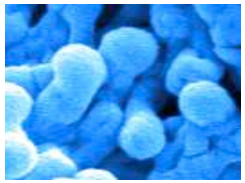
Comité Asesor de Vacunas

MTBVAC

¿PARA CUÁNDO UNA SOLUCIÓN A LA TUBERCULOSIS?



TBVI
TuBerculosis Vaccine Initiative

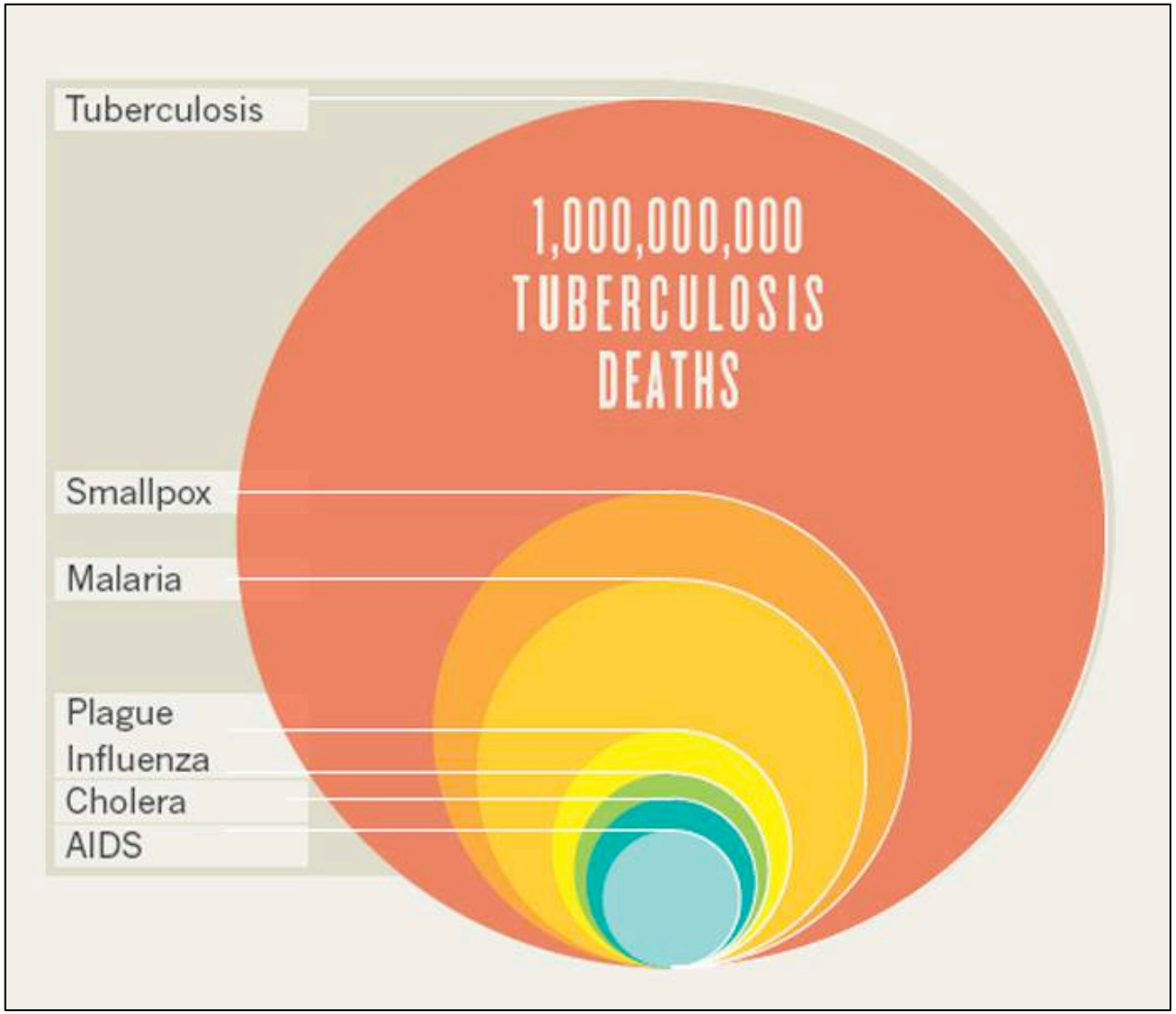
Universidad Zaragoza

BIOFABRI

Carlos Martín
carlos@unizar.es

"TUBERCULOSIS THE BIGGEST KILLER "

Paulson Nature 2013



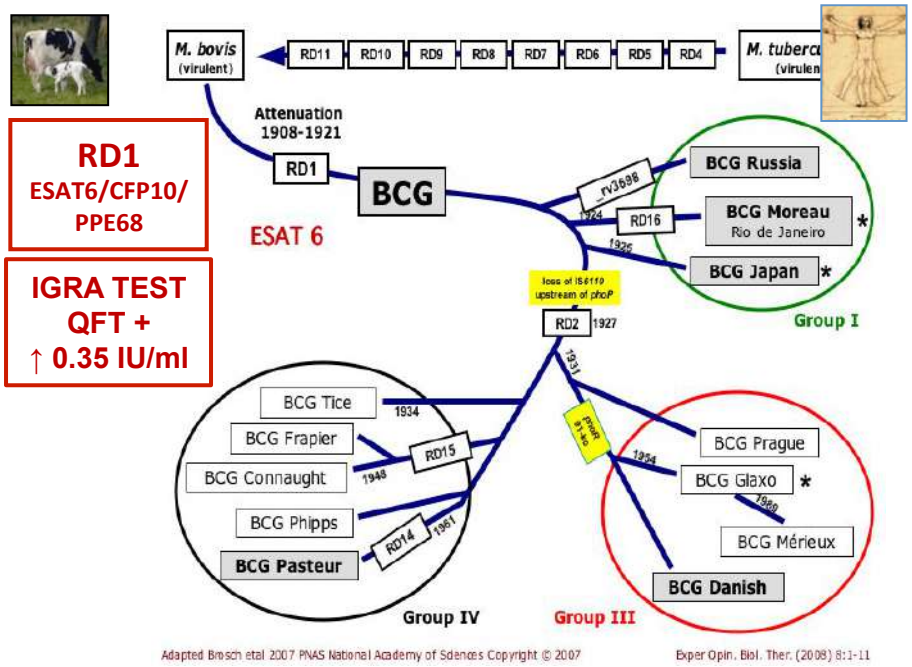
Tuberculosis has caused more deaths than any other infectious disease
More than a Billion dead in the last 200 years

VACCINE BCG

Albert CALMETTE & Camille GUÉRIN
***Mycobacterium bovis* 1908-1921**
230 Passages

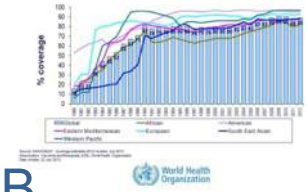
BCG INITIALLY ADMINISTRATED ORALLY
1921-1926: 50.000 infants vaccinated:
25 % Non vaccinated mortality *vs*
1.8 % Vaccinated mortality

Different BCG isolates distributed between the different laboratories around the World



Adapted from Brosch *et al* PNAS 2007

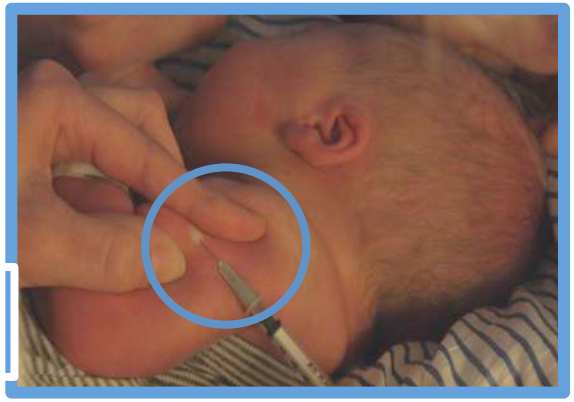
BCG global coverage at birth 89% worldwide



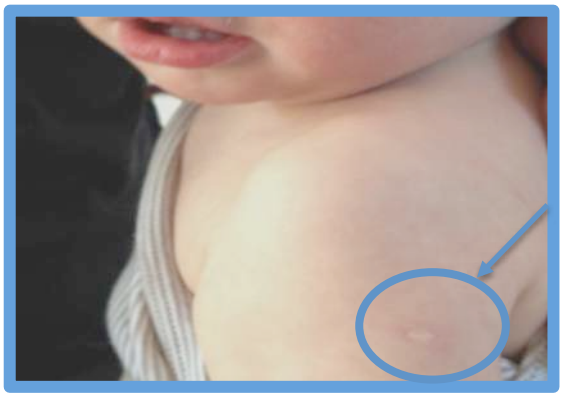
Provides variable protection against respiratory forms of TB

Intradermal administration at birth

BCG 0.05 ml
20 doses



Scar after vaccination



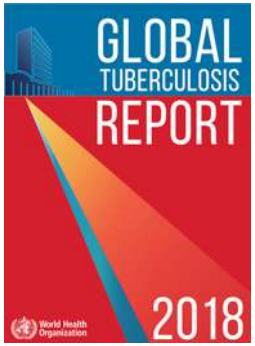
European textbook of pediatric vaccines and vaccination. Springer 2017 TB vaccines and vaccination F Martinon & C Martin

