BMJ Open

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

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To cite: Singh M, Mehendale S, Guleria R, *et al*. 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

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-082916).

Received 06 December 2023
Accepted 06 August 2024

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ABSTRACT

Introduction Tuberculosis (TB) continues to be one of the deadliest infectious diseases over the centuries, killing more people worldwide than any other single infectious disease. There is an urgent need for additional strategies which can expedite efforts to combat TB including a preventive vaccine. In this endeavour, we have developed a protocol for a multisite, double-blind, placebo-controlled clinical trial in India that aims to evaluate the efficacy and safety of two TB vaccines; namely, VPM1002 and Immuvac (*M.w*) (*Mycobacterium Indicus Pranii*) (MIP) among healthy household contacts (HHCs) of sputum smear-positive pulmonary TB (PTB) patients.

Methods and analysis In the three-arm randomised double-blind placebo-controlled trial study protocol, a total of 12 000 HHCs (aged 6–99 years) of sputum smear-positive PTB patients will be randomised to receive either of the two vaccine candidates VPM1002 and MIP or placebo. The primary efficacy endpoint is the prevention of microbiologically confirmed TB. Secondary endpoints will include (1) prevention against Latent TB infection, (2) incidence of adverse events and serious adverse events in study participants, (3) efficacy of vaccine in prevention of PTB/extra PTB in different age groups (6–18 years, 19–35 years, 36–60 years and above 60 years) and (4) immunogenicity of VPM1002 and MIP at month 2 and month 6 after first vaccination in terms of flow cytometric analysis of *M.Tb* specific CD4+ and CD8+ T cells secreting cytokines and Luminex assays for the presence of different cytokines in the sera and supernatants of peripheral blood mononuclear cells cultures stimulated with whole cell lysates of *M.Tb* and subsequently similar analysis for the cases who develop TB postvaccination during the follow-up period.

Ethics and dissemination Ethics committees' approvals have been 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: (1) 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); (2) All India Institute of Medical Sciences (AIIMS), Delhi (including subsites)-Institute Ethics Committee, ECR/547/Inst/DL/2014/RR-17 ECR/538/

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Two tuberculosis (TB) vaccines are simultaneously being evaluated in a large multicentric trial.
⇒ Household contacts of smear-positive pulmonary TB cases, the most high-risk population to be enrolled for evaluating vaccine efficacy.
⇒ Inclusion of participants with comorbidities, risk factors and wider age range will increase generalisability of the study findings.
⇒ Retention of participants for 38 months follow-up after vaccination may be challenging.
⇒ Subclinical cases are likely to be missed due to the low sensitivity of sputum smear examination at screening.

Inst/DL/2014/RR-20; approval No.IEC-385/06-07-2018, approval OP-28/05.04.2019 and SFH- ECR/593/Inst/DL/2014/RR-20 IEC/VMMC/SJH/project/2019-05/25 ; 23 May 2019; (3) 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; (4) Pune-National AIDS Research Institute (NARI) and subsite-ECR/23/Inst/MH/2013/RR-19; IEC-NARI/EC/approval/2018/196; 29 May 2018; (5) 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. No.ECR/84/Inst/OR/2013/RR-20; approval no.186 dated 7 February 2020; (6) NTI-Bengaluru: Ethics Committee-No-ECR/1819/Inst/KA/2019; approval No NTI-IEC/1.2019/principal investigator, dated 31 January 2019; (7) 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 (8) SJMC-Bengaluru: ECR/238/Inst/KA/2013/RR-19; approval IEC/1/491/2020; 7 August 2020.

The trial findings will be published in accordance with the Consolidated Standards of Reporting Trials guidance. The results of this clinical trial will be presented at scientific conferences and disseminated through publications in peer-reviewed journals, conference presentations and shared with Ministry of Health and Family Welfare, policy-makers and other stakeholders.

Trial registration number CTRI/2019/01/017026.

INTRODUCTION

Tuberculosis (TB) is still considered a major threat to public health around the world. According to WHO 2020 Global TB report, annually 10 million new TB cases are reported, of which an estimated 1.5 million die due to the disease.[1 2] India accounts for 27%, that is, more than a quarter of the global TB burden.[1] These alarming figures call for an urgent need to adopt aggressive strategies for prevention and control of TB. India is committed to develop novel strategies to defeat the disease and envisions elimination of TB by the year 2025. An effective vaccine might prove to be a key tool in this endeavour.[3]

Rationale for the trial

The TB infection is almost exclusively transmitted from active, sputum positive, pulmonary TB (PTB) patient through aerosol route, with the highest risk of transmission to the healthy household contacts (HHCs).[4 5] HHCs at younger age and/or with immunodeficiency have a higher risk of TB acquisition.[6 7] WHO guidelines for prevention of TB in HHCs of PTB patients recommend combinations of isoniazid with rifapentine or rifampicin for shorter period like 3 months and individually rifampicin or isoniazid for 4 and 6 months respectively.[2] However, drug-associated toxicity warrants a need for a preventive TB vaccine that will be immunoprophylatic. There are at least 14 potential vaccine candidates reported for TB prevention with promising results.[2 8]

Currently, BCG, the only available vaccine, is effective in preventing TB in children but not in adults.[9 10] However, a recombinant BCG vaccine VPM1002, expressing listeriolysin (LLO, encoded by the gene hly) of Listeria monocytogenes and deficient in urease C gene (ureC) (BCG _ureC::hly, VPM1002), seems to be promising.[11] The mechanism of action of VPM1002 to combat *M.Tb* has been described in several publications.[11–13] VPM1002 has been developed by Vakzine Projekt Management in Germany and licensed to the Serum Institute of India. Preclinical and clinical data indicate that VPM1002 is immunogenic and may be better than available vaccines in terms of safety. Based on encouraging results of two phase I clinical trials in healthy adults, two phase II clinical trials in newborn babies and a clinical trial for prevention of TB recurrence in cured PTB patients,[11–13] we selected VPM1002 for phase III trial in India.

Another highly promising candidate vaccine for TB is Immuvac, earlier known as *Mycobacterium w (Mw)* and later renamed as *MIP* (*Mycobacterium indicus pranii*). Immuvac is a heat killed suspension of *MIP*, a non-pathogenic, cultivable atypical mycobacterium,[14] which shares cross-reactive antigens with *M. leprae* and *M. Tb*. *MIP* has been shown to provide significant protection against TB in both BCG responder and non-responder strains of mice.[15–17] It has been found to be safe with immunoprophylactic effect in a population-based double-blind placebo-controlled trials against both TB and leprosy.[14 18] *MIP* is approved and is marketed by Cadila Pharma for treatment of leprosy as an adjunct therapy along with multidrug therapy under its commercial name Immuvac. In another landmark study, *MIP* has shown promise as an adjunct to DOTS in treatment of category II PTB.[19] *MIP* is an immunomodulatory vaccine that reduced bacterial load, improved pathology and organised granulomatous response postinfection in the *MIP*-immunised Guinea pigs.[20] *MIP* induced an increase in protective Th1 immune response initially, followed by decrease in the inflammatory response and increase in the immunosuppressive response, resulting in improvement of lung pathology in Guinea pigs.[20 21]

Based on several studies on safety, efficacy and immunomodulatory effects of MIP and VPM1002, we planned to conduct a phase III trial for prevention of TB in HHCs of patients with TB. The present study is designed to evaluate the efficacy, safety and tolerability of both VPM1002 and Immuvac (MIP) vaccines among HHCs, of TB patients who are ≥6 years of age, in a double-blind, randomised placebo-controlled phase III clinical trial.

The primary objective of this trial is to evaluate the efficacy of VPM1002 and Immuvac in reducing the incidence of TB among the HHCs of newly diagnosed sputum positive PTB patients from different parts of India, over 3 years' observational period, after vaccination.

Secondary Objectives of the study are as follows:

- To evaluate the efficacy of VPM1002 and Immuvac in prevention of latent TB infection (LTBI).
- To evaluate the safety of VPM1002 and Immuvac in HHCs.

- To evaluate efficacy of vaccine in prevention of PTB/extra PTB (PTB/EPTB) in different age groups (6–18 years, 19–35 years, 36–60 years and above 60 years).
- To evaluate the Immunogenicity of VPM1002 and Immuvac as compared with placebo against TB.

METHODS

Sample size

We hypothesised that individually each candidate (VPM1002 and Immuvac) will lead to 50% reduction in anticipated incidence of TB among HHCs of newly diagnosed PTB patients as compared with placebo. With cumulative incidence of TB in HHCs during 38 months in the control arm estimated at 2% and anticipating a 50% reduction in TB cases after vaccination in the VPM1002/Immuvac groups compared with placebo arm, approximately 12 000 participants (4000 in each arm) will be randomised to achieve 90% power at 2.5% significance level and adjustment for multiplicity, that is, testing two hypothesis, one for efficacy of VPM1002 and the other for efficacy of Immuvac, as compared with placebo. A 10% drop-out rate has been factored in while calculating the sample size.

Study setting

12 000 participants will be screened as per inclusion and exclusion criteria (table 1) and randomised to 1 of the 3 arms in 1:1:1 allocation at 8 main sites and 10 subsites in 6 states of India.

1. Indian Council of Medical Research (ICMR)-National Institute for Research in Tuberculosis (NIRT), Chennai with satellite centres in Madurai; Vellore and Tambaram.
2. All India Institute of Medical Sciences (AIIMS), New Delhi with subsites, Ballabhgarh and Safdurjung Hospital.
3. National Institute of Tuberculosis and Respiratory Diseases, Delhi,
4. ICMR-National AIDS Research Institute (NARI), Pune with subsite at Gadikhana.
5. Regional Medical Research Centre, Bhubaneshwar and AIIMS, Bhubaneshwar with subsite at SCB Medical College, Cuttack.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
► Healthy household contacts of new index case aged ≥6 years and have not been treated for tuberculosis before. ► Must have a sputum sample negative for AFB staining on smear at the time of screening. ► Female participants who are currently using reliable methods of birth control, have a negative pregnancy test during screening and have no intention to become pregnant for at least 3 months post-vaccination. ► The participant must be able and willing to comply with the study protocol, available and willing to complete all the study assessments and must have signed an informed consent form and assent form (as applicable). ► Participant agrees to stay in contact with the study site for the duration of the study, provide updated contact information. ► Has general good health, as confirmed through medical history and physical examination	► Coprevalent TB diagnosed clinically or microbiologically (ie, baseline sputum smear positive for AFB) ► Any acute febrile illness with oral temperature >100 on day of randomisation ► Reactive serology for HIV. ► Having history of taking antitubercular treatment in previous 6 months ► History of chronic administration (defined as more than 14 days) of immunosuppressants including systemic steroids during last 3 months. Participants on inhaled/topical steroids may be permitted to participate in the study ► History of previous administration of experimental *Mycobacterium tuberculosis* vaccines, other than BCG in childhood. ► History of Administration of any immunoglobulins, any immunotherapy and/or any blood products within the 3 months preceding study vaccination or planned administrations during the study period ► Participation in a clinical trial within 3 months prior to and/or planned concurrent participation in another interventional clinical trial at any point throughout the entire timeframe for this study. ► Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination ► A family history of congenital or hereditary immunodeficiency ► History of any acute or chronic illness or medication that, in the opinion of Investigator, may interfere with evaluation of safety or efficacy of vaccine ► Any chronic drug therapy to be continued during the study period, with the exception of vitamins and/or dietary supplements, birth control pills, antihistamines for seasonal allergies ► History of allergic reactions or anaphylaxis to previous immunisations ► History of allergic disease or reactions likely to be exacerbated by any component of the vaccine ► History of severe alcohol or illicit drug abuse during past 6 months. ► Pregnant and/or lactating female participants. ► Presence of any severe systemic disorder as determined by medical history and/or physical examination, which in judgement of Investigator will compromise participant's health or is likely to result in nonconformance to protocol or a participant's ability to give written informed consent.

AFB, acid-fast bacilli; TB, tuberculosis.

Table 2 Summary of vaccine schedule with respect to vaccine candidates

The vaccines schedule			
Study Arm	Intervention	Dose 1 (intradermal injection in upper arm at insertion of the deltoid) Day 0	Dose 2 (intradermal injection in upper arm at insertion of the deltoid, 2 cm away from first injection site only in one arm.). 4 weeks after the first dose
Arm 1	VPM1002	0.1 mL reconstituted solution [2.8×10^5 Colonu forming Units (CFU)] in either of the upper arm. In the other upper arm, 0.1 mL of Placebo	0.1 mL of placebo will be administered
Arm2	Immuvac	0.2 mL (1×10^9 bacilli) of Immuvac will be administered in two divided dose of 0.1 mL each in both upper arms	0.1 mL (0.5×10^9 bacilli) will be administered (single dose)
Arm 3	Placebo	Two doses each of 0.1 mL of Placebo will be administered in both upper arms	0.1 mL of placebo (single dose) will be administered

6. National Institute of Tuberculosis, Bengaluru with subsites, K C General Hospital and Jaynagar Hospital.
7. Bhagwan Mahavir Medical Research Centre (BMMRC), Hyderabad with subsite at MIMS Medical College Medchal.
8. St. John Medical College, Bengaluru.

Vaccine regimens and dosing

PreVenTB trial is a phase III placebo-controlled, double-blind randomised trial to assess the efficacy and safety of two vaccines compared with placebo where three study arms are candidate vaccines VPM1002, Immuvac (*MIP*) and placebo as described in table 2.

Briefly, VPM1002 is a formulated, lyophilised cake of live recombinant *Mycobacterium bovis*. One vial contains $2–8\times10^5$ CFU. After reconstitution, 1 dose (0.1 mL) of VPM1002 contains live, $2–8\times10^5$ CFU of the investigational product. Similarly, each dose of 0.1 mL of Immuvac contains 0.5×10^9 cells of heat killed *Mycobacterium w* or *MIP* in normal saline. The first dose of the vaccination will be given in both arms and 4 weeks after the first dose, the second dose of the vaccine will be given in one arm which too will be randomised. The placebo will consist of an aqueous solution containing thiomerosal (0.1 mg/mL) in normal saline, that is, pyrogen-free sodium chloride (9 mg/mL of water).

All participants will be included in the study after obtaining written informed consent and Institutional Human Ethics Committee's approval at each site, following the Declaration of Helsinki Principles and guidelines of Indian Council of Medical Research, Government of India. The vaccines will be administered to eligible participants as per the vaccine schedule shown in table 2 after obtaining informed consent.

Randomisation procedures and blinding

Randomisation will be done by statistician not involved in the conduct of this trial. 'Block randomisation with variable block sizes will be used, stratified by enrolment site'. Codes for each site will be kept in individually sealed opaque envelops that are provided to the sites for the execution of the vaccination under blinded codes A, B and C, where nobody except the pharmacist reconstituting the vaccine will know the codes and identity of the intervention. An enrolment number will be allocated to each individual, eligible to be vaccinated, which is specific for the site of enrolment.

Duration of study

48 months.

Study design and recruitment plans

Index case identification

PTB cases presenting to the DOTS centre/clinic/OPD of the implementing institute in the last 4 weeks will be contacted to explain the study. All relevant details of the index case such as name, age, gender, address (corresponding and permanent), contact number, date of diagnosis and initiation of antituberculosis treatment (ATT), sputum smear grade and drug sensitivity pattern will be recorded in site records. A list of HHCs will be obtained from the index cases.

Study procedures

HHCs of newly diagnosed smear-positive PTB patients aged 6 years and above will be screened for inclusion in the trial as per details given in table 1.

HHCs will be screened to assess their eligibility within 6 weeks of detection of PTB or within 3 weeks of starting ATT of the index case. At the time of screening, study participants' demographic information including age, gender, date of birth, weight, height, body mass index, contact address and telephone number, history of alcohol consumption, substance use, smoking status and tobacco use and medical history including comorbid conditions will be noted. Screening IDs will be provided to all HHCs screened.

For all eligible participants, following activities will be implemented:

- An informed consent or assent (as applicable) will be obtained before enrolling any participant in the study. Audio-video recording of the consent/assent process

will be done for children less than 12 years of age. Each individual, eligible to be vaccinated, will be allocated an enrolment number, specific to each site.

- Demographic details including address, medical history, history of concomitant medications will be noted, followed by thorough physical examination at screening and subsequently after enrolment at each visit the detailed history will be taken and examination will be done.
- Two spot sputum samples (if expectorated, at 1-hour interval) to test for acid-fast bacilli (AFB) staining (as per National Tuberculosis Elimination Programme[22] (NTEP) guidelines[22] will be collected from all study participants at screening, second and sixth months and thereafter at every 4 months till 38 months.
- At the time of screening, blood samples will be collected (3–5 mL for participants aged 6–12 years, 7 mL for participants above 12 years) from all participants for liver function test (serum glutamate pyruvate transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase and serum bilirubin), renal function test (serum creatinine and serum urea), random blood sugar test, haemogram and HIV testing. Table 3 and online supplemental table 1 give an overview of all the tests to be performed at different time points.
- Blood for immunological testing (5–7 mL for age 6–12 years and 10 mL for >12 years) will be collected from first 500 consecutively enrolled participants from each of the three sites involved in immunological studies (AIIMS New Delhi, ICMR-NARI Pune, ICMR-NIRT Chennai) at screening. Of these, first 150 consecutively enrolled participants from each of 3 sites who have received both doses of the vaccines will be followed up at second and sixth months for longitudinal evaluation of immunological parameters. Immunological parameters will also be studied for those developing PTB/EPTB during the follow-up.

Immunological parameters to be evaluated will include:

Table 3 Summary of study schedule

	V 1	V 2	V4	V 6	V9	V12	V15
Investigations	**Screening**	**Day 0**	**4 W (M1)**	**8 W (M2)**	**56W (M14)**	**104W (M26)**	**152W (M38)**
Informed consent	√						
Vaccination		√	√				
Demographics*	√	√	√	√	√	√	√
Medical history	√	√	√	√	√	√	√
Concomitant medications	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√
Sputum AFB	√			√	√		√
Liver function test†	√						
Renal function test†	√						
Haemogram†	√						
ELISA for HIV	√						
Random blood sugar	√						
Immunological testing‡	√			√			
Chest radiograph-PA view§	√			√	√	√	√
Urine pregnancy test	√	√	√				
TST¶	√						
Safety assessment for AEs and SAEs		√	√	√	√	√	√

*Demographics: age, gender, date of birth, weight (kg), height (cm), body mass index (kg/m^2), alcohol and smoking status. The address (corresponding and permanent) and contact number should be maintained in site records.
†Will be repeated at V6/month 2, if PI feels necessary.
‡Will be done at AIIMS, New Delhi; Indian Council of Medical Research (ICMR)-NARI, Pune and ICMR-NIRT, Chennai.
§A PA view will be done in all and an additional lateral view will be done in children <14 years. Among children, X-ray will be performed only at baseline and in suspected cases. For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the site study co-coordinator/principal investigator decides it is necessity, in case of presence of clinical symptoms of TB.
¶Will be done at sites—Delhi (NCR), Hyderabad and Chennai. Tuberculin reaction reading will be undertaken at 48–72 hours after administration of the test.
AE, adverse event; AFB, acid-fast bacilli; AIIMS, All India Institute of Medical Sciences; LFT, liver function test; NARI, National AIDS Research Institute; NIRT, National Institute for Research in Tuberculosis; PA, posterior–anterior; PI, principal investigator; RFT, renal function test; SAE, serious AE; TB, tuberculosis; TST, tuberculin skin test.

a. Percentage of CD3, CD4/CD8 cells for intracellular cytokines TNF-α, IFN-γ, IL2 using flow cytometry after stimulation with the whole cell lysates of *M.Tb*.
b. Levels of IL2, IFN-γ, TNF-α, IL 10, IL12, IL17 and IP-10 secreted in the blood and supernatants of aforesaid cultures using multiplex Luminex bead arrays.

- A posterior–anterior view of chest X-ray at screening, at second month post first dose of vaccination and thereafter once every year, that is, months 14th, 26th and 38th will be taken. Additional lateral view X-ray will be done in children between 12 and 14 years of age. For children ≤12years, X-ray will be taken at baseline and only in suspected cases. A protective shield will be used while taking X-ray for females who get pregnant during the course of study, in case of presence of clinical symptoms of TB.
- Urine pregnancy test will be done in females of childbearing age at screening, day 0 and week 4.
- Tuberculin skin test (TST) will be done at screening using a standard product PPD-S (2 TU) in all study participants at three sites—Delhi (NCR), Hyderabad and Chennai. Those who are TST positive (induration ≥10 mm at visit 1, that is, at screening will undergo additional work up as per study schedule. Those who are TST negative (induration <10 mm) at screening will be followed up as per study schedule and TST will be repeated at month 6. The number of participants developing LTBI (TST positive: induration ≥10 mm) will be estimated at the end of 6 months and they will be followed up as per study schedule. Those who are TST negative (induration <10 mm) at month 6 will be followed as per study schedule.
- Day of first vaccination will be day 0 (within 1 week of screening) when the eligible participants receive VPM1002/Immuvac/placebo as an intradermal injection as per randomisation schedule. Second dose of the vaccination will be after one month of the first dose with a window period of – 7 days or + 14 days from the scheduled date of second dose.
- The pharmacist will prepare and dispense the study injection as per the randomisation code (under a physical partition for maintaining blinding) and will hand over the same to the study nurse. The study nurse (vaccine giver), study participants (recipient), investigator (assessor) and sponsor will remain blinded to the nature of intervention (vaccine 1, vaccine 2 or placebo) given.
- Postvaccination, enrolled participants will be observed in the clinic for at least 1 hour to closely monitor any immediate adverse event (AE). In case of no adverse event, the participant will be issued a diary card and will be informed about the next visit (visit 3).
- At every visit, study participant will be issued a diary card by medical officer (MO) for recording all solicited and unsolicited AEs, till 2 months post first dose of vaccination and till completion of follow up (for unsolicited AEs). Necessary training to complete diary card will be provided to the participants. In case of children, parents or guardian will be issued the diary card. In case of old age groups, diary card will be provided to the legal representative (adult relative). The study nurse/investigator will collect and review the diary card and transcribe information about AEs into case report form.
- A central independent data safety monitoring board (DSMB) has been established by ICMR that will monitor the conduct of the trial. The DSMB will periodically examine vaccine safety and provide recommendations to the sponsor regarding continuation of the study.

Trial endpoints

Study endpoints (outcome variables)

Primary endpoint will be microbiologically confirmed incident TB cases (PTB and EPTB) as per NTEP guidelines in the vaccinated and placebo groups after 2 months following first dose of vaccine (VPM1002, Immuvac or Placebo) till 38 months follow-up period.

Secondary endpoints are (1) the number of participants developing LTBI, (2) incidence of AEs and serious AEs (SAEs) in study participants till the end of study period, (3) efficacy of vaccine in prevention of PTB/EPTB in the different age groups of (–18 years, 19–35 years, 36–60 years and above 60 years) and (4) immunogenicity of VPM1002 and Immuvac compared with placebo as measured by immunological parameters using flow cytometry and Luminex.

Exploratory endpoints

Since this is a prospective study with a 3-year follow-up, the following exploratory endpoints will be assessed at the end of study.

- Efficacy against other infectious diseases.
- Efficacy against all-cause mortality.
- Efficacy against all-cause hospitalisations.
- Efficacy in TST positive vs TST negative prior to immunisation.
- Gender-specific efficacy.
- Immunological correlates of protection.

Participant timeline and follow-up

The planned recruitment period will be 1 year from the initiation of the study. All enrolled participants will be followed for 3 years after the first dose of vaccination. An active physical follow-up will be done at weeks 2, 4, 6 and 8, after the first dose of vaccination for safety and thereafter every 4 months up to 152 weeks, that is, until completion of 3 years for early detection of the TB in participants. During the follow-up period, clinical examination and investigations will be done as per schedule. In case, TB is diagnosed within 2 months (±7 days or as early as reported) after the first dose of study vaccination, then such participant will be labelled as Co-prevalent TB cases and withdrawn from study analysis, however, will be

followed up for safety until the end of the study. Such patients will be provided treatment and followed up until the treatment completion by the site as per NTEP guidelines. A close-out visit will be offered to these participants when medical history and physical examination will be carried out.

For convenience of participants, follow-up visits will also be done on weekends and holidays to ensure protocol compliance. In case, any participant does not report to site for follow-up visit, a visit to participant's home will be undertaken. Telephonic follow-up will be done for all visits, if physical follow-up is not possible for any reason.

An unscheduled visit will be conducted and provided to the participants any time during the trial period for protocol compliance (eg, in case of missed visits, safety reasons (AEs), sample collection in case of previous sample deterioration/mishandling, inappropriate health status). This information will be provided to all prospective participants as part of the informed consent procedure.

If the participant migrates away from the study area, he/she will be contacted telephonically for his/her welfare and TB symptoms. All efforts will be made to get a digital X-ray and sputum examination done at the scheduled visits 6, 9, 12 and 15.

Clinical examination, investigations for participants with suspected TB during follow-up

If a participant develops TB symptoms (including but not limited to persistent cough, haemoptysis, fever, unintended weight loss, fatigue or lethargy, night sweats or pleuritic chest pain) at any time point during the physical follow-up visits or weekly telephonic calls after vaccination, he/she will be advised to report to the study clinic where a detailed medical history will be taken and thorough physical examination done and necessary investigations for confirming the diagnosis will be done.

