15.3 to 80.7) when Haldane's modification was applied.

Neither VPM1002 nor Immuvac provided any protection in participants with diabetes (supplementary

tables S-28, S-29, S-30) and those who smoked, probably because the proportions (about 4% and 10%, respectively) were very small and were equally distributed across the three groups (supplementary tables S-28 to S-33). However, the vaccine efficacy of VPM1002 for participants who did not have diabetes was 45.8% (95% CI −9.5% to 73.2%; 90% CI 2.2% to 97.0%) against extrapulmonary TB (supplementary table S-30). For participants who did not smoke, the vaccine efficacy of VPM1002 was 24.8% (−6.8% to 47.0%) against all TB, 23.5% (−12.4% to 47.9%) against pulmonary TB, and 45.5% (−10.1% to 73.1%; 90% CI 1.7% to 69.8%) against extrapulmonary TB (supplementary table S-33). The vaccine efficacy for Immuvac was 36.9% (−23.4% to 67.7%) against extrapulmonary TB in those who did not smoke (supplementary table S-33).

Discussion

We report the findings of one of the largest randomised, double blind, placebo controlled trials in which the efficacies of two different vaccines, VPM1002 and Immuvac, were evaluated for preventing TB, pulmonary TB, and extrapulmonary TB in a high risk population (household contacts of patients with smear positive pulmonary TB). Both vaccines were found to be safe, with local solicited self-healing adverse events in one third of participants in each group, with no serious concerns. The primary outcome was to evaluate the efficacy of VPM1002 and Immuvac against all forms of TB (including pulmonary and extra pulmonary TB), pulmonary TB, and extrapulmonary TB. We observed that neither of the vaccines provided protection against TB in general; however, protection was provided against extrapulmonary TB by both vaccines. Extrapulmonary TB, which occurs at sites other than the lungs,[15] occurs in about a third of patients diagnosed as having TB, and the mortality for this form of TB may increase to about 40% in some countries.[16] However, 15-24% of patients with TB may have extrapulmonary disease, with an increase to over 50% in patients coinfected with HIV in countries like India.[17]

Interpretation of results and comparison with other studies

Although many vaccines in different stages of development have been evaluated for prevention of pulmonary TB, limited reports have examined the efficacy of any vaccine against extrapulmonary TB. One study that evaluated efficacy against pulmonary and extrapulmonary TB reported a vaccine efficacy of 31% (95% CI −12% to 58%) against non-pulmonary TB from one of three sites in Brazil after revaccination with BCG[6]. In the current study, VPM1002 showed a vaccine efficacy of 50.4% (95% CI 0.8% to 75.2%) against extrapulmonary TB (incidence 1.02 *v* 2.06 per 1000 person years in VPM1002 and placebo groups, respectively), reducing the incidence of extrapulmonary TB by more than 50% (in line with our basic assumption to calculate sample sizes assuming that individual vaccines would reduce TB incidence by 50%); however, we observed this finding in extrapulmonary TB and not in all forms of TB.

At present, the only vaccine used for protection against TB is BCG, which protects against severe forms of TB in children <5 years old but does not protect against pulmonary TB in adults.[18] However, in children and adolescents <18 years old within the normal weight range, VPM1002 showed a vaccine efficacy of 45.1% (95% CI 5.4% to 68.2%) against all TB, and 56.9% (19.4% to 77.0%) against pulmonary TB. Immuvac, however, had a vaccine efficacy of 31.6% (−12.9% to 58.6%) against all forms of TB and 38% (−7.1% to 64.2%) against pulmonary TB in children and adolescents within the normal weight range; however, neither vaccine provided protection for children who were underweight. These data emphasise the need for nutritional support along with the vaccination,[19 20] particularly for children >5 years old.

