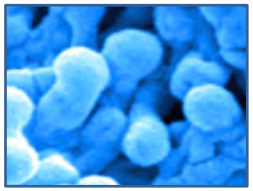
“DE AQUÍ A LA ETERNIDAD,

¿QUÉ NOS ESPERA EN VACUNAS?”

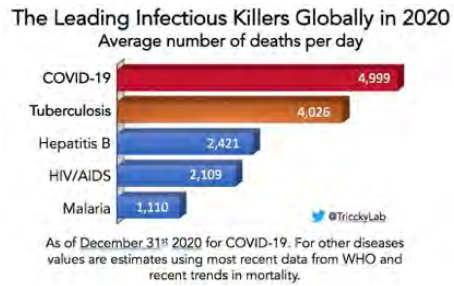


MTBVAC

“TUBERCULOSIS, EL PRINCIPIO DEL FIN”

BIOFABRI

Carlos Martín
15 Abril 2021
carlos@unizar.es



COVID-19

2020 ≈ 1,8 M Deaths
≈ 100 M Cases

TUBERCULOSIS

2020 ≈ 1,4 M Deaths
≈ 10 M TB cases
≈ 100 M TB Infected

(Estimated that an average of 5 M deaths per year in the last 200 years) Paulson Nature 2013

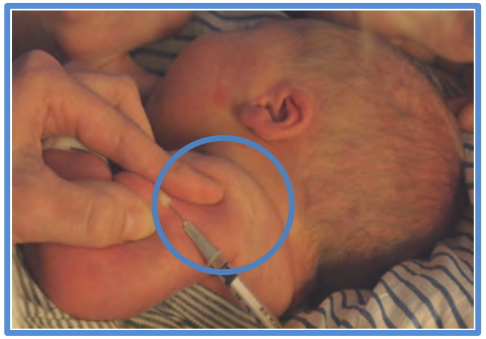
BCG COVERAGE ≥90%

BCG PROVIDES VARIABLE PROTECTION AGAINST RESPIRATORY FORMS OF TB

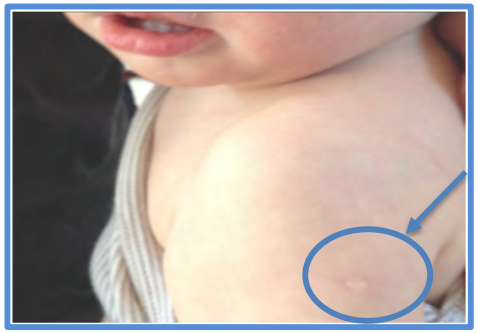
(Needs for impovement: Protection pulmonary forms of TB long term Protection in adolescents

BCG 0.05 ml
20 doses

Intradermal administration at birth



Scar after vaccination



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

BENEFICIAL EFFECTS OF BCG VACCINATION:

1. BCG provides **STRONG PROTECTION AGAINST DISSEMINATED FORMS OF TB** (meningitis, miliary TB). Is estimated that BCG saves 70.000 death per year.

2. BCG vaccination **REDUCES ALL-CAUSE MORTALITY** not related to Mtb and adding reduction in respiratory infections and sepsis also unrelated through **beneficial effects: "Off-target", "Non-specific", "Heterologous"** on the immune system.

CAN THE INNATE IMMUNE SYSTEM LEARN?

Review

Cell

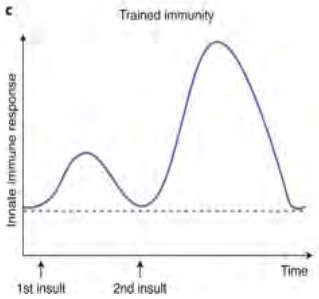
A small jab – a big effect: nonspecific immunomodulation by vaccines

Christine S. Benn[1], Mihai G. Netea[2], Liisa K. Selin[3], and Peter Aaby[4]

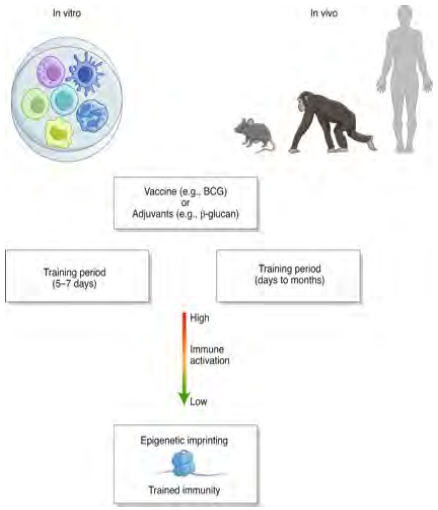
Trends in Immunology, **2013,** Vol. 34, No. 9

The Non-Specific Effects of Vaccines have been studied in randomized controlled clinical trials:

- **Vaccine scarring** has been associated with reductions of more than 40% in overall mortality among adults.
- The **measles vaccine** is associated with more survival benefits than expected.
- **BCG** at birth nearly halves neonatal mortality.



Behavior of innate immune responses during adaptive programs induced in innate immune cells.