Based on the results, the following possible courses of actions will be implemented:

- In suspected PTB, study investigator will undertake investigations (bacteriological, microbiological, radiological) as per NTEP guidelines. Confirmed PTB cases will be provided treatment as per NTEP guidelines and followed up until treatment completion. In suspected EPTB, required investigations for confirming diagnosis of EPTB as per NTEP guideline will be undertaken. Confirmed EPTB cases will be provided treatment as per NTEP guidelines and followed up until the treatment completion.
- In case of presence of symptoms, radiological abnormality and extrapulmonary cases without laboratory confirmation but negative AFB, the participant will be labelled as clinically diagnosed TB. Required treatment will be provided to the participant as per NTEP guidelines and they will be followed up until treatment completion.
- Participants not diagnosed with TB (PTB or EPTB) as per NTEP guidelines will be followed up till the end of the study period.

Criteria for evaluation for safety and efficacy as follows

Safety

- Immediate postvaccination reactogenicity (within 60 min postvaccination).
- Two months postvaccination reactogenicity, that is, the occurrence of solicited reactions (local pain, erythema, swelling, induration, ulcer, subcutaneous abscess, blister formation and regional lymphadenopathy in the participants enrolled in the study).
- Occurrence of all unsolicited AEs after vaccination including grade 3 AEs throughout follow-up period.
- All SAEs, at any time throughout follow-up period.

Efficacy

- All enrolled participants will be followed for incident PTB/EPTB after vaccination. Any suspected cases of PTB/EPTB will be confirmed as per NTEP guidelines. All incident TB cases that are microbiologically confirmed and captured second month—postvaccination onwards in case of VPM1002, Immuvac and Placebo will be considered for the primary outcome to evaluate efficacy.
- TST negative participants at three sites (Delhi-NCR, Hyderabad and Chennai), at screening will be followed for incident LTBI after first dose of vaccination till the end of 6 months using TST.
- ICMR-NIRT, Chennai will store additional samples (blood, plasma and serum)—well characterised and labelled, for future studies.

Adverse events

All AEs and SAEs, occurring at any time, will be recorded and reported. At every visit (including unscheduled visits), a symptom checklist prompting symptoms related to possible side effects will be administered. All participants with symptoms will be evaluated by the MO and discussed with the site principal investigator (PI). Safety laboratory investigations will be performed at baseline and at all visits if clinically indicated. AEs (clinical and laboratory) will be graded using the 2017 Division of AIDS toxicity grading scale.[22] The participants will be followed weekly for AEs and SAEs, telephonically. The site PI will report all SAEs to the Drug Controller General of India, the Sponsor and the Institutional Ethics Committee (IEC), within 24 hours of their occurrence. In addition, the site PI will also send the SAE Report to Chairman of IEC and the Head of the institution where the trial has been conducted within 14 calendar days of occurrence of the event mentioning the relationship with vaccine, if any. Solicited AEs including local events such as pain, erythema, swelling, fever, ulcer, subcutaneous abscess; systemic events such as lymphadenopathy and unsolicited AEs will be assessed during follow-up visits and unscheduled visits.

Statistical analysis

Interim analysis

The primary outcome will be incidence of microbiologically confirmed TB cases among study participants. Interim analysis will be done when 80 microbiologically confirmed incident TB cases will be reported or follow-up of 50% of enrolled subjects will be completed, whichever is earlier. For efficacy, O'Brien Fleming and for SAE's Pocock stopping rules will be followed.[23] DSMB will review the data for efficacy, safety and utility of trial vaccines.

Final analysis

Analysis will be done as per group A, B or C. Efficacy will be assessed using the primary outcome of time from date of randomisation to confirmed incident TB diagnosis. Time-to-event analysis will be performed using Kaplan-Meier survival plots followed by logrank test; and Cox proportional hazards model with incident TB as the outcome and vaccines/placebo as the exposure while adjusting for potential confounders, if any. Above analysis will also be done for all (both microbiological and clinical) incident TB cases. We will confirm the linearity and proportional hazards assumptions before using Cox's proportional hazards model. Results will be described as unadjusted and adjusted HR along with 95% CIs. Analysis will take into account the multiplicity as in the sample size for two hypothesis. AEs and SAE will be analysed as categorical outcome.

Both modified intention-to-treat (mITT) and per-protocol (PP) analyses will be performed. The primary analysis, that is, mITT will include all randomised participants who have received at least one dose of vaccine/placebo excluding coprevalent cases. PP analysis will exclude participants with major protocol violations among mITT population. The primary outcome will be censored in case of death, migration or consent withdrawal or end of study, whichever occurs first. All statistical tests will be two sided. Statistical analyses will be performed by using software Stata V.18.0.

Data collection and management

All the sites and subsites will enrol the participants at their respective sites and will be required to enter the data on electronic cloud-based data capture system. The data will be checked by the site PI before final submission. The data will be monitored by the independent monitoring agency for quality control and source data verification. Data management team of ICMR will perform the final data check before the soft lock and hard lock. ICMR will have access and custody of the entire data set. The study sites will have access to their site data, and ICMR headquarter will have access to the overall dataset. The source and electronic data will be retained using archival method with restricted access for 5 years. after completion of study.

Patients and public involvement

The representatives of the organisation representing TB-affected individuals were involved in the review of the study protocol and suggestions regarding research questions and outcome measures were included.

Ethics and dissemination

The Standard Protocol Items: Recommendations for Interventional Trials checklist was used for writing the protocol.[24] Institutional Ethics Committees of all the participating sites have approved the trial following the Declaration of Helsinki Principles. All eligible HHCs will be given a detailed 'participant information sheet' in the local language before written informed consent is taken. The participant consent form will be developed as per the standard country regulatory guidelines.[25]

The confidentiality of the study participants will be maintained throughout the study period as per applicable Good Clinical Practice guidelines.

The results of this clinical trial will be presented at scientific conferences and disseminated through publications in peer-reviewed journals, conference presentations and shared with Ministry of Health and Family Welfare, Government of India, policy-makers and other stakeholders. If any of the two vaccines or both will be found efficacious in preventing incident TB among study participants and safe specific recommendations will be made to the NTEP for programmatic implementation.

Oversight

The trial will be managed and monitored primarily by the Project Management Unit of India TB Research Consortium (ITRC) under Division of Epidemiology and Communicable Diseases, ICMR and will be overseen by the Trial Monitoring Committee. There will be periodic review by the Trial Expert Committee. Sites will also send reports to Ethics Committee of Institutes.

An independent DSMB will oversee confidential and unblinded data for trial and advise on continuation of the trial.

Trial status

Recruitment in the trial started on 15 July 2019 at one site and subsequently all the sites started enrolling by end of December 2019. In spite of COVID-19 pandemic and subsequent lockdown and restrictions to travel, the enrolment has been completed and a total of 12 721 participants have been enrolled till 31 December 2020 of which 12 717 received 1st dose of vaccination. Additional participants (above the calculated sample size of 12 000) were recruited after due approvals to compensate for the loss to follow-up at V4, that is, second dose of vaccination due to COVID-19 pandemic lockdown. Of all the enrolled participants, a total of 11 829 have received 2nd dose of vaccination. The recruitment has been completed and the follow-up of the participants who could not come for the 38 months of FU is ongoing. Besides follow-up for confirmation of TB is being done for the participants suspected

to have TB during February–May 2024. The anticipated study end date will be July 2024. The sites are expected to be closed by December 2024 after document archival.

The current protocol is ICMR/ITRC/VAC/001/2018 Version 1.5, dated 3 October 2018.

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Acknowledgements The authors would like to acknowledge all trial staff, as well as all families and participants included in the trial and their communities. We gratefully acknowledge the critical inputs of the members of the Expert Committee on TB vaccines including the CEO of The Global Coalition of TB Advocates (GCTA) and members of the International Scientific Advisory Group of 'India TB Research Consortium' of ICMR. We acknowledge PreVenTB trial team and the members of DSMB, Dr Y.K.Gupta, Former Dean Research & Former HOD-Pharmacology, AIIMS, Delhi, Chairman, Professor J.P. Muliyil, Former Principal, CMC, Vellore and Professor, Epidemiology, CMC, Vellore; Co-Chairperson and other members of DSMB, that is, Professor Shalini Bharat, Professor, Centre for Health & Social Sciences, School of Health Systems Studies, Mumbai, Dr Urmila Thatte, Professor and Head, Pharmacology, KEM Hospital, Mumbai, Dr Ira Shah, Professor Paediatrics and In-charge, Paediatric HIV, TB, Liver Clinics, B. J. Wadia Hospital for Children, Mumbai, Dr R. Solanki, Professor, Pulmonary Medicine, BJMC, Ahmedabad, Dr M. Kalaivani, Scientist-IV, Department of Biostatistics, AIIMS, New Delhi. Vaccine supply: VPM1002 is manufactured and provided free of cost by Serum Institute of India and the Immuvac (MIP) and matching placebo are manufactured by Cadilla Pharmaceuticals, Ahmadabad, India and provided free of cost.

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Contributors MS conceived the research question and contributed to the development of the trial protocol. She wrote the first draft and final version of the manuscript. SM, RG, RS, ST, RRG, KK, RMP, SS, SPanda and SB contributed to the development of the Trial Protocol and provided critical inputs to the article and approved the final version. SPati, PRM, SJ and NS provided input to the article. PK contributed to the first draft and final version of the article. RR contributed to final version of the article and provided critical inputs. SS contributed to the development of the trial protocol and provided critical inputs to the article. AMK contributed intellectually with inputs in shaping the final version of the manuscript. PreVenTB team contributed to development of the study CRFs and provided inputs during protocol development. MS is responsible for the overall content (as guarantor).

Funding Indian Council of Medical Research (ICMR), New Delhi is the sponsor of the PreVenTB Trial and the study is also funded by ICMR, New Delhi (Grant number-ECD/NTF/41/2018-19, dated 28 February 2019).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The study sponsor is Indian Council of Medical Research (ICMR) and study is funded by ICMR under ITRC (Indian TB Research Consortium) programme (grant number-ECD/NTF/41/2018-19, dated 28 February 2019). The study will be conducted by specialised Institutes in different parts of India, as per the current ICH Good Clinical Practice after getting Institutional Ethical approvals following the Declaration of Helsinki Principles and ICMR's National Ethical Guidelines For Biomedical And Health Research Involving Human Participants.

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Supplementary Table 1: Study Schedule

Investigations	**V1**	**V2**	**V3**	**V4**	**V5**	**V 6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**
	Screening	**D0**	**2 w**	**4 w (M1)**	**6 w**	**8 w (M2)**	**24 w (M6)**	**40 w (M10)**	**56w (M14)**	**72 w (M18)**	**88w (M22)**	**104w (M26)**	**120w (M30)**	**136w (M34)**	**152w (M38)**
Informed consent	√														
Vaccination		√		√											
Demographic#, alcohol & smoking status	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medical history	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medications	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Sputum AFB	√					√	√		√		√		√		√
LFT* (SGPT, SGOT, ALP, S. Bilirubin	√														
RFT*(Serum Creatinine, Serum Urea)	√														
Hemogram*	√														

ELISA for HIV	√														
RBS	√														
Immunological Testing##	√					√	√								
Chest adiograph -PA view###	√					√			√			√			√
Urine Pregnancy test	√	√		√											
TST### #	√						√								
Safety Assessment for AEs & SAEs		√	√	√	√	√	√	√	√	√	√	√	√	√	√

AE: Adverse Event, ELISA: Enzyme Linked Immunosorbent Assay, HIV: Human Immunodeficiency Virus, LFT: Liver Function Test, PA: Posterior-Anterior, RBS: Random Blood Sugar, RFT: Renal Function Test, SAE: Serious Adverse Event, SGPT: Serum glutamate pyruvate transaminase, SGOT: Serum glutamic oxaloacetic transaminase

V: Visit; D-Day; W-Week; M-Month

*Will be repeated at V6/Month 2, if PI feels necessary.

#Demographics: age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2]. The address [corresponding and permanent] and contact number should be maintained in site records.

##Will be done at AIIMS, New Delhi; ICMR-NARI, Pune; and ICMR-NIRT, Chennai.

###A postero-anterior view will be done in all and an additional lateral view will be done in children <14 years. Amongst children, X-ray will be performed only at baseline and in suspected cases. For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the site study co-coordinator / Principal Investigator decide its necessity, in case of presence of clinical symptoms of TB.

####Will be done at sites - Delhi (NCR), Hyderabad and Chennai. Tuberculin reaction reading will be undertaken at48-72 hours after administration of the test.

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Indian Council of Medical Research

CLINICAL TRIAL PROTOCOL

Study Title	A Phase III, Randomized, Double-blind, Three arm Placebo controlled Trial to Evaluate the Efficacy and Safety of two vaccines VPM1002 and Immuvac(M*w*) in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients.
Protocol Number	ICMR/ITRC/VAC/001/2018
Protocol Version	1.5
Date	3rd October 2018
Investigational Drug (s)	VPM1002 and Immuvac (Mw)
Sponsor	ICMR Headquarters, Ansari Nagar, New Delhi

CONFIDENTIALITY STATEMENT

This document is confidential and is to be distributed for review only to Investigators, potential Investigators, Consultants, study staff, and applicable independent ethics committees or institutional review boards, contract research organization and relevant regulatory authorities such as DCGI. The contents of this document shall not be isclosed to others without written authorization from SPONSOR(or others, as applicable), unless it is necessary to obtain written informed consent from potential study participants.

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Contents

Confidential

Confidential

Confidential

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AFB	Acid Fast Bacilli
AIIMS	All India Institute of Medical Science
ATT	Anti-Tuberculosis Treatment
BCG	Bacillus Calmette Guerin
BMMRC	Bhagwan Mahavir Medical Research Centre
BSL1	Biological Safety Level 1
CAT	Category
CDSCO	Central Drugs Standard Control Organization
CFU	Colony Forming Units
CNS	Central Nervous System
CRF	Case Report Form
CVS	Cardiovascular System
DCGI	Drug Controller General of India
DSMB	Data Safety Monitoring Board
dL	decilitre
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immuno Spot
ENT	Ear, Nose and Throat
EPI	Expanded Programme of Immunization
EPTB	Extra-Pulmonary Tuberculosis
FBS	Fetal bovine serum
g	gram
GCP	Good Clinical Practices
GIS	Gastrointestinal System
GOI	Government of India
GMERS	Gujarat Medical Education and Research Society
GUS	Genito-Urinary System
HHC	Healthy Household Contact
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee

IGMC	Indira Gandhi Government Medical College
IMP	Investigational Medicinal Product
INH	Isonicotinic Acid Hydrazide
INF-γ	Interferon gamma
IP	Investigational Product
ITRC	India TB Research Consortium
ITSU	Immunization Technical Support Unit
IRB	Institutional Review Board
LFT	Liver Function Test
LTBI	Latent Tuberculosis Infection
MAPK	Mitogen Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MIP	*Mycobacterium indicuspranii*
mg	miligram
mITT	Modified Intention-To-Treat
ml	mililitre
MOHFW	Ministry of Health and Family Welfare
Mtb	*Mycobacterium tuberculosis*
Mw	*Mycobacterium w*
NARI	National AIDS Research Institute
NIRT	National Institute for Research in Tuberculosis
NITRD	National Institute of Tuberculosis and Respiratory Diseases
NTI	National Tuberculosis Institute
PA	Posterio-Anterior
PAN	Permanent Acount Number
PBMC	Peripheral Blood Mononuclear Cells
PGIMER	Postgraduate Institute of Medical Education and Research
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per Protocol
PPD	Purified Protein Derivative
PTB	Pulmonary Tuberculosis
PvPI	Pharmacovigilance Programme of India
RBS	Random Blood Sugar
RNTCP	Revised National Tuberculosis Control Programme
RBS	Random Blood Sugar
RFT	Renal Function Test
RMRC	Regional Medical Research Centre
RPMI	Roswell Park Memorial Institute
RS	Respiratory System

SAE	Serious Adverse Event
SDV	Source Data Verification
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SII	Serum Institute of India
SOC	System Organ Class
SOP	Standard Operating Procedure(s)
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
UID	Unique Identification
UIP	Universal Immunization Programme
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

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Telangana	Dr. Md. Ansari (BMMRC, Hyderabad) Dr. VijayaValluri (BMMRC, Hyderabad) Dr. Chitra Iravatham (BMMRC, Hyderabad) Dr. Shilpa Rakh (BMMRC, Hyderabad) Dr. Aparna Sykam (BMMRC, Hyderabad)

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Maharashtra	Dr. Sheela Godbole (ICMR-NARI, Pune) Dr. Seema Sahay (ICMR-NARI, Pune) Dr. Suchit Kamble (ICMR-NARI, Pune) Dr. Megha Mamulwar (ICMR-NARI, Pune) Dr. Sandeep Patil (ICMR-NARI, Pune) Dr. Arati Kishor Mane (ICMR-NARI, Pune) Dr. Ashwini VinodShete (ICMR-NARI, Pune) Dr. Abhijit Vasantrao Kadam (ICMR-NARI, Pune) Dr. Vijay Kumar Naringrekar (GTB Hospital, Sewree, Mumbai) Dr. Daksha Shah (GTB Hospital, Sewree, Mumbai) Dr. Keskar (GTB Hospital, Sewree, Mumbai) Dr. Karanjkar (Group of T.B. Hospital, Sewree, Mumbai) Dr. KiranKeny (Group of T.B. Hospital, Sewree, Mumbai) Dr. Lalit Kumar Anande(Group of T.B. Hospital, Sewree, Mumbai) Dr. Gajanan Dattatray Velhal(Group of T.B. Hospital, Sewree, Mumbai) Dr. Solanki Mridula Jorawar (Group of T.B. Hospital, Sewree, Mumbai)
Karnataka	Dr. Vineet Chadha (former Head NTI, Bengaluru, now at National Leprosy Training and Research Institute, Chinglepattu, Tamil Nadu) Dr. Uma Shankar S, NTI, Bengaluru Dr. C. Ravichandra, NTI, Bengaluru Dr. S. K. Tripathy, NTI, Bengaluru Dr. Parvathi, NTI, Bengaluru
Odisha	Dr. Dasarathi Das (RMRC, Bhubaneshwar) Dr. Tahziba Hussain (RMRC, Bhubaneshwar) Dr. B Dwibedi (RMRC, Bhubaneshwar) Dr. Subrata Kumar Palo (RMRC, Bhubaneshwar) Dr. P.R Mohapatra (AIIMS, Bhubaneshwar) Dr Sourin Bhuniya (AIIMS, Bhubaneshwar) Prof. Baijayantimala Mishra (AIIMS, Bhubaneshwar) Prof.Debasish Hota (AIIMS, Bhubaneshwar) Dr. Sudipta Mohakud (AIIMS, Bhubaneshwar)
Tamil Nadu	Dr. BanuRekha (ICMR-NIRT, Chennai) Dr. Padmapriyadarshini (ICMR-NIRT, Chennai) Dr. Devarajulu Reddy S (ICMR-NIRT, Chennai) Dr. Dina Nair (ICMR-NIRT, Chennai) Dr. Mohan Natarajan (ICMR-NIRT, Chennai) Dr. PK Bhavani (ICMR-NIRT, Chennai) Dr. D.Bella Devaleenal (ICMR-NIRT, Chennai) Dr. Paul Kumaran (ICMR-NIRT, Chennai) Dr. Sriram Selvaraju (ICMR-NIRT, Chennai)
Reserved Sites*	GMERS, Vadodara PGIMER, Chandigarh IGMC, Nagpur
Project Management Unit at ICMR	Dr. Manjula Singh, Scientist _E', ICMR
	Dr. Ritu Gupta, Consultant, ITRC

*** Satellite sites**

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PROTOCOL SYNOPSIS

Study Title	A Phase III, Randomized, Double-blind, Three arm Placebo controlled Trial to Evaluate the Efficacy and Safety of two vaccines VPM1002 and Immuvac(Mw) in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients
Sponsor	India TB Research Consortium, Indian Council of Medical Research
Clinical Development Phase	Phase III clinical trial
Study Hypothesis	We hypothesize that individually each candidate (VPM1002 and Immuvac) will lead to 50% reduction in anticipated incidence of TB among household contacts of newly diagnosed PTB patients as compared to placebo.
Indication	Healthy household contacts of newly diagnosed PTB patients
Participants	12000 healthy household contacts of newly diagnosed PTB patients at six states in India. Approximately, 2000 participants will be enrolled at each state.
Duration of Study	48 months.
Study Definitions	Refer to Section 7.4 of Protocol (on Page 65)
Investigational Products	
VPM1002	The active ingredient of the recombinant BCG vaccine, VPM1002 is *Mycobacterium bovis* rBCGΔureC: Hly+, freeze-dried/lyophilized and standardized to number of viable mycobacteria (colony forming units; CFU) per application. This investigational product is supplied by Serum Institute of India, Pune, India.
Immuvac (Mw/MIP)	Immuvac is a heat killed suspension of Mycobacterium w, a non-pathogenic, cultivable atypical mycobacterium. This investigational product is supplied by Cadila Pharmaceuticals, Ahmedabad, India. The product license of this investigational product is under name –Mycobacterium w‖ and is commercially available as Immuvac. It has been renamed as MIP (*Mycobacterium indicuspranii)*.
Placebo	Aqueous solution containing thiomerosal (0.1 mg/ml), sodium chloride (pyrogenfree – 9 mg/ml) and water for injection (q.s. to 1.0 ml). This investigational product is supplied by Cadila Pharmaceuticals, Ahmedabad, India.
Study Arms	
Study Arm 1	Candidate vaccine 1: VPM1002 + Placebo
Study Arm 2	Candidate vaccine 2: Immuvac
Study Arm 3	Candidate vaccine 3: Placebo
Dosage Schedule	
Study Arm 1	**Dose 1** (day 0): 0.1 ml reconstituted solution (2-8 x 10^5 CFU) of VPM1002 will be administered intradermally in either of the upper arm at the insertion of the deltoid. In the

	other upper arm, 0.1 ml of Placebo will be administered intradermally at the insertion of the deltoid. **Dose 2** (04 weeks after the first dose): 0.1 ml of Placebo will be administered intradermally at least 2 cm away from first injection site.
Study Arm 2	**Dose 1**: At day 0: 0.2 ml (1 x 10^9 CFU) of Immuvac will be administered intradermally in two divided dose of 0.1 ml each in both upper arms at the insertion of deltoid. **Dose 2**: 04 weeks after the first dose: 0.1 ml (0.5 x 10^9 CFU) of Immuvac is administered intradermally (single dose) at least 2 cm away from first injection site.
Study Arm 3	**Dose 1**: At day 0: Two doses each of 0.1 ml of Placebo will be administered intradermally in both upper arms at the insertion of deltoid. **Dose 2**: 04 weeks after first dose: 0.1 ml of placebo (single dose) will be administered intradermally at least 2 cm away from first injection site.
Study Objectives	
Primary Objective	To evaluate the efficacy of VPM1002 and Immuvac by comparing the reduction in incidence of TB over 3-year period among Indian healthy household contacts of newly diagnosed sputum positive PTB patients vaccinated with VPM1002 and Immuvac in comparison to placebo.
Secondary Objective	• To evaluate the efficacy of VPM1002 and Immuvac in prevention of LTBI in healthy household contacts of newly diagnosed sputum positive PTB patients in comparison to placebo [in a sub-set of population at Sites – Delhi (NCR), Hyderabad and Chennai]. • To evaluate the safety of VPM1002 and Immuvac in Indian healthy household contacts. • To evaluate the Immunogenicity of VPM1002 and Immuvac in healthy household contacts as compared to placebo against tuberculosis. (in a sub-set of population at Sites – Delhi (NCR), Pune and Chennai].
Study Endpoints (Outcome Variables)	
Primary Endpoint	To compare the percentage of confirmed TB cases (PTB and EPTB) as per RNTCP guidelines in the vaccinated and placebo groups from two months after first dose of vaccine till 38 months follow-up period (VPM1002, Immuvac and Placebo).
Secondary Endpoints	• Number of participants developing LTBI* • Incidence of adverse events and serious adverse events in study participants till the end of study period. • Efficacy of vaccine in prevention of PTB/EPTB in the different age groups of (6 to 18 years, 19-35 years, 36 to 60 years and above 60 years). • To determine the protective effect for both forms of TB (PTB and EPTB). • Immunogenicity of VPM1002 and Immuvac will be compared with placebo as measured by** ➢ **FACS (Fluorescence activated cell sorting)**: CD3, CD4/CD8, TNFα, IFNγ, IL2 [Time Frame: screening, month 2, month 6, and those who have developed