The available data on BCG vaccination remain controversial[21] and revaccination shows variable results.[22] While some data did not show any protection against TB,[23] a multicentre study on BCG revaccination in school age children from Brazil showed a low level of protection against all forms of TB, with a small increase in vaccine efficacy from 9% (95% CI −16% to 29%) at the end of five year follow-up to 12% (−2% to 24%) at the end of nine year follow-up, with slightly higher efficacy (19%; 3% to 33%) at one of the sites in Salvador.[6] Reanalysis of BCG revaccination data at Chingleput showed that BCG was not protective until 10 years after vaccination, however it showed 36% protection at the end of 15 years after vaccination.[24] In contrast, the results of our study showed a vaccine efficacy of recombinant BCG against extrapulmonary TB in all age groups and against all TB and pulmonary TB in a younger age group (6 to <14 years). Our post hoc analysis showed that in children aged 6 to <14 years, VPM1002 provided more than 60% protection against all forms of TB in general and pulmonary TB in particular. VPM1002 provided more than 70% protection against extrapulmonary TB in children aged 6 to <14 years and Immuvac provided a similar level of protection against extrapulmonary TB in the age group 6 to <10 years, highlighting the protective effects of both the vaccines in younger age groups (table 6).

VPM1002 and Immuvac showed protection against microbiologically confirmed extrapulmonary TB, not only in younger age groups, but also in those aged 36-60 years (table 5). Prevention of extrapulmonary TB could have a major impact on public health by reducing the burden of disease, which causes high morbidity and mortality owing to associated diagnostic challenges.[17] VPM1002 also showed protection against extrapulmonary TB in participants without a BCG scar (supplementary tables S-25, S-26, S-27), a finding that could be investigated further. Even though the numbers of participants in the mITT analysis for the VPM1002 and placebo groups were 1605 and 1579, respectively, for BCG negative participants (supplementary table S-26), the findings have enough power as evident from

the 90% confidence intervals (vaccine efficacy 64.2%, 90% CI 6.4 to 86.3).

A trial of candidate TB vaccine, M72/AS01$_E$, showed a vaccine efficacy of 49.7% in participants aged 18-50 years with latent *M tuberculosis* infection based on interferon γ release assay (IGRA) positivity.[25] However, the current study included all household contacts irrespective of latent TB infection status. VPM1002 and Immuvac provided more than 60% protection against extrapulmonary TB in patients with TST positivity (ie, those with latent TB). VPM1002 also protected participants who were TST negative against pulmonary TB with a vaccine efficacy of 44.2% (90% CI 6.5% to 66.7%; table 3). Neither VPM1002 nor Immuvac protected against *M tuberculosis* infection, as evident from TST conversion observed at six months in participants who were negative at baseline, a result similar to that recently published in a meta-analysis of BCG vaccination.[26] However, VPM1002 was highly protective against all TB, pulmonary TB, and extrapulmonary TB and Immuvac was protective against all TB and extrapulmonary TB, even in those who recently acquired the infection (ie, participants with TST conversion from negative to positive six months after vaccination; table 4). This finding shows that even if the vaccines could not prevent infection, they could prevent progression to disease even in those who acquired the infection within six months of vaccination.

The results indicate that both vaccines may help in reducing the burden of extrapulmonary TB because they provide protection in different scenarios, leading to reduction in mortality and morbidity owing to diagnostic challenges[17] and delay in identification. VPM1002 protects against all TB and pulmonary TB in children and adolescents <18 years old who are well nourished. Nutrition has been shown to be an integral component for improvement in treatment outcomes in adults[19]; the same may apply in those <18 years old. Vaccines along with nutritional support in developing countries could result in reducing smear positivity in young adults and so protect the younger work force.

A previous TB trial with M72 and Ag85A reported a vaccine specific increase in polyfunctional CD4+ T cells after vaccination, contributing to the vaccine efficacy against pulmonary TB.[25 27] However, in our study, instead of vaccine specific immune responses, *M tuberculosis* specific immune responses were studied. Immune correlates of protection provided by VPM1002 seem to be through *M tuberculosis* specific polyfunctional CD4+ T cells expressing IFN-γ and IL-2, IL-2 and TNF-α, and all three cytokines, IFN-γ, IL-2, and TNF-α. However, Immuvac showed a higher frequency of CD4 T cells expressing TNF-α and IFN-γ. These data are in concordance with earlier reports on the immunogenicity of VPM1002.[28] CD4+ T cells, which express the cytokines IL-2 and TNF-α, have central memory phenotype (T_{CM}) and VPM1002 has been shown to induce higher frequencies of T_{CM} compared with BCG.[29] VPM1002, in the current study too, seems to induce *M tuberculosis* specific T_{CM}, which may result in long lasting protection against *M tuberculosis*. Antigen 85A specific polyfunctional CD4 T cells producing cytokine IFN-γ, TNF-α, and IL-2 have been reported to be highly promising.[27] IFN-γ and TNF-α help in recruiting monocytes and granulocytes to the site of infection, and are also involved in the antimicrobial activity of macrophages,[30 31] a mechanism that could also be working through polyfunctional CD4+ T cells in those protected by these vaccines.