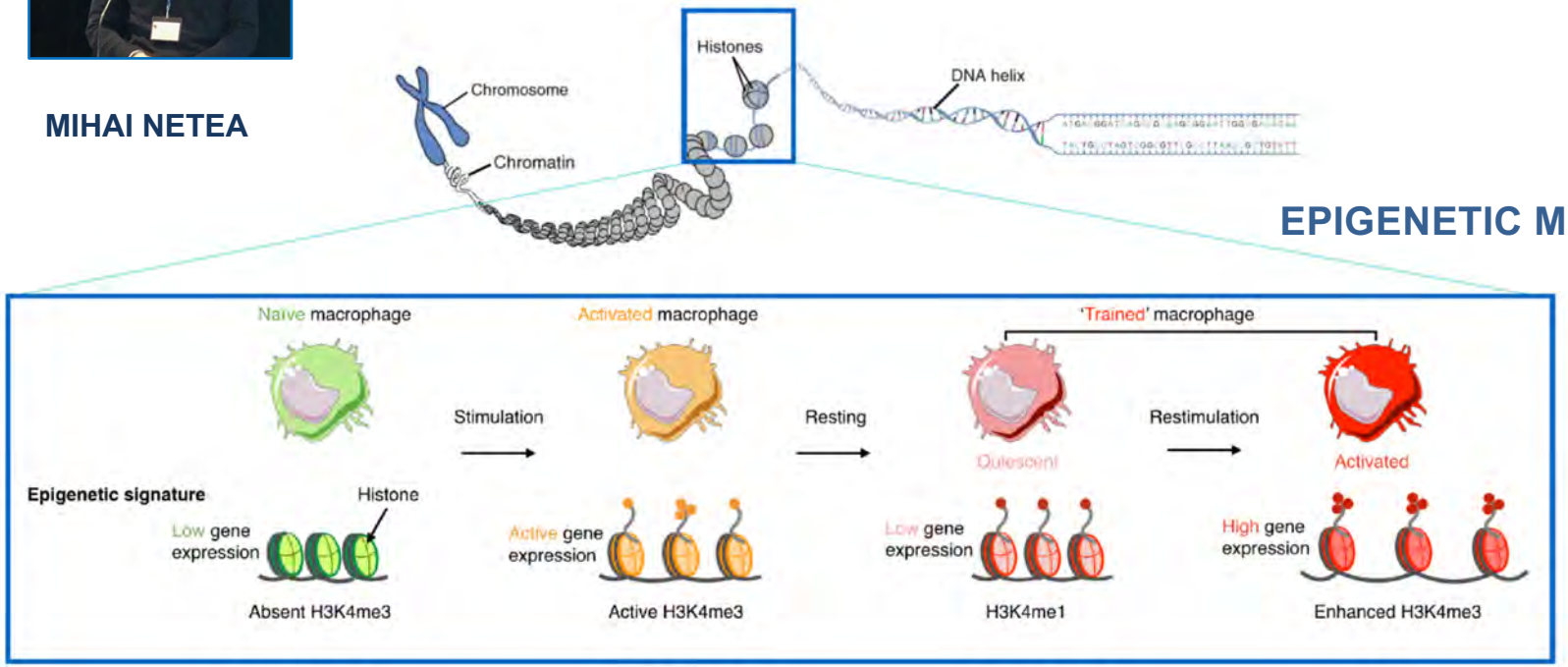


The models used to study the adaptive programs in innate immunity, including trained immunity

Divangahi et al Trained immunity, tolerance, priming and differentiation: distinct immunological processes. ***Nat Immunol* 2021**, *22*, 2–6.

MIHAI NETEA

BCG Trained Immunity : Innate Immune Memory



TRI-METHYLATION AT THE **4TH LYSINE** RESIDUE OF THE **HISTONE H3**

Resting **Infection** **Resting** **Re-infection**

- **IL-1β**
- **IL-6**
- **TNFα**

PROSPECTIVE STUDIES OF NON SPECIFIC EFFECT OF BCG:

ADULTS ADOLESCENTS UPPER RESPIRATORY TRACT INFECTIONS :

ORIGINAL ARTICLE

NEJM 2018

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

- NON SPECIFIC EFFECT OF LIVE ATTENUATED VACCINE BCG
- RATE OF UPPER RESPIRATORY TRACT INFECTIONS WAS: LOWER IN THE BCG REVACCINATED GROUP (2.1%) P<0.001

  9.4% in subunit vaccine H4:IC31 group or
  7.9% in Placebo group

NEONATES ON ALL-CAUSE INFECTIOUS DISEASE MORBIDITY

BCG HAD A PROTECTIVE EFFECT AGAINST, NON-TUBERCULOUS INFECTIONS IN INFANTS WITH A BIRTH WEIGHT OF 2.500 grames or less

Articles

Lancet Resp Dis 2021

BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial

Sarah Prentice, Beatrice Nassanga, Emily L Webb, Florence Akello, Fred Kiwudhu, Helen Akurut, Alison M Elliott, Rob J W Arts, Mihai G Netea, Hazel M Dockrell, Stephen Cose, for The Delayed BCG Study Team*

