MTBVAC vaccine
as newborns BCG replacement and
as boosting BCG in adolescents / adults

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CONSTRUCTION OF MTBVAC: GENEVA CONSENSUS CRITERIA

TWO STABLE INDEPENDENT MUTATIONS
NO ANTIBIOTIC RESISTANCE MARKERS

LIVE ATTENUATED FROM a *M. tuberculosis* Clinical Isolate LINEAGE 4

PRECLINICAL & PROOF-OF-CONCEPT STUDIES (2001-2012)

GMP DEVELOPMENT OF FREEZE-DRIED MTBVAC (2008-2011)

MTBVAC

*phoP*  
*fadD26*
MTBVAC, 519 MORE EPITOPEs THAN BCG WHICH REPRESENTS AN INCREASE OF 48%
Improved protection of MTBVC as compared to BCG is associated with T-cell mediated response to CFP10/ESAT6

*M85B*: BCG a polymorphism unstable protein  
(Copin et al. 2014)

**ESAT6/CFP10 present in RD1**

**Culture-Filtrate Protein**

**Intracellular Protein**

**Culture-Filtrate Protein**

MHC Haplotype:  
- H-2b  
- H-2d  
- H-2k

Protection in lungs (very low-dose H37Rv challenge: ≈ 20 CFU)
**Newborn mice vaccination:** MTBVAC is safe and efficacious conferring greater immunogenicity and protective efficacy than BCG

(Aguilo et al Tuberculosis 2016)

**Guinea Pigs revaccination** with MTBVAC improves BCG's protection

(Clark et al J Infect Dis. 2017)

**NON HUMAN PRIMATES:**

**Adult Study:** MTBVAC given as a single vaccination to adult macaques resulted in a significant reduction in the level of pathology, compared to unvaccinated or vaccinated with BCG at birth

**Neonatal BCG Vaccination:** MTBVAC delivered as a booster vaccination, 4 years later, to macaques primed in infancy with BCG resulted in a significant reduction in TB-induced pathology when vaccinated with MTBVAC

Efficacy studies of MTBVAC in Non Human Primates at PHE (Study 5449, sponsored AERAS)
Sally Sharp et al personal communication Preliminary unpublished results
VACCINE TARGET:

1. **NEWBORNS** (BCG replacement): **ideal for efficacy studies** since are not pre-exposed, not TB infected, (avoiding potential masking and blocking effect)

2. **ADULTS/adolescents** (previous BCG vaccination): **More complex efficacy trial**, infected with TB or other mycobacteria, potential masking and blocking effect
R&D MTBVAC VACCINE:

MTBVAC as a vaccine for newborns as BCG replacement (Vaccine Effectiveness)

MTBVAC as vaccine in adolescents and adults who have previously receive BCG vaccination, with and without LTBI (Vaccine Impact)
MTBVAC CLINICAL DEVELOPMENT

2010
MTBVAC final lot May 2011

2011
Non-clinical studies to support clinical evaluation 25 Aug’10 – 20 Dec’11

2012
Phase I CTA Preparation Oct’11 – April ‘12

2013
Long-term, real time stability studies

2014
First ever live attenuated M. tuberculosis vaccine to enter clinical trial

2015
Approval 3 Oct 2012

2016
PHASE 1a HEALTHY ADULTS in CHUV Switzerland PPD+, BCG+, HIV- (18-45 yrs) Vaccination phase: 23 Jan - 6 Nov 2013

2017
PHASE 1b in NEWBORNS With a safety arm in adults (BCG+, PPD, HIV-)

New born vaccination phase 16 Feb - 21 Sep 2016

Report End 2018

Data Published Spertini et al Lancet Resp Med Dec 2015

ClinicalTrials.gov: NCT02013245

ClinicalTrials.gov NCT02729571

PDT: Product Development Team TBVI
CDT: Clinical Development Team TBVI
Phase 1a (first in man) randomized, double-blind, safety, immunogenicity, and dose-escalation study in healthy individuals in a Non-endemic region