Based on a detailed landscape analysis of published data, this study has evaluated the protective efficacy of two vaccines against all forms of confirmed TB among the most vulnerable group of household contacts of patients with smear positive pulmonary TB. The data showing protection from pulmonary TB in a younger age group and from extrapulmonary TB in general will help to reduce the burden of TB. Sputum collection in a younger age group and sample collection for extrapulmonary TB pose difficulties and so infection often remains undetected or there is a delayed diagnosis owing to limited facilities in peripheral and rural settings. Although VPM1002 and Immuvac show better levels of protection compared with BCG revaccination, VPM1002 seems to show better protection than Immuvac.

Statement of principal findings

The data show that VPM1002 did not provide protection from microbiologically confirmed pulmonary TB in general but protected against microbiologically confirmed extrapulmonary TB. VPM1002 provided protection against all TB, pulmonary TB, and extrapulmonary TB in participants aged 6 to <14 years. VPM1002 also provided protection against TB and pulmonary TB in participants <18 years old within a normal weight range. VPM1002 protected against extrapulmonary TB in participants who were TST positive and against TB, pulmonary TB, and extrapulmonary TB in those who were recently infected with *M tuberculosis*.

Immuvac did not provide protection against TB in general. However, it provided protection against all TB and extrapulmonary TB in participants aged 6-10 years, from pulmonary TB in those aged <18 years within a normal weight range, and from extrapulmonary TB in participants aged 36-60 years. Immuvac protected against extrapulmonary TB in those who were TST positive and also in those with a recent *M tuberculosis* infection. Supplementary tables S-34 and S-35 respectively show summaries of the efficacy analysis for VPM1002 and Immuvac (with lower confidence limit ≥0).

Strengths and weaknesses of the study

This study has many strengths. It was a large study that evaluated the efficacy of two vaccines in a single trial performed across six states of India and included vulnerable household contacts (aged 6 years and older) of patients with a recent TB diagnosis, irrespective of their *M tuberculosis* infection status. The study evaluated vaccine efficacy against all TB,

pulmonary TB, and extrapulmonary TB, was well designed, and was registered. A paediatric population was included, as were participants with comorbidities like diabetes, those who smoked, those with alcohol dependence and other metabolic disorders, with equal distribution across the three groups representing a real world setting and fulfilling the needs currently being emphasised.[32] Inclusion of participants who were TST positive, TST negative, BCG scar positive, and BCG scar negative adds to the value of the study in view of the data generated, especially in high TB burden states.[32] The study was done with domestic funding, following all ethical guidelines, and building capacity of 18 sites in different states for conducting phase 3 trials, with community engagement during trial design. A very important strength is that despite the covid-19 pandemic, we could follow up 96.68% of the participants for 38 months.

A weakness of the study was that owing to the covid-19 pandemic, some participants could not be given the second dose of the vaccine, so they had to be excluded from the per protocol analysis. Although strict follow-ups were done, at times, it was difficult to perform physical follow-ups, which were sometimes delayed owing to lockdowns. Therefore, telephone follow-ups were done within required timeframes during the pandemic. Because the study was conducted in different states of India, applicability of our findings in other countries with different ethnicities needs to be determined.

Strengths and weaknesses relating to other studies, discussing important differences in results

Most recent studies have been done in a defined age group of adults and excluded vulnerable populations and those with comorbidities. Our study included participants ≥6 years and also older populations, those with comorbidities, people who smoked, had alcohol dependence, were TST positive, TST negative, BCG scar positive, and BCG scar negative, which represented the general population in any state. Because BCG, in general, provides protection only up to 5 years of age, this study shows that VPM1002 and Immuvac provide protection in participants aged 6-18 years, who are not underweight, suggesting the need for proper nourishment along with the vaccine. Most recent studies have been done in people who are IGRA positive or TST positive, whereas our study included household contacts irrespective of their infection status (TST positive and negative). Additionally, the data show that the vaccines do not protect against infection, however both vaccines protect against developing overt TB, even in those who have converted from being TST negative to TST positive; these data are lacking in other studies.

