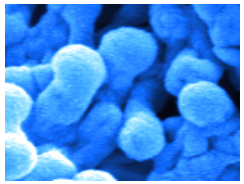
RiCC
RePORT INTERNATIONAL COORDINATING CENTER

Suzhou City, China

4th Annual RePORT International Meeting

MTBVAC



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

TBVI
TuBerculosis Vaccine Initiative

13th September 2018

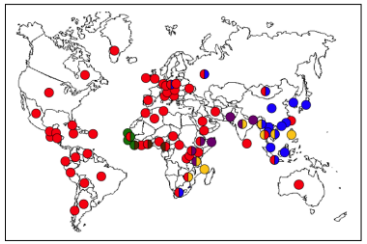
Universidad Zaragoza

Carlos Martín
(University of Zaragoza, Spain)
carlos@unizar.es

BIOFABRI

CONSTRUCTION OF MTBVAC: GENEVA CONSENSUS CRITERIA

TWO STABLE INDEPENDENT MUTATIONS
NO ANTIBIOTIC RESISTANCE MARKERS



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

ELSEVIER

Vaccine

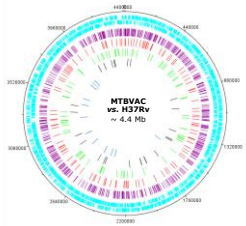
Volume 23, Issue 29, 31 May 2005, Pages 3753-3761

New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development ☆

Arun T. Kamath [a], Uli Fruth [b], Michael J. Brennan [c], Roland Dobbelaer [d], Peter Hubrechts [e], Mei Mei Ho [f], Ronald E. Mayner [g], Jelle Thole [h], K. Barry Walker [i], Margaret Liu [j], Paul-Henri Lambert [a]

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

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



MTBVAC

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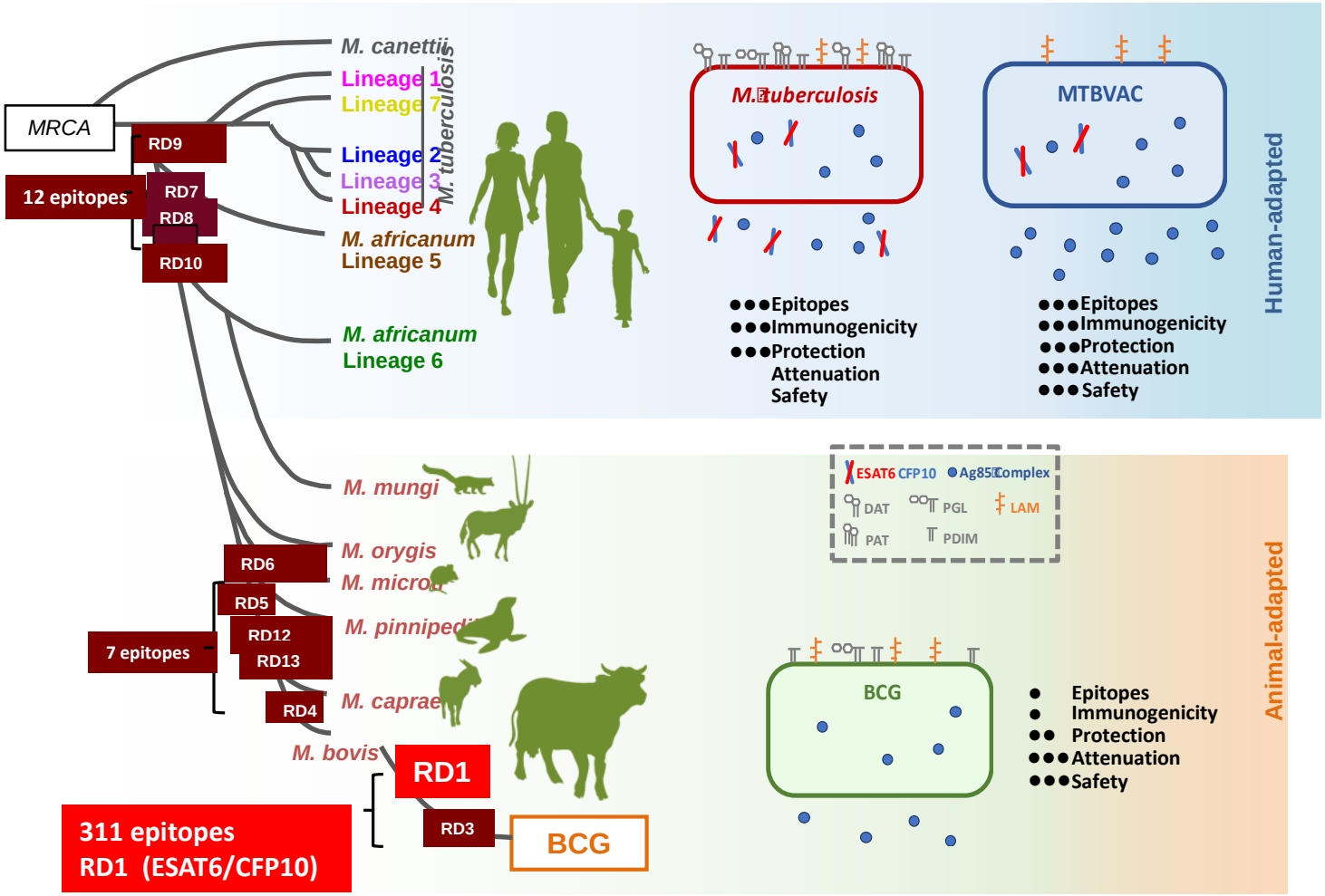
MTBVAC, 519 MORE EPITOPES THAN BCG WHICH REPRESENTS AN INCREASE OF 48%