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	PTB/EPTB will be followed up during the course of study]. ➢ **LUMINEX**: IL2, IFNγ, TNFα, IL 10, IL12,IL17 [Time Frame: screening, month 2, month 6 and those who have developed PTB/EPTB will be followed up during the course of study].
Exploratory Endpoints	Since this is a prospective study with a 3 year follow up, hence the following exploratory endpoints will be assessed at the end of study. • Efficacy against other infectious diseases. • Efficacy against all-cause mortality. • Efficacy against all-cause hospitalizations. • Efficacy in TST positive versus TST negative prior to immunization. • Gender specific efficacy • Immunological correlates of protection.
Inclusion Criteria	i. Healthy household contacts age ≥ 6 years at the time of enrollment. *ii.* No evidence of active TB disease during screening – Normal chest radiograph with no abnormalities and no bacteriological positivity by smear testing for *M.tb* iii. Female participants who are currently using reliable methods of contraception (barrier methods and intrauterine contraceptive device), with a negative urine pregnancy test during screening and agree to informed compliance of contraceptive method until at least 4 months post-vaccination. iv. The participant must be able and willing to comply with the study protocol, available and willing to complete all the study assessments and must have signed an Informed Consent Form.**** v. Participant agrees to stay in contact with the study site for the duration of the study, and provide updated and an alternate contact information. vi. Has general good health, as confirmed through medical history and medical evaluation (which includes physical examination and laboratory tests).
Exclusion Criteria	i. Any chronic febrile illness with oral temperature > 100°F on the day of randomization. ii. Prior or present anti-TB treatment iii. Any laboratory abnormalities (haematological and biochemical), at the time of screening, which is of clinical significance as determined by the Investigator. iv. Pregnant and / or lactating female participants. v. Presence of any illness requiring short hospital referral (temporary exclusion). vi. Reactive serology for HIV. vii. Any confirmed or suspected immunodeficient condition based on medical history and physical examination and a family history of congenital or hereditary immunodeficiency. viii. History of chronic renal failure/dialysis, silicosis, gastrectomy, jejunoileal bypass, solid organ transplantation such as renal or cardiac transplants, carcinoma of the head and neck, and disorders of the liver, kidney, lung, heart, or nervous system, or other metabolic inflammatory conditions, psychiatric, occupational problems that make it unlikely the volunteer will comply with the protocol as determined by the local investigator. ix. History of previous administration of experimental MTB vaccines. x. History of administration of any immunoglobulins, any immunotherapy (antineoplastic chemotherapy, radiation therapy, immunosuppressants to induce

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	tolerance to transplants, and corticosteroids use) and/or any blood products within the 3 months preceding study vaccination, or planned future administrations during the study period. Participants on inhaled/topical steroids may be permitted to participate in the study. xi. Participation in any clinical trial within 3 months prior to and/or planned concurrent participation in another interventional clinical trial at any point throughout the entire timeframe for this study. xii. History of allergic reactions or anaphylaxis to any vaccine or component of the vaccine. xiii. Presence of any severe systemic/autoimmune disorders as determined by medical history and / or physical examination/ or lab investigations at the time of screening, which in the judgment of the Investigator would compromise the participant's health or is likely to result in nonconformance to the protocol or a participant's ability to give written informed consent/assent.
Study Design and Plans	• The study is designed as a multicenter, double-blinded, randomized, placebo-controlled trial with three groups of healthy household contacts of new index case of PTB (n=4000 per group) receiving either VPM1002/Immuvac / Placebo (three arm study). • The study will be started only after the approval from the Drug Controller General of India (DCGI) and the Institutional Ethics Committee (IEC) from the respective study sites. • The details of the sputum positive PTB cases presenting to the DOTS centre/clinic/OPD of the implementing institute in the last 4 weeks will be obtained. The index case will be contacted and visited to explain about the study and required to provide details of HHC. All relevant details of the index case such as name, age, gender, address (corresponding and permanent), contact number, date of diagnosis and initiation of anti-tuberculosis treatment (ATT), sputum smear grade and drug sensitivity pattern will be recorded in site records. A list of household contacts will be obtained from the index case by the health staff. Household contacts who will be willing to be screened will be registered. • Screening of healthy household contacts to assess eligibility for the trial will take place essentially within 6 weeks of detection of PTB or within 3 weeks after Index case is put on ATT. A screening consent will be taken from the willing participants after describing the rationale of the study in brief and the procedures that will be done for screening the participants. At the time of screening, study participant's demographic information (age, gender, date of birth, weight [kg], and height [cm], body mass index, address (corresponding and permanent), contact number, alcohol consumption /substance use and smoking status/tobacco use) and medical history, co-morbid conditions will be noted. • If the participant qualifies for the study criteria, a written/oral consent or assent (as applicable) will be obtained before enrolling the participant in the study. Audio-video recording of the consent/assent process will be done for vulnerable participants (children less than 12 years of age). • Demographic details (age, gender, date of birth, weight [kg], and height [m], body mass index [kg/m^2], alcohol consumption/substance use and smoking

	status/tobacco use) will be captured at all visits in case report forms. All sites should maintain the name, address [corresponding and permanent] and contact numbers of all participants in the site records. • Medical history, history of concomitant medications and thorough physical examination of the participants will be carried out at screening and at all study visits. • Two spot Sputum samples (at 1 hour interval) will be collected for Acid Fast Bacilli (AFB) staining (as per Revised National Tuberculosis Control Programme [RNTCP] guidelines) at screening, month 2, month 6, thereafter every 8 months till month 38 from all study participants. • At the time of screening, 3-5 ml (for participants age 6-12 years) or 7 ml (for participants age >12 years) of blood sample will be collected from all the participants for Liver Function Test (SGPT, SGOT, Alkaline Phosphatase and Serum Bilirubin), Renal function test (Serum Creatinine and Serum Urea), Hemogram and Human Immunodeficiency Virus(HIV) testing (Enzyme Linked Immunosorbent Assay [ELISA]).Random Blood Sugar (RBS) test will be done. • Blood for immunological testing (5-7 ml for age 6 to 12 years and 10 ml for >12 years) for immunological testing will be collected from 1500 (first 500 consecutive enrolled participants from each of 3 sites- AIIMS New Delhi, ICMR-NARI Pune, ICMR-NIRT Chennai) study participants at screening. Of the 1500 study participants, only 450 study participants (first 150 consecutive enrolled participants from each of 3 sites) will be followed at month 2 and month 6 for estimation of immunological parameters. Those who have developed PTB/EPTB will also be followed up for immunological testing during the course of study. • Chest X-ray will be performed at screening and month 2 post first dose of vaccination, thereafter once a year till month 38. A postero-anterior view will be done in all and an additional lateral view will be done in children <14 years. Amongst children (6-12years) X-ray will be performed only at baseline and in suspected cases.For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the study site co-ordinator / site Principal Investigator decide its necessity, in case of presence of clinical symptoms of TB in the pregnant females. • Urine Pregnancy test will be carried out in females of child bearing age at screening, Day 0 and Month 1(week 4). • Tuberculin Skin Test (TST) will be done at screening using a standard product PPD-S (3 TU) in all study participants at sites - Delhi (NCR), Hyderabad and Chennai. Those who are TST positive (induration ≥10 mm) at screening will be worked up as per study schedule. Those who are TST negative (induration <10 mm) at screening will be followed up as per study schedule and TST will be repeated at Month 6. The number of participants developing LTBI (TST positive: induration ≥10 mm) will be estimated at the end of 6 months and will be followed up as per study schedule. Those who are TST negative (induration ≤10 mm) at Month 6 will be followed

as per study schedule.

- Day of vaccination will be Day 0 (as soon as possible or within one week of screening) for the healthy household contact. The eligible participants will receive either VPM1002/Immuvac/Placebo as an intradermal injection as per randomization schedule.
- The pharmacist will prepare and dispense the injection as per the randomization code (under a physical partition for maintaining blinding) and hand it to the study nurse. The study nurse (vaccine giver), study participants (recipient), investigator (assessor), and sponsor will be blinded to the intervention given.
- Post vaccination, enrolled participants will remain in the clinic for sometime (at least 1 hour) for observation when they will be closely monitored for any immediate adverse event. In case of no adverse event, the participant will be issued a diary card and will be informed about the next visit (visit 3).
- All adverse events and serious adverse events will be recorded and reported, occurring at any time, throughout the follow up period. The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The Site Principal Investigator should report all Serious Adverse Events (SAEs) to the Drug Controller General of India (DCGI), the Sponsor and the Institutional Ethics Committee (IEC), within 24 hours of their occurrence. In addition, the Site Principal Investigator will send the SAE Report to Chairman of IEC and the Head of the institution where the trial has been conducted within 14 calendar days of occurrence of the event mentioning the relationship with vaccine if any. Solicited adverse events including local [pain, erythema, swelling, fever, ulcer, subcutaneous abscess] and regional lymphadenopathy and unsolicited adverse events will be assessed during follow-up visit or unscheduled visit.
- At every visit, the study participant will be issued a diary card[***]by Site Principal Investigator/Medical Officer for recording solicited adverse events, at the time of screening and at all the visits till 2 months post first dose of vaccination. The study participant will also be issued a diary card for recording unsolicited adverse events, at the time of screening and at all the visits till completion of follow up post first dose of vaccination. Necessary training to complete the diary card will be provided. In case of children, parents or guardian will be issued the diary card. In case of old age groups, diary card updating training should be provided to legal family representative (adults/relative).The study nurse/investigator will collect and review the diary card and will transcribe the information about adverse events into the Case Report Form.
- A central independent Data Safety Monitoring Board (DSMB) will be established by ICMR to monitor the conduct of the trial. The DSMB will periodically examine vaccine safety and provide recommendations to the Sponsor regarding continuation of the study.

During follow-up period, if TB is diagnosed within 2 months (± 7 days or as early as reported) after first dose of study vaccination then such participant will be labeled as Co-

	prevalent TB and withdrawn from the study and will be excluded for outcome analysis, yet followed up for safety till the end of study and will be provided treatment by Site Principal Investigator/Co-investigator as per RNTCP guidelines, and the investigator will ensure follow-up until the treatment completion. A close out visit will be offered to this participant. During close out visit medical history and physical examination will be carried out. At a minimum, all participants will be followed for 2 months post vaccination. Telephonic follow up will be done for all the visits. Follow up will be done on weekends and holidays to ensure protocol compliance for the convenience of participants. In case the participant does not report to site for follow up visit, a visit to the participant's home will be undertaken. An unscheduled visit can be conducted at any time during the trial period for protocol compliance (e.g. in case of missed visits, safety reasons (adverse events), sample collection in case of previous sample deterioration / mishandling, inappropriate health status etc.). **Investigations for study participants with suspected TB during follow up:** If a participant develops TB symptoms (including but not limited to: persistent cough, hemoptysis, fever, unintended weight loss, fatigue or lethargy, night sweats, or pleuritic chest pain) during the follow-up after vaccination, he/she will be advised to report to the study clinic. A detailed medical history with detailed thorough physical examination will be done. Based on the results participants will be classified as follows: In suspected PTB, the study investigator will undertake investigations (bacteriological, microbiological and radiological) as per RNTCP guidelines for confirming PTB. If confirmed, the study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion. In suspected EPTB, the study investigator will undertake required investigations for confirming diagnosis of EPTB as per RNTCP guideline. If confirmed, the study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion. In case of presence of symptoms ,radiological abnormality and extra pulmonary cases without laboratory confirmation but negative AFB, the participant will be labeled as clinically diagnosed TB. The study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion. If the participant is not diagnosed with TB (PTB or EPTB) as per RNTCP guidelines, he/she will be continued into the study and followed up till the end of the study period.
Study States (including Sites)	1. Delhi-NCR – • AIIMS, New Delhi [Civil Hospital, Ballabgarh; Rajan Babu TB Hospital, Nehru nagar TB Hospital] • Safdarjung Hospital, Delhi

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- NITRD, Delhi

2. Telangana – BMMRC, Hyderabad [Secunderabad Tuberculosis Unit, District TB Centre, Hyderabad].
3. Maharashtra –
   - NARI, Pune [Gadikhana Hospital, Pune]
   - Group of TB Hospital, Sewree, Mumbai
4. Karnataka – NTI, Bengaluru [KC General Hospital, Bengaluru; Jayanagara Hospital, Bengaluru; CV Raman Hospital, Bengaluru; Govt. General Hospital Yelahanka, Bengaluru]
5. Odisha –
   - RMRC, Bhubaneshwar
   - AIIMS, Bhubaneshwar
6. Tamil Nadu – NIRT, Chennai; Government Raja ji Hospital, Madurai
7. Reserved Sites:
   - IGMC, Nagpur
   - GMERS, Vadodara
   - PGIMER, Chandigarh

Study Schedule [Refer to Section 4 of Protocol for details]

Investigations	**V 1**	**V 2**	**V 3**	**V4**	**V 5**	**V 6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**
	Screening	**Day 0**	**2 W**	**4 W (M1)**	**6 W**	**8 W (M2)**	**24 W (M6)**	**40 W (M10)**	**56W (M14)**	**72 W (M18)**	**88 W (M22)**	**104 W (M26)**	**120 W (M30)**	**136 W (M34)**	**152 W (M38)**
Informed consent	√														
Vaccination		√		√											
Demographics #, alcohol and smoking status	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medical history	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medications	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Sputum AFB	√					√	√		√		√		√		√
LFT* (SGPT, SGOT, Alkaline Phosphatase, Serum Bilirubin)	√														
RFT* **(Serum Creatinine, Serum Urea)**	√														
Hemogram*	√														
ELISA for HIV	√														
RBS	√														
Immunological Testing##	√					√	√								
Chest radiograph-PA view###	√					√			√			√			√
Urine Pregnancy test	√	√		√											
TST### #	√						√								
Safety Assessment for AEs and SAEs		√	√	√	√	√	√	√	√	√	√	√	√	√	√

AE: Adverse Event, ELISA: Enzyme Linked Immunosorbent Assay, HIV: Human Immunodeficiency Virus, LFT: Liver Function Test, PA: Posterior-Anterior, RBS: Random Blood Sugar, RFT: Renal Function Test, SAE: Serious Adverse Event, SGPT: Serum glutamate pyruvate transaminase, SGOT: Serum glutamic oxaloacetic transaminase

V: Visit; D-Day; W-Week; M-Month

*Will be repeated at V6/Month 2, if PI feels necessary.

#Demographics: age, gender, date of birth, weight [kg], and height [m], body mass index [kg/m^2]. The address [corresponding and permanent] and contact number should be maintained in site records.

##Will be done at AIIMS, New Delhi; ICMR-NARI, Pune; and ICMR-NIRT, Chennai.

###A postero-anterior view will be done in all and an additional lateral view will be done in children <14 years. Amongst children, X-ray will be performed only at baseline and in suspected cases. For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the site study co-coordinator / Principal Investigator decide its necessity, in case of presence of clinical symptoms of TB.

####Will be done at sites - Delhi (NCR), Hyderabad and Chennai. Tuberculin reaction reading will be undertaken at48-72 hours after administration of the test.

<table>
<tr><th colspan="2">Criteria for Evaluations</th></tr>
<tr><td>Safety</td><td>Participants will be evaluated for:
Immediate post-vaccination reactogenicity (within 60 min post-vaccination) – all participants
2 months post-vaccination reactogenicity, i.e. the occurrence of solicited reactions [local (pain, erythema, swelling, ulcer, subcutaneous abscess, induration, blister formation) and regional lymphadenopathyamong all participants enrolled early in the study
Occurrence of unsolicited adverse events until 2 months after vaccination – reactogenicity cohort
Occurrence of all unsolicited including grade 3 adverse events throughout follow up period.
All serious adverse events, at any time throughout follow up period – all participants</td></tr>
<tr><td>Efficacy</td><td>At all sites, the enrolled participants will be followed for incident PTB/EPTB after vaccination in the trial. Any suspected cases of PTB/EPTB will be confirmed as per RNTCP guidelines. All incident TB cases captured from month 2 - post vaccination onwards in case of VPM1002, Immuvac and Placebo will be included to evaluate efficacy.
At sites at Delhi-NCR; Hyderabad; and Chennai the TST negative participants at screening will be followed for incident LTBI from the first dose of vaccination till the end of 6 months using TST.</td></tr>
<tr><td>Blood Sampling for immunology</td><td>At the time of screening, 5-7 ml blood for age 6 to 12 years and 10 ml blood for >12 years for immunological tests will be collected by the immunological department and processed as soon as possible from 1500 (first consecutive 500 of the enrolled participants from 3 sites each, namely AIIMS, New Delhi; ICMR-NARI, Pune; and ICMR-NIRT, Chennai) study participants. Of the 1500 study participants, only 450 study participants (first consecutive 150 from each of 3 sites) will be followed at month 2 and month 6 for estimation of immunological parameters. Those who have developed PTB/EPTB will also be followed up during the course of study.

ICMR-NIRT, Chennai would store additional samples (blood, plasma, and serum) – well characterized and labeled, at their own cost for future studies.</td></tr>
<tr><td>Sample Size</td><td>The sample size was calculated taking into account the following parameters:

<table><tr><th>INPUTS</th><th></th></tr><tr><td>3 year Incidence of TB in Placebo</td><td>0.02</td></tr><tr><td>Reduction in VPM1002/Immuvac</td><td>50%
(0.01)</td></tr><tr><td>Observed/Expected difference in proportion in 3 year incidence</td><td>0.01</td></tr><tr><td>Alpha level (%) Two sided
(adjusting for multiplicity i.e. two hypothesis)</td><td>0.025</td></tr></table></td></tr>
</table>

	Power (%)	90
	Per Group Required Sample Size	3562
	Sample Size with 10% drop-out	3918≈4000
	Total study size (=Per group x 3)	12000 (=4000 x 3)
Statistical Analysis / Considerations	**Interim Analysis** Interim analysis will be done at the time when 80 incident TB cases are observed in the trial or follow up of 50% of enrolled subjects is completed, whichever is earlier. For efficacy, O'Brian Flaming and for SAE's Pocock stopping rules will be followed. DSMB will review the data for efficacy, safety, and utility of the trial vaccines. **Final Analysis** Final analysis will be done at the time when 160 incident TB cases are observed in the trial or end of follow up period whichever is earlier. Incidence of new cases for each of the three arms will be estimated in person years of time. Time to event (event of interest for efficacy analysis - incident TB and for safety analysis - ADR and Death) analysis for confirmed TB cases will be performed using Cox proportional hazards model. Safety data will be summarized by vaccine and placebo arms using descriptive statistics. Effect size (95% CI) would be computed for each study outcome. Statistical analyses will be performed using SPSS version 20 or higher or R version 3.3 or higher.	
Statistical and Data Management Centre (SDMC)	All the sub-sites will be required to collect and send data to the co-coordinating site on daily basis which will be vetted by Site Principal Investigator. The sites will transfer the data to ICMR, Headquarters for the Central Data Management on weekly basis.	

*Will be evaluated at sites - Delhi (NCR), Hyderabad and Chennai.

**Will be done at AIIMS, Delhi; NARI, Pune; and NIRT, Chennai

*** One page diary card (front page having information about adverse events and back page having instructions which are required to be followed for filling the diary card) for both solicited and unsolicited adverse events.

****For children less than 7 years of age, parental consent is sufficient. For children between 7 (84 months and above) and 11 years of age, oral assent will be obtained in the presence of parent/Legally Acceptable Representative. Children between 12 and 18 years of age, should give written assent. If the study participant becomes 13 years old during the course of the study, then he/she must be willing to provide a written assent in addition to parent/LAR consent. During the course of the study period, when the child crosses the stipulated age band, re-consent will be taken appropriately.

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1. BACKGROUND AND INTRODUCTION

DISEASE DEFINITION

Tuberculosis (TB) is an infectious disease caused by bacteria (*Mycobacterium tuberculosis*) that commonly affect the lungs. It is considered as one of the top 10 causes of death worldwide. The general symptoms of active lung TB include cough with sputum and blood, chest pain, weakness, weight loss, fever, and night sweats. In latent TB, individuals are infected by the causative organism but are not (yet) ill with the disease and thus cannot transmit the disease.1

BURDEN OF DISEASE

Worldwide approximately 2 billion people2,3are infected with *Mycobacterium tuberculosis* (*M.tuberculosis*). In most cases, infection with *Mtb* is initially limited by host defenses and the infection remains latent/subclinical. However, latent TB infection has the potential to develop into active TB disease at any time. Individuals with active TB become sources and contribute to transmission of the disease and new infections.

In 1993, World Health Organization (WHO) declared tuberculosis (TB) as a global emergency.In 2014, the number of new cases of disease was reported to be 9.6 million.4Approximately 1.5 million people die from tuberculosis each year. Consequently, active tuberculosis along with other infectious disorders like HIV, gonorrhea, infectious leprosy, chancroid*etc*.5 is considered as a communicable disease of public health significance as it is a major public health problem in nearly all resource-constrained countries and has considerably increased in sub-Saharan Africa as a result of the impact of HIV infection.[1,6]

India has the highest burden of TB (due to the huge population size), as per WHO report for 2014 with approximately 2.2 million new cases of TB occurring in India out of the global incidence of 9.6 million. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB disease. It is also estimated by the WHO that 220,000 people die from TB each year in India.[1,4,7]

As per WHO report for 2017, TB was considered as the ninth leading cause of death worldwide. In particular, 6.3 million new cases of TB were reported in 2016. Additionally, 6,00,000 new cases of drug resistant (resistance to rifampicin) were reported, out of which 490,000 cases had multidrug-resistant TB.8

In an Indian study, the prevalence of LTBI observed according to TST was found to be 42%.9

The TB infection is almost exclusively transmitted through air from patients with active pulmonary disease. The risk of transmission to household contacts is greatest when index case is sputum smear positive, close to the contacts, living conditions are overcrowded, bacillary density in respiratory secretions is high, and degree of lung fields involved are more. Therefore, those living within the same household are at higher risk than casual contacts. Further, among the household contacts, younger age and absolute or relative immunodeficiency states increase the

risk of acquiring infection from their index case. Several studies from high burden countries have shown that active case finding among household contacts yields significantly more TB cases than passive case detection.[10]

In a study carried out in a peri-urban population of South Delhi, India Co-prevalent and Incident TB was found in 4.3% and 2.6%household contacts of pulmonary TB patients respectively. In incident cases, the diagnosis was made between 4 to 24 months of follow-up, after index case was diagnosed. The age-wise distribution of incident TB cases was 12.9% in ≤ 12 years, 48.4% in 13-25 years, 22.6% in 25-40 years and 16.1% in > 40 years age group.[10]

A prospective cohort study carried out in South Africa reported overall TB incidence rate of per 100 person years among household contacts (all age groups) of TB index patients. TB incidence for individuals who were HIV-infected and HIV sero-negative at baseline was 5.4per 100 person years and 0.7 per 100 person years respectively.[11]

In a prospective cohort study, 1,206 household contacts of 302 index cases with TB were enrolled in Uganda between 1995 and 1999. All contacts were systematically evaluated for active TB and risk factors for active disease. Among the 1,206 household contacts, 76 secondary cases (6.3%) of TB were identified. Of these cases, 51 (4.2% had co-prevalent TB) were recognized in the baseline investigation, and 25 (2.1% had incident TB) developed during follow-up period. As compared with index cases, secondary cases were present more often with minimal disease. In addition, the risk for secondary TB was greater amongst young children than adults (10% vs. 1.9%) and among HIV-seropositive than -seronegative contacts (23% vs. 3.3%).[12]

In China, with a similar high-burden of TB in India, the yield for active TB case finding through contact investigation ranged from 0to 6.9% in household contacts.[13, 14]

A systematic review and meta-analysis of all studies reporting the prevalence of TB and latent TB infection, and the annual incidence of TB among contacts of patients with TB has reported 3.1% prevalence of TB among household contacts. Incidence of TB in household contacts of index case has been reported to be higher in the first year after exposure.[15]

In addition to the above studies, a prospective, observational study investigating adult household contacts for active TB by culture and drug susceptibility testing of index case at the time of diagnosis and again one year lateral so revealed that incidence rates of multidrug-resistant and extensively drug-resistant tuberculosis among household contacts were extremely high.[16]

There is an increased risk of exposure to the disease causing organism among the household contacts of TB patients than the general population.[17]

A systematic review has shown that among household contacts or other close contact of an index TB case, around 3.5–5.5%are found to have previously undiagnosed and active TB .Despite this potential benefit, routine contact investigation is performed rarely and inconsistently in resource-limited settings probably due to constraints in finance and human resources.[18]

Thus, in the present Phase III clinical trial study we have considered HHC as active participants in contrast to community as a whole.

NEED FOR TB VACCINES

Bacille Calmette-Guerin vaccine (BCG), an attenuated strain of *M. bovis*, has been in use as a TB vaccine in studies since 1921. To date, approximately 4 billion doses have been administered.[19]It is used in routine Expanded Programme of Immunization (EPI) in countries across the world. It is generally given at birth or in the first year of life. A double blind randomized controlled trial to investigate the protective effect of BCG against bacillary forms of pulmonary tuberculosis carried out in Chingelput district in South India and involving 281,161 individuals showed that BCG offered no overall protection in adults and a low level of overall protection in children.[20]

Since BCG clearly has inadequate efficacy against adult TB and also against most forms of childhood TB, the overall burden of childhood TB remains unaltered. Also, it does not have a significant impact on TB control. There is therefore a perceived need and an ongoing drive to develop more effective vaccines.