Despite the covid-19 pandemic, this study completed recruitment during the peak of the pandemic and was successfully completed within the expected timeframe without much delay. The physical follow-up visits were made despite the pandemic and lockdown restrictions, and when possible, home visits were made. In all participants who were suspected to have TB, efforts were made to confirm the diagnosis microbiologically and by other confirmatory tests for extrapulmonary TB according to NTEP guidelines.

A weakness of the study is that it was conducted during the covid-19 pandemic, therefore some participants could not be given their second dose and so were excluded from the per protocol analysis, as mentioned above. However, the data were not affected because all those suspected of having TB were tested according to NTEP guidelines.

Meaning of the study: possible explanations and implications for clinicians and policy makers

Currently, the only licenced vaccine available against TB is BCG, which protects against the severe form of TB in children <5 years old. Policy makers should consider our study findings that VPM1002 showed a vaccine efficacy of 50.4% compared with placebo in all age groups in reducing extrapulmonary TB over a period of time and the potential economic benefits of this reduction. Recombinant BCG (VPM1002) and Immuvac may be used for protection against pulmonary TB and extrapulmonary TB in children and adolescents aged >5 to 18 years along with nutritional supplements, and against extrapulmonary TB in all age groups. Because neonatal BCG is given in many countries, booster doses with recombinant BCG (VPM1002) at 5-8 years, 12-14, and 18-35 years may provide protection against pulmonary TB and extrapulmonary TB in the most vulnerable groups and in the general population as well. Elimination of TB would only be possible if boosters are given at younger ages.

Unanswered questions and future research

Because both vaccines gave better efficacy in well nourished children and in adults with a body mass index ≥18, future research of vaccines could include additional nutrition or energy dense nutritional supplements in undernourished children and in adults with a body mass index <18.

Our study included participants with diabetes, those who smoked, had alcohol dependence, low body mass index, and other metabolic disorders distributed across the three groups and representing a real world scenario. Therefore, efficacy against specific high risk groups could not be determined. Additionally, this study was carried out in a population that had already been vaccinated at birth with BCG. Further research on common targeted high risk groups for TB could be undertaken.

AUTHOR AFFILIATIONS

[1]Indian Council of Medical Research, Delhi, India
[2]Bhagwan Mahavir Medical Research Centre (BMMRC), Hyderabad, India
[3]National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India
[4]National Institute of Translational Virology & AIDS Research (Formerly National AIDS Research Institute, Pune), Pune, India
[5]National Institute for Research in Tuberculosis, Chennai, India
[6]All India Institute of Medical Sciences, New Delhi, India
[7]Regional Medical Research Center, Bhubaneshwar, India

[8]S C B Medical College and Hospital, Cuttack, India
[9]All India Institute of Medical Sciences, Bhubaneshwar, India
[10]National Tuberculosis Institute, Bengaluru, India
[11]Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India
[12]St John's Medical College, Bengaluru, India
[13]SHARE INDIA Mediciti Institute of Medical Sciences (MIMS), Medchal, Malkagiri, India
[14]Clinical Development Services Agency (CDSA), THSTI, Faridabad, India

This work was supported by the Indian Council of Medical Research (ICMR). The authors acknowledge and thank all the study participants and their families without whom the study could not have been undertaken. The authors thank Rajiv Bahl, secretary, Department of Health Research, and director general, ICMR for his support and critical input on data analysis of the study. The authors thank R M Pandey for conducting independent performance analysis of the data. The authors thank the expert committee and the monitoring committee for their support in following up the progress of the sites throughout enrolments and follow-up period. The authors also thank Balram Bhargava, former secretary, Department of Health Research, and director general, ICMR for his support of the study. The authors are thankful to data safety monitoring board members for evaluation of the safety of the vaccines under study from time to time. The authors acknowledge all the trial staff and committees for their contribution; a detailed list is given in the supplementary materials. Study vaccines and placebo were provided free of cost: VPM1002 by Serum Institute of India, Pune, Immuvac and placebo by Cadila Pharmaceuticals. The Electronic Data Capture system (Velos-eResearch Platform) was provided pro bono by Aithent Technologies Private.

