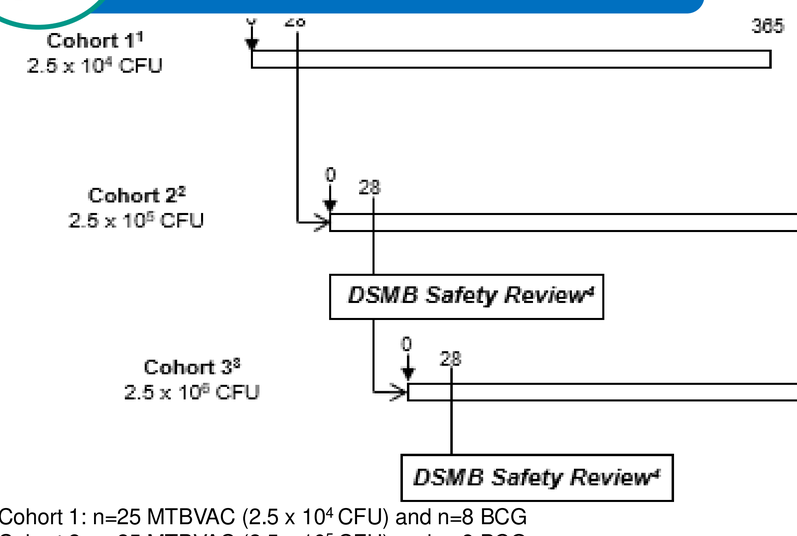
A PHASE 2A RANDOMIZED, DOUBLE-BLIND, DOSE-DEFINING TRIAL OF MTBVAC IN NEWBORNS IN A TB ENDEMIC AREA:

Michele Tameris[1#], Virginie Rozot[1#], Claire Imbratta[1#], Ingrid Murillo[2], Hennie Geldenhuys[1], Justin Shenje[1], Angelique Luabeya[1], Simon Mendelsohn[1], Nicolette Tredoux[1], Michelle Fisher[1], Nicole Bilek[1], Humphrey Mulenga[1] ,Carly Young[1] , Asma, Toefy[1], Ashley Veldsman[1], Natasja Botes[1], Jelle Thole[2], Bernard Fritzell[2], Rajat Mukherjee[4], Juana Doce[2], Nacho Aguilo[3], Dessislava Marinova[3], Jesus Gonzalo-Asensio[3] ,Eugenia Puentes[2], Carlos Martin[3], Thomas Scriba[1#], Mark Hatherill[1#]
[1]South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine, Department of Pathology, University of Cape Town, South Africa, [2]Biofabri S.L., Porriño (Pontevedra), Spain, [3]Department of Microbiology, Faculty of Medicine, University of Zaragoza, Spain, [4] Mukherjee-Consultants, Barcelona, Spain

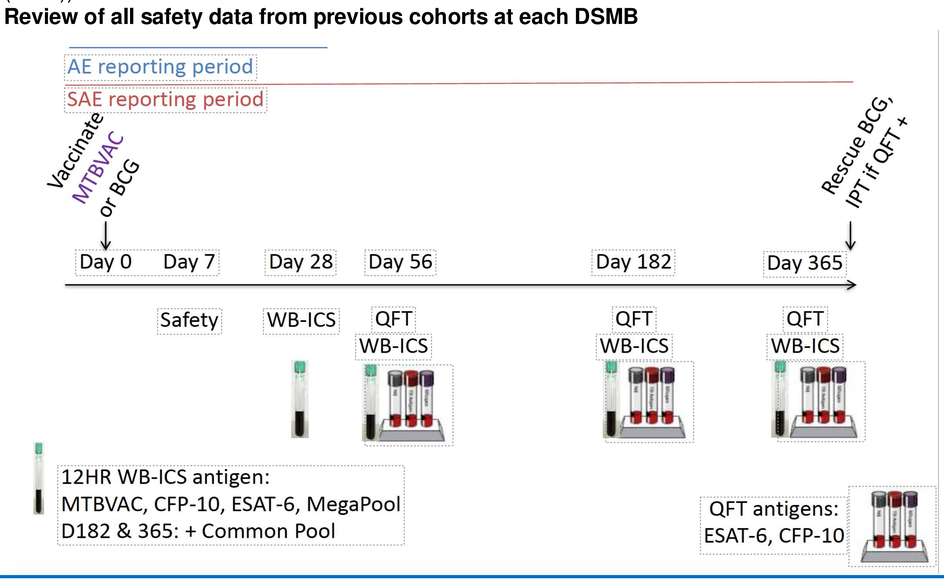
AIMS

- Vaccination at birth with **three escalating doses** of the live-attenuated *Mycobacterium tuberculosis* (*Mtb)* vaccine candidate, **MTBVAC**, in comparison to BCG in South African newborns.
- Safety and reactogenicity outcomes: frequencies of solicited systemic and local injection site AE, unsolicited AE, and SAE.
- Immunogenicity endpoints: frequencies of antigen-specific IFN-g, TNF, IL-2, IL-17, and/or IL-22 expressing CD4 and CD8 T cells, measured by 12-hour whole blood intracellular cytokine staining (WB-ICS) at Days 28,56,182, and 365.
- Secondary aim: to evaluate quantitatively and qualitatively IGRA responses on Days 56, 182, and 365.