Additionally, new TB vaccines are also urgently required to achieve the goal of considerably reducing the incidence of tuberculosis by 2050.[21]In this context, there is critical necessity for greater diversity in the antigens targeted and immune responses generated by TB vaccine candidates in order to maximize the chances of obtaining a successful vaccine candidate by 2025.[22]

At present, there is no intervention available for prevention of TB in household contacts of pulmonary TB patients (except for isoniazid or Isonicotinic Acid Hydrazide [INH] for the high risk HIV + population and paediatric population [<6 years]).Therefore in this study, we aim to evaluate the efficacy, safety, tolerability and immunological biomarkers of VPM1002 and Immuvac to prevent TB among household contacts of TB patients of age ≥ 6 years.

RATIONALE FOR INCLUDING INVESTIGATIONAL PRODUCTSVPM1002 ANDIMMUVAC IN THE CURRENT TRIAL

A Detailed landscape analysis of anti-tubercular entities was done and the most advanced candidates were shortlisted (Immuvac {Mw}, VPM1002, DAR901, M72/ AS01, and ID93/ GLA-SE). Based on the following data, VPM1002 and Immuvac (Mw) were selected.

1.4.1 VPM1002

VPM1002 is a live recombinant BCG (rBCG) in which the urease C gene has been replaced by the listeriolysin O (LLO) encoding gene (hly) from Listeria monocytogenes. Urease C drives neutralization of phagosomes containing mycobacteria by generation of ammonia, thereby inhibiting phagolysosomal maturation and contributing to the survival of mycobacteria inside the macrophage. Its depletion allows for rapid phagosome acidification, which promotes phagolysosome fusion and provides the optimal pH for LLO stability. LLO is a cholesterol-dependent cytolysin that forms transmembrane β-barrel pores in the phagolysosome membrane, allowing escape of L. monocytogenes into the cytosol. Its expression in VPM1002 results in the release of antigens and bacterial DNA into the cytosol, triggering autophagy, inflammasome activation, and apoptosis.[24]It is developed by VakzineProjekt Management in Germany and licensed to the Serum Institute of India (SII). It is currently being tested in two Phase I clinical trials in healthy adults and two Phase II clinical trials in newborn babies .A Phase II/III clinical trial is currently ongoing in India for prevention of TB recurrence in pulmonary TB patients who have successfully completed first line anti-TB treatment and declared as cured.

PRIOR NON-CLINICAL AND CLINICAL STUDIES WITH VPM1002

Preclinical efficacy and safety

A non-clinical study was carried out to investigate the protective capacity of BCG ΔureC::hly immunizations as single vaccination post-Mtb exposure in female BALB/c mice. In this study, Female Balb/c mice were grouped and were aerosol-infected with 100–200 CFUs Mtb H37Rv. Once chronic infection had been established (day 42), animals received drinking water supplemented with antibiotics (100 mg/L rifabutin and 100 mg/L isoniazid) until day 84, which reduced the burden of TB to a subclinical level mimicking LTBI.

To avoid impact of chemotherapy on survival of live vaccines, subcutaneous vaccination with $1x10^6$ CFU of BCG or rBCG was performed on day 88. Groups of five mice were used to profile the progress of pulmonary TB at designated time points. Organ homogenates were plated onto agar for Mtb CFU determination. To evaluate protection at the end of the experiment (day 250), groups of 16 mice were used.

The results of three independent biological experiments indicated that mice vaccinated with BCG ΔureC::hly were, with varying statistical significance, better protected than animals that received BCG SSI or PBS. Pooled data of the three experiments showed that immunization of mice with BCG SSI and BCG ΔureC::hly after Mtb exposure reduced load of TB in lungs by 0.55 logs and 76 1.12 logs, respectively, as compared to mock-vaccinated controls. Our data suggests that BCG ΔureC::hly provides 10-fold better protection over the mock-vaccinated control group in the murine Mtb post-exposure model. BCG SSI vaccination reduced the TB burden by approximately five fold. The BCG ΔureC::hly vaccine candidate has demonstrated superior protective efficacy over canonical BCG in pre-exposure mouse studies.[23]

The safety profile of VPM1002 has been evaluated in animal models including mice, guinea pigs, rabbits, and non-human primates. VPM1002 demonstrated substantially lower virulence in severe combined immunodeficiency mice, most likely due to the reduced intracellular persistence of this strain.After immunization of wild type BALB/c or C57BL6 mice, VPM1002 was more rapidly cleared from the draining lymph nodes than BCG and disseminated less to the spleens, where it was also quickly cleared. Dissemination to the lungs was observed in BCG vaccinated but not VPM1002 vaccinated mice. Enhanced adaptive immune responses after VPM1002 vaccination are therefore likely to play a role in the reduced dissemination of VPM1002 in immunocompetent mice. Overall, the data demonstrate increased safety and protective efficacy of VPM1002 compared to parental BCG in mice. In guinea pigs and non-human primates, the safety of VPM1002 was comparable to that of BCG.[24]

Clinical trials with VPM1002

VPM1002 human data is available from five clinical trials.

In the **first** (**Phase 1**) clinical trial**VPM1002-GE-1.01TB**(ClinicalTrials.gov Identifier: NCT00749034),conducted in Germany, **healthy male Caucasian adult volunteers with or without pre-exposure to BCG** were vaccinated with VPM1002 (N=30 + 30) or BCG (N=10 + 10) and followed for six months. This study revealed that a single vaccination with VPM1002 up to 5 x $10e^5$ CFU was safe and well tolerated. VPM1002 was also shown to be immunogenic; it induced multifunctional CD^{4+} and CD^{8+} T cell subsets, which are thought to play a crucial role in protection against TB.[25,26,27] Regarding multifunctional CD^{8+} T cells, VPM1002 showed a trend of superiority over BCG at comparable dosage. The immunogenicity of VPM1002 as detected by IFN-γ release by stimulated T-cells was dose dependent.[28]

In the **second (Phase 1 b)** clinical trial,**VPM1002-ZA-1.10TB**(ClinicalTrials.gov Identifier: NCT01113281) was given to 24 **healthy male or female adults, all with prior exposure to BCG** and predominantly from the indigenous African population, were vaccinated in South Africa. The safety data concurred with that of the German clinical trial. Data from this study suggest that vaccination with VPM1002 is at least as safe as, and possibly better tolerated than that with an equivalent dose of BCG in healthy volunteers from a TB endemic population. A single vaccination with VPM1002 (2-8 x $10e^5$ CFU) resulted in an immune response to mycobacterium antigens that is at least equivalent to that precipitated by a single vaccination with an equivalent dose of BCG. This was measured by the change from baseline in the IFN-γ concentrations of the whole blood samples, measured by ELISA after stimulation with PPD.[29]

The **third (Phase II)**clinical trial was the first investigation of VPM1002 as a **TB prime vaccine in newborns in a setting with a high burden of TB**(South Africa: ClinicalTrials.gov Identifier: NCT01479972), the population at highest risk of TB and which stands to benefit from a safe and effective new vaccine. The clinical trial, **VPM1002-ZA-2.12TB**, was conducted in Cape Town, South Africa. Around 48 HIV-unexposed, BCG-naive newborn infants were vaccinated with either VPM1002 (n=36) or BCG (n=12). The trial followed an open label, randomized,

controlled design to assess the safety and immunogenicity of a single dose of VPM1002 in comparison to the commercially available BCG vaccine. Neonates of both sexes from an endemic region were vaccinated with VPM1002 2.5 x $10e^5$ CFU (n=36) in comparison to BCG 2.5 x $10e^5$ CFU (n=12). Data from this study suggest that vaccination with VPM1002 is at least as safe as, and possibly better tolerated than that with an equivalent dose of BCG in the target population. A single vaccination with VPM1002 resulted in an immune response to mycobacterial antigens that was similar to that precipitated by a single vaccination with an equivalent dose of BCG in HIV-unexposed, BCG-naive infants, as assessed by the change in IFN-γ concentrations post-vaccination, and cytokine expression on CD4+ and CD8+ T-cells.[11]30

The **fourth** (**Phase II**)clinical trial **VPM1002-ZA-2.13TB**is currently being conducted in South Africa (ClinicalTrials.gov Identifier: NCT02391415). It is a phase II double-blind, randomized, controlled study to evaluate the safety and immunogenicity of VPM1002 as **a TB prime vaccine in comparison with BCG in HIV-exposed and HIV-unexposed, BCG-naive newborn infants.** BCG is routinely recommended to be administered at or around birth by the World Health Organization (WHO), but generally HIV-exposed babies are at increased risk of severe side effects. Due to the observed comparability between VPM1002 (Hyg+) and VPM1002 a clinical bridging study is incorporated into this study. The study has been started in June 2015;recruitment and study follow up is completed.[24]

The **fifth** clinical trial **VPM1002-IN-3.01TBR**(ClinicalTrials.gov Identifier: NCT03152903)**,** is currently ongoing in India. It is a phase II/III double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of VPM1002in prevention of TB recurrence in 2000 adults who were pulmonary TB patients but had received drug treatment and were cured of disease. This study has been approved by Drug Controller General of India (DCGI) and other institutional bodies. The study will also expand the safety database on VPM1002. Few of the sites included are: Mahavir Hospital & Research Centre, Hyderabad; B.J. Govt. Medical College and Sassoon General Hospitals Pune, Maharashtra; Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, Christian Medical College and Hospital, Ludhiana; MV Hopsital for Diabetes Pvt Ltd, Chennai.[24]

Thus, the available preclinical and clinical data revealed that VPM1002 is immunogenic and may be better than available vaccines in terms of safety.[24]

1.4.2 IMMUVAC (Mw)

Immuvac is a heat killed suspension of Mycobacterium w, a nonpathogenic, cultivable atypical mycobacterium. The vaccine is already approved and is marketed by Cadila Pharma for treatment of leprosy cases with MDT and has shown promise of protection in contacts of index leprosy cases. In addition, the contacts also had lower incidence of pulmonary TB and has shown promise when added to DOTS in treatment of polyresistant Category II cases of pulmonary TB.

The product license of this investigational product is under name –Mycobacterium w‖ and is commercially available as Immuvac. It has been renamed as MIP (*Mycobacterium indicuspranii*).

PRIOR NON-CLINICAL AND CLINICAL STUDIES WITH IMMUVAC

Preclinical efficacy and safety

Mycobacterium w (Mw) as stand-alone or adjunct immunotherapeutic in treatment of experimental animal tuberculosis.

In a study conducted on BALB/c mice, the effectiveness of Immuvac was examined as a therapeutic agent with or without the chemotherapy against drug sensitive *M.tuberculosis* H37Rv. The infection was inducted via respiratory route in the mice using the aerosol chamber with a dose of 200 bacilli. After 4 and 6 weeks of the chemotherapy it was observed that Immuvac along with the chemotherapy was more effective to reduce the bacterial load in lungs of the mice post chemotherapy duration of one month (5 days /week). Further, there was significant reduction in the CFU in both lungs and spleen of the animals. This study clearly indicates role of Immuvac as an adjuvant therapy in the tuberculosis management.[31]

Effect of Immuvac immunization in animals on immune cells: p38 marker

Naïve Balb/C mice were randomized in six groups and immunized with 1 mL of PBS in group one, group two to six received 1 mL Immuvac (10^9 cells) intravenous. The group 1 and 2 were sacrificed on day 1, while group three on 7day, group four on 14day, group five on 21day, group six on 28day and spleens were isolated. The Splenocyte were isolated and cultured in RPMI 1640 media with 10%FBS and 1% antibiotics in microtitre plate. After 48 hrs cells were harvested and the MAPK ELISA were performed as per manufacturer‘s instructions, using the commercial kits (Cat no # DYC869-5) from R & D Systems.

The result depicted in the Table below shows p38 level down regulated when immunization with Immuvac cells from 24 h to 28th day. The maximum down regulation of p38 occurs till 14 days. P38 level remains down regulated for the entire period of study (*i.e.* 28 days)[In-house study of Cadila Pharma].

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Table 1: Inhibition of p38 MAPK by *in vivo* stimulation with *Mycobacterium w* intravenous immunization in mice

Normal cells (Splenocytes 10^6)	% inhibition
0 hrs after immunization	-
1 day after immunization	17.4
7 days after immunization	20.2
14 days after immunization	25.1
21 days after immunization	14.1
28 days after immunization	17.3

Resistance to intravenous inoculation of Mycobacterium tuberculosis H37Rv in mice of different inbred strains following immunization with a leprosy vaccine based on Mycobacterium w.

Immuvac was found to provide protection against the tuberculosis for in mice of different strains (Balb/c, C57BL/6 NCrl (Bcgs), C3H/He NCrl and CBA/N (Bcgr) when heat killed 10^7 Mycobacterium suspension was given to the mice in the experiment as immunization. Further, study also suggested that Immuvac appears to have protective action pertaining to the Mycobacterium tuberculosis in the mice whose immune system was less reactive when intravenous BCG injection was given to them.[32]

Clinical trials with Immuvac

Immuvac human data is available from three clinical trials.

First clinical trial was a prospective, randomized, double blind, placebo controlled, multicentric clinical study. The immunotherapeutic potential of Immuvac as an adjunct to ATT in 890 sputum smear positive CAT II pulmonary TB patients was evaluated. Patients were randomized to receive either six intra-dermal injections (2 as 1^{st} dose followed by 4 more doses at 2 weekly intervals till 8 weeks) of heat-killed Immuvac at a dose of 5×10^8 bacilli or placebo once in 2 weeks for 2 months. Sputum smear and culture examinations were carried out initially every 2 weeks and later on at end of treatment and every 6 months for 2 years after RFT. The study results showed that Immuvac was safe with no adverse effects, except the self-limiting, local reaction at the site of inoculation. While sputum smear conversion did not show any statistically significant difference between the two groups, notably higher number of patients (67.1%) in the

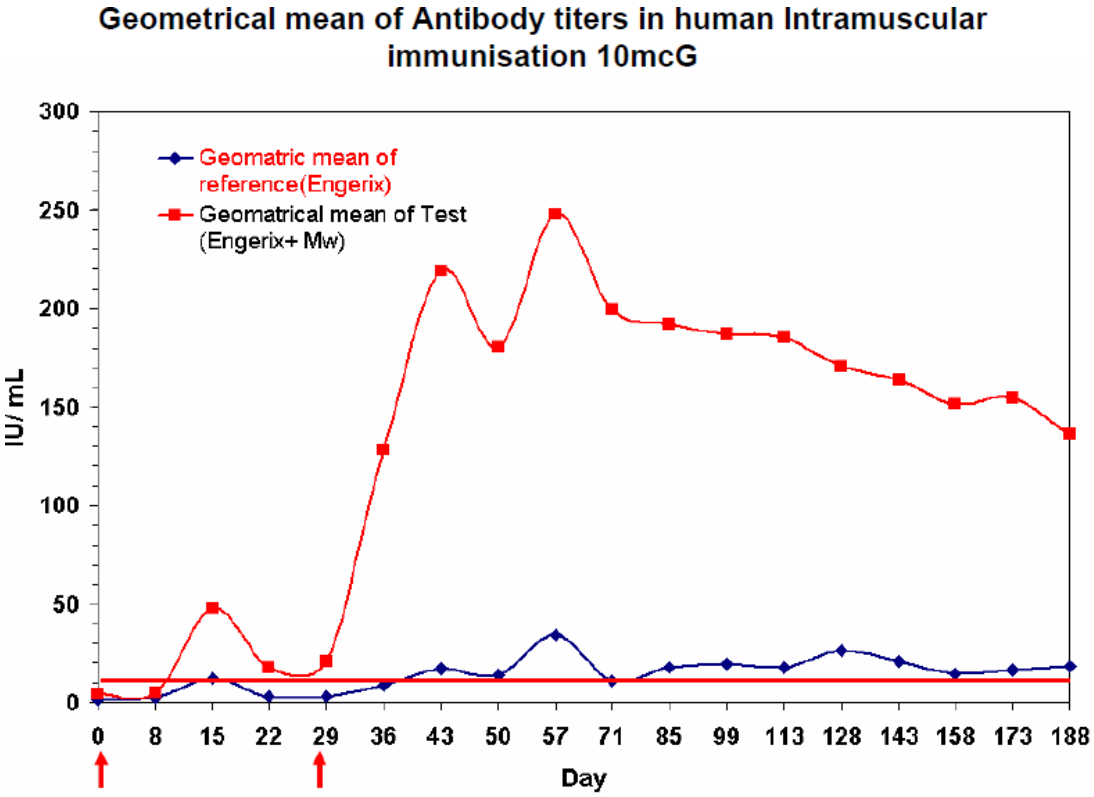
Immuvac group achieved sputum culture conversion at fourth week compared to the placebo (57%) group ($p = 0.0002$), suggesting a role of Immuvac in clearance of the bacilli. The study was funded by Department of Biotechnology, Department of Science and Technology, Government of India.[33]

In the **second** clinical study, which was done earlier, to examine the protective efficacy of Immuvac against tuberculosis was investigated in 28,948 populations belonging to 272 villages in Ghatampur, Kanpur (India) were examined 10 to 13 years after initial vaccination. The vaccinated population were contacts of index cases of leprosy, and they were injected with two doses (1^{st} dose of 1×10^9 heat killed organisms followed 6 months later with a 2^{nd} dose of 5×10^8 organisms) of *Immuvac* 10–13 years ago originally to evaluate its effect against leprosy. The vaccine/placebo was administered to healthy contacts of leprosy patients who had no indication of suffering from tuberculosis. The prevalence and occurrence of PTB was investigated in a blinded manner by an active field survey and also retrospectively by history of ATT received by the subject in the intervening period, which was also supported by analyzing the medical records. A standard clinical and bacteriological criterion was used to confirm diagnosis. Survey results depicted that a total of 69 patients had PTB which included 17 new sputum smear positive cases and 52 previously partially treated (but still active PTB) cases. The difference in the new sputum positive cases between the vaccinated (5/17) and placebo groups (12/17) was noteworthy. Around 75% (52/69) of the cases who had PTB, but had not taken sufficient, complete treatment. All the cases diagnosed during the vaccination period were recorded and re-analysed 10 to 13 years after vaccination. The differences are found to be more significant at 1% level of significance for 1 tail test ($Z>2.59$) when all cases were analysed as a group. Around 12.85% (total number=3036) of the contacts in the study population had BCG scars. In this group, protective effect of BCG against tuberculosis ($p<0.01$) was observed. In the placebo group, the occurrence of TB was 1.11% when compared to 0.70% among those who received Immuvac vaccine ($p<0.01$), and 0.53% in subjects who had BCG scars had received Immuvac. It was thus concluded that Immuvac has protective effect against pulmonary tuberculosis besides leprosy. The study was funded by Department of Biotechnology, Government of India.[34]

In a **recent** clinical study, IMMUVAC as adjuvant shows best results when administered on Day 0 and 1 month in humans. The human volunteers were immunized intramuscularly with 1 ml of Engerix-B (n = 15) or 1 ml of Engerix B mixed with 108 cells of Immuvac (n = 32) at two sites, one on each arm. Blood samples were collected at regular intervals for assessment of antibody titers. All the volunteers received a booster injection on day 28. The protective titers in Immuvac adjuvanted group between day 8 and day 15 reached 5 fold above protective levels, while the commercial preparation just managed to achieve protective levels. The titers were further elevated in Immuvac adjuvanted group to well above 20 fold higher than the protective levels after first booster and the levels were maintained above 10 fold over a period of 8 months with peak on 60^{th} day. The commercial preparation alone showed protective antibody titers two fold

higher than the protective titers at the end of study. The difference between the antibody titers of the two groups in the entire study was always maintained at 6 fold in the beginning starting from day 21 to day 233 (~8 months). The difference was even higher with a peak on day 70 at more than 18 fold. In humans the results suggested that the antibody titers reached were much higher in the Immuvac adjuvanted group at any point of time and the response was faster, stronger and long lasting than in the absence of Immuvac.[In-house study of Cadila Pharma].

Figure 1: Geometrical means of Antibody titers in human intramuscular immunization 10mcG



From the above mentioned data we can conclude that Immuvac vaccine merits serious consideration as one of the alternatives when new generation TB vaccines are tried in randomised controlled trials and population-based observational studies.

Thus in the present study we propose to test all of these vaccine candidates – VPM1002 and Immuvac in a phase III clinical trial aimed at prevention of TB infections from newly diagnosed TB index cases among Indian people.

Hence, we have designed a clinical trial to decide whether individually each of the above mentioned two TB vaccine candidates will lead to 50% eradication in the presumed incidence of 3% (*reference: based on study done by NIRT, Chennai, India -"Incidence of tuberculosis disease among household contacts of adult pulmonary tuberculosis patients in India- a multi centric cohort study": the results of the study demonstrated the cumulative incidence of TB as 1.5% and TB incidence density as 8.93/1000 person-years follow-up*) in 38 months among healthy household contacts of newly diagnosed sputum positive TB patients when compared with placebo.

POST-TRIAL BENEFIT

It is preferred that the household contacts are vaccinated at the earliest after diagnosis of TB in the index case to prevent breakdown of TB disease. The participants in the placebo arm in this clinical trial will not be benefited if the vaccine is proved efficacious since by then they would have crossed the period of vaccination post TB diagnosis in the index TB patient. However, the contacts in the placebo arm will be benefitted by close follow-up for early diagnosis of TB disease and appropriate treatment in this trial.

The Sponsors and PIs will make attempts to ensure that the vaccines VPM1002 and Immuvac are made available to the household contacts of TB patients in future in India if they are found to be beneficial in this trial.

2 HYPOTHESIS, OBJECTIVES AND BASIC STUDY DESIGN

STUDY HYPOTHESIS

We hypothesize that individually each candidate (VPM1002 and Immuvac) will lead to 50% reduction in anticipated incidence of TB among household contacts of newly diagnosed PTB patients as compared to placebo.

OBJECTIVES

PRIMARY OBJECTIVE

To evaluate the efficacy of VPM1002 and Immuvac by comparing reduction in the incidence of TB over 3-year period among Indian healthy household contacts of newly diagnosed sputum positive PTB patients vaccinated with VPM1002 and Immuvac in comparison to placebo.

SECONDARY OBJECTIVES

To evaluate the efficacy of VPM1002 and Immuvac in prevention of LTBI in healthy household contacts of newly diagnosed sputum positive PTB patients in comparison to placebo[in a sub-set of population at Sites at– Delhi (NCR), Hyderabad and Chennai].

To evaluate the safety of VPM1002 and Immuvac in Indian healthy household contacts.

To evaluate the immunogenicity of VPM1002 and Immuvac in healthy household contacts as compared to placebo against tuberculosis.

2.3 STUDY DESIGN

The study is designed as a multicenter, double-blinded, randomized, placebo-controlled trial with three groups of healthy household contacts of PTB patients (approximately n= 4000per group) receiving either of the vaccine candidates (VPM1002/Immuvac) or placebo.

Table 2: STUDY ARMS

Study Arm 1	Candidate vaccine 1: VPM1002 + Placebo
Study Arm 2	Candidate vaccine 2: Immuvac
Study Arm 3	Candidate vaccine 3: Placebo

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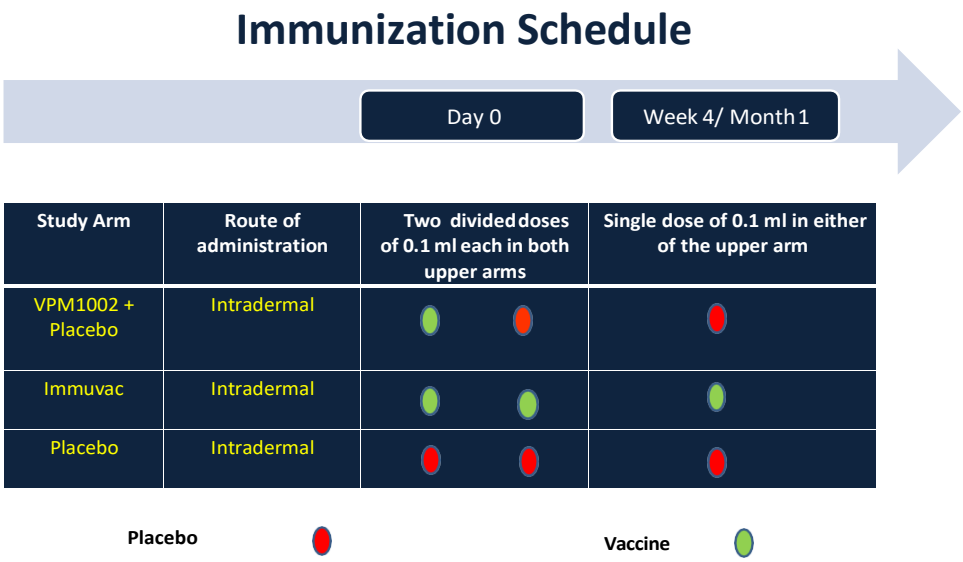
Figure 2: Immunization Schedule



STUDY SITES: Delhi-NCR – AIIMS, New Delhi(Civil Hospital, Ballabhgarh;RajanBabu TB Hospital, Delhi, Nehru Nagar TB Hospital Delhi),Safdarjung Hospital, Delhi, NITRD, Delhi; Telangana – BMMRC, Hyderabad (Secunderabad Tuberculosis Unit, District TB Centre,

Hyderabad); Maharashtra – NARI, Pune (Gadikhana Hospital, Pune); Group of T.B.Hospital,Sewree, Mumbai& IGMC, Nagpur(reserved site); Karnataka – NTI, Bengaluru (KC General Hospital, Bengaluru; Jayanagara Hospital, Bengaluru; CV Raman Hospital, Bengaluru; Govt. General Hospital, Yelahanka, Bengaluru); Odisha – RMRC, Bhubaneshwar, AIIMS, Bhubaneshwar; and Tamil Nadu – NIRT, Chennai (Government Raja ji Hospital, Madurai);

Gujarat – GMERS, Vadodara (reserved site); Chandigarh– PGIMER(reserved site).