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 IMPOVEMENT :
PROTECTION PULMONARY FORMS OF TB
LONG TERM PROTECTION IN ADOLESCENTS

The Global Burden of TB, 2017



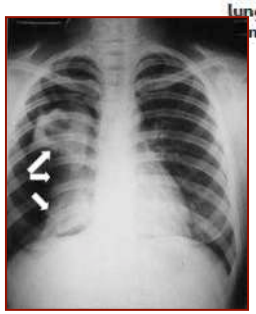
Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS)

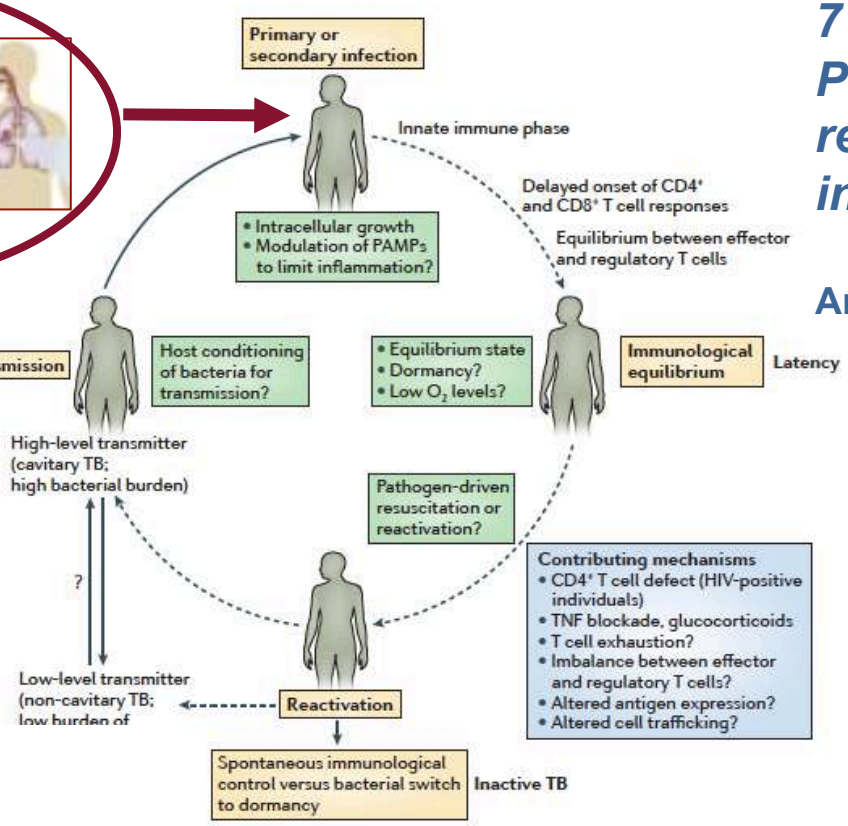
	Estimated number of cases	Estimated number of deaths
All forms of TB	**10.0 million** • 1.0 million children • 3.2 million women • 5.8 million men	**1.7 million** 22 per 100.000 • 250,000 in children • 490,000 in women • 930,000 in men
HIV-associated TB	**1.0 million**	300,000
Multidrug-resistant TB MDR/RR	**558,000**	

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

NATURAL HISTORY OF TUBERCULOSIS

95%
MTB strains
Human
origin





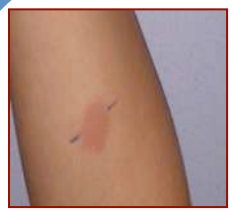
TB DISEASE

HUMAN RESERVOIR

MORTALITY 50%
WITHOUT TREATMENT

"Individuals with LTBI had 79% lower risk of Progressive TB after reinfection than uninfected individual"

Andrews *et al* CID 2012



TB INFECTION

only 5-10%
will develop
TB disease

THE STAGES IN THE IMMUNOLOGICAL LIFE CYCLE OF TB

Modified from J. D Ernst 2012 NATURE REVIEWS IMMUNOLOGY

Lancet. 2013 Mar 23;381(9871):1021-8.

Articles

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team*

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

Lancet Respir Med 2017
Published Online
February 15, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30060-7

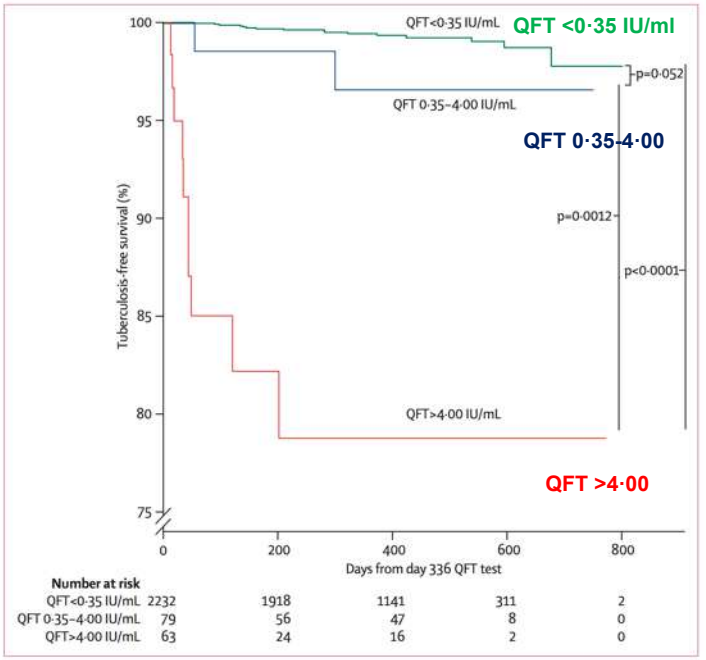
Summary

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.

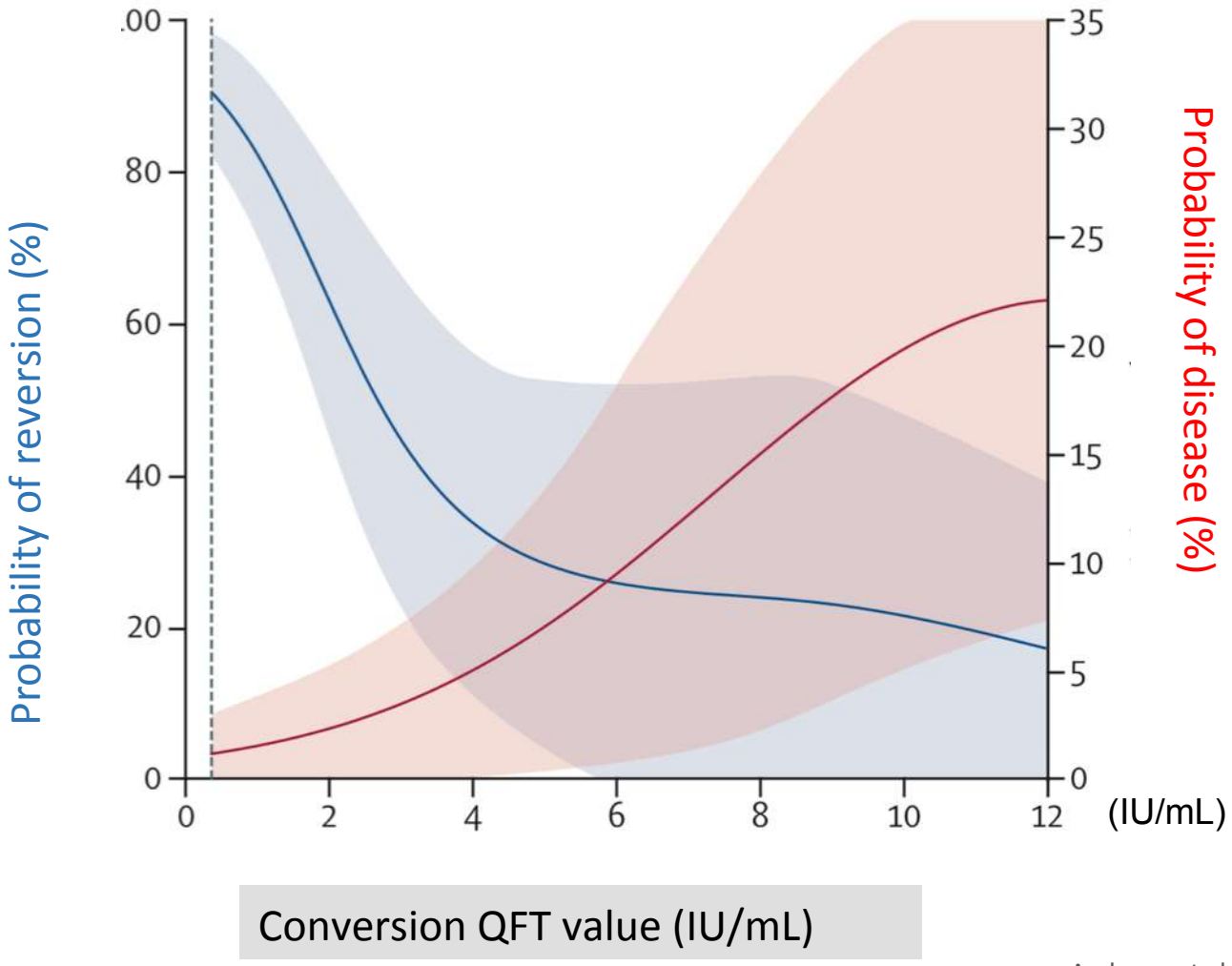
	N	Cases	Incidence (95% CI)	IRR (95% CI)	p value
Revised case definition 1					
<0·35 IU/mL	2232	16	0·7 (0·4–1·1)	Ref	Ref
0·35–4·00 IU/mL	79	2	2·5 (0·4–9·4)	3·7 (0·4–15·8)	0·23
>4·00 IU/mL	63	10	28·0 (14·9–45·7)	42·5* (17·2–99·7)	<0·0001