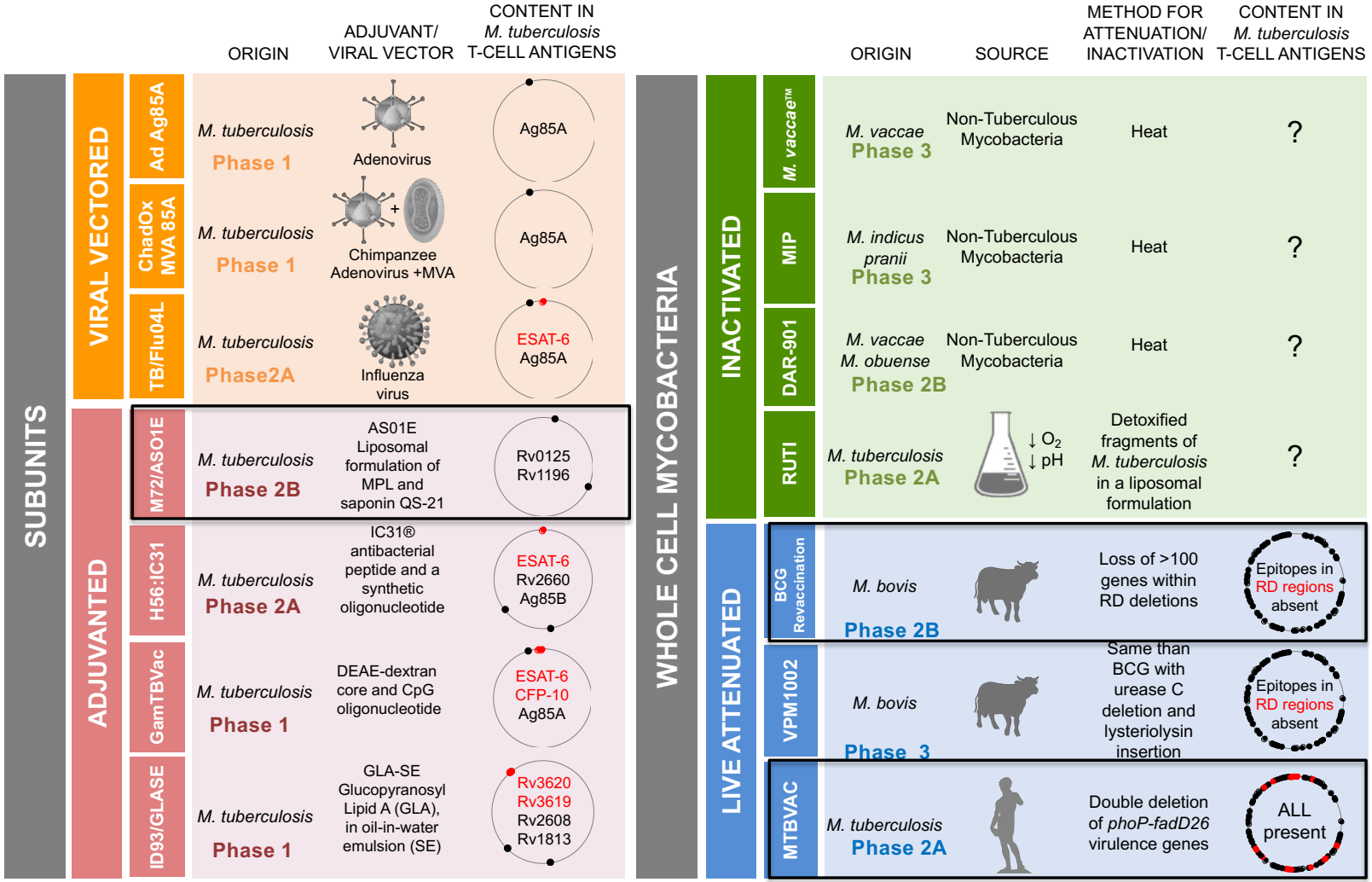
Summary

Background Trials done in infants with low birthweight in west Africa suggest that BCG vaccination reduces all-cause mortality in the neonatal period, probably because of heterologous protection against non-tuberculous infections. This study investigated whether BCG alters all-cause infectious disease morbidity in healthy infants in a different high-mortality setting, and explored whether the changes are mediated via trained innate immunity.

Lancet Infect Dis 2021
Published Online
February 17, 2021
https://doi.org/10.1016/S1473-3099(20)30676-8