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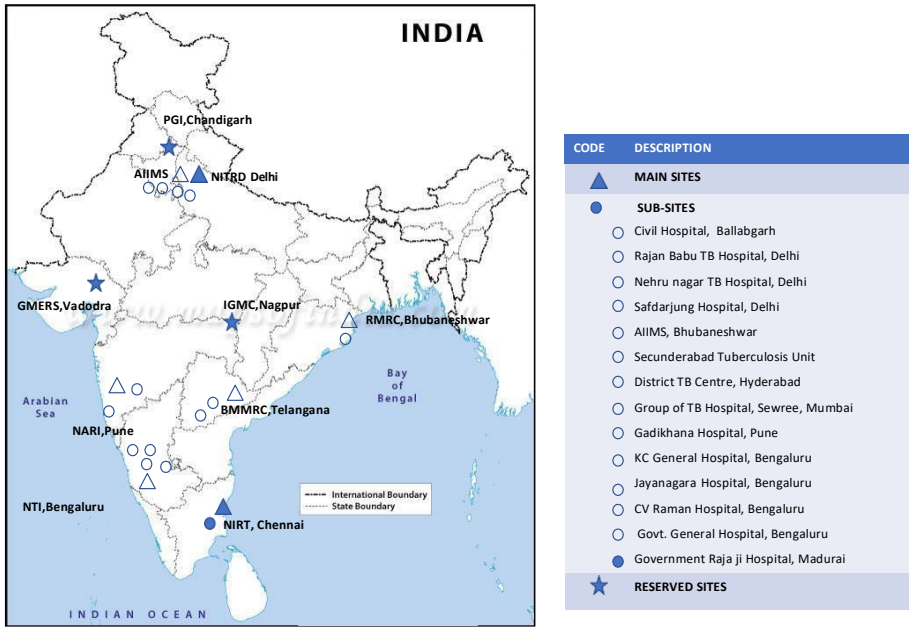
Figure 3: STUDY SITES MAP



3 STUDY POPULATION

Healthy household contacts (refer to section 7.4 for definition) of newly diagnosed index sputum positive pulmonary TB patients(within 4 weeks of anti-TB treatment initiation in the Index TB patients).

ELIGIBILITY

INCLUSION CRITERIA

Fulfillment of all of the following criteria is required to accept aparticipant in the study:

i. Healthy household contacts age ≥ 6 years at the time of enrollment.
ii. No evidence of active TB disease during screening – Normal chest radiograph with no abnormalities and no bacteriological positivity by smear testing for *M.tb*
iii. Female participants who are currently using reliable methods of contraception (barrier methods and intrauterine contraceptive device), with a negative urine pregnancy test during screening and agree to informed compliance of contraceptive method until at least 4 months post-vaccination.

iv. The participant must be able and willing to comply with the study protocol, available and willing to complete all the study assessments and must have signed an Informed Consent Form.**
v. Participant agrees to stay in contact with the study site for the duration of the study, and provide updated and an alternate contact information.
vi. Has general good health, as confirmed through medical history and medical evaluation (which includes physical examination and laboratory tests).

Note: **For children less than 7 years of age, parental consent is sufficient. For children between 7 (84 months and above) and 11 years of age, oral assent will be obtained in the presence of parent/Legally Acceptable Representative. Children between 12 and 18 years of age, should give written assent. If the study participant becomes 13 years old during the course of the study, then he/she must be willing to provide a written assent in addition to parent/LAR consent. During the course of the study period, when the child crosses the stipulated age band, re-consent will be taken appropriately.

EXCLUSION CRITERIA

Any of the following will exclude a participantfrom taking part in the study:

i. Any chronic febrile illness with oral temperature > 100°F on the day of randomization.
ii. Prior or present anti-TB treatment.
iii. Any laboratory abnormalities (haematological and biochemical), at the time of screening, which is of clinical significance as determined by the Investigator.
iv. Pregnant and / or lactating female participants.
v. Presence of any illness requiring short hospital referral (temporary exclusion).
vi. Reactive serology for HIV.
vii. Any confirmed or suspected immunodeficient condition based on medical history and physical examination and a family history of congenital or hereditary immunodeficiency.
viii. History of chronic renal failure/dialysis, silicosis, gastrectomy, jejunoileal bypass, solid organ transplantation such as renal or cardiac transplants, carcinoma of the head and neck, and disorders of the liver, kidney, lung, heart, or nervous system, or other metabolicinflammatory conditions, psychiatric, occupational problems that make it unlikely the volunteer will comply with the protocol as determined by the local investigator.
ix. History of previous administration of experimental MTB vaccines.
x. History of administration of any immunoglobulins, any immunotherapy (antineoplastic chemotherapy, radiation therapy, immunosuppressants to induce tolerance to transplants, and corticosteroids use) and/or any blood products within the 3 months preceding study vaccination, or planned future administrations during the study period. Participants on inhaled/topical steroids may be permitted to participate in the study.
xi. Participation in any clinical trial within 3 months prior to and/or planned concurrent participation in another interventional clinical trial at any point throughout the entire timeframe for this study.
xii. History of allergic reactions or anaphylaxis to any vaccine or component of the vaccine.

xiii. Presence of any severe systemic/autoimmune disorders as determined by medical history and / or physical examination/ or lab investigations at the time of screening, which in the judgment of the Investigator would compromise the participant‘s health or is likely to result in nonconformance to the protocol or a participant‘s ability to give written informed consent/assent.

4 STUDY PROCEDURES

The study will be initiated only after the approval from the DCGI and the Institutional Ethics Committee (IEC) from the respective study sites. The details of the sputum positive PTB cases presenting to the DOTS centre/clinic/OPD of the implementing institute in the last 4 weeks will be obtained. The index case will be contacted and visited to explain about the study and required to provide details of HHC. All relevant details of the index case such as name, age, gender, address (corresponding and permanent), contact number, date of diagnosis and initiation of anti-tuberculosis treatment (ATT), sputum smear grade and drug sensitivity pattern will be recorded in site records. A list of household contacts will be obtained from the index case by the health staff. Household contacts who will be willing to be screened will be registered.

The study procedures will include three phases: screening phase, enrollmentphase and follow-up phase.(All the participating sites will make provision for enrollment and follow-up on Sundays/Holidays to ensure compliance/follow-up by study participants.)

SCREENING PHASE

Visit 1: Screening (6 weeks of detection of PTB or within 3 weeks of anti-TB treatment initiation in the Index TB patient)

A screening consent will be taken from the willing participants after describing the rationale of the study. This will include a general overview of the trial purpose and procedures as well as the samples to be collected at this visit. Each participant will be asked to sign (or provide a thumb print in the presence of a witness if illiterate) for the screening procedures and will be given a copy of the signed Informed Consent Form (ICF) and a Participant Information Sheet (PIS) to take home.If the participant qualifies for the study criteria, a written /oral consent or assent (as applicable)will be obtained before enrolling the participant in the study.Audio-video recording of the consent / assent process will be done for vulnerable participants (children less than 12 years of age).

The screening evaluation will aim at collecting the following information and performing the following assessments:

- Demographic data
- Medical history
- History of Concomitant medications

- Physical examination
- Two spot Sputum samples (at 1 hour interval) will be collected (wherever available) for AFB staining (as per Revised National Tuberculosis Control Programme [RNTCP] guidelines). Participant should have negative sputum smear result at the time of randomization. (Sputum will be collected if available. Since the participants are healthy household contacts there are chances of not having cough or expectoration)
- Blood collection (3-5 ml [for participants age 6-12 years] or 7 ml [for participants age >12 years]for Hemogram, Renal Function Test [Serum Creatinine and Serum Urea], Liver Function Test[SGOT, SGPT, Alkaline Phosphatase, Serum Bilirubin] andHIV ELISA.Blood collection (5- 7 ml for age 6 to 12 years and 10 ml for >12 years) for Immunological tests.
- Random Blood Sugar test.
- Blood for immunological testing (5-7 ml for age 6 to 12 years and 10 ml for >12 years) for immunological testing will be collected from 1500 (first 500 consecutive enrolled participants from each of 3 sites - AIIMS New Delhi, ICMR-NARI Pune, ICMR-NIRT Chennai) study participants at screening.
- Chest X-ray will be performed at screening and month 2 post first dose of vaccination, thereafter once a year till month 38. A postero-anterior view will be done in all and an additional lateral view will be done in children <14 yrs. Amongst children (6-12yrs) X-ray will be performed only at baseline and in suspected cases. For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the study co-ordinator / Principal Investigator decide its necessity, in case of presence of clinical symptoms of TB in the pregnant females.
- Urine Pregnancy test will be carried out in females of child bearing age.
- Tuberculin Skin Test (TST) will be done at screening using a standard product PPD-S (3 TU) in all study participants at sites - Delhi (NCR), Hyderabad and Chennai. Those who are TST positive (induration ≥ 10 mm) at screening will be worked up as per study schedule.

Methodology of TST

The tester will administer exactly 0.1 ml of tuberculin intra-dermally (Mantoux technique) on the mid-anterior aspect of the left forearm. The left forearm is to be chosen by convention to avoid error in locating the test site during reading. However, in case of injury or scar on left forearm, the test will be given on right forearm and a note is made in remarks column of child card. Similarly, the anterior side is preferred since in people with dark complexion, the test site may be difficult to locate if given on dorsal side.

The injections are to be given with 1-ml disposable tuberculin syringe with graduations of one-tenth of a mm, fitted with a 26-gauge needle of 1 cm length and 20o bevel. The needlepoint will be inserted with the bevel upward in the superficial layer of the skin of the forearm while the skin is slightly stretched in the direction of the needle. The syringe should be held by the barrel; the plunger should not be touched until the needlepoint has been satisfactorily inserted. A volume of 0.1 ml will be slowly injected and the finger should be removed from the end of the plunger before the needle is withdrawn.

The test as recorded as satisfactory if it raises a flat pale wheal with clearly visible pits and well demarcated borders. It is recorded as unsatisfactory in case of leakage or if it is a subcutaneous injection as shown by a less anemic dome-shaped papule rather than a flat pale wheal) at screening (visit 1).

Reading of tuberculin reactions

The reading of tuberculin reaction should be undertaken by readers about 72 hours after administration of the test and should be captured in the case report form. All efforts should be made to read the reactions at about 72 hours and only in case of utmost exigency it may be undertaken at any other time between 48-72 hours. While reading the reactions, the BCG scar status of the child should not be known to the reader.

The reader identifies the margins of induration by carefully palpating the edges of the reaction. The induration may be easily recognizable when firm and well circumscribed or it may be a soft ill-defined swelling in which case its margins must be identified very carefully. The maximum transverse diameter of the induration is then measured in millimeters, using a transparent ruler. A small ruler of 10-15 cm length and calibrated in mm should be used for this purpose. Care is taken not to measure the erythema. The reader should also examine the test site for presence of bullae, vesicles, necrosis or lymphangitis.

Transport of PPD vials and cold chain

The cold chain has to be maintained during supply and transportation of tuberculin vials from the point of manufacture to the point of usage in the field.The vaccine will be

directly shipped by the manufacturer to the sites. During storage, PPD vials should be refrigerated at 2-8 C and not allowed to freeze. Vaccine carriers should be used to transport tuberculin vials, which must be used within the expiry period as specified. During the field work, maximum care should be taken to protect the tuberculin from heat and sunlight and vials once opened must be used on the same day or at latest on the following day

Demographic data: This will includeage, gender,date of birth, weight (kg), and height (m), body mass index (kg/m^2), alcoholconsumption/substance use and smoking status/tobacco use. All sites should maintain the name, address [corresponding and permanent] and contact numbers of all participants in the site records

Medical history: This will include history of participation in a drug research study/clinical trial, or other illness. Also, it will include details of current medication if any, past medical/surgicalhistory, previous hospitalizations, history of any allergy to food or drugs, menstrual history (in case of females of child-bearing age), and family history, including history of immunodeficiency in any household.

Physical examination: Physical examination will include vital signs (axillary body temperature, pulserate,blood pressure and respiratory rate), previous BCG vaccination scar and general examination including pallor,odema,cyanosis,lymph nodes and systemic examination includingcardiovascular system (CVS), respiratory system (RS), gastrointestinal system (GIS), genito-urinary system (GUS), central nervous system (CNS), and musculoskeletal system.

Furthermore, the participant will be enquired about TB symptoms (including but not limited to: persistent cough, hemoptysis, fever, unintended weight loss, fatigue or lethargy, night sweats, or pleuritic chest pain).

Review of laboratory results: This will include evaluation of lab test results of Hemogram,LFT, RFT, RBS, HIV,Bacteriological results and chest X-ray for any abnormality.

All the samples (sputumandblood) will be collected by a trained clinical research nurse/technician at the hospital site at the specified intervals(study schedule page).

In case HIV ELISA test is positive, the participant will be excluded from the study and will be referred to Anti-retroviral treatment clinic.

If sputum is positive for AFB then such participant will be labeled as inappropriate enrolment (co-prevalent TB). He/she will be referred for further investigations and treatment as per RNTCP guidelines and the investigator will ensure and follow up the participant‘s treatment.

DIARY CARD

At every visit, the study participant will be issued a diary card by Site Principal Investigator/Medical Officer for recording solicited adverse events, at the time of screening and at all the visits till 2 months post first dose of vaccination. The study participant will also be

issued a diary card for recording unsolicited adverse events, at the time of screening and at all the visits till completion of follow up post first dose of vaccination. In one page diary card the front page contains information need to fill about adverse events and the back page have instructions which are required to be followed for filling the diary card.Necessary training to complete the diary card will be provided. In case of children, parents or guardian will be issued the diary card. In case of old age groups, diary card updating training should be provided to legal family representative (adults/relative). The study nurse/investigator will collect and review the diary card and will transcribe the information about adverse events into the Case Report Form.

ENROLLMENT AND RANDOMIZATION

After all the screening assessments are complete and the study investigator confirms that all of the protocol defined eligibility criteria are met, participants will be enrolled in the study arm following centrally randomized allocation to either VPM1002-Placebo/Immuvac/Placebo arms.

The participants will be questioned regarding any new TB symptoms since the Visit 1. Thereafter, the medical history and physical examination will be carried out. Information on concomitant medications will be captured. In female participants of childbearing age, urine pregnancy test will be repeated.

Visit 2 (Day 0: as soon as possible or within one week of screening): Randomization

- Demographic details (age, gender, date of birth, weight [kg], and height [m], body mass index (kg/m^2), alcohol consumption/substance use and smoking status/tobacco use, address (corresponding and permanent), contact number, alcohol and smoking status) will be captured.
- Urine Pregnancy test will be carried out in females of child bearing age.
- The eligible participants will receive VPM1002-Placebo/Immuvac/Placebo as an intradermal injection as per central randomization.
- In Study Arm 1, VPM1002 and Placebo will be administered at day 0 and Placebo will be administered at 4 weeks (month 1).
- In Study Arm 2, Immuvac will be administered in two divided doses at day 0 and a single dose at 4^{th} week (month 1).
- In Study Arm3, Placebos will be administered in two doses at day 0and a single dose at 4^{th} week (month 1).

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VACCINATION PHASE

Study Arm 1 (VPM1002 + Placebo)

Dose 1 (day 0): 0.1 ml reconstituted solution (2-8 x 10^5 CFU) of VPM1002 will be administered intradermally in either of upper arm at the insertion of the deltoid.

ml of Placebo will be administered intradermally in the upper arm, at the insertion of the deltoid.

Dose 2 (04 weeks after the first dose): 0.1 ml of Placebo will be administered intradermally at least 2 cms. away from first injection siteon the same arm (only pharmacist will know the dose 1 placebo arm*)

Study Arm 2 (Immuvac)

Dose 1: At day 0: 0.2ml (1 x 10^9 CFU)of Immuvac will be administered intradermally in two divided dose of 0.1 ml each in both upper arms at the insertion of deltoid.

Dose 2: 04 weeks after the first dose: 0.1 ml (0.5 x 10^9 CFU) of Immuvac (single dose) is administered intradermally at least 2 cms. away from first injection site.

Study Arm 3 (Placebo)

Dose 1: At day 0: Two doses each of 0.1 ml of Placebo will be administered intradermally in both upper arms at the insertion of deltoid.

*The Pharmacist will mark R/L (for right and left arm) while filling the syringes with IP and will keep a note of it with details of the arm in which placebo is given for each subject during 1st dose of the IP. He will ensure that the subject gets the 2nd dose of placebo in same arm as during 1st dose.

Dose 2: 04 weeks after first dose: 0.1 ml of placebo (single dose) will be administered intradermally at least 2 cms. away from first injection site.

Visit 2 (Day 0: as soon as possible or within one week of screening): Vaccination

- The first dose of vaccination will be given.
- Demographic details (age, gender, date of birth, weight [kg], and height [m], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Urine Pregnancy test will be carried out in females of child bearing age.
- Post-vaccination, all study participants will be observed at the clinic site for sometime (at least 1 hour) for any immediate reactions. In case of no adverse event, the participant will be issued a diary card.

- Before check-out post-vaccination, vital signs will be recorded and the local examination of the injection site will be done.
- Participants will be informed about the follow up visit.

Visit 3: Day 14 (with a -7 to +7 days window) after first dose of vaccination:

- The participants will visit the study clinic 14 dayspost-vaccination for assessment which will include demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use); medical historyand physical examination and local examination of vaccination site.
- The participant will be interviewed for any suspectedTB symptoms and concomitant medication.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will review the diary card for safety reporting (in case any adverse event or serious adverse event has occurred within 14 days after vaccination).
- Participants will be informed about the follow up visit.

Visit 4: 4 weeks/Month 1 (*i.e*. 30 days with a -7 to +14 days window) after first dose of vaccination:

- The participants will visit the study clinic 4 weeks/Month 1 post-vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Urine Pregnancy test will be carried out in females of child bearing age.
- Detailed medical history will be taken with special mention to any adverse events,suspected TB symptoms, menstrual history for females (child-bearing age), concomitant medications followed by physical examination.
- In female participants, pregnancy test will be carried out. All study participantswill receive 2nd dose of vaccine/placebo as per the study schedule.
- After vaccination, study participants will be observed at the clinic site for sometime (at least 1 hour) for any immediate reactions.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary card for data entry.

If any solicited reaction persistsat week 4/ month 1, surveillance will be continued and recorded on the diary card until reaction is resolved/stabilized.

- Participants will be informed about the follow up visit.

Visit 5: 6 weeks (*i.e*. 42 days with a -7 to +14 days window) after first dose of vaccination:

- The participants will visit the study clinic 6 weeksafter first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken including questions asked for any adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- The field worker will telephonically fol low-up weekly for any adverse events and serious adverse events. The study personnel will review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 6: 8 weeks/Month 2 (*i.e*. 60 days with a -7 to +14 days window) after first dose of vaccination:

- The participants will visit the study clinic 8 weeks/Month 2 post first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken including questions asked for any adverse events, suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples(at 1 hour interval) will be collected for AFB staining.
- Chest X-ray will be done to exclude any abnormality.
- Blood for immunological tests (5-7 ml for age 6 to 12 years and 10 ml for >12 years) will be collected, labeled and immediately processed by the immunology department at the three sites namely AIIMS, New Delhi; ICMR-NARI, Pune; and ICMR-NIRT, Chennai.
- Hemogram, LFT/RFT may be repeated, if PI feels necessary.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary card for data entry.

If any solicited reaction persists on day 60, surveillance will be continued and recorded on the diary card until reaction is resolved/stabilized.

- Participants will be informed about the follow up visit.

IMMEDIATE POST-VACCINATION REACTOGENICITY ASSESSMENT

After vaccination, all study participants will be kept at the clinic site for sometime (at least 1 hour) to check for anyimmediatereactogenicity. Before check out post-vaccination, vital signs and local examination of the injection site will be done.

Study participant will be asked to promptly contact the site staff in the event of any illness occurring after vaccination.

FOLLOW-UP PHASE

Visit 7: At Month 6th(*i.e*. 180 days with a -7 to +14days window) after first dose of vaccination:

- The participants will visit the study clinic 6 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention to any adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples (at 1 hour interval) will be collected for AFB staining.
- TST will be repeated at sites - Delhi (NCR), Hyderabad and Chennai. In individuals wherein TST was negative (induration <10 mm) at screening, TST will be repeated at Month 6. The number of participants developing LTBI (TST positive: induration ≥10 mm) will be estimated at the end of 6 months and will be followed up as per study schedule.

  Those who are TST negative (induration ≤10 mm) at Month 6 will be followed up as per study schedule.
- Blood for immunological tests (5-7 ml for age 6 to 12 years and 10 ml for >12 years)willbe collected, labeled and processed by the immunology department.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 8: At Month 10th(*i.e*. 300 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 10 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention to any adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 9: At Month14th(*i.e*. 420 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 14 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention to anyadverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples(at 1 hour interval) will be collected for AFB staining.
- Chest X-ray will be done to exclude any abnormality.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 10: At Month18th(*i.e*. 540 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 18 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.

- Medical history will be taken with special mention to any adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 11: At Month 22nd(*i.e*. 660 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 22 months after first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention toany adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples (at 1 hour interval) will be collected for AFB staining.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 12: At Month 26th(*i.e*. 780 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 26months post first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention toany adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Chest X-ray will be done to exclude any abnormality.

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- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 13: At Month 30th (*i.e*. 900 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 30 months after first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention toany adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples (at 1 hour interval) will be collected for AFB staining.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 14: At Month 34th (*i.e*. 1020 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 34 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention toany adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events. The study personnel will collect and review the diary cardfor safety reporting.
- Participants will be informed about the follow up visit.

Visit 15: At Month 38th (*i.e*. 1140 days) after first dose of vaccination (each with a -7 to +14 days window):

- The participants will visit the study clinic 38 monthspost first dose of vaccination.
- Demographic details (age, gender, date of birth, weight [kg], and height [cm], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use) will be captured.
- Medical history will be taken with special mention toany adverse events,suspected TB symptoms and concomitant medications followed by physical examination.
- Two spot Sputum samples (at 1 hour interval) will be collected for AFB staining.
- Chest X-ray will be done to exclude any abnormality.
- The field worker will telephonically follow-up weekly for any adverse events and serious adverse events.The study personnel will collect and review the diary card for safety reporting.

During follow-up period, if TB is diagnosed within 2 months (± 7 days or as early as reported) after first dose of study vaccination then such participant will be labeled as Co-prevalent TB and withdrawn from the study and will be excluded for outcome analysis, yet followed up for safety till the end of study and will be provided treatment by Site Principal Investigator/Co-investigator as per RNTCP guidelines, and the investigator will ensure follow-up until the treatment completion. A close out visit will be offered to this participant. During close out visit medical history and physical examination will be carried out.

At a minimum, all participants will be followed for 2 months post vaccination.

Telephonic follow up will be done for all the visits. Follow up will be done on weekends and holidays to ensure protocol compliance for the convenience of participants. In case the participant does not report to site for follow up visit, a visit to the participant‘s home will be undertaken.

An unscheduled visit can be conducted at any time during the trial period for protocol compliance (e.g. in case of missed visits, safety reasons (adverse events), sample collection in case of previous sample deterioration / mishandling, inappropriate health status etc.).

Investigations for study participants with suspected TB during follow up:

If a participant develops TB symptoms (including but not limited to: persistent cough, hemoptysis, fever, unintended weight loss, fatigue or lethargy, night sweats, or pleuritic chest pain) during the follow-up after vaccination, he/she will be advised to report to the study clinic.

A detailed medical history with detailed thorough physical examination will be done.

Based on the results participants will be classified as follows:

In suspected PTB, the study investigator will undertake investigations (bacteriological, microbiological and radiological) as per RNTCP guidelines for confirming PTB. If confirmed, the study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion.

In suspected EPTB, the study investigator will undertake required investigations for confirming diagnosis of EPTB as per RNTCP guideline. If confirmed, the study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion.

In case of presence of symptoms, radiological abnormality and extrapulmonary cases without laboratory confirmation but negative AFB, the participant will be labeled as clinically diagnosed TB. The study investigator will provide the participant the required treatment as per RNTCP guidelines, and will ensure follow-up until the treatment completion.

If the participant is not diagnosed with TB (PTB or EPTB) as per RNTCP guidelines, he/she will be continued into the study and followed up till the end of the study period

Concomitant vaccinationsand Other Treatments

At each study visit, the Investigator/designee should ask about concomitant vaccinations/medication.Other medications that are considered necessary for participant‘s welfare and that will not interfere with the vaccine may be given at the discretion of the Investigator (prohibited medication is indicated below).