% 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



Andrews et al, Lancet RespMed 2017

AUTHORS RECOMENDATION: 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

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 379;17
October 25, 2018

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

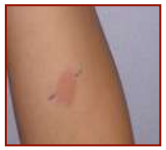
METHODS **phase 2b trial** of the **M72/AS01E** TB vaccine in **Kenya, South Africa, and Zambia** (HIV)–negative adults 18 to 50 years of age **with LTBI *M. tuberculosis*** (in a 1:1 ratio) to receive **two doses** of either M72/AS01E or placebo intramuscularly 1 month apart **(previously BCG)**

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.

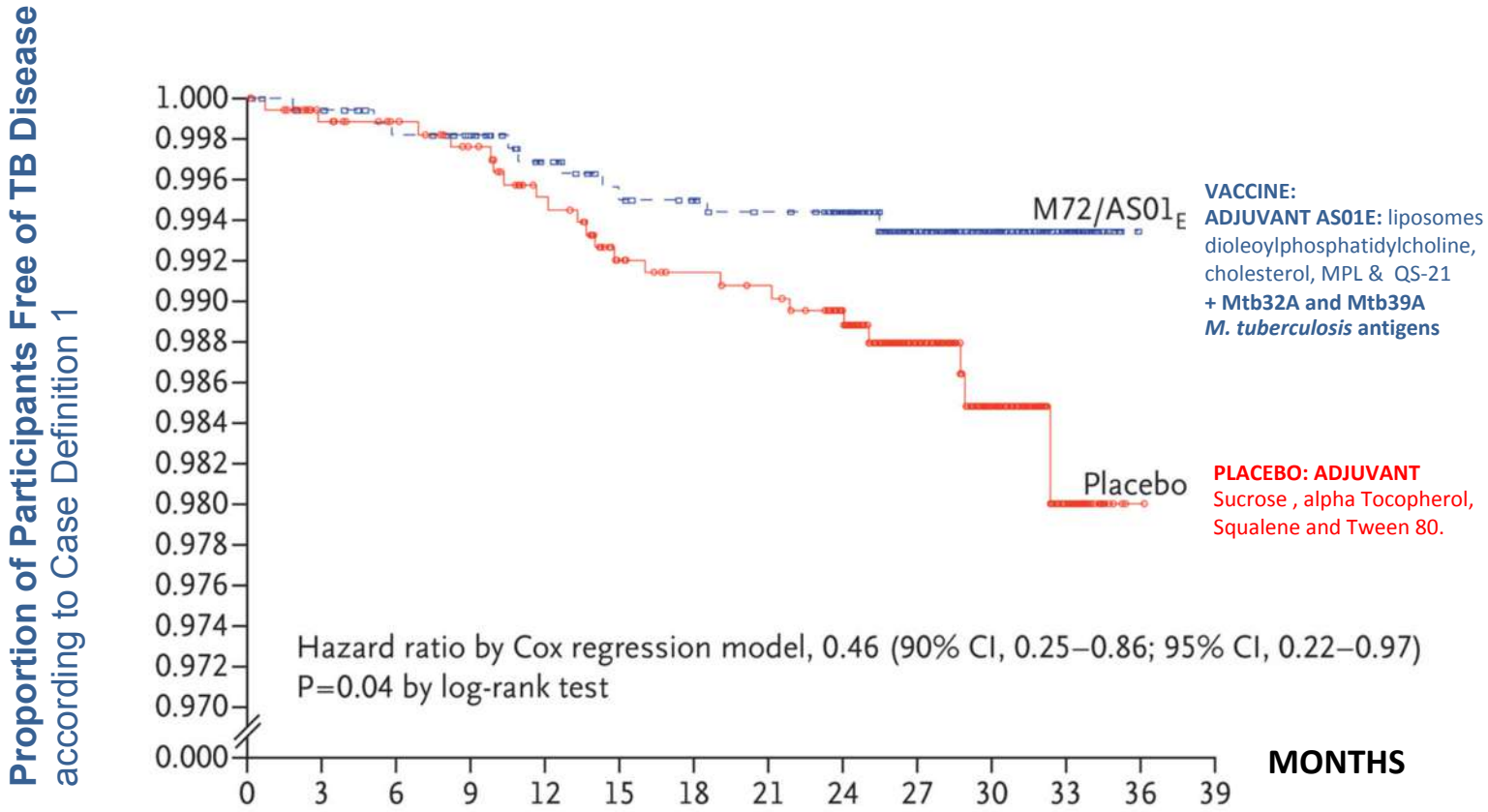
PLACEBO: **ADJUVANT** Sucrose 20 mg/dose in Phosphate Buffer pellet reconstituted with alpha Tocopherol, Squalene and Tween 80.

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.**



LTBI adults



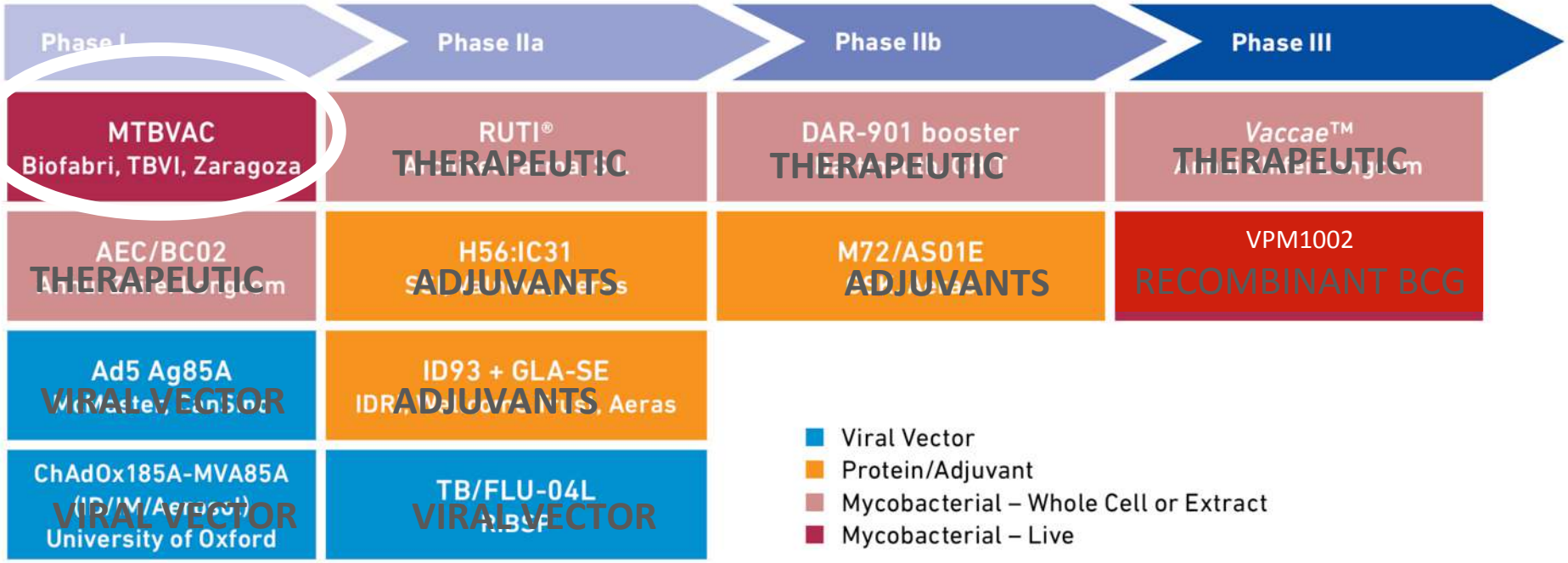
N ENGL J MED October 25, 2018

CONCLUSION: M72/AS01E provided 54.0% protection
for *M. tuberculosis* **–infected LTBI adults against active pulmonary TB disease**