36 clinically healthy, HIV-negative, QuantiFERON (QFT)-negative, non BCG vaccinated, 18-45 yrs. old volunteers

Randomized 3:1 to receive:

- MTBVAC (2.5x $10^3$ CFU) or BCG SSI (2.5x$10^5$ CFU) (9+3)
- MTBVAC (2.5x$10^4$ CFU) or BCG SSI (2.5x$10^5$ CFU) (9+3)
- MTBVAC (2.5x$10^5$ CFU) or BCG SSI (2.5x$10^5$ CFU) (9+3)

Objectives

- To evaluate safety and reactogenicity of MTBVAC at escalating dose levels compared to BCG
- To evaluate the immunogenicity of MTBVAC at escalating dose levels (as compared to BCG)

RESULTS PUBLISHED Lancet Respiratory Medicine Spertini et al Dec 2015
MTBVAC 5x10^5 group greater induction of 3 cytokines+ compared to BCG and higher number of responders were observed after MTBVAC vaccination with a peak at D28

Spertini et al 2015 Lancet Respiratory Medicine
ELISPOT ASSAY ESAT-6/CFP-10: Negative 7 months after MTBVAC immunization.

MTBVAC induces a CFP10-specific immune response in humans.

MTBVAC and BCG were compared for their ability to induce a CFP10-specific immune response. The positive cut-off for TB infection was determined to be 50 SFC (Spot-Forming Cells) per million cells.

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Dose-escalation Safety and Immunogenicity Study to Compare MTBVAC to BCG in Newborns With a Safety Arm in Adults

**Phase 1b**

**SAFETY AND IMMUNOGENICITY IN NEWBORNS**

**ClinicalTrials.gov**
NCT02729571
Phase 1b randomized, double-blind, safety, immunogenicity and dose-escalation study in NEWBORNS living in a TB ENDEMIC REGION

18 healthy adults
- randomized 1:1 to receive:
  - MTBVAC (5 x 10^5 CFU) or BCG SSI (5 x 10^5 CFU) (9+9)
  - HIV negative, QuantiFERON (QFT) negative, previously BCG-vaccinated

36 healthy, HIV-unexposed, BCG-naïve, newborns
- randomized 3:1 to receive:
  - MTBVAC (2.5 x 10^3 CFU) or BCG SSI (2.5x10^5 CFU) (9+3)
  - MTBVAC (2.5x10^4 CFU) or BCG SSI (2.5x10^5 CFU) (9+3)
  - MTBVAC (2.5x10^5 CFU) or BCG SSI (2.5x10^5 CFU) (10+2)

Within 96 hrs of birth

Objectives
- To evaluate safety and reactogenicity of MTBVAC at escalating dose levels compared to BCG
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Newborn vaccination phase
Feb - Sep 2016
PHASE 1B STUDY IN NEWBORNS

- MTBVAC is as safe as BCG
- MTBVAC is less reactogenic as compared to same dose of BCG
- MTBVAC induces a dose dependent, and stronger Th1 response as compared to BCG at peak response
- QFT conversion was observed close to 80% in infants at M6 with MTBVAC highest dose reverting to less than 50% in M12 (QFT lower than 4 IU/ml!)

- FURTHER TRIALS IN THESE POPULATIONS ARE WARRANTED

(Michele Tameris personal communication preliminary unpublished data)
ACTIVE CLINICAL DEVELOPMENT MTBVAC

2017

MTBVAC PHASE Ib in NEWBORNS FINISHED
Results end 2018

2018

MTBVAC
Long-term, real time stability studies

NHP Efficacy Non-clinical studies to support clinical evaluation

2019

MTBVAC Phase1b/2a IN ADULTS DOSE FINDING SAFETY AND IMMUNOGENICITY

2020

MTBVAC Phase2a IN NEWBORNS DOSE FINDING SAFETY AND IMMUNOGENICITY

ClinicalTrials.gov
NCT02729571

ClinicalTrials.gov
NCT02933281

ClinicalTrials.gov
NCT03536117
Phase 2a randomized, double-blind, safety, immunogenicity, and dose-finding study in newborns living in a tuberculosis endemic region