Contributors: MS contributed to conceptualisation of study and trial protocol development, was involved in supervision, coordination, project administration, data curation, and wrote the first draft and final version of the manuscript. SJ, VV, RS, SVK, BV, AM, UBS, RK, SPat, MP, PRM, US, SN, GY, SH, RR, AVK, PKP, SK, AN, NAP, SDR, AS, LEH, DKM, SPan, RG, ST, NR, GDS were involved in trial conduct, recruitment of participants, data acquisition, and site project administration. KK was involved in monitoring and supervision of the study. RRG, AMK were involved in supervision and project administration. SS and MK were involved in project monitoring, medical monitoring, and data cleaning. MB was involved in data audit and data verification. NW was involved in study monitoring and data verification. RMP was involved in efficacy and safety data analysis. VT was involved in data cleaning and contributed to efficacy and safety analysis. RR was involved in immunogenicity data analysis, data verification, and contributed to original and final version of the manuscript. All authors reviewed, provided critical inputs and approved the final version of manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no other persons meeting the criteria have been omitted. MS is the guarantor.

Funding: India TB Research Consortium (ITRC), Indian Council of Medical Research (ICMR), New Delhi is the sponsor of the PreVenTB trial and the study is funded by ICMR, New Delhi (grant No ECD/NTF/41/2018-19, dated 28 February 2019). Study vaccines and placebo were provided free of cost: VPM1002 by Serum Institute of India, Pune, Immuvac, and placebo by Cadila Pharmaceuticals. The Electronic Data Capture (EDC) system (Velos-eResearch Platform) was provided pro bono by Aithent Technologies Private. The vaccine manufacturers had no role in design, conduct, analysis, and reporting of the trial.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: funding support from the Indian Council of Medical Research (ICMR), New Delhi for the submitted work; Study vaccines and placebo were provided free of cost: VPM1002 by Serum Institute of India, Pune, Immuvac, and placebo were provided by Cadila Pharmaceuticals. The Electronic Data Capture system (Velos-eResearch Platform) was provided pro bono by Aithent Technologies Private. The vaccine manufacturers had no role in design, conduct, analysis and reporting of the trial. India TB Research Consortium (ITRC), ICMR is the sponsor of the study and was involved in study design, coordination, monitoring and DSMB meetings to ensure compliance to protocol and timely completion, however had no role in participant enrolment and data acquisition. The authors declare that they have no competing interests; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval and consent of participants was done as per guidelines. Ethics committee approvals were granted by the institutional human ethics committees of all participating centres in this study and the names of the ethics committees and approvals are as follows: National Institute for Research in Tuberculosis (NIRT) Chennai (including subsites): ECR/135/Inst/TN/2013/RR-19, approval No 390/NIRT-Institutional Ethics Committee (IEC)/2018 dated 5 December 2018 (NIRT-Madurai-ECR/1365/Inst/TN/2020; approval dated 8 June 2020; NIRT, Vellore: ECR/1215/Inst/TN/2019; approval dated 26 September 2020); All India Institute of Medical Sciences (AIIMS), Delhi (including subsites): Institute Ethics Committee, ECR/547/Inst/DL/2014/RR-17 ECR/538/Inst/DL/2014/RR-20; approval No IEC-385/06-07-2018, approval OP-28/05.04.2019, SFH-ECR/593/Inst/DL/2014/RR-20 IEC/VMMC/SJH/project/2019-05/25; 23 May 2019; National Institute of Tuberculosis and Respiratory Diseases (NITRD), Delhi: ECR/315/Inst/DL/2013/RR-19; approval IEC-No-NITRD/EC/2019/9004; 8 January 2019; Pune-National AIDS Research Institute (NARI) and subsite ECR/23/Inst/MH/2013/RR-19; IEC-NARI/EC/approval/2018/196; 29 May 2018; Regional Medical Research Centre-Bhubaneshwar-ECR/911/Inst/OR-2017/RR-21; approval dated 25 April 2018; subsites AIIMS, Bhubaneshwar ECR/534/Inst/OD/2014/RR-17 and 20, approval No T/EMF/Pulm. Med/19/01 dated 13 May 2019; SCB, Cuttack No ECR/84/Inst/OR/2013/RR-20; approval No 186, dated 7 February 2020; NTI-Bengaluru: Ethics Committee-No-ECR/1819/Inst/KA/2019; approval No NTI-IEC/1.2019/principal investigator, dated 31 January 2019; BMMRC, Hyderabad-ECR/450/Inst/AP/2013/RR-16, approval No 779/BMMRC/2018/IEC, dated 11 June 2018 (subsite Share India-Mediciti Ethics Committee-ECR/283/Inst/AP/2013/RR-20; approval No EC/11/VII/2K20(1), dated 11 July 2020); and SJMC-Bengaluru: ECR/238/Inst/KA/2013/RR-19; approval IEC/1/491/2020; 7 August 2020.