World Health Organization

VACUNAS CONTRA LA TUBERCULOSIS EN ENSAYOS CLINICOS

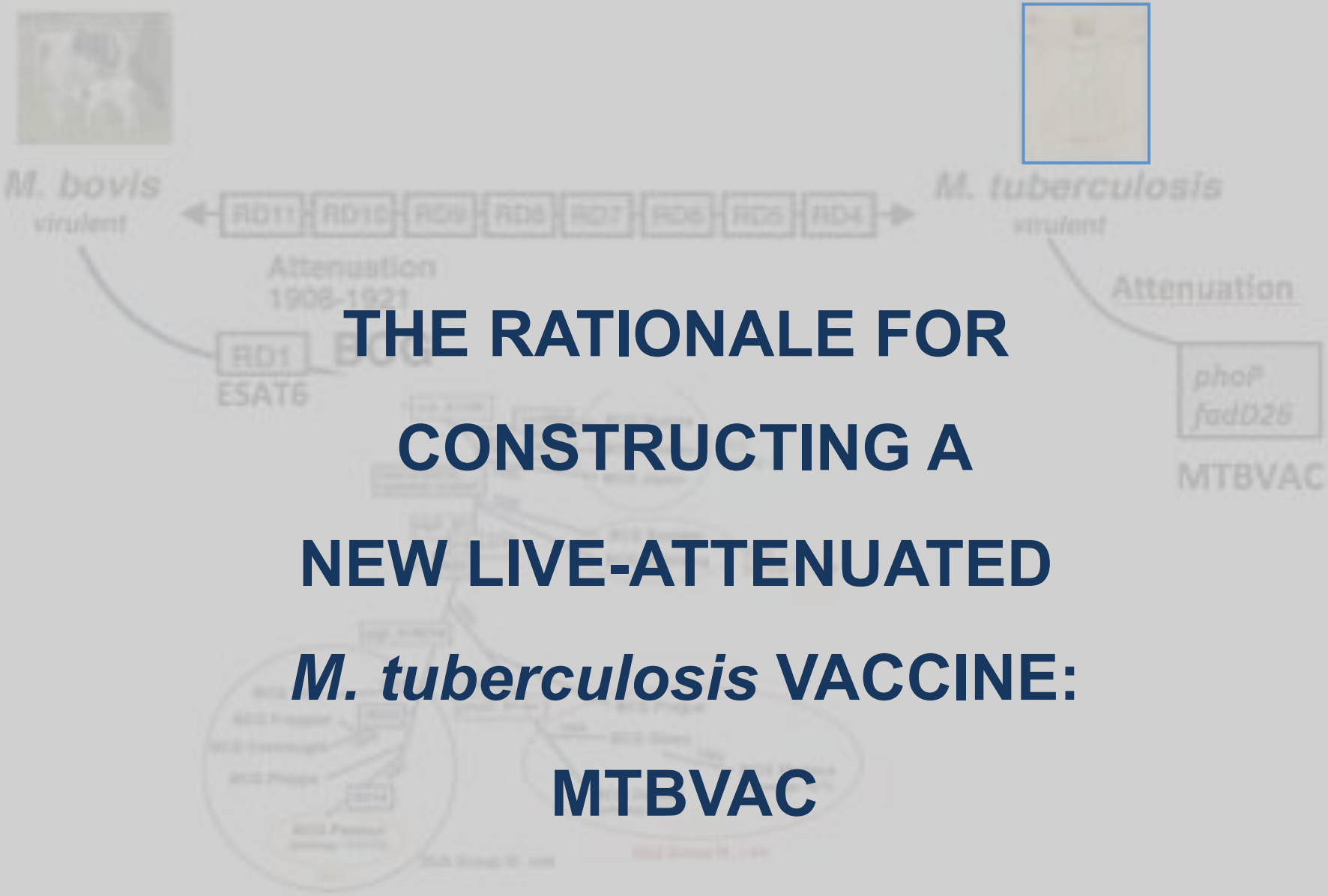
The global development pipeline for new TB vaccines, August 2018[a]



TBVI
TuBerculosis Vaccine Initiative

AERAS
GLOBAL TB VACCINE FOUNDATION

GLOBAL TUBERCULOSIS REPORT 2018

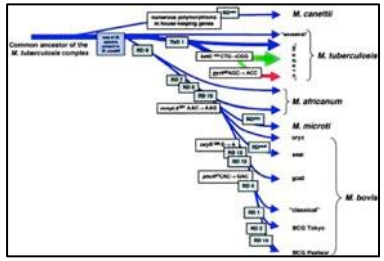


THE RATIONALE FOR CONSTRUCTING A NEW LIVE-ATTENUATED *M. tuberculosis* VACCINE: MTBVAC

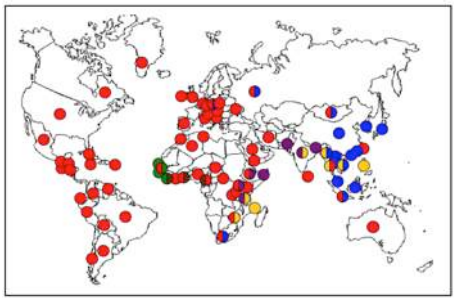
Universidad Zaragoza
1542

RATIONALE FOR DEVELOPING MTBVAC

Fulfilling Pasteur's Postulates for attenuated vaccines. Learning from BCG



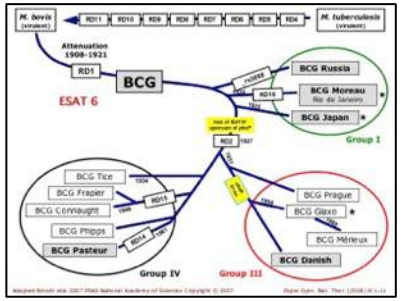
1.- ATTENUATE A PATHOGEN FROM HUMAN ORIGIN



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

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

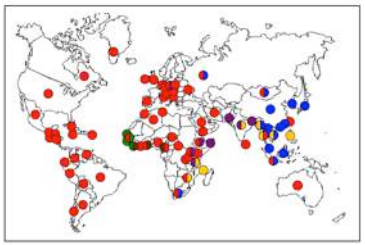
phoP: Outbreak MDR-TB in HIV 1990´s
fadD26: PDIM essential for virulence



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

Ainhoa Arbues

ELSEVIER

Vaccine

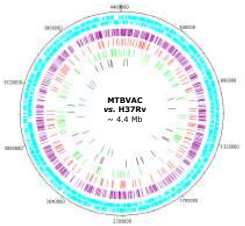
Volume 23, Issue 29, 31 May 2005, Pages 3753-3761

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)



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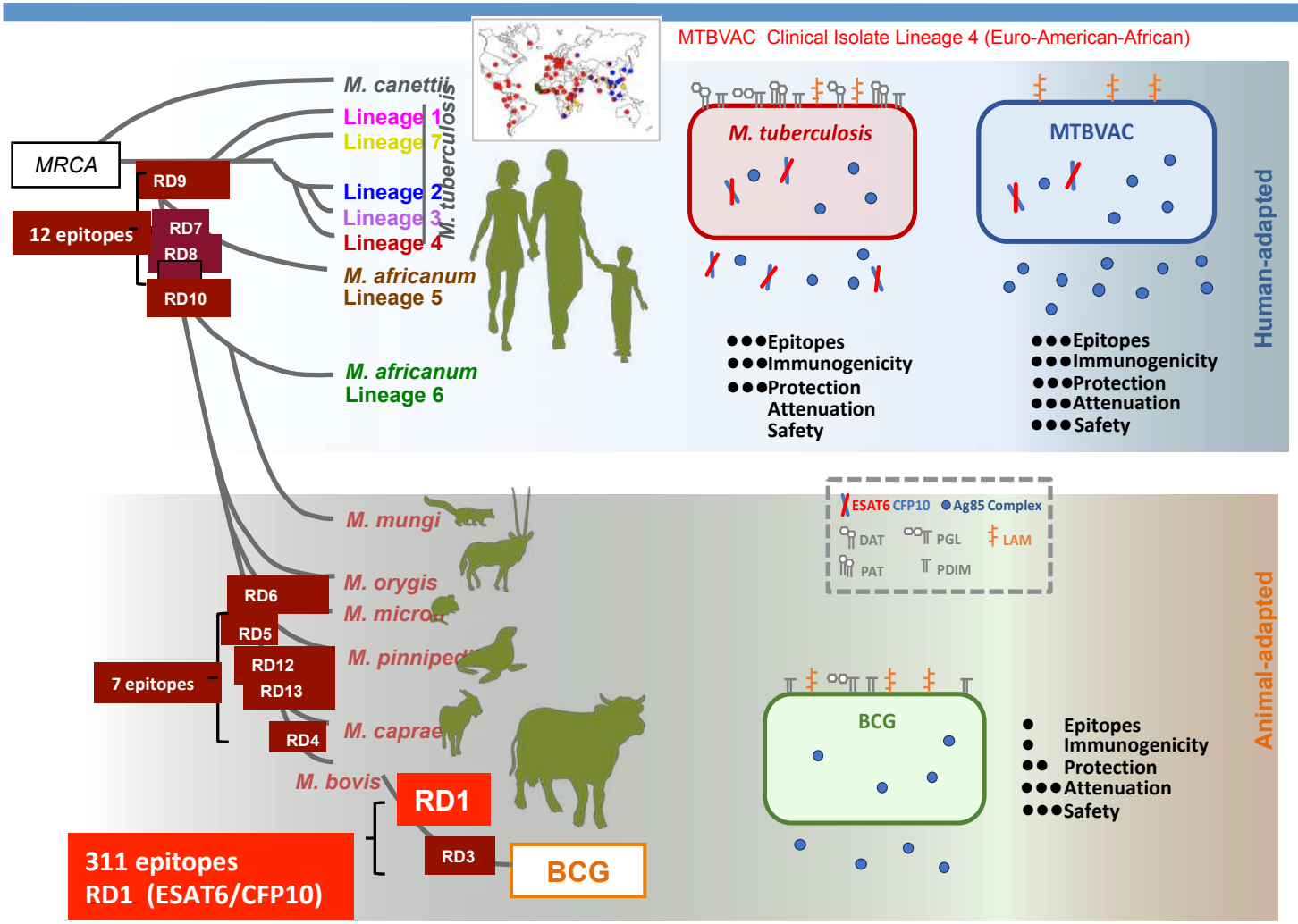
MTBVAC