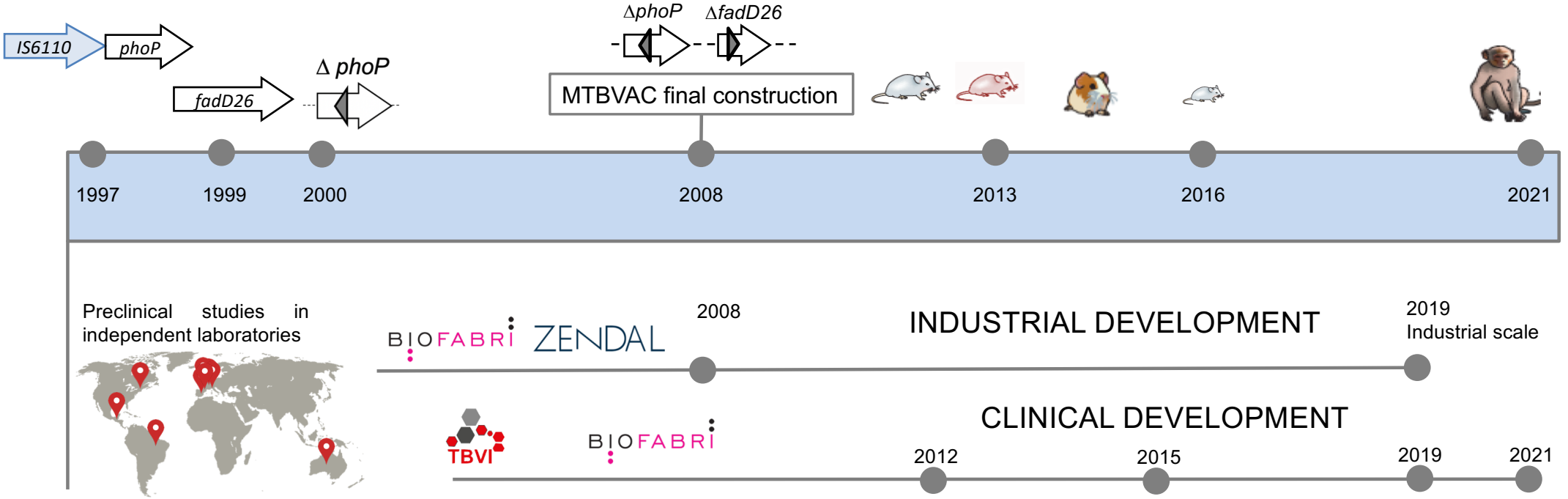
	Before delayed BCG (age 0–6 weeks)*				After delayed BCG (age 6–10 weeks)†				Total follow-up period			
	Frequency in BCG at birth group	Frequency in BCG at 6 weeks group	Hazard ratio (95% CI)	p value	Frequency in BCG at birth group	Frequency in BCG at 6 weeks group	Hazard ratio	p value	Frequency in BCG at birth group	Frequency in BCG at 6 weeks group	Hazard ratio	p value
Infectious presentations												
Total	98	129	0·71 (0·53–0·95)	0·023	88	76	1·10 (0·87–1·40)	0·43	186	205	0·91 (0·76–1·10)	0·33
Male	42	62	0·57 (0·36–0·89)	0·013	41	33	1·11 (0·78–1·59)	0·56	83	95	0·84 (0·63–1·11)	0·22
Female	56	67	0·87 (0·59–1·27)	0·47	47	43	1·11 (0·81–1·52)	0·53	103	110	0·99 (0·78–1·25)	0·93
p_interaction between BCG and sex	..	..	..	0·16	..	..	..	0·99	..	..	..	0·37
Birthweight >2500 g	97	115	0·79 (0·59–1·07)	0·12	88	72	1·16 (0·9–1·48)	0·22	185	187	0·99 (0·82–1·19)	0·89
Birthweight ≤2500 g	1	14	0·10 (0·01–0·75)	0·026	0	4	1·31* (5·64*–3·03*)	<0·0001	1	18	0·07 (0·01–0·45)	0·0061
p_interaction between BCG and birthweight	..	..	..	0·044	..	..	..	<0·0001	..	..	..	0·0045