99 HIV-unexposed, BCG-naïve, healthy newborns Intradermally within 96hrs of birth
– randomized 3:1 to receive:
  • MTBVAC (2.5x10^4 CFU) or BCG (2.5x10^5 CFU) (25+8)
  • MTBVAC (2.5x10^5 CFU) or BCG (2.5x10^5 CFU) (25+8)
  • MTBVAC (2.5x10^6 CFU) or BCG (2.5x10^5 CFU) (25+8)

**PRIMARY OBJECTIVES**

- To evaluate safety and reactogenicity of MTBVAC at escalating dose levels compared to BCG vaccine in healthy, BCG naïve, HIV unexposed, South African newborns
- To evaluate the immunogenicity of MTBVAC at escalating dose levels compared to BCG vaccine in healthy, BCG naïve, HIV unexposed, South African newborns

**SECONDARY OBJECTIVES**

- To evaluate QFT conversion rates in neonates receiving escalating dose levels of MTBVAC

Center de Recherche Biomedical e Espoir Pour La Santé (BRC-EPLS)/ Senegal
Institut Pasteur de Madagascar (IPM)/ Madagascar
Phase 1b/2a DOSE FINDING SAFETY AND IMMUNOGENICITY IN ADULTS 2018
Re-VACCINATION IN ADOLESCENTS / ADULTS
Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and
Dose-escalation Study in Adults with and without LTBI in South Africa.

Trial Population – 144 (96 +48 )

QFT negative individuals:
- Cohort 1: n =12 MTBVAC (2.5 x 10^3 CFU) and n=6 BCG
- Cohort 2: n= 12 MTBVAC (2.5 x 10^4 CFU) and n=6 BCG
- Cohort 3: n= 12 MTBVAC (2.5 x 10^5 CFU) and n=6 BCG
- Cohort 4: n= 12 MTBVAC (2.5 x 10^6 CFU) and n=6 BCG

QFT positive individuals:
- Cohort 5: n =12 MTBVAC (2.5 x 10^3 CFU) and n=6 BCG
- Cohort 6: n= 12 MTBVAC (2.5 x 10^4 CFU) and n=6 BCG
- Cohort 7: n= 12 MTBVAC (2.5 x 10^5 CFU) and n=6 BCG
- Cohort 8: n= 12 MTBVAC (2.5 x 10^6 CFU) and n=6 BCG

ClinicalTrials.gov
NCT02933281

Site PI Angelique Luabeya
OBJECTIVES

Phase 1b/2a, double-blind, randomized, BCG-controlled, dose-escalation safety and immunogenicity study in healthy adults with and without LTBI

Primary:
Adverse events, injection site reactions

Secondary:
**Immunogenicity** of MTBVAC at escalating dose levels measured by 12 hour whole blood (WB) intracellular cytokine staining (ICS) assay 180 D

QuantiFERON® TB (QFT) conversion rates in QFT-negative adults, receiving escalating dose levels of MTBVAC measured with QFT Gold Plus assay.

QFT-negative adults, receiving escalating dose levels of MTBVAC in comparison to BCG measured by QFT Gold Plus assay.
LOOKING FOR CLINICAL EFFICACY TRIALS IN ENDEMIC AREAS

- EFFICACY STUDIES FOR BCG REPLACEMENT
MTBVAC ID Vaccination at birth
WILL BE DESIGNED TO DEMONSTRATE SUPERIOR PROTECTION AGAINST DISEASE COMPARED TO BCG

(Tameris et al. The Lancet 2013)

- EFFICACY STUDIES IN ADULT / ADOLESCENTS ??
MTBVAC ID Vaccination in adults/adolescents previously BCG vaccinated
WILL BE DESIGNED TO DEMONSTRATE SUPERIOR AGAINST DISEASE COMPARED TO PLACEBO

POI: (Differential QFT test need to be studied at present Phase1b/2a)
Participants, their parents and the community