phoP *fadD26*

BIOFABRI

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



MTBVAC →
1603 epitopes

BCG →
1084 epitopes

Marinova *et al* Expert Rev Vaccines 2017

Gonzalo-Asensio et al Frontiers Immunology 2017

THE MECHANISMS OF PROTECTION AND ATTENUATION OF MTBVAC

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MECHANISMS OF ATTENUATION OF MTBVAC:

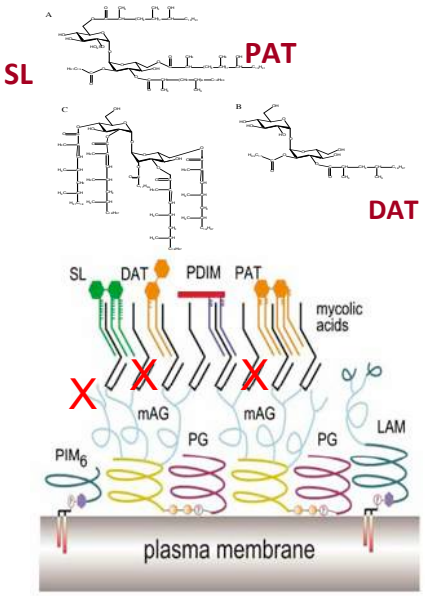
Transcription factor PhoP plays an essential role in MTB *virulence*

~2-4% ORFS MTB genome under **PhoP control** (Microarrays, RNAseq & Chipseq):
mainly genes implicated in virulence or inmunomodulation

SINTHESIS POLYKETIDE-DERIVED LIPIDS Immunomodulators

LIPID METABOLISM
SL, DAT, PAT + ... *lipF*

MTB Glycolipids TLR2 ANTAGONIST INHIBITS INNATE IMMUNE. Blanc *et al* PNAS 2017



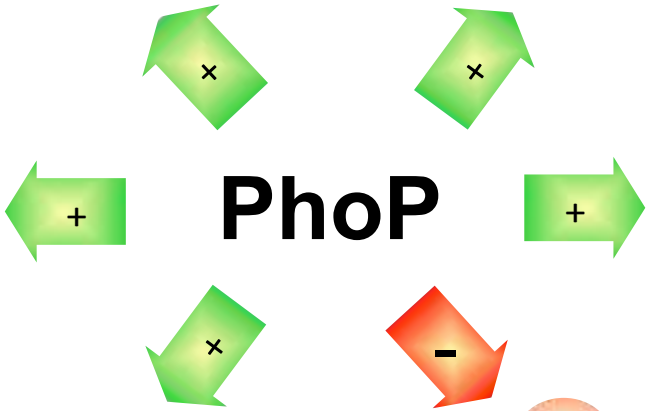
Brigitte Gicquel

INSTITUT PASTEUR

Gonzalo Asensio *et al*. JBC 2006

RESPIRATION
***narK1*, *nirA*, *cysH*, *ald*, *nuo*BCDK**

STRESS PROTEINS
(hsp) groEL2



HYPOXIC RESPONSE

1.- INITIAL (*dosS*/R)
2.- ENDURING

icl

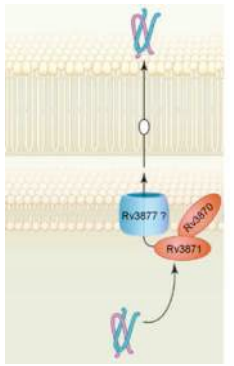
PERSISTENCE

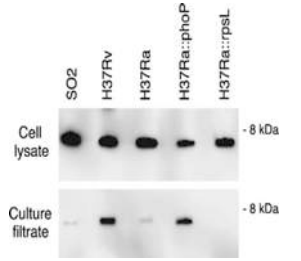
Marcel Behr

McGill

Gonzalo-Asensio *et al*. PLoS ONE 2008

ESAT 6 SECRETION Virulence factor





Frigui *et al*. PLoS Path 2008

Roland Brosh

INSTITUT PASTEUR

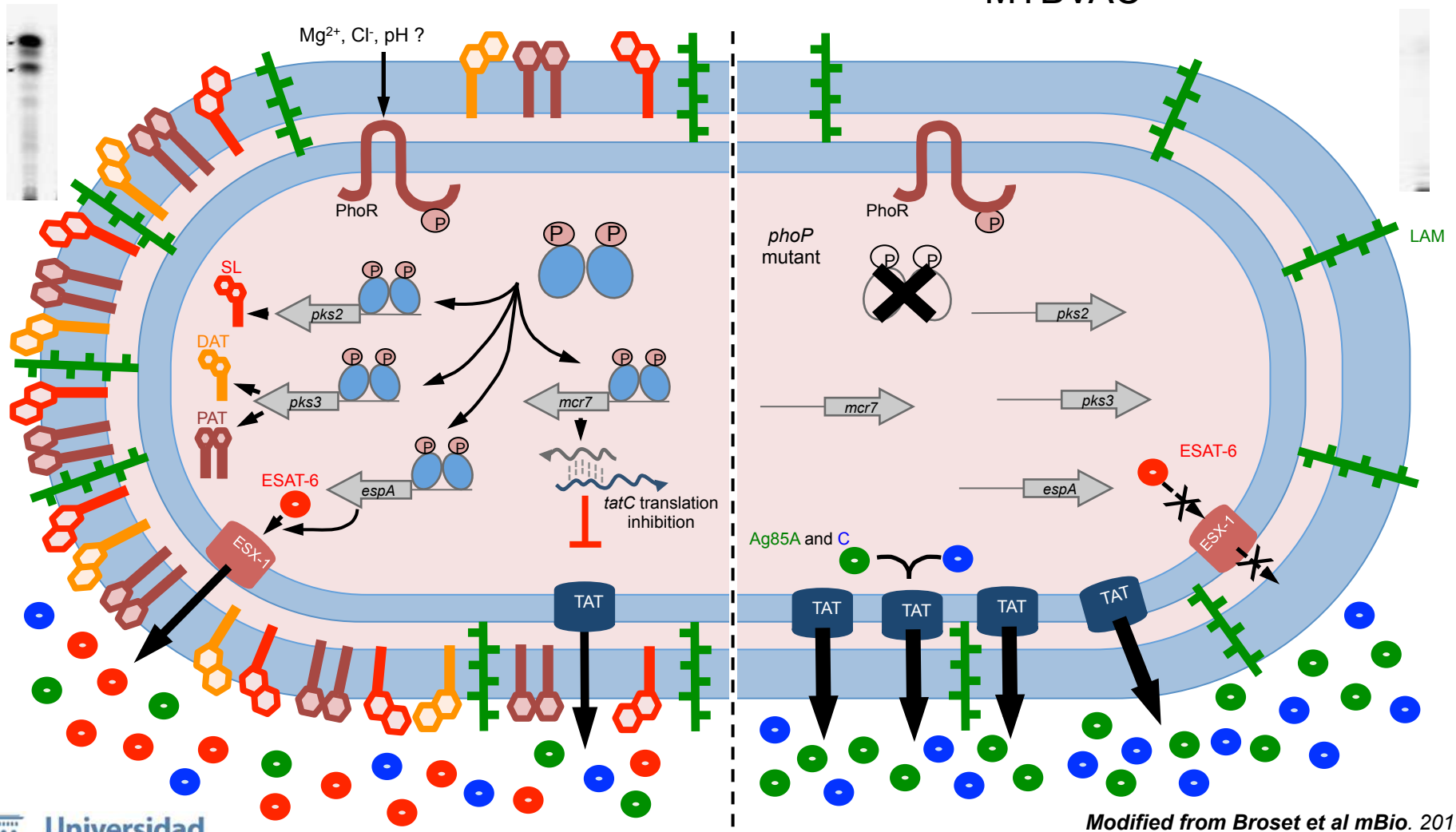
Stewart Cole

EPFL ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

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)

Jesús Gonzalo-Asensio



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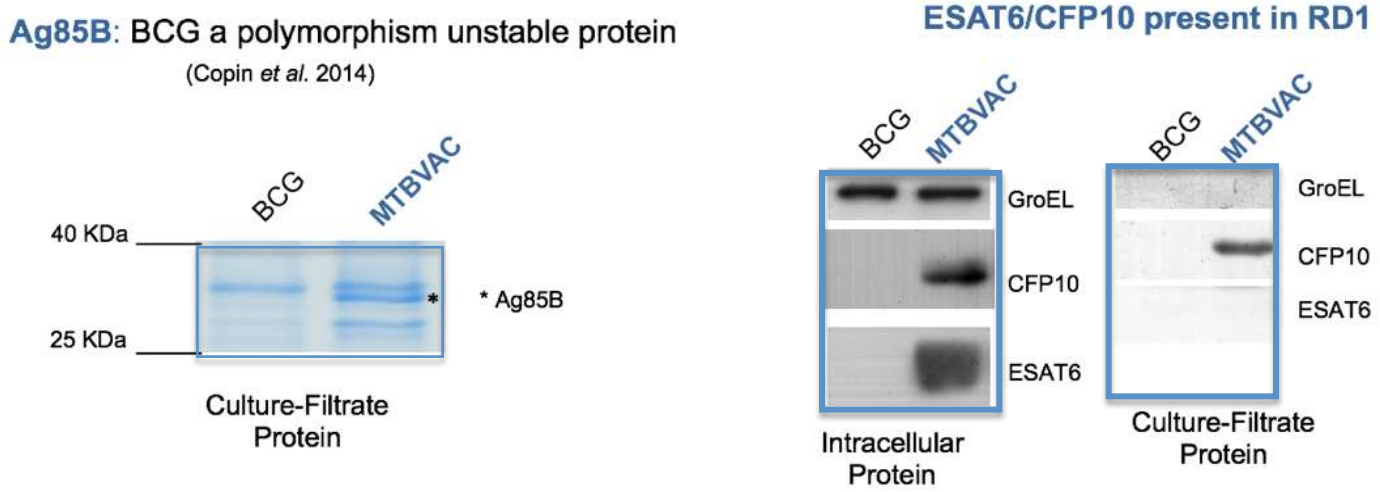
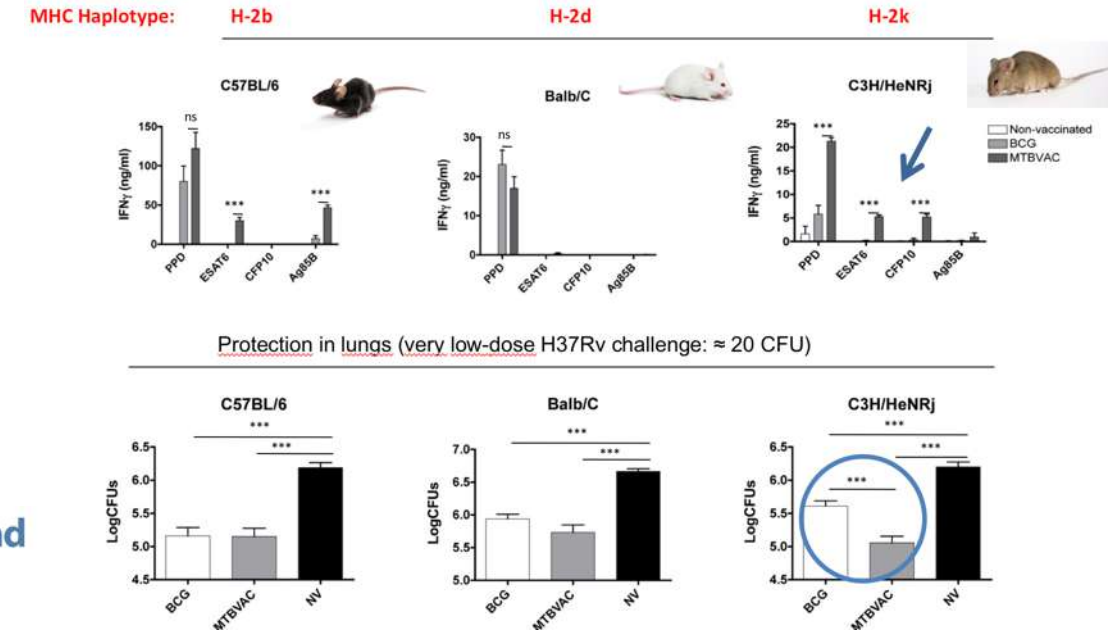
***Modified from Broset et al mBio**. 2015*
Solans et al. PLoS Pathogen 2014
Gonzalo et al Plos One 2008

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





Nacho Aguilo

Universidad Zaragoza

Aguilo *et al 2017 Nature Communications*

BIOFABRI

Zendal

INDUSTRIAL & CLINICAL DEVELOPMENT OF MTBVAC

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Brigitte Gicquel

MTB GENETIC TOOLS
1987-1992 WHO
1992-2000 EU
EU FP3/FP4

ATTENUATION, PROTECTION & IMMUNOGENICITY




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

Douglas Young "road map"

Eugenia Puentes

BIOFABRI

INDUSTRIAL DEVELOPMENT FREEZE-DRIED MTBVAC (2008-2011)

Original lab strain MTBVAC (P0) 2008

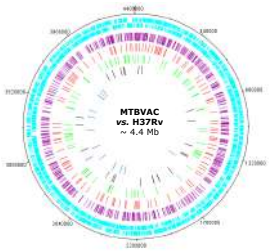
Master Seed Lot (MSL)

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***

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Arbues et al ***Vaccine 2013***

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

BIOFABRI

Esteban Rodriguez

ELSEVIER

Vaccine

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

Conference report

The second Geneva Consensus: Recommendations for novel live TB vaccines ☆

K.B. Walker, M.J. Brennan, M.M. Ho, J. Eskola, G. Thiry, J. Sadoff, R. Dobbelaer, L. Grode, M.A. Liu [a, b], U. Fruth, P.H. Lambert

Jelle Thole

PDT: Product Development Team **TBVI**

CDT: Clinical Development Team **TBVI**

PLAN DE DESARROLLO CLÍNICO DE MTBVAC

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

BIOFABRI

Health Protection Agency

Universidad Zaragoza

charles river

FECYT FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA

Phase I CTA Preparation
Oct'11 – April '12

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

CHUV Centre Hospitalier Universitaire Vaudois

CTA Evaluation

swissmedic

Approval
3 Oct 2012

PHASE Ia HEALTHY ADULTS in CHUV Switzerland
PPD-, BCG-, HIV-
(18-45 yrs)

Last visit V10
End of study
6 Jun 2014

Vaccination phase:
23 Jan - 6 Nov 2013

ClinicalTrials.gov : NCT02013245

Unblinded data
March 2015

Published Dec 2015
The Lancet Respi Medi

mcc MEDICINES CONTROL COUNCIL

CTA Evaluation
11 May 2015

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

Approval
13 May 2015
HREC+ DAFF
5 Agust 2015

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

ClinicalTrials.gov NCT02729571

Dessi Marinova

Universidad Zaragoza 1542

INNOCASH

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

FECYT FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA

BIOFABRI

BIOFABRI

CLINICAL DATA OF MTBVAC DEVELOPMENT

Zendal

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

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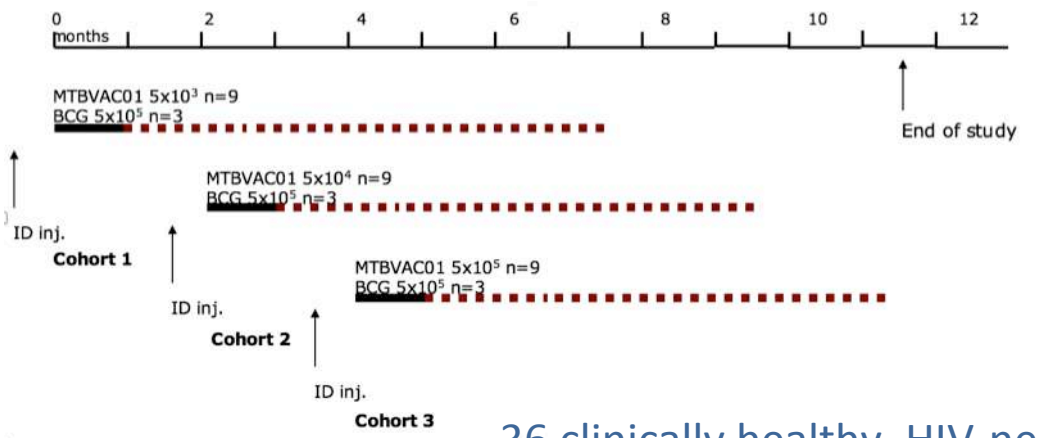


ClinicalTrials.gov: NCT02013245

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

Lancet Respir Med 2015;
3: 953–62

Safety of human immunisation with a live-attenuated *Mycobacterium tuberculosis* vaccine: a randomised, double-blind, controlled phase I trial

François Spertini*, Régine Audran, Reza Chakour, Olfa Karoui, Viviane Steiner-Monard, Anne-Christine Thierry, Carole E Mayor, Nils Rettby, Katia Jaton, Laure Vallotton, Catherine Lazor-Blanchet, Juana Doce, Eugenia Puentes, Dessislava Marinova, Nacho Aguilo, Carlos Martin*

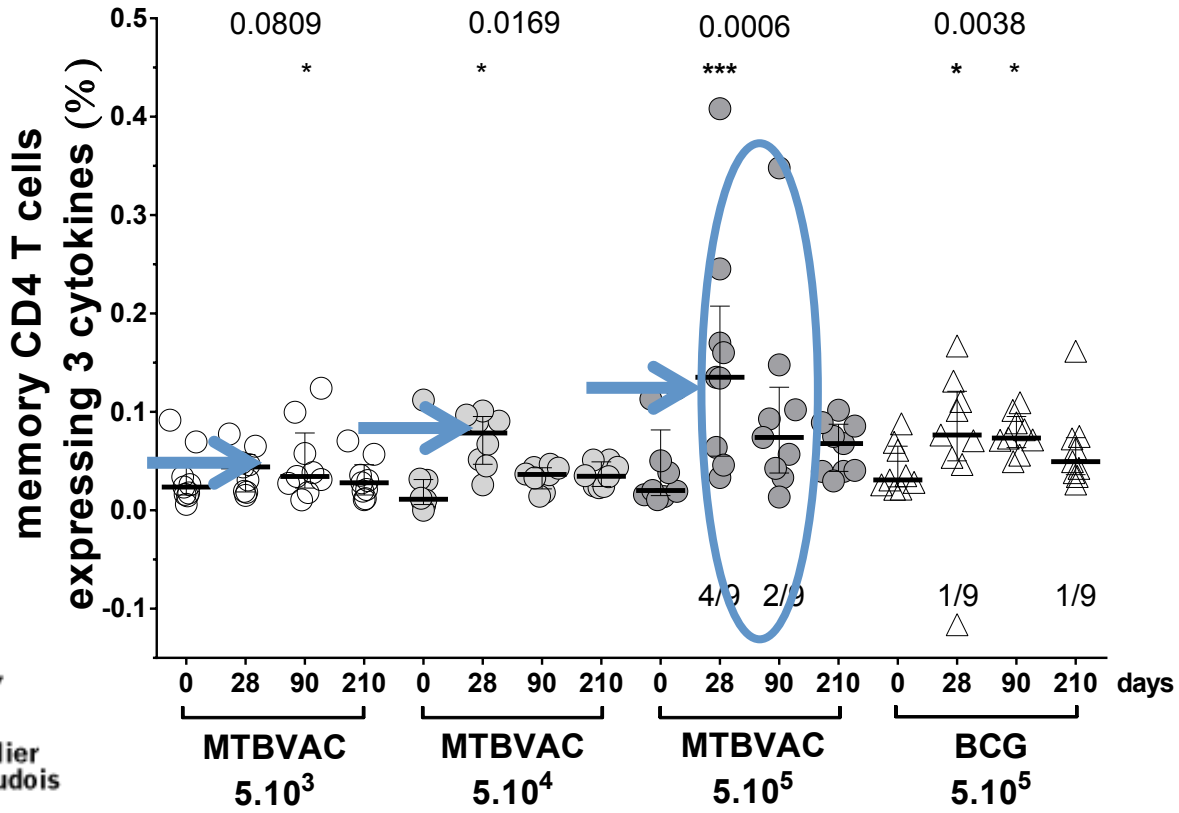
Methods:

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 10e5 CFUS BCG and **dose escalation 10e3, 10e4, 10e5 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)

live MTBVAC-specific response



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

WBA stimulation with MTBVAC

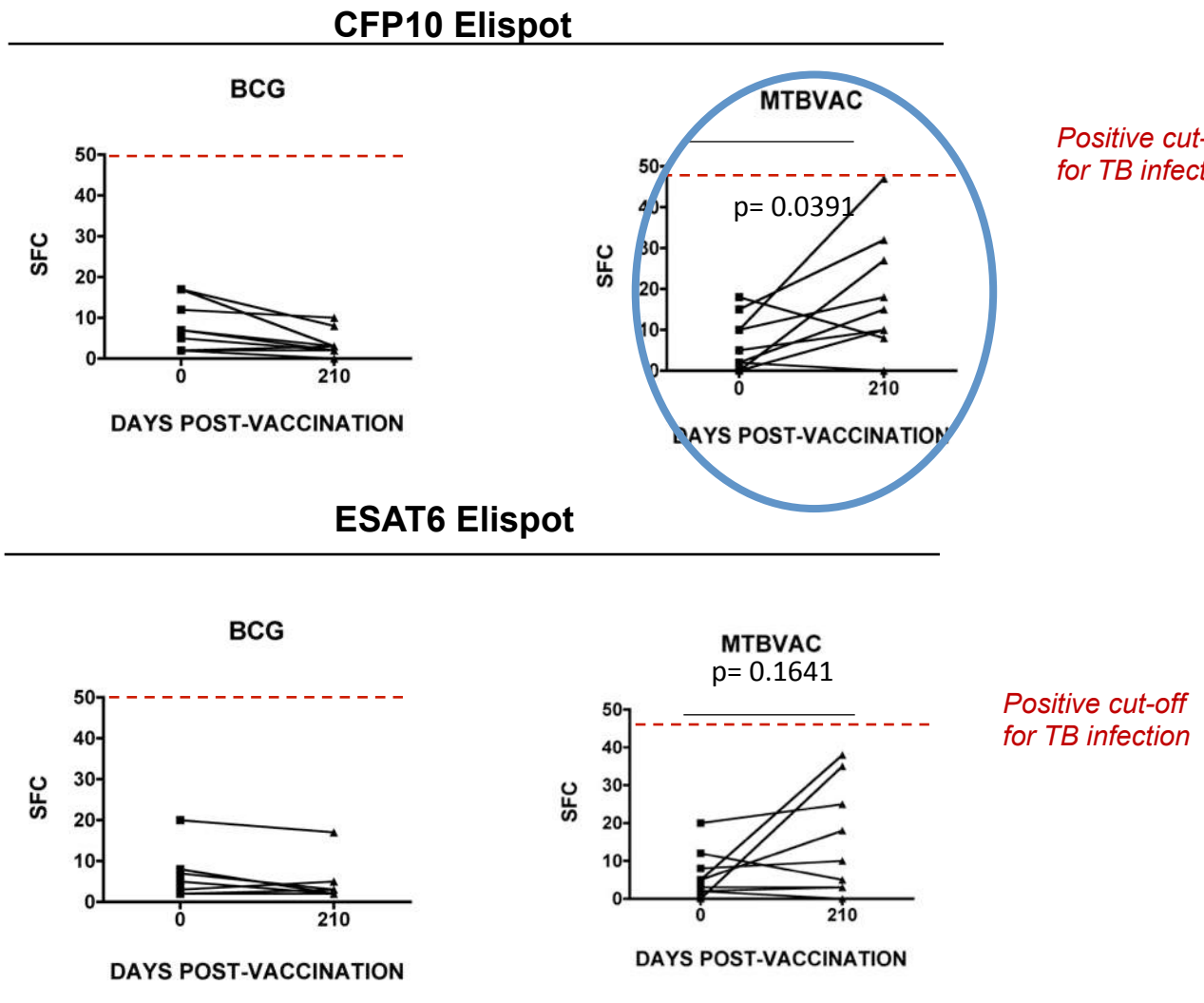
Centre Hospitalier Universitaire Vaudois

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

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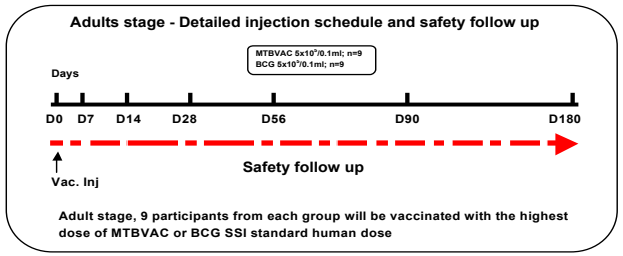
SAFETY ARM IN ADULTS WITH HIGHEST DOSE MTBVAC PREVIOUSLY VACCINATED WITH BCG



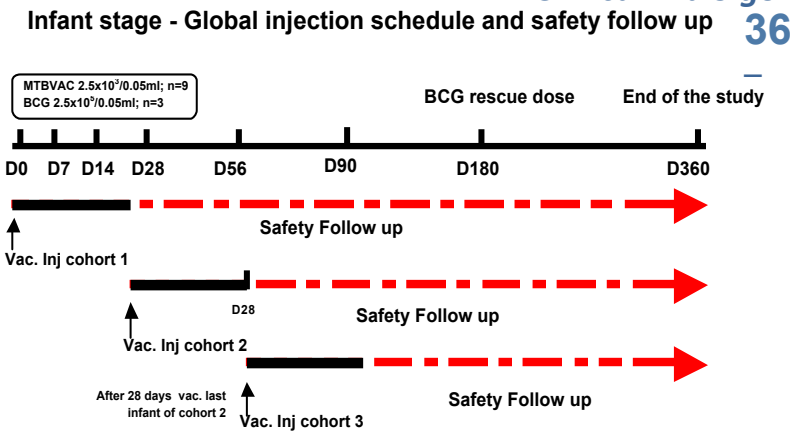
Sept 2015

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

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



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

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ACTIVE CLINICAL DEVELOPMENT OF MTBVAC

AERAS

iavi International AIDS Vaccine Initiative

CDMRP

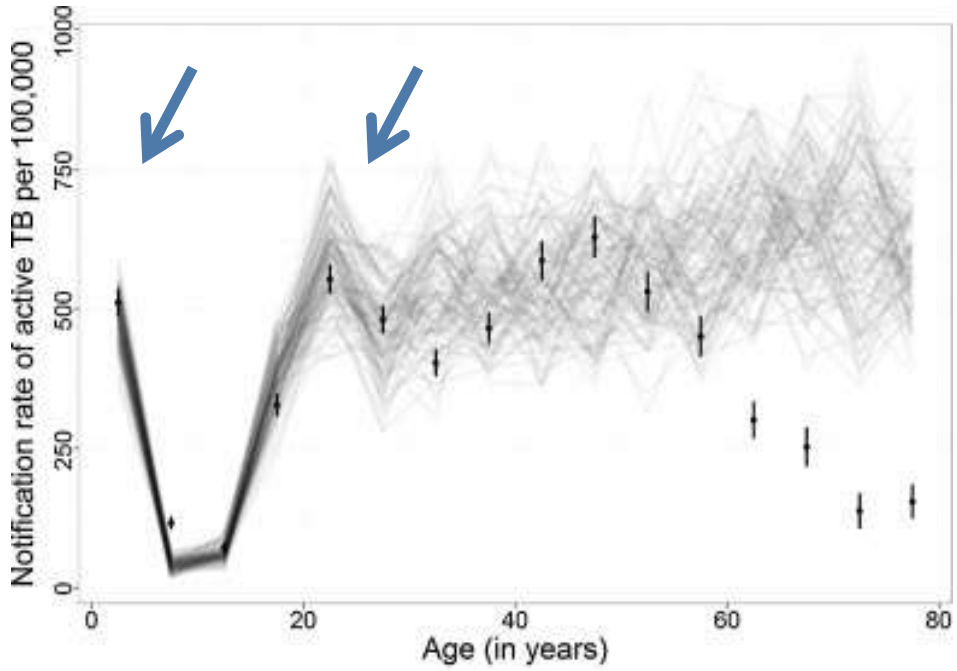
NIH National Institutes of Health

EDCTP

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/IVB/18.06

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**

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.**

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AERAS

avi International AIDS Vaccine Initiative

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

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

Phase 2a DOSE FINDING SAFETY AND IMMUNOGENICITY IN NEWBORNS **2018**

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

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Clinical Research Director: Ingrid Murillo

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

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

EDCTP
RIA2016V-1637

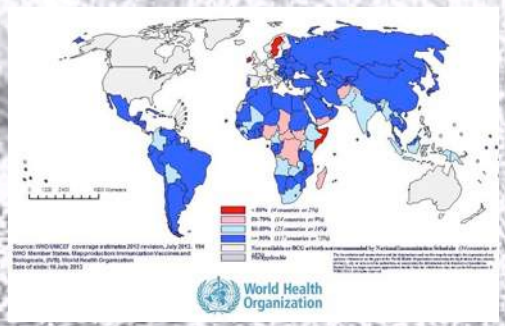
Trial Steering Committee: A. Ginsberg , F. Martinon, B. Kampmann & D. Moreno

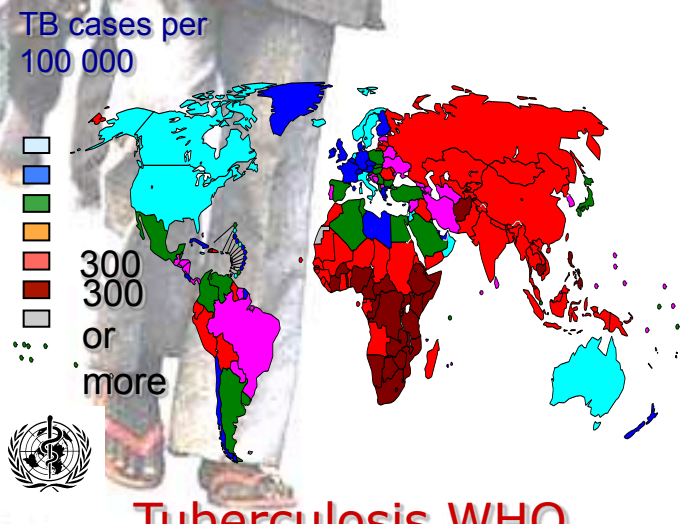
NEW LIVE ATTENUATED TB VACCINE

with a better protection pulmonary TB than BCG

ADVANTAGE BCG EXPERIENCE: Distribution/Use

BCG at birth global coverage close 90%





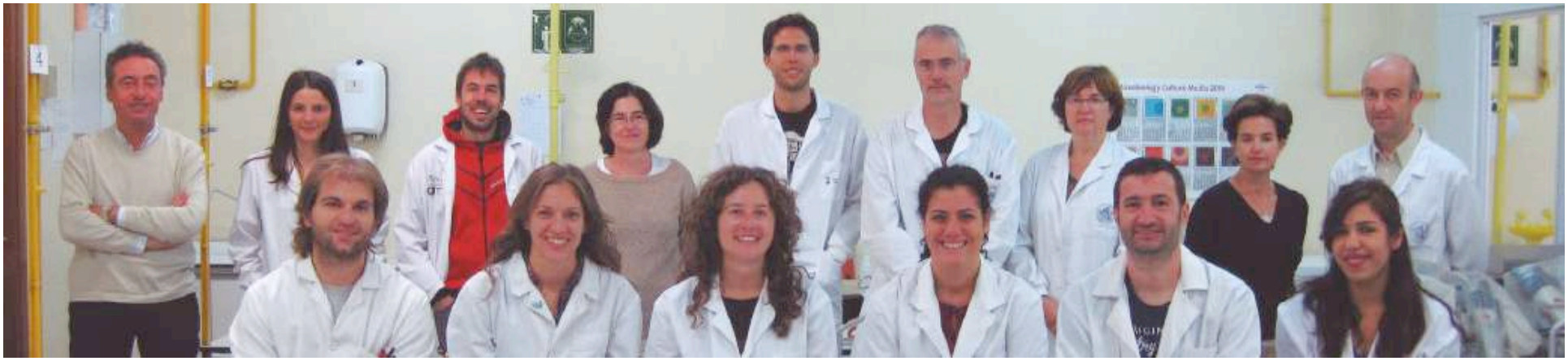
MTBVAC EN ENSAYOS CLÍNICOS:

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



Esther Pérez

Ainhoa Arbues

TBVAC 2020

ciberes Centro de Investigación Biomédica en Red Enfermedades Respiratorias

Clara Aguilar
Ignacio Aguiló
José Antonio Aínsa*
Esther Broset
Alberto Cebollada
Ana Belén Gómez
Jesús Gonzalo
Begoña Grácia
Daniel Ibarz Bosque
Mª José Iglesias Gozalo*
Carmen Lafoz

* IP coordinadores de línea

Carlos Lampreave
Ainhoa Lucia
Elena Mata
Dessi Marinova
*Isabel Otal**
Irene Pérez
Ana Pico
Sofía Samper *
Luis Solans
Santiago Uranga
Samuel Álvarez
Raquel Tarancón

Microbiología Clínica
Mª José Revillo Pinilla
Asunción Vitoria

IIS Aragón Instituto de Investigación Sanitaria Aragón

Dirección General de Salud Pública

Grupo de Apoptosis, Inmunidad y Cancer
Alberto Anel
Julian Pardo

Centro de Encefalopatías y Enfermedades Emergentes
Marta Monzón
Juan J Badiola

Universidad Zaragoza 1542

universidad de zaragoza

University of Zaragoza
Nacho Aguilo
Jesus Gonzalo
Dessi Marinova
Carlos Martin

TBVI
Jelle Thole
Bernard Fritzell
Emmanuèle Gerdil
Brij Patel
Georges Thiry
Mei Mei Ho

Biofabri
Esteban Rodríguez
Eugenia Puentes
Juana Doce
Ingrid Murillo

PHE
Ann Rawkins
Sally Sharp
Simon Clark
Andrew White

CHUV
François Spertini
Régine Audran
Reza Chakour
Olfa Karoui
Viviane Steiner-Monard
Anne-Christine Thierry
Carole E Mayor
Nils Rettby
Katia Jaton
Laure Vallotton
Catherine Lazor-Blanchet

AERAS
Jacqueline Shea
Ann Ginberg
Dereck Tait
Kristin Croucher
Domminique Laddy

SATVI Lab
Tom Scriba
Helen Mearns
Virginie Rozot
Adam Penn Nicholson
Munya Musmosvi
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