DIVERSITY OF THE PIPE LINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS



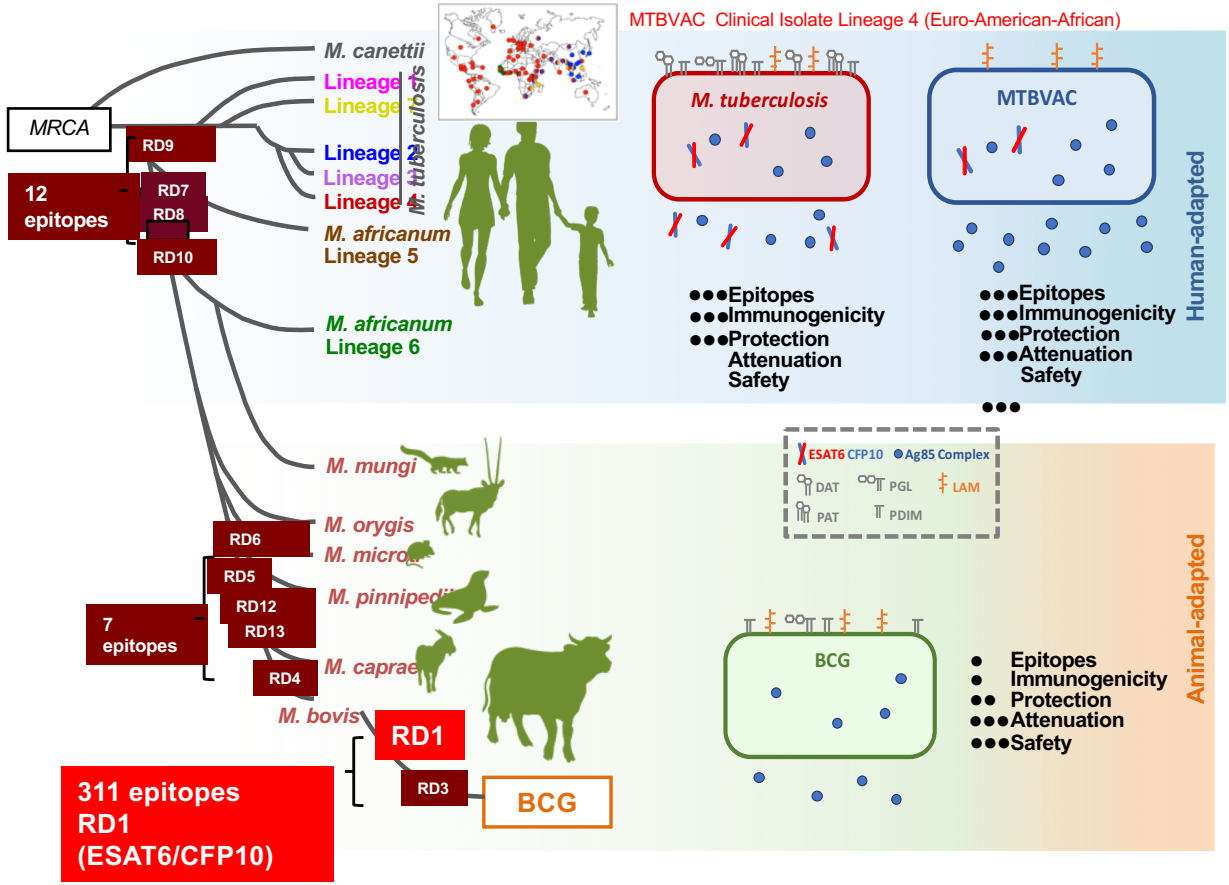
Update on TB Vaccine Pipeline. Martin et al Applied Sciences 2020

MTBVAC : PRECLINICAL DEVELOPMENT AND VACCINE CHARACTERIZATION



Universidad Zaragoza
1542

BCG *Mycobacterium bovis* isolated from cows attenuation RD1 deletion
MTBVAC, *Mycobacterium tuberculosis* isolated from a human clinical isolate.
MTBVAC, 519 MORE EPITOPES THAN BCG WHICH REPRESENTS AN INCREASE OF 48%