The following drugs/vaccines are prohibited during the study:

- Any investigational or non-registered drug or vaccine within 30 days prior to administration of study vaccine as well as during the entire study participation.
- Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying agents during the study period. For corticosteroids, this means prednisone or equivalent ≥0.5 mg/kg/day. However, topical or inhaled steroids will be allowed.

- Administration of any vaccine during the study period.
- Administration of immunoglobulin and/or any blood products during the study period.

History of receipt of vaccines or medications such as other live vaccines, immune-modifying agents, immunoglobulin‘s and blood or blood products taken 30 days prior to vaccination must be captured with trade name and/or generic name, dose, indication, start and end dates.

Any of the medication taken at any time during the study participation must be captured with trade name and/or generic name, dose, indication, start and end dates.

Administration of all rescue medications must be recorded in the appropriate section of the electronic Case Report Forms (eCRFs).

Safety Follow-Up

Safety assessments of solicited adverse reactions [local (pain, fever, erythema, swelling, ulceration, subcutaneous abscess, induration, blister formation) and regional lymphadenopathy] and unsolicited events during each scheduled visit or during unscheduled visit/s (the participants will be instructed to report to site in case of any adverse event or serious adverse events). In case of lost to follow up, every possible effort will be made to contact the lost to follow up participant.

All serious adverse events will be recorded and reported, occurring at any time, throughout follow period.

Study Schedule

The study schedule of this trial is provided in Appendix 1.

Withdrawal and Early Termination From The Study

The participants may be withdrawn from the study for any of the following situations:

- If aparticipant wishes to withdraw consent and stop participation.
- If a participant moves away from the study site permanently and is not willing to continue participation.
- If, in the Principal Investigator‘s (PI‘s) opinion, the further participation in the study may be detrimental to the participant‘s health.

In all such cases, the participant will be withdrawn from the study and the reason for withdrawal will be documented in an appropriate section of the eCRF. However, the data collected up to the last contact will be part of the analysis.

All participants who withdraw early from the study for any reason will be encouraged to follow-up until the end of study for complete assessments. At close-out visit medical history and physical examination will be carried out for all participants.

PI should ensure that after the participant withdraw from study, he/she should be in a soundphysical and mental health and further treatment provided to the study participant should be unbiased and as per PI‘s clinical opinion and participant‘s condition.

Premature Termination of The Study

The Sponsor(DG, ICMR and Secretary, DHR)may terminate the trial in consultation with DSMB for safety, administrative, or other reasons. Documentation explainingpremature termination of the study must be forwarded to the site, regulatory authority, DSMBand Ethics Committees of all participating sites.

The Sponsor reserves the right to terminate or curtail this clinical study at a site or all sites for any reason (s), including but not limited to the following:

- Risk to participants‘ safety.
- Adverse events occur with such severity and frequency that the proposed schedule can no longer be adhered to.
- The scientific question is no longer relevant or the objectives will not be met (*i.e.* slow accrual).
- Failure to comply with Good Clinical Practice (GCP) or terms of Clinical Trial Agreement.
- Risks that cannot be adequately quantified.
- Ethical concerns raised by the local community or local medical care/health care authorities.
- Failure to remedy deficiencies identified through site monitoring, substandard data or failure to meet identified Sponsor performance standards.
- The Sponsor decides to discontinue the development of the formulation.
- It becomes apparent that participant enrollment is unsatisfactory with respect to quality and/or quantity.
- Data recording is inaccurate and/or incomplete on a longterm basis.
- Lack of performance or adherence to GCP can lead to termination of a study site. In such an event, the study site will continue to follow the enrolled participants as per the study protocol, however, the deficit enrollments will be distributed to other well-functioning sites.

If the study is prematurely discontinued by the Sponsor for any reason, a summary report will be submitted to the DCGI. The summary report will provide a brief description of the study, the number of participants exposed to the vaccine, dose and duration of exposure, details of adverse drug reactions if any, and the reason for discontinuation of the study or non-pursuit of the new drug application.

5. LABORATORY EVALUATIONS

5.1 COLLECTION OF BLOOD

- At the time of screening, 3-5 ml (for participants age 6-12 years) or 7 ml (for participants age >12 years) of blood sample will be collected from all the participants for Liver Function Test (SGPT, SGOT, Alkaline Phosphatase and Serum Bilirubin), Renal function test (Creatinine and Urea), Hemogram and Human Immunodeficiency Virus (HIV) testing (Enzyme Linked Immunosorbent Assay [ELISA]).
- Atvisit 1 (screening) andat visit 6 (month 2)blood for immunological tests (5-7 ml for age 6 to 12 years and 10 ml for >12 years)willbe collected and labeled.
- An experienced phlebotomist will collect blood from a vein under aseptic techniques.Laboratory personnel involved in testing plasma/PBMC samples will be blinded to the vaccination of the study participant.
- All fresh blood samples will be processed as soon as possible after collection. Storage of samples is not advisable.

IMMUNOGENICITY ASSESSMENTS

Immunological assessments will allow us to know the immunological profiles that will be maximally benefited by vaccination.

Blood for immunological tests (5-7 ml for age 6 to 12 years and 10 ml for >12 years)willbe collected from 1500 (first 500 consecutive enrolled participants from each of threesites*viz.*, AIIMS, New Delhi;ICMR-NARI, Pune;ICMR-NIRT Chennai) study participants at screening. Of the 1500 study participants, only 450 study participants (first 150 consecutive enrolled participants from each of 3 sites) will be followed at month 2 and month 6 for estimation of immunological parameters. Those who have developed PTB/EPTB will also be followed up during the course of study.

The study nurse collect blood sample from participants at various time points, provided that the participant has given the informed consent. The consent form clearly provides the information

regarding collection of the blood samples at all time points and also the quantity of the samples that would be collected.

All fresh blood samples will be processed as soon as possible after collection. Storage of samples is not advisable.

Only ICMR-NIRT, Chennai would store additional samples (blood, plasma, and serum) – well characterized and labeled, at their own cost for future studies.

BIOHAZARD CONTAINMENT

As blood-borne pathogens can infect through contact with contaminated needles, blood, and blood products, appropriate precautions will be ensured by all personnel in shipping and handling of all specimens for this study as recommended. All biological specimens will be transported using appropriate packaging. Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

6. INVESTIGATIONAL PRODUCTS (IP)

TEST AND COMPARATOR VACCINES

Table 3: INVESTIGATIONAL PRODUCTS

Test Vaccine: **VPM1002**	The active ingredient of the recombinant BCG vaccine, VPM1002is *Mycobacterium bovis*rBCGΔureC::Hly+, freeze-dried and standardized to number of viable mycobacteria (CFU) per application.
Immuvac	Immuvac is a heat killed suspension of *Mycobacterium w*,a non-pathogenic, cultivable atypical mycobacterium.
Comparator: **Placebo**	Aqueous solution containing thiomerosal (0.1 mg/ml), sodium chloride (pyrogen free – 9 mg/ml) and water for injection (q.s. to 1.0 ml).

Investigational Product

i. VPM1002

The Investigational Medicinal Product (IMP) is a formulated, lyophilized cake of live recombinant *Mycobacterium bovis*; VPM1002. One vial contains 2-8 x 10^5 CFU of the IMP.

VPM1002 is the active pharmaceutical ingredient. It is a genetically modified BCG vaccine derived from the *Mycobacterium bovis*BCG subtype Prague.

VPM1002 is sensitive to antibiotics commonly used in treatment of mycobacterial infection, *i.e*. Isoniazid, Rifampicin, and Ethambutol.

A more detailed description of the study medication can be found in the Investigator's Brochure.

Qualitative and quantitative composition:
After reconstitution 1 dose (0.1 ml) contains:
VPM1002, live, 2-8 x 10^5 CFU

Pharmaceutical particulars**:**
List of excipients:
Powder:Dextran, Glucose
Solvent:Water for injection

Shelf life:
The stability program (+2°C to +8°C) for the investigational vaccine is still ongoing.The product will be stable for 18 months from the date of manufacture based on the data available thus far.

Storage conditions:
Store at +2°C to +8°C. Protect from direct sunlight.

ii. Immuvac

Immuvacis a heat killed suspension of Mycobacterium w,a non-pathogenic, cultivable atypical mycobacterium.

Qualitative and quantitative composition:

Each vial contains ready to use 0.6 ml suspension of heat killed Mycobacterium w (Immuvac) (3×10^9) in normal saline (0.9% w/v).

Each dose of 0.1 ml of Immuvac contains Mycobacterium w*(*Immuvac) (Heat Killed): 0.5 x 10^9 cells, sodium chloride IP: 0.9% W /v, Thiomersol IP (As a preservative): 0.01% W/v, Water for injection IP: q.s.

Pharmaceutical particulars**:**
List of excipients:

Heat killed *Mycobacterium w* Bulk
Thiomersal
Sodium chloride (Pyrogen free)
Water for Injection

Shelf life:36 months.

Confidential

Storage conditions:
Store at +2°C to +8°C.

Reference Product

Placebo:

Aqueous solution containing thiomerosal (0.1 mg/ml), sodium chloride (pyrogen free – 9 mg/ml) and water for injection (q.s. to 1.0 ml) in 2 ml amber colour USP-type I glass vials closed with 13 mm butyl rubber stoppers & sealed with 13 mm aluminium tear off seals.

Composition:Please refer the below table:

Table 4: PLACEBO COMPOSITION

Sr. No.	Ingredients	Spec.	Qty. (mg/ml)	Use
1.	Thiomerosal	IP	0.1	Preservative
2.	Sodium chloride (Pyrogen Free)	IP	9.0	Osmogen
3.	Water For Injection	IP	q.s. to 1.0 ml	Vehicle

Volume per vial: 0.8 ml/vial –Fill volume

Not less than 0.6 ml/vial -Extractable volume

Shelf life: 36 Months.

Storage conditions:

2-8°C.

STUDY DRUG PREPARATION AND ADMINISTRATION

***VPM1002*:**The content of the VPM1002vials should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. The investigational productmust not be mixed with other medicinal products.

VPM 1002 preparation instructions:

Preparation

VPM1002 will be reconstituted with 1 ml sterile water for injection. After reconstitution, the vial willbe allowed to stand for 15 minutes. Dispensing into suitable syringes will be done with the help of a filling needle(15/20 mm). The investigational product should be administered to the participants within maximal 3 hours after reconstitution of the vial. One vial of VPM1002 will be used for one participant only.

The injection site should be clean and dry. If antiseptics (such as alcohol) are applied to swab the skin, they should be allowed to evaporate completely before the injection is given.

The vaccine will be injected intradermally in theupperarm, over the distal insertion of the deltoid muscle onto the humerus (approx. junction of upper 1/3rd and lower 2/3rd of upper arm), as follows:

- The skin is stretched between thumb and forefinger.
- The needle should be almost parallel with the skin surface and slowly inserted (bevel upwards), approximately 2 mm into the superficial layers of thedermis.
- The needle should be visible through the epidermis during insertion.
- The injection is given slowly.
- A raised, blanched bleb will appear
- The injection site should not be rubbed.

VPM1002is classified as genetically modified organisms with biological safety level 1 (BSL1) and has to be handled in accordance with the applicable local requirements.

VPM1002contains viable attenuated mycobacteria and should be handled as an infectious agent at all times. Any VPM1002 vials must be stored for monitoring drug accountability. Any partially or completely used VPM1002 and all other equipment, packaging and materials exposed to the product should be immediately placed in a container for biohazardous material and disposed off as biohazardous waste. Any unused vaccine or waste material should be disposed in accordance with local requirements.

***Immuvac*:**

Each Vial contains 0.6ml of vaccine which is ready to use. Each vial contains suspension of heat killed *Mycobacterium w* (3×10^9) in normal saline (0.9% w/v).

The vaccine is administered by intradermal route twice, at the interval of 0 days and 4 weeks.

Placebo: Aqueous solution containing thiomerosal (0.1 mg/ml), sodium chloride (pyrogen free – 9 mg/ml) and water for injection (q.s. to 1.0 ml).

VPM1002, Immuvac, and Placebo vials must be stored for monitoring of drug accountability.

The handling of Immuvac does not need special biosafety precautions other than general hygiene practice followed by health workers for handling injections and medicines.On spillage, it must be cleaned with large amount of water and surface disinfectants. Immuvac is non-hazardous, non-infective, non-corrosive and non-toxic substance.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

LOGISTICS

SUPPLY

The Manufacturers and Sponsor will provide sufficient quantities of the IP (VPM1002, Immuvac and Placebo)packed uniformly to all study sites at the beginning of the study to ensure blinding.

PACKAGING AND LABELING

VPM1002/Immuvac/Placebo:

Both the vaccines and placebo will be packed uniformly.

The vials used for administration of the study drugs will be labeled according to the local regulations and requirements of the study protocol. All labels will contain the following information**:**

- Name of Sponsor / manufacturer,
- Protocol number,
- Storage conditions between 2^{o}C -8^{o}C, Protect from direct sunlight
- Imprint –For Clinical Trial Use Only‖,
- Unique kit/batch number
- Dosage and Route of administration
- Expiry date
- Randomization number / Participant unique ID no.

The kits/cartons label will include provision for the site tocapture the date of vaccination after use and the participant‘s unique ID to whom the vial was assigned/administered. The kit/carton label will also include a second panel which can be peeled/torn off and stuck on the participant‘s source document; this second label will include the unique kit number as well as provision for the site to capture the date of vaccination and participant‘s unique ID.

Confidential

RECEIPT AND ACCOUNTABILITY

Upon receipt of the study supplies,the receiver should ensure its storage conditions are strictly met. In case, the storage condition/temperature was not maintained as per protocol, same should be communicated to the sponsor and IP should not be used. An inventory must be maintainedand a drug receipt log should be filled out and signed by the person accepting the shipment. It is important that the designated study staff verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study product in a given shipment will be documented in the study files. The Investigator must immediately notify the Sponsor of any damaged or unusable vials that have been supplied to the Investigator‘s site. The damaged vials should be immediately returned to Sponsor by the study coordinator or investigator.

Following documents will be included in eachshipment to site:

1. Investigational product shipmentform stating the details of thevialssent in the shipment.
2. Courier Air Way Bill provided by courier.

After receipt of each shipment and completion of reconciliation and inspection at site, site personnel will provide acknowledgement of receipt of shipment to Sponsor/designee in cases where there is no temperature excursion and shipment is received in good condition(The acknowledgement section of the investigational products shipment form should be completed and forwarded to the Sponsor/designee).

In case there is anytemperature excursion during shipment, follow the steps given below:

1. Quarantine the shipment in appropriate storage area (2°C -8°C).
2. Immediately report to Site Monitor and Sponsor/designee about the excursion.
3. Send completed acknowledgment forms to Sponsor/designee.
4. Wait to hear on usage decision from Sponsor.
5. In case Sponsor confirms use, release vialsfor study use.
6. In case usage decision is _To be Rejected‘, transfer the affected vials back to the sponsor or to therejected/Biodegradationare after confirmation from the sponsor. The copy of the confirmation and details of such vials should be maintained at site and shared to the sponsor whenever required.

Designeewill provide temperature data to the site/Sponsor for each shipment.

The site PI (or designee) must maintain 100% accountability for all investigational products received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all containers used/broken/unused/lost are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

During the monitoring visit, the Study monitor will ensure that the site has sufficient investigational product required for research purpose. The monitor will do the investigational product accountability by reviewing the investigational product shipment, storage, and dispensing logs and will retrain the study staff in case of any deviation or discrepancy observed while storage or dispensing of the investigational product.

STORAGE

The study vaccines must be protected from light and refrigerated between +2°C to +8°C, which will be under close temperature monitoring (temperature logger) and connected to a source with reliable back-up power. Changes in temperature outside the allowed range should be immediately reported and any vaccine lots experiencing such out of range changes will be brought to the attention of the Sponsor for determination of procedures to follow. Diluent ampoules should be stored at ambient temperatureandnot to be frozen.

After reconstitution, the vaccine VPM1002 should be stored at +2°C to +8°C and protected from lightunless administration is done immediately after reconstitution. Administration of VPM1002 / Placebo has to be performed within 3 hours after reconstitution. VaccineImmuvac should be administered immediately when the vial is opened as they are ready to use vials.

In case there is temperature excursion during storage, follow the steps given below:

1. Quarantine the exposed investigational products in appropriate storage area (2°C to 8°C).
2. Immediately report to Site Monitor and Sponsor/designee about excursion.
3. Send completed temperature excursion form to Sponsor who will send it to the respective vaccine manufacturers.
4. Wait to hear on usage decision from Sponsor.
5. In case Sponsor confirms use, release product for study use.
6. In case usage decision is _To be Rejected‘, transfer the products to rejected area.

DISPENSING /METHOD OF ASSIGNING TREATMENTS TO SUBJECTS AND THE SUBJECT IDENTIFICATION CODE NUMBERING SYSTEM

After the inclusion and exclusion criteria check, the PI or designated personnel must confirm the eligibility and then randomize the participant.The pharmacist will prepare and dispense the injection as per the randomization code (under a physical partition for maintaining blinding) and

hand it to the study nurse after marking R/L (for right and left arms) and keep a record of arm in which placebo was administered (in case of study arm 1) to ensure administration of placebo in Dose 0 and 1 in same arm. The study nurse (vaccine giver), study participants (recipient), investigator (assessor), and sponsor will be blinded to the intervention given. The used vaccines/placebo vials must be kept for the accountability.

RETURN OR DESTRUCTION

The site will receive instruction from the Sponsor regarding the final disposition of any remaining investigational products. The used vaccine/placebo vials must be kept separately for the accountability. At completion of the study (after the last visit of the last participant), there will be a final reconciliation of investigational products shipped, investigational products consumed, and investigational products remaining. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused investigational products. All unused vials will be returned to the Sponsor. If the investigational products are destroyed on the site, it will be documented in the study files and a certificate will be provided to the Sponsor.

BLINDING AND BREAKING THE CODE

BLINDING

The study will be double-blinded (*i.e.* the study participants, investigator, study staff, and sponsor will be blinded to treatment assignment).

Double blinding will be ensured by:
(i) Similar immunization schedule of all three arms.
(ii) Separate person for dispensing the vaccine and for immunization.
(iii) Physician observing for safety will not be aware of the vaccine administered.

However, it is possible thatover time participants, investigators and/or study staff maybecome aware of treatment allocation onlyin cases where a local reaction to the vaccine occurs and/or a scar forms. This is not preventable. The study will not be formally un-blinded until all participants have reached the 38 months follow-up period and the database is locked.

TheDSMB, the designated statistician, third party vendor packaging personnel (including IP packaging, labeling, storage & distribution personnel) who are not involved in the conduct of the trial will be un-blinded to treatment assignments.

BREAKING THE CODE / EMERGENCY UNBLINDING

The code for an individual participant should be broken only in case of medical emergency where the identification of the investigational productsmust be known in order to properly treat the study participant. All such cases must be fully documented by the Investigator and written

notification should be provided to Sponsor and theInstitutional Review Board / Institutional Ethics Committee (IRB/IEC).

6.5 ASSESSMENT OF COMPLIANCE

The investigational product/ placebo will be administered by qualified staff only to participants included in this study. The date and time of the vaccinations must be recorded. The Investigator must track vaccines received, used and wasted and will retain all unused or expired products.

7. STATISTICAL DESIGN AND ANALYSIS

OVERVIEW AND GENERAL DESIGN

This is a multi-center, phase III, randomized, double-blinded, placebo-to evaluate the efficacy and safety of VPM1002 and Immuvac in the prevention of TB in healthy household contacts of TB patients.

RANDOMIZATION PROCEDURES

Block randomization with variable sample size will be generated with sequence of random number for each enrollment sites. Codes for each site will be kept in individually sealed opaque envelop. All the states will be allocated a number in the alphabetical sequence [*e.g.*: Delhi-**1**] and the sites will be numbered as a decimal place to the state number [*e.g.* AIIMS, Delhi – **1.0**] (Appendix 2)**.** A randomization series will be allotted to each site of the state with randomization codes. The details of Randomization are provided in SOP.

STUDY ENDPOINTS (OUTCOME VARIABLES)

PRIMARY ENDPOINT

To compare the percentage of confirmed TB cases (PTB and EPTB) as per RNTCP guidelines in the vaccinated and placebo groups from 2 months after first dose of vaccine till 38 months follow-up period (VPM1002, Immuvac and Placebo).

SECONDARY ENDPOINTS

- Number of participants developing LTBI (Will be evaluated at sites - Delhi (NCR), Hyderabad and Chennai).
- Incidence of adverse events and serious adverse events in study participants till the end of study period.

- Efficacy of vaccine in prevention of PTB/EPTB in the different age groups of (6 to18 years, 19 to 35 years, 36 to 60 years and above 60 years).
- To determine the protective effect for both forms of TB (PTB and EPTB).
- Immunogenicity of VPM1002 and Immuvac will be compared with placebo to be measured by (Will be done at AIIMS, Delhi; NARI, Pune; and NIRT, Chennai):
  - **FACS (Fluorescence activated cell sorting)**: CD3, CD4/CD8, TNFα, IFNγ, IL2[Time Frame: screening, month 2, month 6,and those who have developed PTB will be followed up during the course of study]
  - **LUMINEX**:IL2, IFNγ, TNFα, IL 10, IL12, IL17 [Time Frame: screening, month 2,month 6and those who have developed PTB/EPTB will be followed up during the course of study]

EXPLORATORY ENDPOINTS

Since this is a prospective study with a 3 year follow up, hence the following exploratory endpoints will be assessed at the end of study.

- Efficacy against other infectious diseases.
- Efficacy against all-cause mortality.
- Efficacy against all-cause hospitalizations.
- Efficacy in TST positive versus TST negative prior to immunization.
- Gender specific efficacy
- Immunological correlates of protection.

IMPORTANT DEFINITIONS

New Index case:

The identified case of newly diagnosed sputum positive pulmonary TB of any age in a specific household or other comparable setting in which others may have been exposed. The index case is either untreated or may have taken anti-tuberculosis treatment (ATT) for less than one month. *(*WHO and RNTCP*)*

Household contacts:

Household contacts were defined to be those people who shared meals with the index case; stayed together as a family with the index case; spent 8 or more hours per day with the patient in a single room and/or resided with the index case for any 7 consecutive days during 3 months before the diagnosis of TB.[35]

Bacteriologically confirmed TB case:

A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics such as Xpert MTB/RIF.

Clinically diagnosed TB case:

A clinically diagnosed TB case is one who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the participant a full course of TB treatment. This definition includes cases diagnosed on the basis of radiological abnormalities and extra pulmonary cases without laboratory confirmation.

Co-prevalent TB:

If active TB is diagnosed in the household contact of Index case at the time of the baseline investigation or within 2 months after first dose of study vaccine, then it is called as Co-prevalent TB case.

Incident TB:

If active PTB/EPTB is absent in the household contact of Index case at the time of the baseline investigation but develops/diagnosed as TB after 2 months after first dose of study vaccine till 38monthsof follow-up period then the case is called as Incident PTB/EPTB.

ANALYTIC METHODOLOGY

The planned statistical analyses for this study are outlined below. A detailed statistical analysis plan for preparation of the final study report will be created and made final prior to database lock and un-blinding procedure. All statistical analyses will be performed using SPSS software Version 20 or higher or R version 3.3 or higher. Medical history and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Prior and concomitant medications will be coded as per World Health Organization Drug Dictionary (WHO DD).

ANALYSIS POPULATION

Definitions of analysis populations to be analyzed are:

Screened Population

All screened participants who provided informed consent/assent, regardless of the participant‘s randomization and treatment status in the trial.

Modified Intention-To-Treat (mITT) Population

All participants who were randomized and vaccinated, did not develop TB within the first 2 months after vaccination, completed at least 2 months of follow-up after vaccination, and were baseline staining negative will be included in this population. Participants will be analyzed as

randomized. This will serve as the primary analysis population for the primary and secondary (except for safety and immunogenicity) endpoints.

Safety Population

All participants who were randomized and vaccinated are to be included. The analysis based on this population will serve as the primary population for safety endpoints. Participants will be analyzed as treated.

Per Protocol (PP) population

All participants in the mITT population with no major protocol violations that are determined may potentially interfere with the assessment of the study vaccine‘s efficacy and immunogenicity will be included in the PP population.

The criteria for exclusion of participants from the PP Population will be established before database is locked. This will be based on the blinded review of protocol violations by the Sponsor.

The primary and secondary (except safety) analyses will be repeated using the PP; these will serve as supportive analyses. The PP analysis data set is a subset of the mITT population and will include the participants not showing major protocol violations in aspects such as

- meeting all eligibility (inclusion/exclusion) criteria;
- receiving the vaccine or placebo;
- with no premature discontinuation criteria during the follow-up visits post vaccination; and
- not taking any prohibited concomitant medication during the study period.

The mITT and PP data set will be used for the analysis of efficacy data. The mITT data set will be the primary data set for efficacy analysis. Safety analysis will be done using the safety data set and may be repeated for PP data set if deemed necessary.

STATISTICAL METHODS AND ANALYSIS

Interim Analysis

Interim analysis will be done at the time when 80 incident TB cases are observed in the trial or follow up of 50% of enrolled subjects is completed, whichever is earlier. For efficacy, O‘Brian Flaming and for SAE‘s Pocock stopping rules will be followed. DSMB will review the data for efficacy, safety, and utility of the trial vaccines.