Data sharing: The protocol for PreVenTB trial is publicly available (doi:10.1136/bmjopen-2023-082916). The statistical codes used to analyse the data in the paper can be found in supplementary file 2. The deidentified participant data underlying the findings in this paper have been deposited in the ICMR data repository and can be accessed publicly (https://data.icmr.org.in/datasets/preventb-trial-data). If you encounter problems accessing the data, please contact the corresponding author.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and all relevant explanations have been provided; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: The results of this clinical trial will be presented at scientific conferences and disseminated by widely circulating the publication published in peer reviewed journals. The publication will also be shared with the Ministry of Health & Family Welfare, government of India, and will be widely circulated to researchers and policy makers, and all relevant stakeholders. The final report has been submitted to the regulatory authorities as per regulatory requirements.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Harding E. WHO global progress report on tuberculosis elimination. *Lancet Respir Med* 2020;8:19. doi:10.1016/S2213-2600(19)30418-7
2 World Health Organization. *Global Tuberculosis Report*2024. https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024
3 *India TB Report2024National TB Elimination Programme*. https://tbcindia.mohfw.gov.in/wp-content/uploads/2024/10/TB-Report_for-Web_08_10-2024-1.pdf
4 Kaufmann SHE. Fact and fiction in tuberculosis vaccine research: 10 years later. *Lancet Infect Dis* 2011;11:633-40. doi:10.1016/S1473-3099(11)70146-3
5 Singh M, Dutta M, Kodan P, Tripathy S. Vaccination against tuberculosis: beyond BCG. *J Respir Dis Med* 2020;2.