MTBVAC →
1603 epitopes

BCG →
1084 epitopes

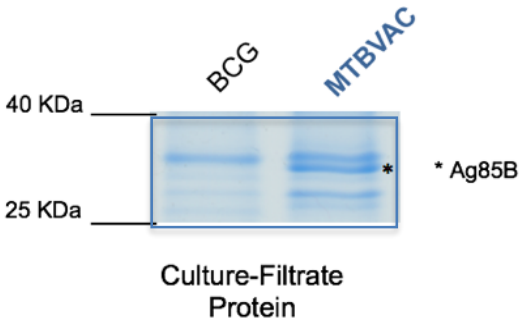
Marinova *et al* Expert Rev Vaccines 2017

Gonzalo-Asensio et al Frontiers Immunology 2017

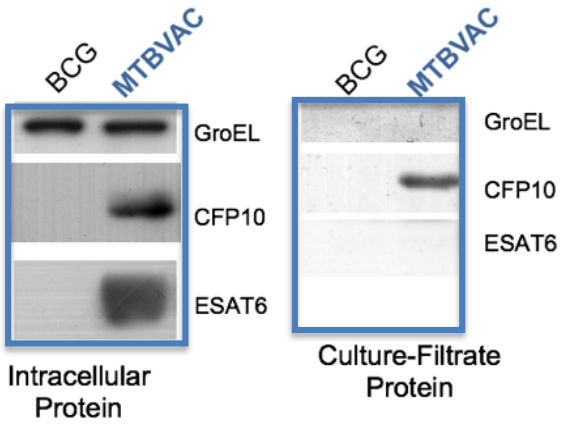
Improved protection of MTBVAC as compared to BCG is associated with T-cell mediated response to CFP10/ESAT6

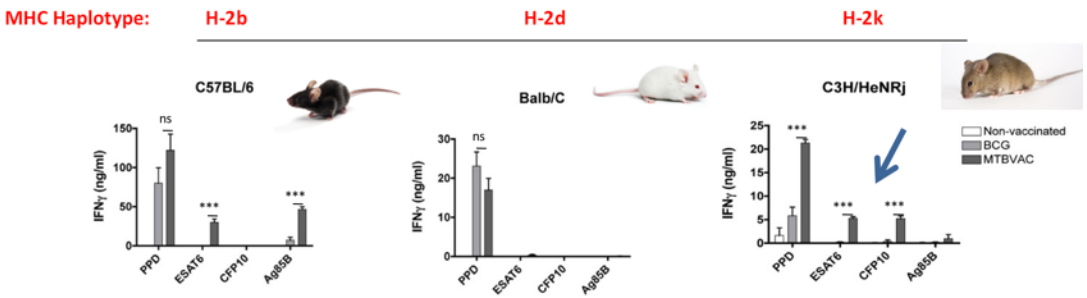
Ag85B: BCG a polymorphism unstable protein