Final Analysis

Final analysis will be done at the time when 160 incident TB cases are observed in the trial or end of follow up period whichever is earlier. Incidence of new cases for each of the three arms will be estimated in person years of time. Time to event (event of interest for efficacy analysis - incident TB and for safety analysis - ADR and Death) analysis for confirmed TB cases will be performed using Cox proportional hazards model. Safety data will be summarized by vaccine and placebo arms using descriptive statistics. Effect size (95% CI) would be computed for each study outcome. Statistical analyses will be performed using SPSS version 20 or higher or R version 3.3 or higher.

SAMPLE SIZE CALCULATION

Sample size was estimated based on the primary study endpoint of confirmed TB cases (PTB and EPTB) in the three arms at 38 months after vaccination. Based on literature review, cumulative incidence of TB in household contacts during 38 months in the control arm is estimated as 2%. Anticipating a 50% reduction in TB cases during the 38 months of follow-up after vaccination in the VPM1002/Immuvac, approximately 12000 participants (4000 in each arm) will be randomized to achieve 90% power at 1% significance level. This calculation is based on continuity corrected one-sided test. A 10% drop out rate has been factored while calculating the sample size.

Thus, approximately 12000 healthy household contacts of newly diagnosed PTB patients will be enrolled at six states in India. Around, 2000 participants will be enrolled at each state.

8. SAFETY ASSESSMENTS AND REPORTING

SAFETY MONITORING

The Investigators at each study site will be responsible for continuous close safety monitoring of all study participants, and for alerting the protocol/study safety review team if concerns arise. An internal team, the Protocol/Study Safety Review Team, will be set up to examine safety across the participating sites. Furthermore, an independent DSMB will be established to monitor the conduct of the trial. The DSMB will periodically examine vaccine safety and provide recommendations to the Sponsor. This will be laid down in a separate DSMB charter.

PROTOCOL/STUDY SAFETY REVIEW TEAM

Safety will be monitored during the study by on-site clinical staff on ongoing basis and routinely by the Protocol/Study Safety Review Team, an internal group of physicians which includes the Sponsor Medical Officers, a biostatistician and designated pharmacovigilance medical officer from the ICMR Headquarters. The Protocol/Study Safety Review Team may seek independent expert medical opinion as dictated by the occurrence of certain events. There will be periodic reviews of accruing safety data by the Protocol/Study Safety Review Team. The reports will be

prepared by the ICMR Headquarters, blinded by treatment assignment and will include but not be limited to:

- Participant status data with regard to completion/discontinuation of study visits.
- Summaries of solicited reactogenicity data by severity grade and duration.
- Vaccine-related solicited adverse events sorted by MedDRA system organ and class(SOC) and grade.
- Hospitalization and deaths.
- Reported serious adverse events.
- Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up, *etc.*)

The reports will be analyzed by the Protocol/Study Safety Review Team as needed.

DATA AND SAFETY MONITORING BOARD

A central DSMB formed entirely by independent vaccine and infectious diseases experts, and including a biostatistician, will be set up by ICMR to periodically review cumulative data. Items reviewed by the DSMB will include (but will not be limited to):demographic information on study, interim/cumulative data for evidence of study-related adverse events, protocol deviations, data quality, completeness and timeliness of visits, factors that might affect the study outcome or compromise the confidentiality of the trial data (such as treatment and endpoint un-blinding), and factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics issues of the study.

The membership of the DSMB should reflect the disciplines and medical and dental specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/participant population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

The DSMB reviews will be summarized with recommendations to the study Sponsor. In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study product for all and stop accrual into the study, the protocol team will request a review of the data by the DSMB before recommending that the study be stopped.

If at any time, a decision is made to discontinue study product in all participants, Sponsor will notify DCGI and the site investigators will notify the responsible IRBs/IECs expeditiously.

DSMB recommendations will be carefully considered by the sponsor. If a disagreement arises between the sponsor and the DSMB, the sponsor will discuss it with the DSMB in order to reach consensus. If attempts to reach consensus fail, the sponsor‘s opinion will prevail. In such situation, the sponsor will inform the regulatory authorities.

All paperwork, CRFs, essential documents, master file *etc.* will be maintained for a period of five years after completion of the trial.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. Usually, only voting members of the DSMB should have access to interim analyses of outcome data by treatment group. Exceptions may be made when the DSMB deems it appropriate. The reason and to whom the exceptions for access to interim analyses is granted will be documented in the Closed Session Report. DSMB members must maintain strict confidentiality concerning all privileged trial results ever provided to them. The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the identities of the groups are necessary for their decision-making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

A named statistician, not involved with the final data analysis or with the study, shall receive the relevant codes and perform the interim analysis. A record shall be kept in the Investigator Trial Master File of the name of the statistician, the date they were supplied the relevant code breaks and the location of the results. The un-blinded data and the results supplied to the DSMB shall not be accessible by the Principal Investigator or trial staff.

The frequency of DSMB meetings depends on several factors including the rate of enrollment, safety issues or unanticipated adverse events, availability of data, and, where relevant, scheduled interim analyses. Unless the Clinical Terms of Award for the grant specifically identify this as the responsibility of the grantee, the Program official (PO) or designee is responsible for convening meetings, selecting a venue when the meeting is not convened by teleconference, and coordinating the distribution of meeting materials to DSMB members and other meeting participants.

The initial DSMB meeting should occur preferably before the start of the trial or as soon thereafter as possible. At this meeting the DSMB should discuss the protocol and the DSMB charter which includes triggers set for data review or analyses, definition of a quorum, and guidelines for monitoring the study. Guidelines should also address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol.

Once a study is implemented, the DSMB should convene as often as necessary, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed. A DSMB meeting may be requested by DSMB members, the PO, industrial collaborator, IRB, or study Principal Investigator at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the PO and DSMB Chair. Meetings may be held by conference calls or videoconferences or as face-to-face meetings. In the event a DSMB

member cannot attend a meeting, he/she may receive a copy of the closed session DSMB report and either participate by conference call or provide written comments to the DSMB Chair for consideration at the meeting.

VACCINE REACTOGENICITY

- Following vaccination, enrolled participants will stay in the clinic for at least 1 hour for observation. During this time, they will be closely monitored for any immediate hypersensitivity reaction. Safety assessments solicited adverse events-local (pain, erythema, swelling, fever, ulcer, subcutaneous abscess, indurations, blister formation) and regional lymphadenopathy reactogenicity events, unsolicited events, vital signs will be recorded.
- Safety assessments also will be performed at all visits and at any unscheduled visit.

All adverse events and serious adverse events will be recorded and reported, throughout follow up period.

ADVERSE EVENTS

DEFINITIONS

An Adverse Event is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

An Adverse Drug Reaction (ADR) is any untoward and unintended response to an investigational medicinal product causally related to study product administered.

An adverse event does not include:

- Medical or surgical procedures (*e.g.* surgery, endoscopy, tooth extraction, transfusion) but the condition that leads to the procedure is an adverse event.
- Situations where an untoward medical occurrence has not occurred (*e.g.*, hospitalization for elective surgery, social and / or convenience admissions).
- Overdose of either study drug or concomitant medication without any signs or symptoms.

The participants will be requested to record injection site reactions (local reactions) and regional reactions for the first 2 months following vaccination using pre-printed diary card. All solicited and unsolicited adverse events in all study participants from day of vaccination to 2 months after vaccination will be recorded and reported (reactogenicity cohort).All Unsolicited adverse events will be recorded throughout follow-up period in all study participants.

Injection site reactions (local reaction) and regional reactogenicity events for the first 2 months following vaccination will be designated as solicited reactions.

Solicited reactions, such as the formation and resolution of the vaccine-associated local reaction, are pre-specified and will be actively monitored during the trial.

SOLICITED REACTIONS OF THE IP:

Local reactions: Fever, pain, erythema, blister formation, induration, swelling, ulcer, subcutaneous abscess, keloid formation

Regional: evidence of lymphadenitis

Unsolicited adverse events are not specified for active monitoring, but spontaneously reported as untoward events occurring in a participant. All such events will be recorded in the Adverse event ‘pages in the CRF.

SEVERITY OF ADVERSE EVENTS

The severity of all adverse events / serious adverse event occurring during the course of the study will be graded as per the clinical judgment of the Investigator taking into account information provided by participants.

For severity grading of adverse reaction/events, criteria given will be used. The Investigator/designee will record all adverse events for their maximum severity. For events measured with continuous variables such as fever or diameters, the severity grades will be provided for completeness. The Investigator will report the highest measured value.

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Table 5: Assessment of severity for all adverse events (including solicited reactions)

Local reactions (at the injection site)	**Severity grade**
Injection Site pain or tenderness	
Pain or tenderness causing no or minimal limitation of use of limb	**1 (Mild)**
Pain or tenderness causing greater than minimal limitation of use of limb	**2 (Moderate)**
Pain or tenderness causing inability to perform usual social and functional activities	**3 (Severe)**
Pain or tenderness causing inability to perform basic self-care function OR hospitalization is indicated	**4 (Potentially Life Threatening)**
Redness (Erythema)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**
Potentially life-threatening consequences (*e.g.* abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissues)	**4 (Potentially Life Threatening)**
Swelling (Induration)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**
Potentially life-threatening consequences (*e.g.* abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissues)	**4 (Potentially Life Threatening)**
Ulceration, Subcutaneous abscess (collection of pus	

beneath the skin), Blister, Keloid (overgrowth of scar)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**
Potentially life-threatening consequences	**4 (Potentially Life Threatening)**
Fever(axillary temperature measured once daily even in the absence of signs)	
38°C to <38.6°C	**1 (Mild)**
≥38.6°C to <39.3°C	**2 (Moderate)**
≥39.3°C to <40°C	**3 (Severe)**
≥ 40°C	**4 (Potentially Life Threatening)**
Other adverse events	
Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	**1 (Mild)**
Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	**2 (Moderate)**
Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated	**3 (Severe)**
Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death	**4 (Potentially Life Threatening)**

An adverse event that is assessed as severe should not be confused with the term serious adverse events. Severity is a category utilized for rating the intensity of an event; and both adverse events and serious adverse events can be assessed as severe.

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OUTCOME CATEGORIES

The outcome of adverse event will be categorized as following:

- **Recovered** – If the participant recovered from the event occurred.
- **Recovered with squeal** – If the participant recuperated and retained the pathological condition resulting from previous disease or injury.
- **Recovering** – If the participant is recovering from the existing event occurred
- **Not recovered** – If the participant continuing with the event occurred
- **Fatal** – If the participant dies due to adverse event or the ADR is associated with fatal outcome.
- **Lost to follow-up / unknown** – If the outcome is not known.

CLASSIFICATION OF ADVERSE EVENTS*

*Only for reference

Adverse events will be grouped into five categories.

- **Vaccine-product related reaction**: An adverse event that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

  Example: Extensive limb swelling following DTP vaccination.

- **Vaccine quality defect-related reaction:** An adverse event that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.

  Example: Failure by the manufacturer to completely inactivate a vaccine/ lot of inactivated polio vaccine leads to cases of paralytic polio.

- **Immunization error-related reaction**: An adverse event that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

  Example: Transmission of infection by contaminated multi dose vial.

- **Immunization anxiety-related reaction:** An adverse event arising from anxiety about the immunization.

  Example: Vasovagal syncope in an adolescent during/following vaccination.

- **Coincidental event:** An adverse event that is caused by something other than the vaccine product, immunization error or immunization anxiety.

  Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria.

Coincidental events reflect the natural occurrence of health problems in the community with common problems being frequently reported.

RELATIONSHIP TO STUDY DRUG

Investigator will evaluate and assess the causality of adverse event and will send scanned copy of adverse event notification form with all required information to ICMR (Sponsor) and Institutional Ethics Committee and if needed will send to the Causality Assessment Committee (if required in case of compensation), and then committee will take responsibility to assess it.

The likelihood of the relationship of the adverse event to study product is to be recorded as follows as per WHO causality assessment criteria.

Table 6: ADVERSE EVENT CAUSALITY ASSESSMENT CRITERIA

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (*i.e*. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required

Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*WHO-UMC System

MEDICATION ERRORS

A medication error is any preventable event that may cause or lead to inappropriate investigational product use or participant harm while the investigational products are in control of study staff.

Examples ofmedication error that will require reporting to the Sponsor and Ethics Committee as Protocol Violation:

- Administration of unassigned treatment.
- Administration of expired study product.

- Any deviation from the recommended route of administration of the investigational product.
- Administration of investigational products from a damaged vial.

RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Participants will be monitored throughout follow up period for adverse events. The adverse event will come to the attention of site clinicians (Principal Investigator / Co-Investigator) through interim medical histories, physical examinations and laboratory testing. All adverse events will be closely monitored in the safety visits. In addition, the participants will be advised to contact study staff immediately at any time throughout the follow up period if they observe an adverse event in the participant of the study. The possible occurrence of any adverse event and serious adverse event will also be asked and noted during the scheduled study visits.

All solicited and unsolicited adverse events in all study participants from day of vaccination to 2 months after vaccination will be recorded and reported (reactogenicity cohort). All unsolicited adverse events will be recorded upto month 38 for all study participants. All serious adverse events will be recorded and reported, occurring at any time, throughout the study, *i.e*. up to 38months follow-up period.

Adverse events will be managed in accordance with good medical practices by the clinical study site team (Principal Investigator/ delegated personnel) who will assess and treat or refer the participant for medical care, free of cost, as appropriate. Where feasible and medically appropriate, the participant will be encouraged to seek medical care at the facility where the study clinician is based, and to request that the clinician be contacted upon their arrival. If needed to monitor or treat an adverse event, additional study visits may be conducted.

All Adverse events and Serious Adverse Event will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up, whichever is earlier. Every possible effort will be made to contact the lost to follow up participant. Once resolved or stabilized, the appropriate Adverse Event/ Serious Adverse Event, the form(s) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and / or causality of the Adverse event or Serious Adverse Event. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.

Sponsor may request that the Investigator perform or arrange for the conduct of supplemental laboratory analysis and/or evaluations to elucidate as fully as possible, the nature and / or cause of the Adverse Event or Serious Adverse Event. The Investigator is obliged to comply with this request. If participant‘s death occurs during the follow up period or during a recognized follow-up period, Sponsor will be provided, by the Site Principal Investigator, with a copy of any post-mortem findings, including histopathology.

All related baseline safety parameters will be performed before vaccination at screening. Moreover, the PI may repeat any lab parameter if deemed necessary post-vaccination.

Any abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as adverse events or Serious Adverse Event as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after investigational drug administration or that are present at baseline and worsen following the administration of investigational drug are included as adverse events and Serious Adverse Events. The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

Any participant who develops any adverse reactions or clinically significant laboratory test values will be evaluated by the respective site Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the Adverse Event /Serious Adverse Events and not the individual signs/symptoms.

NOTE: *All diagnosed TB cases up to 2 months after vaccination will be reported Co-prevalent TB. After that period, TB cases will be captured as study end-points. However, hospitalization for suspected TB case will be regarded as Serious Adverse Events*.

ADVERSE EVENT AND SERIOUS ADVERSE EVENT (SAE) REPORTING

- Trial study participants should be instructed to report any adverse event that they experience to the Investigator immediately
- Investigator should assess Adverse Event at each visit
- Adverse event is to be considered as SAE, if it is - Fatal, Life-Threatening, causes permanent disability, cause or prolongs hospitalization, or causes congenital anomaly and other medically significant event as per PI‘s decision.
- Investigator must ensure safety of the trial study participants.
- When study participant experiences an adverse event, following actions should be taken:
    - Occurrence of Adverse Event must be monitored carefully
    - Investigator must provide the best possible care available and follow-up trial study participant‘s AE until it disappears completely. Adverse event/SAE likely to be related to the IP and persisting to the end of the trial should also be followed- up.
    - A thorough investigation should be there to determine the causality

  - The adverse event must be recorded in detail during the course of the trial irrespective of the possible causal relationship with the IP.
- All adverse events occurring during the trial should be accurately reported in the appropriate section of the CRF.
- If adverse event is serious, a Serious adverse event case notification form shall be filled by Site Principal Investigator for reporting of Serious adverse event case, which shall be notified to the simultaneously to ICMR headquarter/Sponsor, DCGI, Chair of Ethics Committee within 24 hours.
- As per the regulations (Schedule Y of Drugs & Cosmetics Rules), all serious adverse events initial report has to be reported within 24 hours and follow up report has to be reported to CDSCO within 14 calendar days.
- Every report (both initial as well as follow-up reports) should be submitted along with a covering letter.
- All the sections of the covering letter should be completed. When some information is not available at the time of report *e.g.* causality assessment by medical monitor of Sponsor / CRO, compensation provided for study related injury or death, the same has to be provided as a follow-up report.
- Covering letter of every report arising from the clinical trials (CT) has to capture DCGI CT file number, complete address of Sponsor including phone & e-mail address, Phase of clinical trial, Category of clinical trial, Protocol or Study No. / Code / ID and the study title, Adverse event term / diagnosis (whenever possible provide a preferred term), a brief narrative of the event, not exceeding 10 lines and a detailed narrative may be enclosed, if available.
- The assessment report should clearly mention whether the SAE occurred is related or not related (situations like unlikely, possibly, suspected, doubtful *etc.* should not be used) and whether the outcome is fatal.
- Details of compensations provided for injury or death. In case no compensation has been paid, reason for the same should be submitted. It is pertinent to mention that in case of study related injury or death, complete medical care as well as compensation for the injury or death should be provided.
- Capture whether it is ―initial‖ or ―follow-up‖ report. For follow-ups, clearly mention the follow-up report number *e.g.* Follow-up #01, Follow-up #02, *etc.*
- In case of follow-up reports, please mention the date of submission of initial (first) report somewhere in narrative.

DOSE MODIFICATION

No modification of the dose is allowed.

9. DATA MANAGEMENT

A Data Management Plan describing the tools and processes for generation of the clinical database and data management activities from project set-up through database lock and transfer will be developed by the Sponsor.

The Sponsor will build, validate and maintain EDC, an ICH-GCP compliant Electronic Data Capture System.

Internal data quality checks such as automatic range checks, checks to identify data that appear inconsistent, incomplete or inaccurate are programmed into EDC. This allows for real-time review of the data as and when clinical data is entered into the system by the site staff.

The Sponsor will review the data for quality and will provide several quality assurance reports to ensure that study data is clean and complete. All adverse events will be coded using the latest version of MedDRA and concomitant medications using the latest version of WHO Drug dictionaries. Quality assurance reports will include, but are not limited to, the following: missing forms, missing values and out of range values, automated data queries, and manual review of study data. Data queries will be distributed to the sites at scheduled time period for the site staff to review and update the data.

DATA ENTRY

The eCRFs will be developed by the Sponsor and should be handled in accordance with eCRF completion guidelines. All study data must be verifiable to the source documentation. Source documents for each study participant will be maintained at the study site. Source documentation will be available for review to ensure that the data collected in eCRF is consistent with source documents. A study monitor appointed by Sponsor will review all eCRFs entered into the data base. Source documents and other supporting documents will be kept in a secure location to ensure confidentiality. Standard ICH-GCP practices will be followed to ensure accurate, reliable and consistent data collection.

DATA COLLECTION

An Investigator is expected to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. The Site Investigator is responsible for ensuring the accuracy, completeness, and timelines of the data reported. Data collection is the responsibility of the clinical trial staff at the study site under the supervision of the site Investigator.

Data will be entered electronically by site study staff over the internet in electronic data platform. The data system includes password protection and internal quality checks, such as automatic range checks to identify data that appears inconsistent, incomplete or inaccurate.

Clinical data will be entered directly from the source documents. Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All the information required by the study protocol must be entered into eCRF. An explanation must be provided for any missing data. Source documentation supporting the eCRF data should document the dates and details of study procedures, adverse events and participant status. The PI/site staff will maintain information in the eCRFs and all source documents that support the data collected from each participant.

The study monitor will check for completeness and accuracy of eCRF during the monitoring visits.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). Each individual having written access to electronic CRFs must meet the training requirements and must only access the electronic data capture tool using the unique user account provided by ICMR Headquarters. User accounts are not to be shared or reassigned to other individuals.

The Investigator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documentation. The study database will identify study participants only by a participant identifier and will not contain any identifying information such as name, address or personal contact information, or any other regional / State / national identification number (Ration Card, Permanent Account Number [PAN], Unique Identification [UID], *etc.*).

All the sub-sites will be required to collect and send data to the coordinating sites on daily basis which will be vetted by Site Principal Investigator. The sites will transfer the data to ICMR, Headquarters for the Central Data Management on weekly basis.

Database will be locked after all the participants data have been entered in the database, all data anomalies have been resolved, study monitoring activities are completed, all the listings in the database. After the database lock, the eCRFs may no longer be modified by the site staff. The final data will be sent to the Protocol Statistician for statistical analysis.

DATA ACCESS

The study site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, Sponsor and institutional requirements for the protection of confidentiality of participants. The site will permit authorized representatives of the Sponsor(s), IEC / IRB, monitor, auditor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

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DATA STORAGE AND ARCHIVAL

The study monitor will provide each Investigator with a Site Master File, which will be used to file the IB, protocol, drug accountability records, correspondence with the IEC / IRB, Sponsor and other study-related documents *etc*. The Investigator will maintain, and store securely, complete, accurate and current study records throughout the study.

The Investigator will keep essential documents until at least 5 years after the last approval of a marketing application in compliance with Indian GCP guidelines. In addition, the Investigator will make provision for the participant‘s medical records to be kept for the same period of time.

No data will be destroyed without the permission of the Sponsor. The Sponsor will inform the Investigator in writing of the need for record retention and will notify the Investigator in writing when the trial related records are no longer needed.

SOURCE DOCUMENTS

Source documents include but are not limited to:

- Documentation of the study eligibility evaluation.
- Signed Informed Consent Documents.
- Visit documentation that includes dates of study visits and dates of study vaccinations.
- Reported laboratory results.
- Adverse event evaluations.
- Concomitant medications.
- Diary card
- Certified copies of hospital records.

10. STUDY MONITORING

SITE INITIATION VISIT

Before the first participant is enrolled into the study, the Sponsor, designated monitors and a Data Manager will conduct a site initiation visit to:

- Brief Investigator and site personnel on study protocol and procedures.
- Train the site PI and site staff on EDC and on safety reporting procedures.
- Ensure the qualifications, resources, staff, and facilities are adequate to properly conduct the study.
- Discuss the responsibilities of the Investigator and other site personnel involved with the study with regard to protocol adherence and GCPs.

- Verify site has current protocol, SOPs, other essential documents and study supplies to conduct the study properly.
- Verify site procedures and training is adequate and ready to properly conduct the study.

STUDY MONITORING

Sponsor or Sponsor‘s authorized representatives are responsible for contacting and visiting study sites for the purpose of monitoring the facilities and inspecting the trial records. For that purpose, the Sponsor will engage a monitoring agency independent of the sites. Site Investigators will allow study monitors and Sponsor‘s staff to inspect study facilities and documentation (*e.g.*, informed consent forms, clinic and laboratory records, other source documents, eCRFs), as well as observe the performance of study procedures.

Mutually agreed monitoring visits between sponsor and the Monitoring Contractor will be scheduled to take place before entry of the first participant (site initiation visit), during the study at appropriate intervals (on study site visit) and after the last participant is completed (closeout visit). Communication by telephone and e-mail will be used, as needed, to supplement site visits. Monitoring will be conducted according to ICMR‘s SOPs and study specific monitoring plan. The Sponsor will be responsible for reviewing and approving the monitoring reports.

MONITORING VISITS

After the study is initiated, the designated monitors will contact the Investigator to obtain information on the performance of the study. These monitoring visits will take place at regular intervals during the entire study. Subsequent to start of recruitment, the first routine Monitoring Visit will occur as soon as possible after recruitment of the first participant. The Investigator and his / her staff are obliged to set aside adequate time and place for the monitoring visits. All original source documents and certified copies of external sources such as hospital records / other records will be reviewed to verify compliance with human participants protection and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation.

The Sponsor-designated study monitors will perform the source data verification (SDV) of the data recorded in the eCRFs against the source documents available at the site to ensure consistency between the source data and the data present in the eCRFs. In addition to source data verification, the monitoring agency will assess adherence to the study protocol, study-specific procedures, confirm the quality and accuracy of information collected at the study site including the validation of data reported on eCRFs, and assess the resolution of any past or ongoing issues identified at previous monitoring visits.

During the visits the monitors will verify the following, from comparing source documents with the data entered:

- Appropriate informed consent/assent was obtained.
- Inclusion / exclusion criteria are properly fulfilled.
- The participant screening logs are filled and maintained properly.
- Quantity and dosing schedule of the investigational products is in accordance with the protocol.
- Quantity and dosing schedule of concomitant medication is documented in the records.
- The study vaccines are being stored correctly and its supply being properly accounted for and recorded accurately in the medication log.
- The eCRF details consistent with the physician's original records, which also have to clearly indicate that the participant is included in the clinical study.
- All relevant information (*e.g.* adverse event) has been recorded in the appropriate place in the eCRF.
- Check that the study product is being stored, dispensed and accounted for according to procedures and specifications.