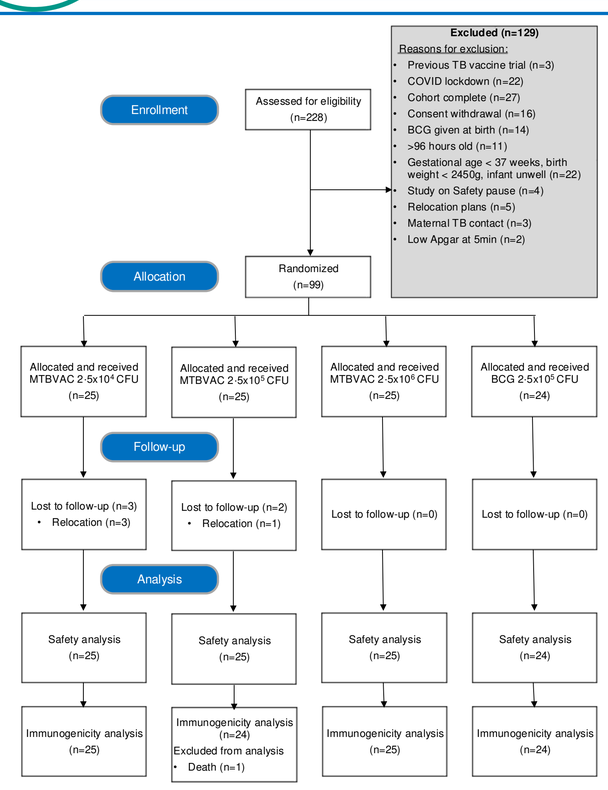
METHODS

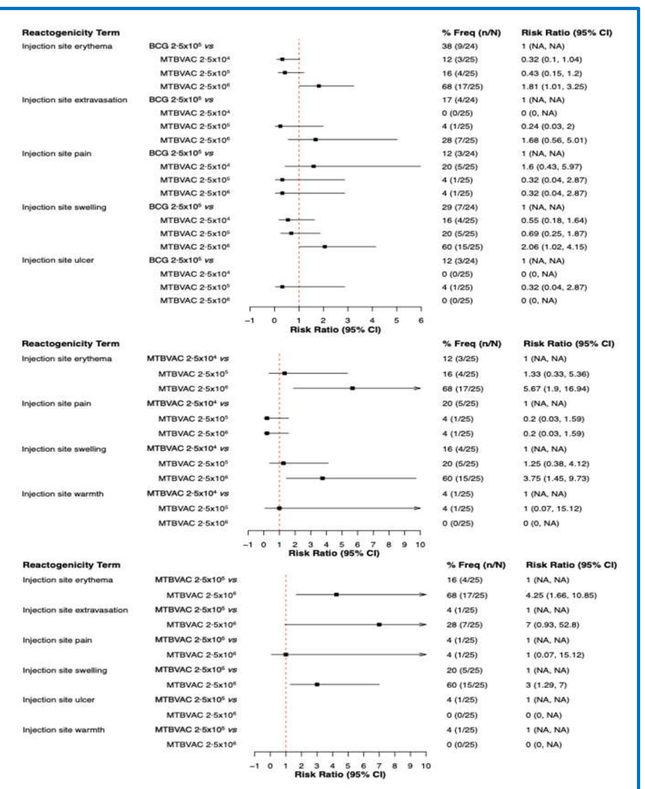


Cohort 1: n=25 MTBVAC (2.5 x 10^4 CFU) and n=8 BCG
Cohort 2: n=25 MTBVAC (2.5 x 10^5 CFU) and n=8 BCG
Cohort 3: n=25 MTBVAC (2.5 x 10^6 CFU OR 2.5 x 10^5 CFU (n=13) plus 2.5 x 10^4 CFU (n=12)) and n=8 BCG
Review of all safety data from previous cohorts at each DSMB



RESULTS





63 of 99 infants across all three cohorts had solicited AE through Day 56
- all rated mild except one grade 2 erythema in an MTBVAC 2·5×10^5 CFU recipient.
- **Induration, swelling, and erythema** were more frequent with increasing MTBVAC dose.
- **Redness, swelling, pain, ulceration, and discharge** were less frequent in receiving MTBVAC 2·5×10^5 CFU compared to BCG
- **tion and swelling** were more frequent in infants receiving MTBVAC 2·5×10^6 CFU than those receiving BCG.

Solicited and unsolicited systemic AE reflected common early childhood ailments and were evenly distributed between study vaccines across groups.

12 infants (3 BCG and 9 MTBVAC (6 in cohort 1, 2 in cohort 2, and 1 in cohort 3 groups) experienced **14 vaccine-unrelated SAE including**
- **1** death of an MTBVAC 2·5×10^5 CFU recipient, due to bronchopneumonia, confirmed at autopsy.
- **6** hospitalisations for respiratory tract infection
- **3** for gastroenteritis; **2** for neonatal jaundice; and **1** each for breast abscess, pertussis, and possible TB meningitis.

9 infants (9%) were treated for **TB.**
- 4 of 24 **BCG** recipients (**16.7%**) and 4 [all cohort 1] of 75 **MTBVAC** recipients (**5.3%**), were treated for unconfirmed pulmonary TB.
- 1 infant in each of the MTBVAC cohort 1 and BCG groups were Xpert MTB/RIF Ultra positive on induced sputum, which was classified as unconfirmed TB.
- No infants in the MTBVAC 2·5×10^5 or 2·5×10^6 CFU cohorts were treated for TB.
- 1 BCG recipient (4.2%) was diagnosed with unconfirmed TB meningitis nine days post-vaccination

MTBVAC is safe and well-tolerated at all three dose levels in infants, with the 2·5×10^5 CFU MTBVAC dose being less reactogenic and more immunogenic than the licensed BCG vaccine.

In concordance with WHO recommendations, the 2·5x10^5 CFU MTBVAC dose was selected for phase 3 efficacy evaluation compared to BCG vaccination in infants

Acknowledgements

Study participants & families, MTBVAC 202 clinical, lab and support teams.
Funders: EDCTP 2, Biofabri

This project is part of the EDCTP2 programme supported by the European Union