6 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;29:4875-7. doi:10.1016/j.vaccine.2011.05.023
7 Datta M, Radhamani MP. Revaccination with Bacille Calmette-Guérin: some issues to consider. *Indian J Med Res* 2023;157:160-2. doi:10.4103/ijmr.ijmr_2106_22
8 Singh M, Mehendale S, Guleria R, et al, PreVenTB Trial Team. PreVenTB trial: protocol for evaluation of efficacy and safety of two vaccines VPM1002 and Immuvac (Mw) in preventing tuberculosis (TB) in healthy household contacts of newly diagnosed sputum smear-positive pulmonary TB patients: phase III, randomised, double-blind, three-arm placebo-controlled trial. *BMJ Open* 2024;14:e082916. doi:10.1136/bmjopen-2023-082916
9 Lawson R. Small sample confidence intervals for the odds ratio. *Commun Stat Simul Comput* 2004;33:1095-113doi:10.1081/SAC-200040691.
10 Haldane JB. The estimation and significance of the logarithm of a ratio of frequencies. *Ann Hum Genet* 1956;20:309-11. doi:10.1111/j.1469-1809.1955.tb01285.x
11 Ruxton GD, Neuhäuser M. Review of alternative approaches to calculation of a confidence interval for the odds ratio of a 2×2 contingency table. *Methods Ecol Evol* 2013;4:9-13doi:10.1111/j.2041-210x.2012.00250.x.
12 Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ* 2025;389:e081123. doi:10.1136/bmj-2024-081123.
13 Martinez L, Cords O, Liu Q, et al. Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis. *Lancet Glob Health* 2022;10:e1307-16. doi:10.1016/S2214-109X(22)00283-2
14 Indian Academy of Pediatrics Growth Charts Committee. Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. *Indian Pediatr* 2015;52:47-55.
15 Haulman NJ, Hawn TR, Nolan CM. Tuberculosis in Travelers and Immigrants. In: *The Travel and Tropical Medicine Manual*. Elsevier, 2008: 391-406, doi:10.1016/B978-141602613-6.10024-2.
16 Grønningen E, Nanyaro M, Blomberg B, Hassan S, Ngadaya E, Mustafa T. Mortality among extrapulmonary tuberculosis patients in the HIV endemic setting: lessons from a tertiary level hospital in Mbeya, Tanzania. *Sci Rep* 2024;14:10916. doi:10.1038/s41598-024-61589-z
17 VidyaRaj CK, Vadakunnel MJ, Mani BR, et al. Prevalence of extrapulmonary tuberculosis and factors influencing successful treatment outcomes among notified cases in South India. *Sci Rep* 2025;15:8290. doi:10.1038/s41598-025-92613-5
18 Lange C, Aaby P, Behr MA, et al. 100 years of Mycobacterium bovis bacille Calmette-Guérin. *Lancet Infect Dis* 2022;22:e2-12. doi:10.1016/S1473-3099(21)00403-5
19 Bhargava A, Bhargava M, Meher A, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India. *Lancet Glob Health* 2023;11:e1402-11. doi:10.1016/S2214-109X(23)00324-8
20 Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *Lancet* 2023;402:627-40. doi:10.1016/S0140-6736(23)01231-X
21 Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med* 2011;8:e1001012. doi:10.1371/journal.pmed.1001012
22 Trauer JM, Kawai A, Coussens AK, et al. Timing of *Mycobacterium tuberculosis* exposure explains variation in BCG effectiveness: a systematic review and meta-analysis. *Thorax* 2021;76:1131-41. doi:10.1136/thoraxjnl-2020-216794
23 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. doi:10.1016/S0140-6736(96)02166-6
24 Velayutham B, Thiruvengadam K, Kumaran PP, Watson B, Rajendran K, Padmapriyadarsini C. Revisiting the Chingleput BCG vaccination trial for the impact of BCG revaccination on the incidence of tuberculosis disease. *Indian J Med Res* 2023;157:152-9. doi:10.4103/ijmr.ijmr_1540_22
25 Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2019;381:2429-39. doi:10.1056/NEJMoa1909953
26 Pelzer PT, Stuck L, Martinez L, et al. Effectiveness of the primary Bacillus Calmette-Guérin vaccine against the risk of Mycobacterium tuberculosis infection and tuberculosis disease: a meta-analysis of individual participant data. *Lancet Microbe* 2025;6:100961. doi:10.1016/j.lanmic.2024.100961
27 Beveridge NER, Price DA, Casazza JP, et al. Immunisation with BCG and recombinant MVA85A induces long-lasting, polyfunctional *Mycobacterium tuberculosis*-specific CD4$^+$ memory T lymphocyte populations. *Eur J Immunol* 2007;37:3089-100. doi:10.1002/eji.200737504
28 Desel C, Dorhoi A, Bandermann S, Grode L, Eisele B, Kaufmann SH. Recombinant BCG ΔureC hly+ induces superior protection over parental BCG by stimulating a balanced combination of type 1 and type 17 cytokine responses. *J Infect Dis* 2011;204:1573-84. doi:10.1093/infdis/jir592
29 Nieuwenhuizen NE, Kulkarni PS, Shaligram U, et al. The recombinant Bacille Calmette-Guérin vaccine VPM1002: ready for clinical efficacy testing. *Front Immunol* 2017;8:1147. doi:10.3389/fimmu.2017.01147
30 Pfeffer K. Biological functions of tumor necrosis factor cytokines and their receptors. *Cytokine Growth Factor Rev* 2003;14:185-91. doi:10.1016/S1359-6101(03)00022-4
31 Flynn JL, Chan J. Immunology of tuberculosis. *Annu Rev Immunol* 2001;19:93-129. doi:10.1146/annurev.immunol.19.1.93
32 Moorthy V, Siegfried N, Amuasi J, et al. Improving the clinical trial environment and infrastructure: moving from global resolution to action. *Lancet Glob Health* 2025;13:e608-10. doi:10.1016/S2214-109X(25)00012-9

Web appendix 1: Supplementary materials
Web appendix 2: Supplementary file 2