Incorrect entries/ any discrepancy in the eCRF will be submitted to the Investigator for correction.

The Investigator must ensure the provision of reasonable time, space, and adequate qualified personnel for monitoring visits. Study monitor will also provide information and support to site during such visits. The monitor will also be available between visits should the Investigator or other staff at site need information and advice.

CLOSE OUT SITE VISIT

A final monitoring visit to each of the study site will be performed by the ICMR monitor to:

- Retrieve any specified study materials (*e.g.*, unused investigational products*etc*.) to return to Sponsor.
- Check all study documents and records have been properly filed for archiving.
- Arrange for archiving wherever required.

AUDITS AND INSPECTIONS

In addition to the above outlined monitoring visits, the investigational sites (clinical sites, laboratories, vaccine storage facilities, repositories, *etc.*) may be audited or inspected. Audits and Inspections are conducted to assess systemically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, SOPs, ICH, and GCP guidelines, regulatory requirements, and any applicable guidelines.

The audit may be performed by the contracted monitors or Sponsor designated independent auditor or authorized representatives of the Sponsor. The Sponsor, regulatory authority

Inspectors or their authorized representatives will be responsible for contacting and visiting the study site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial. The Investigator will inform sponsor expeditiously of any inspection requested by a regulatory authority. The Investigators will allow inspection of all study-related documentation by authorized representatives of the Sponsor and local regulatory authorities (DCGI). During the audits or inspections the participants'confidentiality will be maintained at all times to the extent permitted by the law. Site visit logs will be maintained at the study site to document all visits.

11. ETHICAL PRINCIPLES AND INFORMED CONSENT

This study must be carried out in compliance with the protocol and in accordance with the study's Standard Operating Procedures (SOP). These documents are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guideline for Good Clinical Practice (E6) 1996.
2. Declaration of Helsinki, concerning medical research in humans.
3. ‗Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines' issued by Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India in 2005.
4. ‗Requirements and guidelines for permission to import and / or manufacture of new drugs for sale or to undertake clinical trials' (Schedule Y, 2005) and it's amended rules 122DAB [Drugs and Cosmetics (First Amendment) Rules, 2013: Compensation in case of injury or death during clinical trial], 122DAC [Drugs and Cosmetics (Second Amendment) Rules, 2013: Permission to conduct clinical trial], 122DD [Drugs and Cosmetics (Third Amendment) Rules, 2013: Registration of Ethics Committee], and any other applicable amendments to these rules.
5. ‗Ethical Guidelines for Biomedical Research on Human Participants' issued by Indian Council of Medical Research, 2017.

The study will commence only after receipt of a favorable opinion from competent IEC / IRB and approval from the DCGI.

INSTITUTIONAL REVIEW BOARDS / INSTITUTIONAL ETHICS COMMITTEE (IRB / IEC)

Each participating institution is responsible for assuring that this protocol, the associated informed consent documents, and study-related documents are reviewed and approved by a local IEC or IRB prior to implementation of the protocol. Any major amendments to the protocol, informed consents, or other study-related documents must be approved by the IEC / IRB and the Sponsor prior to implementation. Any minor amendments will be notified to the same. The Investigator will notify the IEC / IRB of Serious Adverse Events as noted in the protocol and of protocol deviations according to the Indian regulatory requirements and IEC / IRB requirements. The study will be conducted in full compliance with the protocol.

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INFORMED CONSENT

In this trial, a freely given, informed, written consent is to be obtained from each study participant. The Investigator must provide information about the study verbally as well as using a participant information sheet, in a language that is non-technical and understandable by the study participant. The study participant's consent must be obtained in writing using an 'Informed Consent Form'. If the Study participant or his/her legally acceptable representative is unable to read/write — an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

Prior to any study-related screening procedures being performed, audio-video consenting for the study will be conducted for vulnerable participants(children less than 12 years of age) and a written/oral consent or assent (as applicable) will be obtained from participant before enrolling in the study. The procedures to explain the meaning of informed consent/assent to the participants / impartial witness and to obtain their consent will comply with current Indian regulatory requirements, the ICH-GCP Guidelines, with GCP for Clinical Research in India, 2001; ICMR‘s Ethical Guidelines for Biomedical Research on Human Participants, 2017 and Schedule Y, Amended 2005 under Drugs and Cosmetics Act and Rules there under, and the ethical principles in the amended Declaration of Helsinki (2013). The Investigator or designee will obtain and document the informed consent/assent process in accordance with the requirements for source documentation.

The consent/assent form will include the purpose of the study, the investigational products to be administered, a description of the procedures to be followed, and the risks and benefits of participation.

It is the site Investigator‘s responsibility to ensure that informed consent/assent is obtained after adequate explanation of the aims, methods, and potential risks and benefits of the study to the participants. A signed and dated copy of the consent/assent form will be given to them, and this will be documented in the participant‘s record.

INFORMED CONSENT PROCESS

The informed consent process will give individuals all relevant information they need to decide whether to allow them to participate, or to continue participation. Participants will be encouraged to ask questions and to exchange information freely with the study Investigators. Audio-video recording of the informed consent / assent process will be done for vulnerable participants (children less than 12 years of age). The Investigator has the duty to communicate to the participants, all the information necessary for informed consent. There should not be any restriction on participants‘ right to ask any questions related to the study as any restriction on this undermines the validity of informed consent. Participants will be provided with copies of the informed consent/assent forms. The Investigators will keep participants fully aware of any new

information that could affect their willingness to continue study participation. During the course of the study period, when the child crosses the stipulated age band, re-consent will be taken appropriately.

The informed consent process covers all elements required by research regulations addressing the following topics of importance to this study:

- The importance of adherence to the study visits and procedures schedule.
- The potential risks of study participation (and what do if such risks are experienced).
- The potential social harms associated with study participation (and what do if such harms are experienced).
- The limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.
- Extent to which the records can be maintained confidential and which groups will have access.
- Who can be contacted if the participant has questions about research or rights of research participants.
- The use of stored samples for future research and the risks of specimen storage (ICMR-NIRT, Chennai).

PARTICIPANT CONFIDENTIALITY

The Investigator must ensure that the participants‘ confidentiality is maintained. Personal identifiers will not be included in any study reports. All study records will be kept confidential to the extent provided by national and local laws. Medical records containing identifying information may be made available for review when the study is monitored by the Sponsor or an authorized regulatory agency. Direct access may include examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, administrative forms, laboratory specimens, and other reports will be identified by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with

password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Study information, will not be released without their written permission, except as necessary for monitoring.

REIMBURSEMENT

At the discretion of each of the individual sites, and after approval by the corresponding IEC / IRB, the sites may compensate the participants for any transportation costs, work time associated with visits *etc*. The amount of such compensation, if any, will be determined by the site PI and approved by the IEC / IRB.

INSURANCE AND INDEMNITY

Participants will be insured against injury caused by the study according to legal requirements. The participants will be informed about the insurance. Medical care for all adverse events will be provided by the Sponsor.

In case of an injury or death during the study to the participants, the Sponsor will provide complete medical management and compensation in the case of trial related injury or death in accordance with rule 122 DAB and the procedures prescribed under Schedule Y, and the details of compensation provided in such cases will be intimated to DCGI within thirty days of the receipt of the order of the said authority.

STORAGE OF SPECIMENS

All fresh blood samples will be processed as soon as possible after collection. Storage of samples is not advisable.

Only ICMR-NIRT, Chennai would store additional samples (blood, plasma, and serum) at their own cost for future immunogenicity studies.

12. RESPONSIBILITIES

RESPONSIBILITIES OF SPONSOR

Following are the responsibilities of Sponsor:

- Regulatory submissions.
- Be aware of, and should comply with, GCP and the applicable regulatory requirements.
- Select qualified Investigators to facilitate the communication between Investigators at various sites.
- Provide Investigator with an up-to-date IB or equivalent documents.
- Define and allocate all Study related duties and responsibilities to the respective identified person(s) / organization(s).

- Provide the PI with all information he / she needs for submission to IEC / IRB and / or regulatory authority.
- Provide Investigator with any information of possible relevance to the clinical study that becomes available during a trial.
- Review monitoring reports and resolve outstanding issues.
- Obtain from the Investigator(s) and / or the Institutions confirmation of review by the Ethics Committee.
- Supply investigational products.
- Ensure the preparation and appropriate approval(s) of a comprehensive final clinical study report, whether or not the study has been completed.

RESPONSIBILITIES OF INVESTIGATORS

- Be thoroughly familiar with the appropriate use of the investigational products, as described in the protocol, in the current Investigator‘s Brochure (IB), in the product information and in other information sources provided by the Sponsor.
- Be aware of, and should comply with, GCP and the applicable regulatory requirements
- Permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority (ies).
- Maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related duties.
- Have sufficient time to properly conduct and complete the trial within the agreed trial period.
- Have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- Ensure that all persons assisting with the trial are adequately informed and trained about the protocol, the IP(s), and their trial-related duties and functions.
- A qualified physician, who is an Investigator or a sub-Investigator for the trial, should be responsible for all trial-related medical decisions.
- During and following a participant's participation in a trial, the Investigator should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial.
- Before initiating a trial, the Investigator should have written and dated approval / favorable opinion from the IEC for the trial protocol, written informed consent/assent form, consent form updates, participant recruitment procedures (*e.g.*, advertisements), and any other written information to be provided to participants.

- The Investigator should conduct the trial in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority (ies) and which was given approval / favorable opinion by the IEC.
- The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval / favorable opinion from the IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial [*e.g.*, change in monitor(s), change of telephone number(s)].
- The Investigator should promptly report to the ethics committee, the monitor, and the Sponsor:
    1. Deviations from or changes of, the protocol to eliminate immediate hazards to the participants.
    2. Changes that increase the risk to participant(s) and / or affecting significantly the conduct of the study.
    3. All adverse drug reactions and adverse events those are serious and / or unexpected.
    4. New information that may adversely affect safety of the participants or the conduct of the study.
    5. For reported deaths, the Investigator should supply any additional information (*e.g.*, autopsy reports and terminal medical reports).
- Responsibility for investigational products accountability at the trial site(s) rests with the Investigator.
- The investigational products should be stored as specified by the Sponsorand ensure that the investigational products are used only in accordance with the approved protocol.
- The Investigator is responsible for ensuring the unbiased selection of an adequate number of suitable participants according to the protocol.
- In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the Investigator should have the IEC's written approval / favorable opinion of the written informed consent form and any other written information to be provided to participants.
- The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.
- On availability of study results the Investigator may share and ensure appropriate clinical management based on the individual titre values for the study participants.

- Upon completion of the trial, the Investigator should provide IEC with a summary of the trial‘s outcome.

RESPONSIBILITIES OF MONITOR

The monitor should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- Verifying that the Investigator has adequate qualifications and resources and remain adequate throughout the trial period.
- Should ascertain that the institutional facilities like laboratories, equipment, staff, storage space *etc.* are adequate for safe and proper conduct of the study and that they will remain available throughout the study.
- Verifying, for the investigational products that:
    1. Storage times and conditions are acceptable, and that supplies are sufficient throughout the trial,
    2. The investigational products are administered only to participants who are eligible to receive it and at the protocol specified dose(s),
    3. The receipt, use, and return of the investigational products at the trial sites are controlled and documented adequately,
    4. Verifying that the Investigator follows the approved protocol and all approved amendment(s), if any, and
    5. Verifying that written informed consent was obtained before each participant's participation in the trial.
- Ensuring that the Investigator receives the current IB, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- Ensuring that the Investigator and the Investigator's trial staff are adequately informed about the trial.
- Verifying that the Investigator and the Investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the Sponsor and the Investigator and have not delegated these functions to unauthorized individuals.
- Verifying that the Investigator is enrolling only eligible participants.
- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

- Verifying that the Investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- Checking the accuracy and completeness of the eCRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
    1. The data required by the protocol are reported accurately on the eCRFs and are consistent with the source documents.
    2. Any dose and / or therapy modifications are well documented for each of the trial participants.
    3. Adverse events, concomitant medications, and inter current illnesses are reported in accordance with the protocol on the eCRFs.
    4. Visits that the participants fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the eCRFs.
    5. All withdrawals and dropouts of enrolled participants from the trial are reported and explained on the eCRFs.
    6. The Investigator is informed of any eCRF entry errors or omissions.
    7. Adverse events are appropriately reported within the time periods required by GCP, protocol, IEC, Sponsor, and the applicable regulatory requirement(s).
    8. The Investigator is maintaining the essential documents.
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the Investigator, Sponsor, and the ethics committee (if required) and to take appropriate action designed to prevent recurrence of the detected deviations.
- Submit a written report to the Sponsor and Investigator after each trial-site visit or trial-related communication.

13. PROTOCOL MODIFICATIONS AND AMENDMENTS

The protocol will not be amended without prior written approval by the Sponsor. In case if the protocol is amended the Investigator will submit and, where necessary, obtain approval from the IEC / IRB for all subsequent protocol amendments and changes to the ICF document.

ADMINISTRATIVE MODIFICATIONS

Administrative or technical modifications (like change in study team or telephone numbers), which do not have an impact on the participant's health will be communicated in writing and filed as amendments to the protocol by Sponsor. The IEC / IRB and the DCGI will be notified by the Sponsor / PI, if needed.

CLINICAL MODIFICATIONS

Modifications affecting or interfering with the participant's health interests and involving changes in the design of the study or its scientific significance or quality or safety will require protocol amendments and new approvals by DCGI and IEC / IRB. The Sponsor and Investigator will agree to implement / adhere to such modifications only after written approval from DCGI and IEC / IRB.

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor before implementation. Amendments significantly affecting or interfering with the safety of study participants and involving changes in the design of the study or its scientific significance or quality or safety, the scope of the investigation require additional approvals by the DCGI, local IEC / IRB for the study site. A copy of the written approval of the IEC / IRB must be given to the Sponsor.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all participants included in the trial. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him / her for safety reason (s), the Sponsor should be notified immediately. The IEC / IRB should also be informed immediately.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IEC / IRB approval but the IEC / IRB must be kept informed of such administrative changes.

PROTOCOL DEVIATIONS AND VIOLATIONS

Any changes from protocol-specified procedures and study-related SOPs occurring during the conduct of the trial will be documented and reported as protocol violations or deviations.

A Protocol Violation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the study which may affect the safety of trial participants or the study outcomes. Examples include wrong randomization or enrolment of participants that do not meet inclusion / exclusion criteria.

A Protocol Deviation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes. Examples of deviations include a protocol visit date outside the study visit window or an isolated incident of a missed or incomplete study procedure or study evaluation. Serious or repeated protocol violations or deviations will require assessment of the root cause and implementation of corrective and preventive action plans. They may constitute grounds to interrupt the trial at a study site.

Protocol Violation and Protocol Deviation logs need to be filled by Study Investigator.

Both Protocol violations and deviations will be reported to local Ethics Committees in accordance with the requirements of the involved committees.

ARCHIVING

All raw data generated in connection with this study, together with the original copy of the final report, will be retained in the archives of study site for a period of five years after the last approval of a marketing application in compliance with Indian GCP guidelines. In addition, the Investigator will make provision for the participant‘s medical records to be kept for the same period of time.

No data will be destroyed without the permission of the Sponsor. The Sponsor will inform the Investigator in writing of the need for record retention and will notify the Investigator in writing when the trial related records are no longer needed.

14. FINAL STUDY REPORT AND PUBLICATION

Sponsor shall make an integrated clinical-biometrics final study report according to ICH-E3 guidelines which, after mutual consent, will also be signed by the PI.

Publication of the study will be independent of analysis results. Any formal presentation or publication of study would be considered as a joint publication by the Investigator(s) and the respective Sponsor personnel. Authorship will be determined by mutual agreement following International Committee of Medical Journal Editors (ICMJE) guidelines (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/).

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LIST OF APPENDICES

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APPENDIX 1 –STUDY SCHEDULE

Investigations	**V 1**	**V 2**	**V 3**	**V4**	**V5**	**V 6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**
	Screening	**Day 0**	**2 W**	**4 W (M1)**	**6 W**	**8 W (M2)**	**24 W (M6)**	**40 W (M10)**	**56W (M14)**	**72 W (M 18)**	**88W (M 22)**	**104W (M 26)**	**120W (M 30)**	**136W (M 34)**	**152W (M 38)**
Informed consent	√														
Vaccination		√		√											
Demographics#, alcohol and smoking status	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medical history	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medications	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Sputum AFB	√					√	√		√		√		√		√
***LFT (SGPT, SGOT, Alkaline Phosphatase,**	√														

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Serum Bilirubin)															
***RFT (Serum Creatinine, Serum Urea)**	√														
***Hemogram**	√														
ELISA for HIV	√														
RBS	√														
Immunological Testing##	√					√	√								
Chest radiograph-PA view###	√					√			√			√			√
Urine Pregnancy test	√	√		√											
TST### #	√						√								
Safety Assessment for AEs and SAEs		√	√	√	√	√	√	√	√	√	√	√	√	√	√

AE: Adverse Event, ELISA: Enzyme Linked Immunosorbent Assay, HIV: Human Immunodeficiency Virus, LFT: Liver Function Test, PA: Posterior-Anterior, RBS: Random Blood Sugar, RFT: Renal Function Test, SAE: Serious Adverse Event, SGPT: Serum glutamate pyruvate transaminase, SGOT: Serum glutamic oxaloacetic transaminase

V: Visit; D-Day; W-Week; M-Month.

*Will be repeated at V6/Month 2, if PI feels necessary.

#Demographics: age, gender, date of birth, weight [kg], and height [m], body mass index [kg/m^2], alcohol consumption/substance use and smoking status/tobacco use. The address [corresponding and permanent] and contact number should be maintained in site records.

##Will be done at AIIMS, New Delhi; ICMR-NARI, Pune; and ICMR-NIRT, Chennai.

###A postero-anterior view will be done in all and an additional lateral view will be done in children <14 years. Amongst children, X-ray will be performed only at baseline and in suspected cases. For females who get pregnant during the course of study will be subjected to X-ray with a shield only if the site study co-ordinator / Principal Investigator decide its necessity, in case of presence of clinical symptoms of TB.

####Will be done at sites - Delhi (NCR), Hyderabadand Chennai.Tuberculin reaction reading will be undertaken at 48-72 hours after administration of the test.

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APPENDIX 2 – LIST OF INVESTIGATORS AND STUDY SITES

State	Site No.	Centers and Sub- Centers (Site/Sub site Name)	Name of Principal Investigator (including contact details)	Name of Co-Investigator (including contact details)
Delhi-NCR (1)	1.0	All India Institute of Medical Science Ansari Nagar, New Delhi - 110029	Prof. RandeepGuleria randeepguleria2002@yahoo.com director.aiims@gmail.com 9810184738	Prof. Anant Mohan anantmohan@yahoo.com 9810048204 Dr. Urvashi drurvashi@gmail.com 9811120203 Dr. D. K. Mitra salilmitra2@gmail.com
	1.1	Civil Hospital, Ballabhgarh Faridabad - 121004, Opposite DusheraMaidan	Dr. Anand Krishnan anand.drk@gmail.com 9811500667	
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	2.3	Jayanagara General Hospital, Jayanagar, Bengaluru		Dr. Parvathi parvathi17790@gmail.com 9497472049
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	6.1	District TB Centre, Hyderabad Secunderabad		Dr. Chala Devi 9866415498

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	6.2	Tuberculosis Unit, Secunderabad		

Singh M, *et al. BMJ Open* 2024; 14:e082916. doi: 10.1136/bmjopen-2023-082916

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APPENDIX 3 – CLINICAL LABORATORIES

S.No.	Laboratory
1.	All India Institute Of Medical Science, Ansari Nagar, New Delhi 110029
2.	BhagwanMahavir Medical Research Centre, Plot No. 10-1-1, BhagwanMahavirMarg, AC Guards, Masab Tank, Hyderabad, Telangana 500004
3.	Indian Council of Medical Research - National AIDS Research Institute, Plot No 73, G-block, M I D C, Bhosari, Pune, Maharashtra 411026
4.	Indian Council of Medical Research - National Tuberculosis Institute, 8, Avalon, Bellary Rd, Near Cauvery Theatre, Guttahalli, Bengaluru, Karnataka 560003
5.	Indian Council of Medical Research - Regional Medical Research Centre, Nandankanan Rd, SamantaVihar, Gajapati Nagar, Bhubaneswar, Odisha 751017
6.	Indian Council of Medical Research - National Institute for Research in Tuberculosis, No. 8/1-2, Mayor Sathyamoorthy Street, Korukkupet, Chetpet, Chennai, Tamil Nadu 600031

Singh M, *et al. BMJ Open* 2024; 14:e082916. doi: 10.1136/bmjopen-2023-082916

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APPENDIX 4 – DIARY CARD TEMPLATE FOR SOLICITED ADVERSE EVENTS

Unique ID:

Date of Visit:

Date of Next Visit:

Side effects (if any) details:

Name of Side effect	Side effect Start Date	Side effect Stop Date	Severity 1=Mild 2=Moderate 3=Severe 4=Life threatening	Name of Medication Prescribed for side effect	Medication Start Date	Medication Stop Date
Injection Site pain or tenderness						
Redness (Erythema)						
Swelling (Induration)						
Subcutaneous abscess (collection of pus beneath the skin)						
Blister						
Keloid (overgrowth of scar)						
Fever						

Study Nurse Name and Contact details (e-mail/Mobile):

Study Doctor Name and Contact details (e-mail/Mobile):

Instructions

1. Please use ball point pen only for filling the details.

Singh M, *et al. BMJ Open* 2024; 14:e082916. doi: 10.1136/bmjopen-2023-082916

2. Do not overwrite. Make correction by cancelling the entry with single line. Sign and date over the corrected entry.
3. Dates should be entered in DD-MMM-YY format [Example: 31-JAN-18].
4. Please refer to the following table for assessing the severity of the side effect:

Local reactions (at the injection site)	**Severity grade**
Injection Site pain or tenderness	
Pain or tenderness causing no or minimal limitation of use of limb	**1 (Mild)**
Pain or tenderness causing greater than minimal limitation of use of limb	**2 (Moderate)**
Pain or tenderness causing inability to perform usual social and functional activities	**3 (Severe)**
Pain or tenderness causing inability to perform basic self-care function OR hospitalization is indicated	**4 (Potentially Life Threatening)**
Redness (Erythema)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**
Potentially life-threatening consequences (*e.g.* abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissues)	**4 (Potentially Life Threatening)**
Swelling (Induration)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**

Potentially life-threatening consequences (*e.g.* abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissues)	**4 (Potentially Life Threatening)**
Ulceration, Subcutaneous abscess (collection of pus beneath the skin), Blister, Keloid (overgrowth of scar)	
Longest diameter: 2.5 to < 5 cm	**1 (Mild)**
Longest diameter: ≥ 5 to < 10 cm	**2 (Moderate)**
Longest diameter: ≥ 10 cm	**3 (Severe)**
Potentially life-threatening consequences	**4 (Potentially Life Threatening)**
Fever (axillary temperature measured once daily even in the absence of signs)	
38°C to <38.6°C	**1 (Mild)**
≥38.6°C to <39.3°C	**2 (Moderate)**
≥39.3°C to <40°C	**3 (Severe)**
≥ 40°C	**4 (Potentially Life Threatening)**

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APPENDIX 5 – DIARY CARD TEMPLATE FOR UNSOLICITED ADVERSE EVENTS

Unique ID:

Date of Visit:

Date of Next Visit:

Side effects (if any) details:

Name of Side effect	**Side effect Start Date**	**Side effect Stop Date**	**Severity** 1=Mild 2=Moderate 3=Severe 4=Life threatening	**Name of Medication Prescribed for side effect**	**Medication Start Date**	**Medication Stop Date**

Study Nurse Name and Contact details (e-mail/Mobile):

Study Doctor Name and Contact details (e-mail/Mobile):

Instructions

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1. Please use ball point pen only for filling the details.
2. Do not overwrite. Make correction by cancelling the entry with single line. Sign and date over the corrected entry.
3. Dates should be entered in DD-MMM-YY format [Example: 31-JAN-18].
4. Please refer to the following table for assessing the severity of the side effect:

Unsolicited Adverse event	**Severity grade**
Adverse Event/Side effect	
Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	**1 (Mild)**
Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	**2 (Moderate)**
Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated	**3 (Severe)**
Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death	**4 (Potentially Life Threatening)**

Singh M, *et al. BMJ Open* 2024; 14:e082916. doi: 10.1136/bmjopen-2023-082916

Summary of changes for Version 1.5 dated 03rd October 2018

Protocol No.:	ICMR/ITRC/VAC/001/2018
Title	A Phase III, Randomized, Double-blind,Three Arm, Placebo controlled Trial to Evaluate the Efficacy and Safety of two vaccines, VPM1002 and Immuvac in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients.
Amendment No. :	Amendment 1
Amendment Date:	3rd October 2018
List of changes:	

- Title :added "Three Arm" , two vaccines" and deleted the word 'vaccine'
  A Phase III, Randomized, Double-blind,**Three Arm**, Placebo controlled Trial to Evaluate the Efficacy and Safety of **two vaccines** VPM1002 and Immuvac(M*w*) in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients