¿PARA CUÁNDO UNA SOLUCIÓN A LA TUBERCULOSIS?

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Tuberculosis has caused more deaths than any other infectious disease.
More than a Billion dead in the last 200 years.
Albert CALMETTE & Camille GUÉRIN
*Mycobacterium bovis* 1908-1921
230 Passages

**VACCINE BCG**

Different BCG isolates distributed between the different laboratories around the World

BCG INITIALLY ADMINISTRATED ORALLY
1921-1926: 50,000 infants vaccinated:
25 % Non vaccinated mortality vs
1.8 % Vaccinated mortality

Adapted from Brosch et al. PNAS 2007
**BENEFICIAL EFFECTS OF BCG VACCINATION:**

1. BCG provides **strong protection against disseminated forms** of the disease.
2. BCG vaccination **reduces all-cause mortality** through beneficial non-specific (heterologous) effects on the immune system.

**NEEDS FOR IMPROVEMENT:**
- PROTECTION PULMONARY FORMS OF TB
- LONG TERM PROTECTION IN ADOLESCENTS
The Global Burden of TB, 2017

Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS)

Estimated number of cases

10.0 million
- 1.0 million children
- 3.2 million women
- 5.8 million men

1.7 million

Estimated number of deaths

22 per 100,000
- 250,000 in children
- 490,000 in women
- 930,000 in men

About 1.7 billion people, 23% of the world’s population, are estimated to have a latent TB infection, and are thus at risk of developing active TB disease during their lifetime.
95% MTB strains Human origin

NATURAL HISTORY OF TUBERCULOSIS

"Individuals with LTBI had 79% lower risk of Progressive TB after reinfection than uninfected individual"
Andrews et al CID 2012

THE STAGES IN THE IMMUNOLOGICAL LIFE CYCLE OF TB

Modified from J. D Ernst 2012 NATURE REVIEWS IMMUNOLOGY

TB DISEASE
HUMAN RESERVOIR
MORTALITY 50% WITHOUT TREATMENT

"Individuals with LTBI had 79% lower risk of Progressive TB after reinfection than uninfected individual"
Methods: double-blind, randomised, placebo-controlled phase 2b trial, we enrolled healthy infants (aged 4–6 months) without HIV infection who had previously received BCG vaccination. Followed up infants every 3 months for up to 37 months.

Findings: Enrolled 2797 infants (1399 allocated MVA85A and 1398 allocated placebo). 32 (2%) of 1399 MVA85A recipients meet primary efficacy point tuberculosis as did 39 (3%) of 1395 controls (BCG).

Interpretation: absence of MVA85A efficacy against tuberculosis or M. tuberculosis infection infants need exploration.
Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study

Jason R Andrews, Elisa Nemes, Michele Tameris, Bernard S Landry, Hassan Mahomed, J Bruce McClain, Helen A Fletcher, Willem A Hanekom, Robin Wood, Helen McShane, Thomas J Scriba, Mark Hatherill

Summary
Background The value of quantitative interferon-γ release assay results for predicting progression from Mycobacterium tuberculosis infection to active disease is unknown. We aimed to investigate the relation between QuantiFERON-TB Gold In-Tube (QFT) conversion interferon-γ values and risk of subsequent active tuberculosis disease and of QFT reversion.

QFT: TB antigens specific to M. tuberculosis: ESAT-6, CFP-10 and TB7.7

TB cases according to day 336 QFT interferon-γ value by case definition.

<table>
<thead>
<tr>
<th>Revised case definition 1</th>
<th>N</th>
<th>Cases</th>
<th>Incidence (95% CI)</th>
<th>IRR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0·35 IU/ml</td>
<td>2232</td>
<td>16</td>
<td>0·7 (0·4-1·1)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0·35-4·00 IU/ml</td>
<td>79</td>
<td>2</td>
<td>2·5 (0·4-9·4)</td>
<td>3·7 (0·4-15·8)</td>
<td>0·23</td>
</tr>
<tr>
<td>&gt;4·00 IU/ml</td>
<td>63</td>
<td>10</td>
<td>28·0 (4·9-45·7)</td>
<td>4·25* (17·2-99·7)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>

% percentage Tuberculosis-free

Andrews et al Lancet Respir Med 2017
Probability of QuantiFERON (QFT) **Reversion** (blue line, left axis) and prospective risk of **Disease** (red line, right axis), as a function of the QFT conversion interferon-γ value

**AUTHORS RECOMMENDATION:** Revision of current international guidelines for use of IGRAs in young children. 0.35 IU/mL might therefore be too low. 0.35–4.00 IU/mL might warrant repeat testing if preventive therapy is considered.
METHODS phase 2b trial of the M72/AS01E TB vaccine in Kenya, South Africa, and Zambia (HIV)–negative adults 18 to 50 years of age with LTBI M. tuberculosis (in a 1:1 ratio) to receive two doses of either M72/AS01E or placebo intramuscularly 1 month apart (previously BCG).