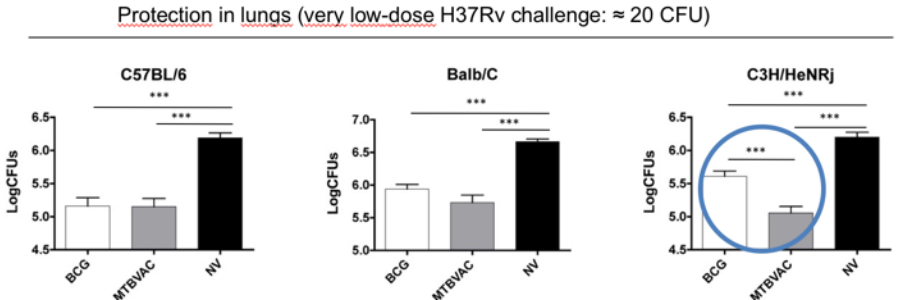
(Copin *et al*. 2014)



ESAT6/CFP10 present in RD1







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Aguilo *et al 2017 Nature Communications*

MTBVAC NON CLINICAL STUDIES SUPORTING TO MOVE TO EFFICACY TRIALS IN HUMANS

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:

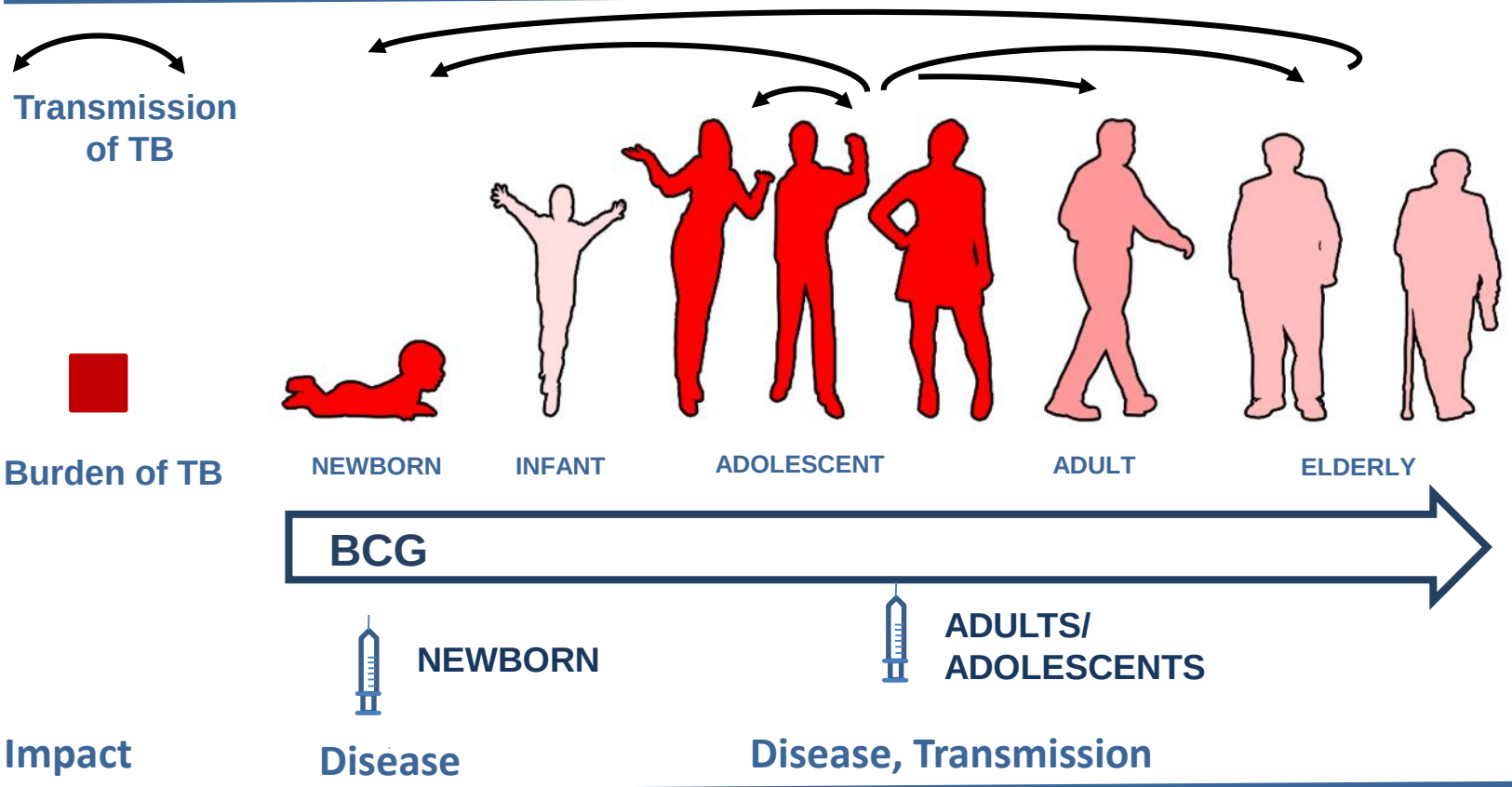
Adult Study: MTBVAC given as a **single vaccination to adult** macaques resulted in a significant reduction in the level of pathology, compared to unvaccinated or vaccinated with BCG at birth

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

PRELIMINARY UNPUBLISHED RESULTS

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

TB DISEASE BURDEN IN AGE GROUPS



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)

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TBVI
TuBerculosis Vaccine Initiative

MTBVAC CLINICAL DEVELOPMENT

BIOFABRI

2010 2011 2012 2013 2014 2015 2016 2017

MTBVAC
final lot
May 2011

Long-term, real time stability studies

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

FECYT Fundación Española para la Ciencia y la Tecnología

charles river · Health Protection Agency · BIOFABRI

Phase I CTA Preparation
Oct'11 – April '12

swissmedic

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

Universidad Zaragoza

CTA Evaluation

swissmedic

Approval
3 Oct 2012

PHASE 1a HEALTHY ADULTS

in CHUV Switzerland PPD$^-$, BCG$^-$, HIV$^-$ (18-45 yrs)

MCC Medicines Control Council

Vaccination phase:
23 Jan - 6 Nov 2013

Centre Hospitalier Universitaire Vaudois

ClinicalTrials.gov: NCT02013245

Bill & Melinda Gates foundation

PHASE 1b in NEWBORNS

With a safety arm in adults (BCG+, PPD-, HIV-)

New born vaccination phase
16 feb - 21 Sep 2016

satvi South African Tuberculosis Vaccine Initiative

ClinicalTrials.gov NCT02729571

NORAD Norwegian Agency for Development Cooperation

Data Published Spertini et al
Lancet Resp Med Dec 2015

Report End 2018

TBVI Tuberculosis Vaccine Initiative

PDT: Product Development Team **TBVI**

CDT: Clinical Development Team **TBVI**

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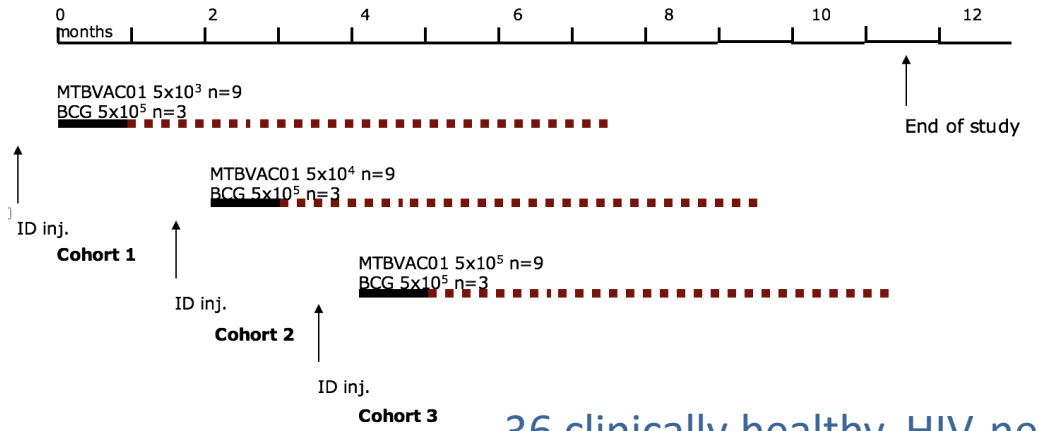
Phase 1a

SAFETY AND IMMUNOGENICITY IN ADULTS

Phase1a (first in man) randomized, double-blind, safety, immunogenicity, and dose-escalation study in healthy individuals in a Non-endemic region

BIOFABRI



ClinicalTrials.gov: NCT02013245

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 (2.5x10^5 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) (9+3)

Prof. F. Spertini

Centre hospitalier universitaire vaudois

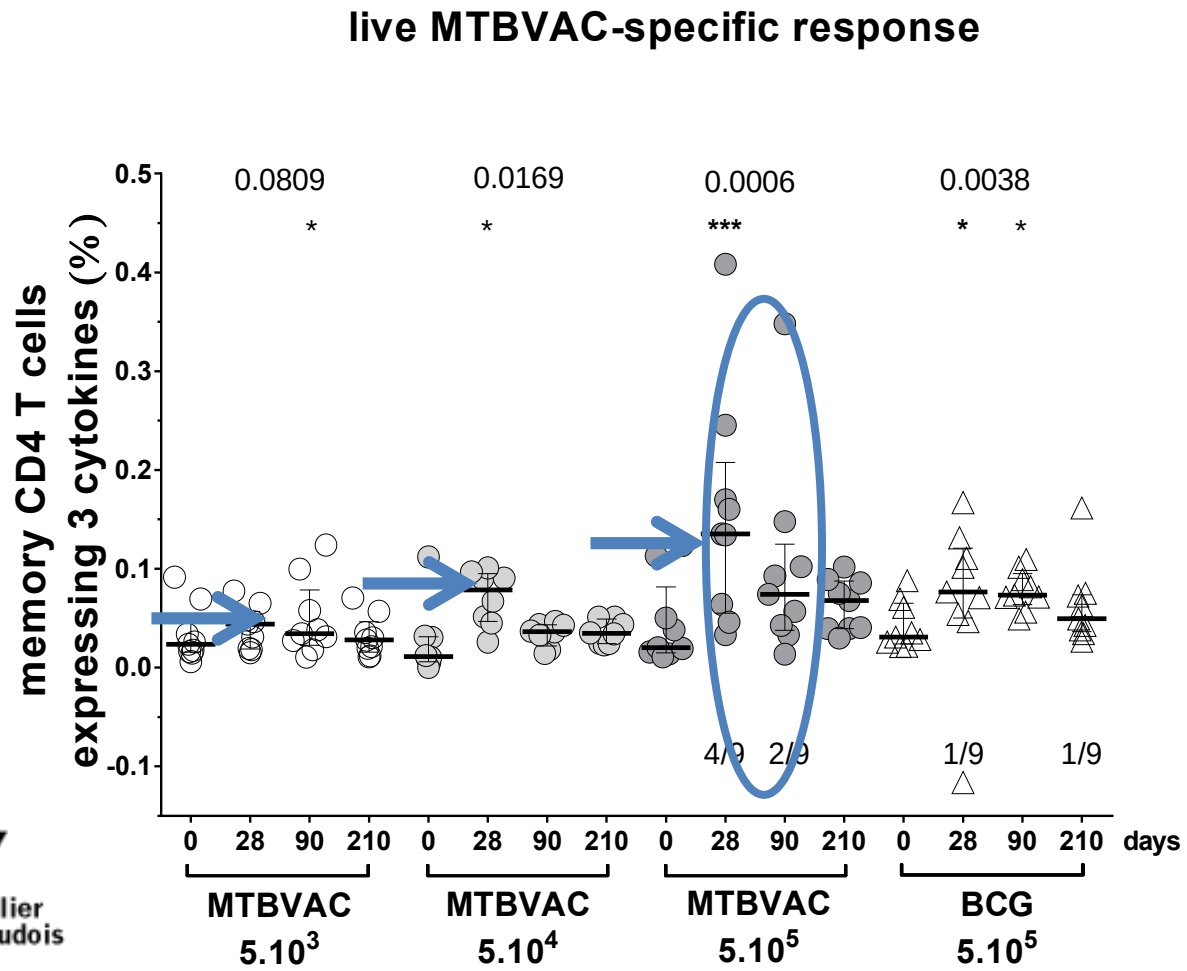
BILL & MELINDA GATES foundation

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

POLYFUNCTIONAL CD4+ T CELL WBA 3 CYTOKINES (IFNY, IL2, TNFα)



Higher number of responders peak at D28 in MTBVAC $5x10^5$ group

WBA stimulation with MTBVAC

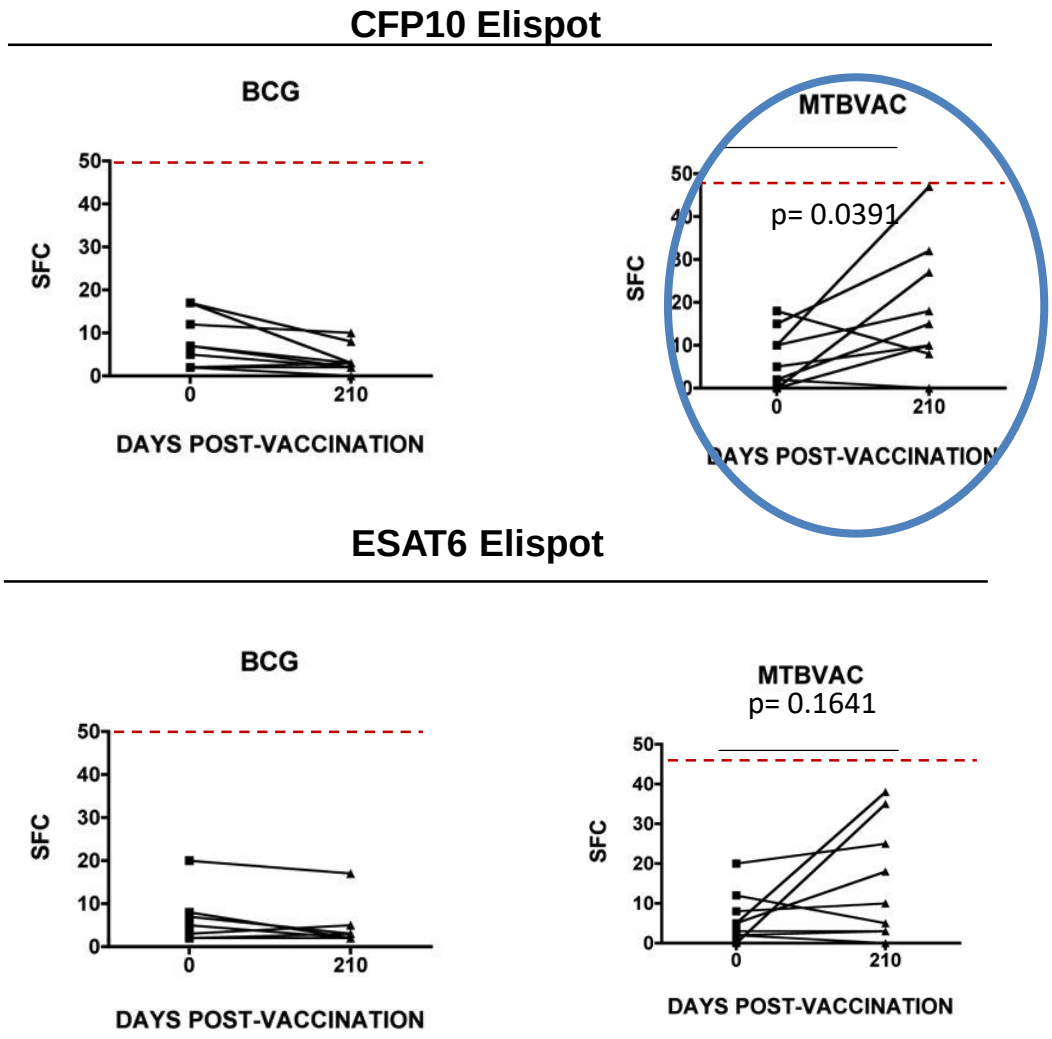
Centre Hospitalier Universitaire Vaudois

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



Aguilo *et al July 2017 Nat Comm*

Phase 1b

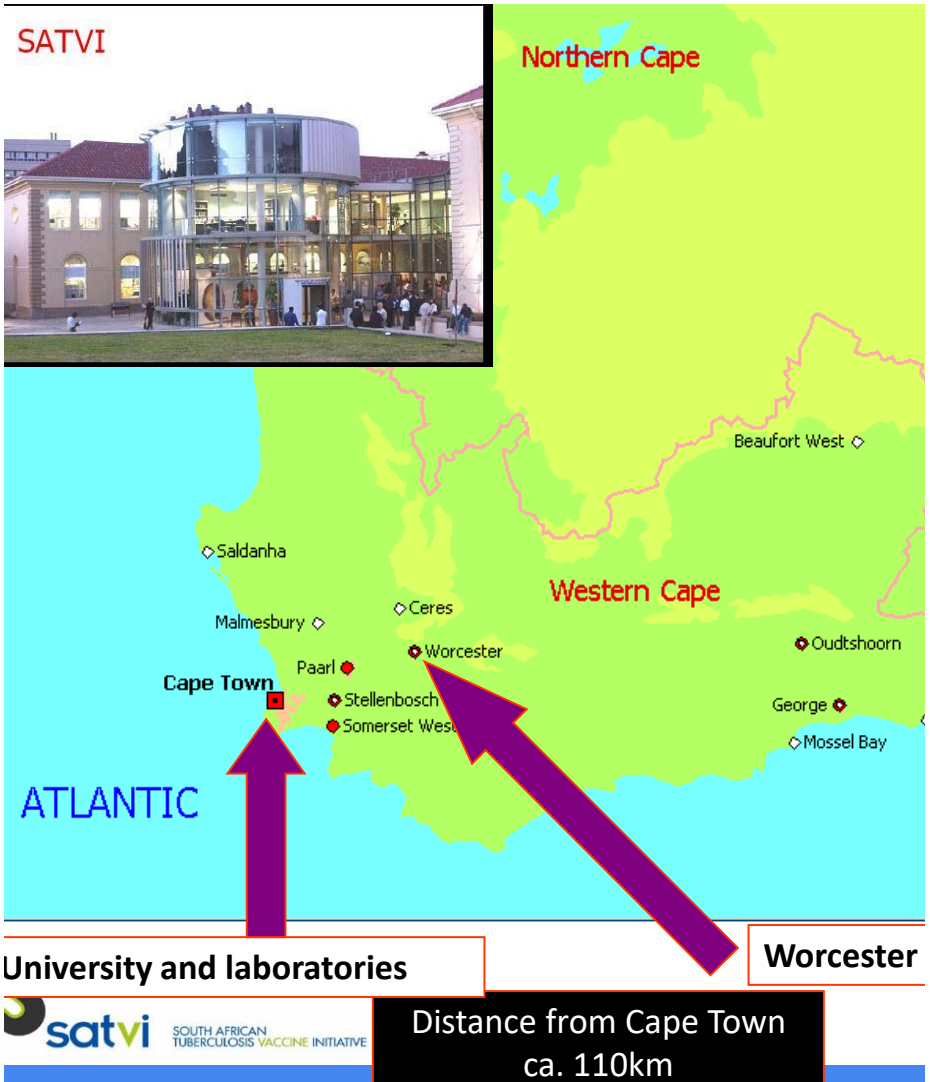
SAFETY AND IMMUNOGENICITY IN NEWBORNS

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

Mark Hatherill

Tom Scriba

Helen Mearns



Michele Tameris

ClinicalTrials.gov
NCT02729571

NORAD
DIREKTORATET FOR UTVIKLINGSSAMARBEID
NORWEGIAN AGENCY FOR DEVELOPMENT COOPERATION

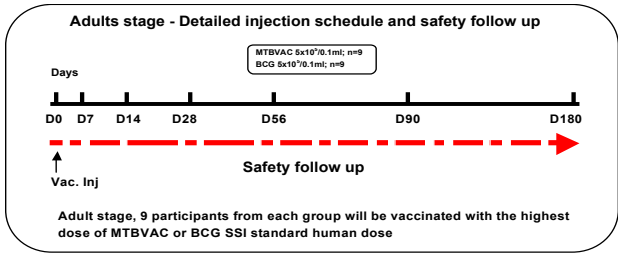
BIOFABRI

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

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

BIOFABRI

SAFETY ARM IN ADULTS WITH HIGHEST DOSE MTBVAC PREVIOUSLY VACCINATED WITH BCG

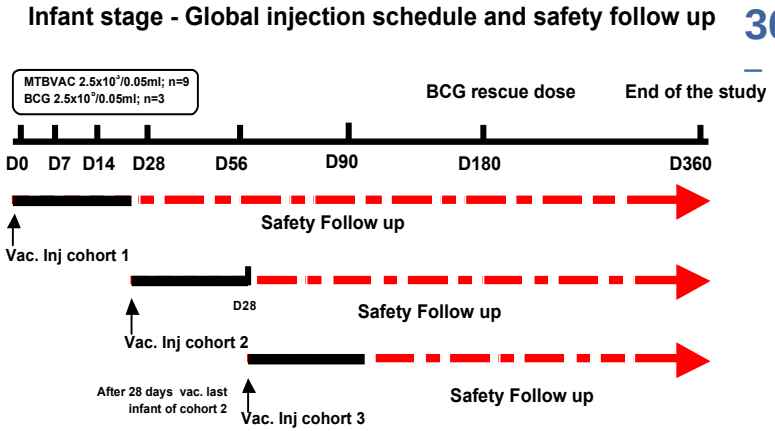


Sept 2015

ClinicalTrials.gov
NCT02729571

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 (2.5x 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
- To evaluate the immunogenicity of MTBVAC at escalating dose levels (as compared to BCG)

Newborn vaccination phase
Feb - Sep 2016

NORAD
DIREKTORATET FOR UTVIKLINGSSAMARBEID
NORWEGIAN AGENCY FOR DEVELOPMENT COOPERATION

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 4IU/ml !)

PRELIMINARY
UNPUBLISHED RESULTS

- FURTHER TRIALS IN THESE POPULATIONS ARE WARRANTED

(Michele Tameris personal communication preliminary unpublished data)

ACTIVE CLINICAL DEVELOPMENT MTBVAC

BIOFABRI

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2017 2018 2019 2020

MTBVAC

Long-term, real time stability studies

NHP Efficacy Non-clinical studies to support clinical evaluation

Public Health England

MTBVAC PHASE Ib in NEWBORNS FINISHED
Results end 2018

ClinicalTrials.gov NCT02729571

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

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

ClinicalTrials.gov NCT02933281

CDMRP

NIH National Institutes of Health

MTBVAC Phase2a IN NEWBORNS DOSE FINDING SAFETY AND IMMUNOGENICITY

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

ClinicalTrials.gov NCT03536117

EDCTP

TBVI TuBerculosis Vaccine Initiative

AERAS

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Phase2a randomized, double-blind, safety, immunogenicity, and dose-finding study in newborns living in a tuberculosis endemic region

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

BIOFABRI

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)

ClinicalTrials.gov
NCT03536117

Site PI Michele Tameris

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

EDCTP
RIA2016V-1637

Center de Recherche Biomedical e Espoir Pour La Santé (BRC-EPLS)/ Senegal
Institut Pasteur de Madagascar (IPM)/ Madagascar

TBVI

Universidad Zaragoza

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.**

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

AERAS

Trial Population – 144 (96 +48)

ClinicalTrials.gov
NCT02933281

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

Site PI Angelique Luabeya

CDMRP NIH National Institutes of Health AERAS BIOFABRI TBVI Tuberculosis Vaccine Initiative Universidad Zaragoza 1542

OBJECTIVES

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

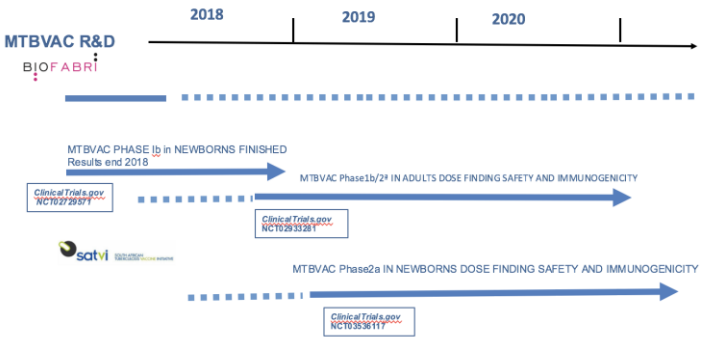
Primary :
Adverse events, injection site reactions

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)

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Simba Mabwe
Nicole Bilek

SATVI Clinical
Mark Hatherill
Michele Tameris
Angelique Luabeya
Hennie Geldenhuys
Justin Shenje
and MTBVAC study team





Participants, their parents and the community

Puente de Piedra (Zaragoza)

Puente de Rande (Vigo)

Tacoma Narrows Bridge (Seattle)

Universidad Zaragoza

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

CTVD The Collaboration for TB Vaccine Discovery

ciberes Centro de Investigación Biomédica en Red Enfermedades Respiratorias

TBVAC 2020

EurolacTB European Latin American-Caribbean Tuberculosis Consortium

SLAMTB Sociedad Latinoamericana de Tuberculosis y otras Micobacteriosis

BILL & MELINDA GATES foundation

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European Commission

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CHUV Centre Hospitalier Universitaire Vaudois

University of Cape Town

Portico de la Gloria (Santiago)