MTBVAC →
1603 epitopes

BCG →
1084 epitopes

QuantiFERON®-TB Gold In-Tub
ESAT6,CFP10 &TB7.7

BIGGEST DIFFERENCE MTBVAC CONTAINS RD1

Marinova *et al* Expert Rev Vaccines 2017

Gonzalo-Asensio et al Frontiers Immunology 2017

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

Michele Tameris

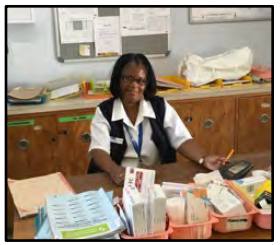
ClinicalTrials.gov
NCT02729571

NORAD

BIOFABRI

SATVI PROJECT OFFICE

WORCESTER SITE

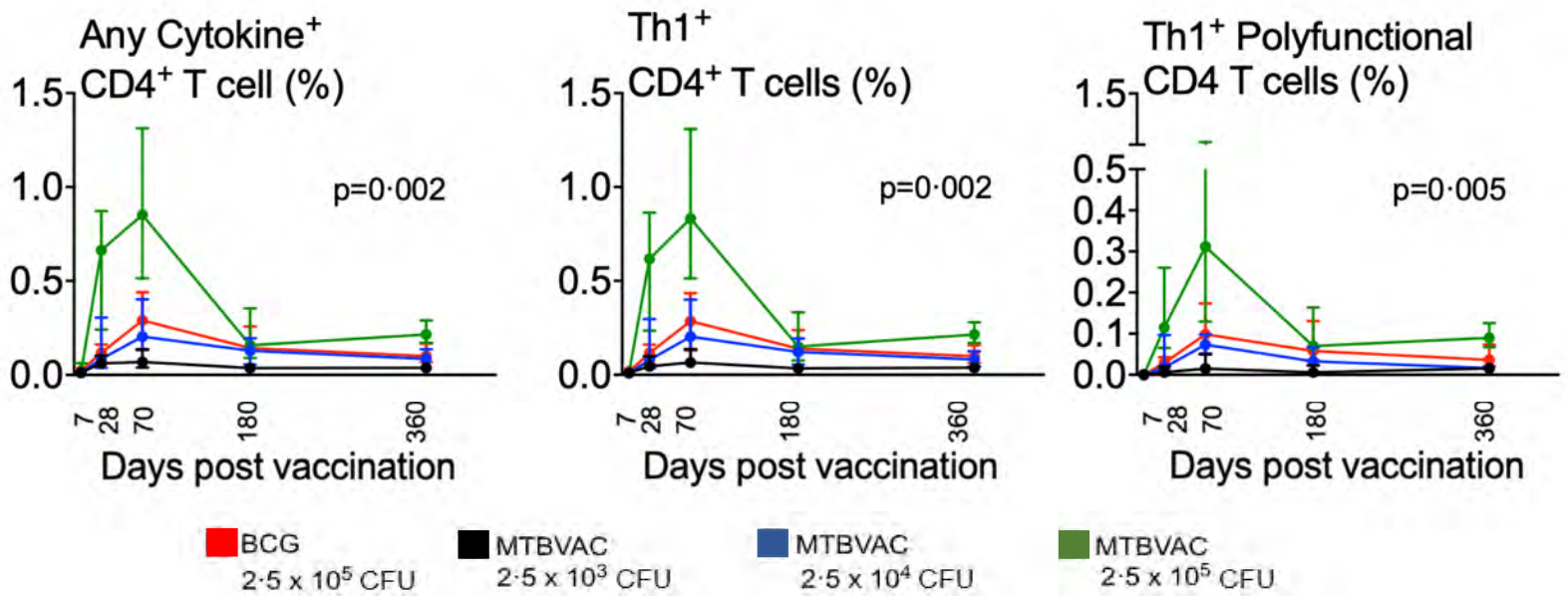


TB CLINIC

TB HOSPITAL

KINETICS OF TOTAL CD4 $^{+}$T-CELL RESPONSES INDUCED BY VACCINATION

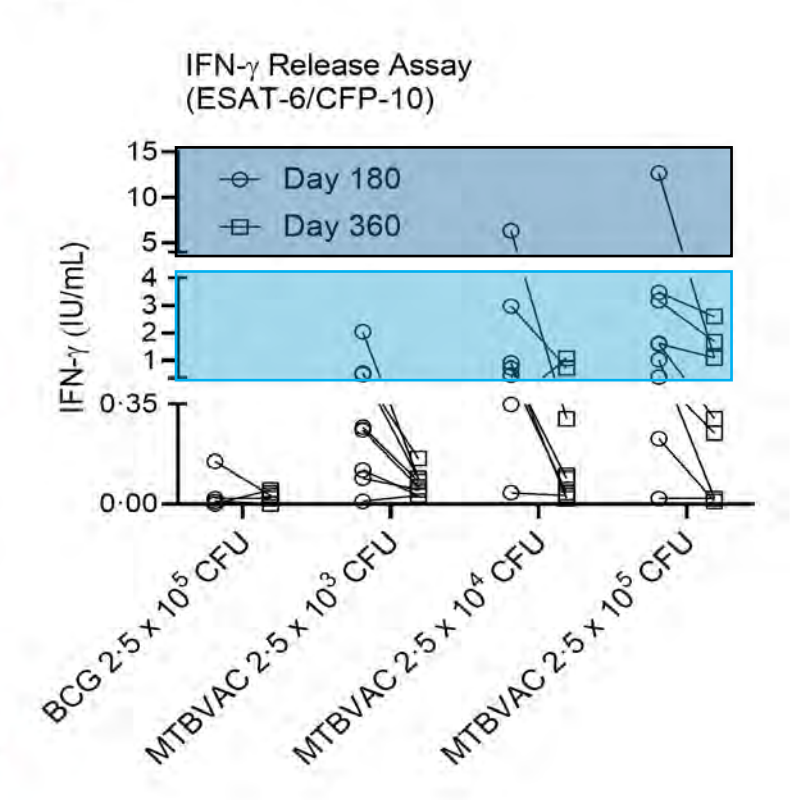
Longitudinal kinetics of antigen-specific CD4 T cells expressing the indicated cytokine responses in participants after vaccination and measured by whole blood intracellular cytokine staining assay.



CD4 T cells indicate a significant difference between the groups: Any Cytokine +, Th1+, Th1 + polyfunctional

ANTIGEN SPECIFIC T CELL RESPONSES: IGRA QFT

QuantiFERON®-TB Gold In-Tub
ESAT6,CFP10 &TB7.7



DOSE RELATED QFT CONVERSION MTBVAC
Up to 0.35 IU per millilitre at day 180:

0 of 8 BCG (0%)
3 of 8 low-dose (10^3) **(37·5%),**
6 of 8 medium-dose (10^4) **(75·0%)**
7 of 9 high-dose (10^5) **(77·8%)**

Day 180 and day 360 interferon-γ values, as measured by **QuantiFERON-TB-Gold** assay, in each trial group, each line represents data for one participant. The pink shaded area represents the manufacturer's threshold for test positivity (0.35 IU per millilitre).

Phase 1b

Lancet Respir Med 2019
Published Online
August 12, 2019
http://dx.doi.org/10.1016/
S2213-2600(19)30251-6

Articles

Tameris et al Lancet Respir Med 2019

Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial

Michele Tameris, Helen Mearns*, Adam Penn-Nicholson, Yolande Gregg, Nicole Bilek, Simbarashe Mabwe, Hennie Geldenhuys, Justin Shenje, Angelique Kany Kany Luabeya, Ingrid Murillo, Juana Doce, Nacho Aguilo, Dessislava Marinova, Eugenia Puentes, Esteban Rodríguez, Jesús Gonzalo-Asensio, Bernard Fritzell, Jelle Thole, Carlos Martin, Thomas J Scriba†, Mark Hatherill†, and the MTBVAC Clinical Trial Team*

- A clear dose-dependent increase in MTBVAC immunogenicity was observed.
- The highest MTBVAC dose of 2·5 x 10^5 CFU induced a response of greater magnitude than the same dose of BCG.
- The induced CD4 T cell immune response was predominantly polyfunctional and comprised a range of different IFN-γ, TNF-α and/or IL-2-expressing subsets higest than in BCG vaccinated.