VACCINE: Mtb32A and Mtb39A M. tuberculosis antigens
ADJUVANT AS01E (gE/AS01E; GSK Vaccines; 500 μg dioleoylphosphatidylcholine, 125 μg cholesterol, 25 μg MPL & 25 μg QS-21) liposomes.
Component MALARIA (RTS,S/A01) & ZOSTER (Shingrix) vaccines GSK.

PLACEBO: ADJUVANT Sucrose 20 mg/dose in Phosphate Buffer pellet reconstituted with alpha Tocopherol, Squalene and Tween 80.

EFFICACY AGAINST PROGRESSION TO BACTERIOLOGICALLY CONFIRMED BY PCR OR MYCOBACTERIAL CULTURE.
RESULTS: A total of 1786 participants received M72/AS01E and 1787 received placebo. A total of 10 participants in the M72/AS01E group met the primary case definition (bacteriologically confirmed ACTIVE PULMONARY TB, as compared with 22 participants in the placebo.

CONCLUSION: M72/AS01E provided 54.0% protection for M. tuberculosis–infected LTBI adults against active pulmonary TB disease.
VACUNAS CONTRA LA TUBERCULOSIS EN ENSAYOS CLINICOS

The global development pipeline for new TB vaccines, August 2018
THE RATIONALE FOR CONSTRUCTING A NEW LIVE-ATTENUATED M. tuberculosis VACCINE: MTBVAC
RATIONALE FOR DEVELOPING MTBVAC
Fulfilling Pasteur’s Postulates for attenuated vaccines. Learning from BCG

1.- ATTENUATE A PATHOGEN FROM HUMAN ORIGIN

2.- WE SELECTED A WORLDWIDE DISTRIBUTED M. tuberculosis CLINICAL ISOLATE (lineage 4)

3.- WHICH GENE(S) TO INACTIVATE?:

   phoP: Outbreak MDR-TB in HIV 1990’s
   fadD26: PDIM essential for virulence

4.- AVOID LABORATORY SUBCULTURE:
   Industrial Development: 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

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%

WORKING HYPOTHESIS: **MTBVAC** HAS A WIDER ANTIGENIC POTENTIAL THAT THE CURRENT VACCINE BCG

Marinova et al Expert Rev Vaccines 2017
Gonzalo-Asensio et al Frontiers Immunology 2017
THE MECHANISMS OF PROTECTION AND ATTENUATION OF MTBVAC
Transcription factor PhoP plays an essential role in MTB virulence  
~2-4% ORFS MTB genome under PhoP control (Microarrays, RNAseq & Chipseq):
mainly genes implicated in virulence or immunomodulation
CONSEQUENCE OF *fadD26* DELETION: loss of virulence factor PDIM

CONSEQUENCE OF *phoP* DELETION: loss of SL, PAT, DAT; impaired ESAT6 SECRETION (*espACD*) and increased secretion of MTB antigens (TAT-C regulation)

*Modified from Broset et al* mBio. 2015
Gonzalo et al Plos One 2008
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

MHC Haplotype: H-Zb H-Zd H-Zk

C57BL/6 Balb/C C3H/HeNRj

Protection in lungs (very low-dose H37Rv challenge: ~20 CFU)

Aguilo et al 2017 Nature Communications
INDUSTRIAL & CLINICAL DEVELOPMENT OF MTBVAC
ATTENUATION, PROTECTION & IMMUNOGENICITY

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

Douglas Young “road map”

INDUSTRIAL DEVELOPMENT FREEZE-DRIED MTBVAC (2008-2011)

Original lab strain
MTBVAC (P0) 2008

Master Seed Lot (MSL)

Working Seed Lot (WSL)

Final Lot (at least 2 clinical lots)

Release of Final Product 2011
FIRST GENEVA CONSENSUS CRITERIA: CONSTRUCTION OF MTBVAC
NO ANTIBIOTIC RESISTANCE MARKERS
TWO STABLE INDEPENDENT MUTATIONS

MTBVAC

phoP  fadD26

Arbues et al Vaccine 2013

SECOND GENEVA CONSENSUS: Criteria for further Clinical Development Phase 1 to 3

Vaccine
Volume 28, Issue 11, 8 March 2010, Pages 2259-2270

Conference report:
The second Geneva Consensus: Recommendations for novel live TB vaccines


PDT: Product Development Team TBVI
CDT: Clinical Development Team TBVI
Non-clinical studies to support clinical evaluation
25 Aug’10 – 20 Dec’11

Phase I CTA Preparation
Oct’11 – April’12

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

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

Unblinded data
March 2015

ClinicalTrials.gov
NCT02013245

PHASE Ib in NEWBORNS
With a safety arm in adults (BCG+, PPD-, HIV-)
Sept 2015 - Jan 2016

New born vaccination phase
16 Feb - 21 Sep 2016

Unblinded data
5 Aug 2015
Published Dec 2015
The Lancet Respi Medi

ClinicalTrials.gov
NCT02729571
CLINICAL DATA OF MTBVAC DEVELOPMENT
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
Methods:
double-blind, controlled phase 1 study at CHUV; Lausanne, Switzerland., we enrolled aged 18–45 years, clinically healthy, HIV-negative and tuberculosis-negative. 4 groups 9 BCG vaccinated with 10^5 CFUS BCG and dose escalation 10^3, 10^4, 10^5 MTBVAC.

The primary outcome was safety in all vaccinated participants. Secondary outcomes included whole blood cell-mediated immune response to live MTBVAC and BCG, and interferon γ release assays (IGRA) of peripheral blood mononuclear cells.
POLYFUNCTIONAL CD4+ T CELL WBA 3 CYTOKINES (IFNY, IL2, TNFα)

MTBVAC 5x10⁵ 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
MTBVAC induces a CFP10-specific immune response in humans.

MTBVAC induces a CFP10-specific immune response in humans.

**ELISPOT ASSAY ESAT-6/CFP-10**

Negative 7 months after MTBVAC immunization

MTBVAC induces a CFP10-specific immune response in humans.
Phase 1b randomized, double-blind, safety, immunogenicity and dose-escalation study in NEWBORNS living in a TB ENDEMIC REGION

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

Sept 2015

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

ClinicalTrials.gov Identifier: NCT02729571
Medical Adviser: Dr. Federico Martinon

ClinicalTrials.gov Identifier: NCT02729571

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 CU) (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)

ClinicalTrials.gov Identifier: NCT02729571
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Newborn vaccination phase
Feb - Sep 2016
ACTIVE CLINICAL DEVELOPMENT
OF MTBVAC
TB notification rates by age in the HIV-negative in Cape Town

Worcester, 2-3 % TB cases in infants BCG vaccinated (Tameris et al Lancet 2013)

Infants / Adolescents / Adults

Tuberculosis in Cape Town: An age-structured transmission model
Blaser et al Epidemics, 2016, 14: 54–61

A BETTER VACCINE THAN BCG IS NEEDED
WHO Preferred Product Characteristics for New Tuberculosis Vaccines

1. PPC FOR NEW TB VACCINES: USE IN ADOLESCENTS AND ADULTS

   PRIME (live attenuated BCG) / BOOST SUBNITS VACCINES

2. PPC FOR NEW TB VACCINES: USE IN NEONATES AND INFANTS

   REPLACE BCG VACCINE: NEW LIVE ATTENUATED VACCINES

Schrager et al  Lancet Infectious Disease Vol 18 August 2018
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

**Objectives:**  
**Primary:** Adverse events, injection site reactions  
**Secondary:** Immunology, in QFT negatives: QTF Conversion/Reversion

Site PI Angelique Luabeya
Phase 2a randomized, double-blind, safety, immunogenicity, and dose-finding study in newborns living in a tuberculosis endemic region

Clinical Research Director: Ingrid Murillo

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
NEW LIVE ATTENUATED TB VACCINE
with a better protection pulmonary TB than BCG

ADVANTAGE BCG
EXPERIENCE: Distribution/Use
BCG at birth global coverage close 90%
MTBVAC EN ENSAYOS CLÍNICOS:

Fase 1 A Adultos Suiza  “
Dose-Escalation Study to Evaluate the Safety and Immunogenicity of MTBVAC Vaccine in Comparison With BCG Vaccine”
(ClinicalTrials.gov : NCT02013245) Resultados Lancet Respiratory Disease Spertini et al Dec 2015

Fase 1 B Recién nacidos Sudáfrica
“Dose-escalation Safety and Immunogenicity Study to Compare MTBVAC to BCG in Newborns With a Safety Arm in Adults (MTBVAC-Ph1b)”
ClinicalTrials.gov : NCT02729571) Finalizada 2018
Resultados pendientes de publicar

Fase 1B/2A Adultos Sudáfrica
“MTBVAC Study in Adults With and Without Latent Tuberculosis Infection in South Africa” (ClinicalTrials.gov NCT02933281 ) Inicio Enero 2019

Fase 2 A Recién nacidos Sudáfrica
“Dose-Defining Safety and Immunogenicity Study of MTBVAC in South African Neonates” (ClinicalTrials.gov: NCT03536117) Inicio Febrero 2019
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