DATA SUPPORT ADVANCED CLINICAL DEVELOPMENT OF MTBVAC

Funding BIOFABRI and Norwegian Agency for Development Cooperation (NORAD) , TuBerculosis Vaccine Initiative (TBVI), UK Department for International Development

npj | Vaccines

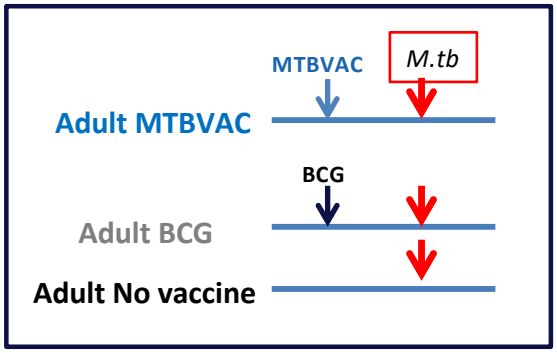
www.nature.com/npjvaccines

ARTICLE OPEN

Check for updates

MTBVAC vaccination protects rhesus macaques against aerosol challenge with *M. tuberculosis* and induces immune signatures analogous to those observed in clinical studies

Andrew D. White[1✉], Laura Sibley[1], Charlotte Sarfas[1], Alexandra Morrison[1], Jennie Gullick[1], Simon Clark[1], Fergus Gleeson[2], Anthony McIntyre[2], Cecilia Lindestam Arlehamn[3], Alessandro Sette[3], Francisco J. Salguero[1], Emma Rayner[1], Esteban Rodriguez[4], Eugenia Puentes[4], Dominick Laddy[5], Ann Williams[1], Mike Dennis[1], Carlos Martin[6] and Sally Sharpe[1]



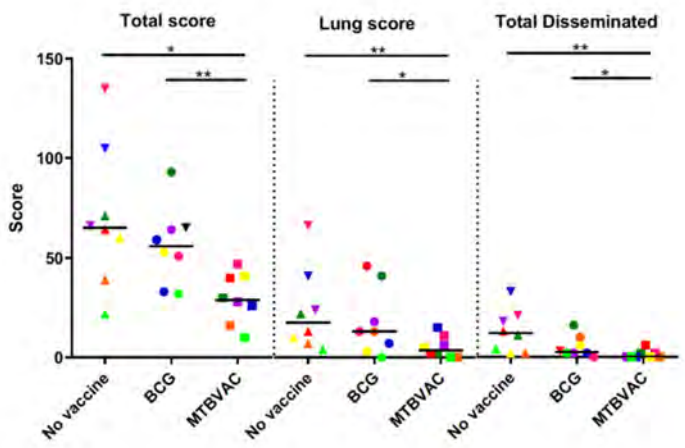
White *et al* npj Vaccines 4 January (2021) 6:4 ;
https://doi.org/10.1038/s41541-020-00262-8

Public Health England

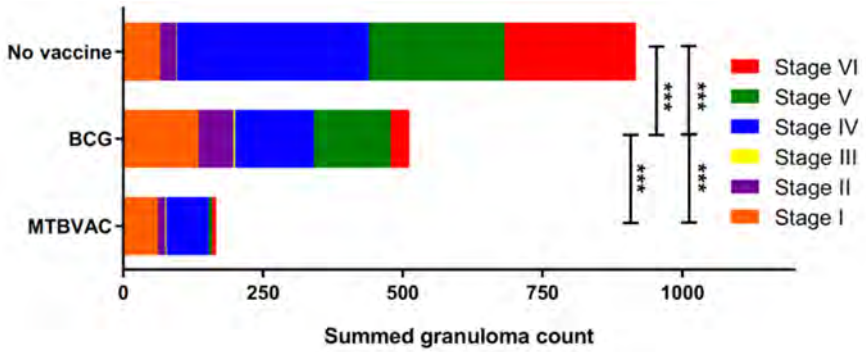
Objectives:

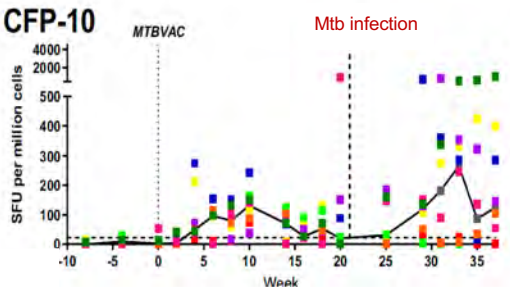
- To study the protective efficacy conferred by a single intradermal vaccine with MTBVAC or BCG against exposure to low doses of aerosol with *M. tuberculosis* in rhesus macaques.

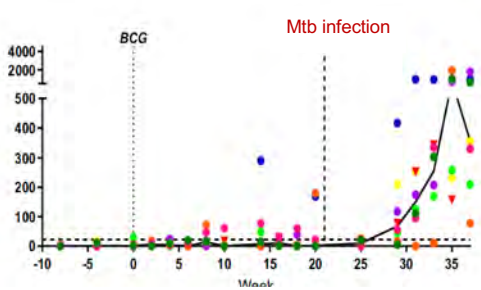
- Characterize the immune response induced after vaccination and compare the immune responses in macaques with the responses in humans immunized with BCG and MTBVAC.

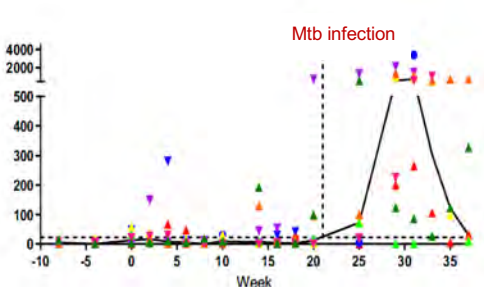


EFFICACY

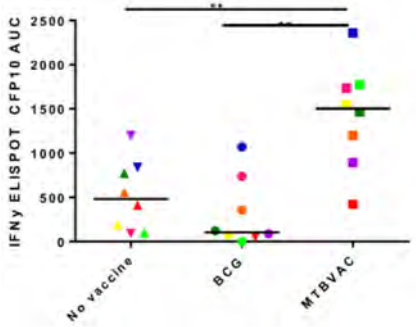








IMMUNOGENECITY



Concordance between immune profiles measured in clinical trials and a preclinical study of macaques demonstrating a significantly improved outcome after exposure to *M. tuberculosis* as evidence to support the continued development of MTBVAC as an effective prophylactic vaccine for vaccination against TB.

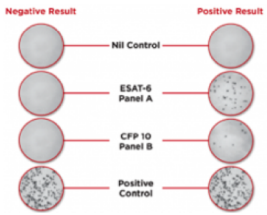
Centre Hospitalier Universitaire Vaudois

Phase1a Adults (NCT02013245)

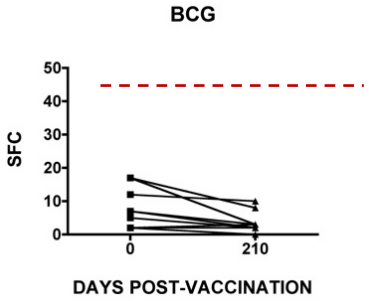
Elispot ESAT6/CFP10 (CHUV)

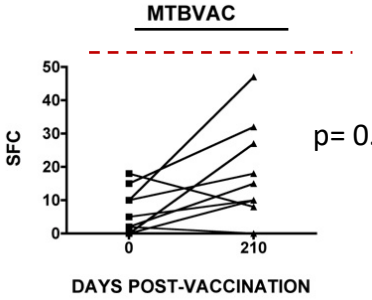
ELISPOT CFP10 and ESAT6-specific responses in MTBVAC-vaccinated adults

ELISPOT



CFP10 Elispot



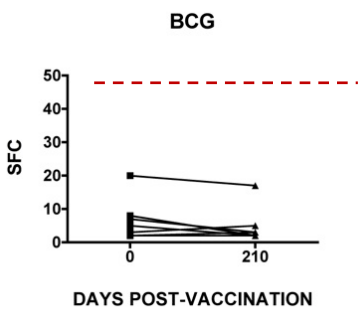


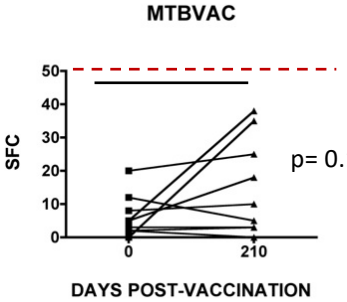
Positive cut-off for TB infection

p= 0.0391

CFP10 significative higer but, **Negative** for the 3 doses of MTBVAC and the end of the study (7M)

ESAT6 Elispot





Positive cut-off for TB infection

p= 0.1641

Aguilo *et al 2017 Nat Comm*

Spertini et al Lancet Resp Medicine 2015

ESAT-6 and CFP-10 as positive if the number of SFUs was at least 55 SFU per 10^6 cells

BIOFABRI

Phase 2 ADULTS

satvi

Phase 1b/2a — DOSE FINDING SAFETY AND IMMUNOGENICITY IN ADULTS 2019

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 — avi

Trial Population – 144 (96 +48) END VACCINATION PHASE SEPT2020

ClinicalTrials.gov NCT02933281

QFT negative individuals:

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

QFT positive individuals:

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

Site PI Angelique Luabeva

EDCTP — NIH — avi — BIOFABRI — TBVI — Universidad Zaragoza

2019 **CLINICAL DEVELOPMENT** 2021/2022

Phase 2 NEWBORNS

satvi

Phase 2a — DOSE FINDING SAFETY AND IMMUNOGENICITY IN NEWBORNS 2019

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

satvi — BIOFABRI

END VACCINATION PHASE MARCH 2021

99 HIV-unexposed, BCG-naïve, healthy newborns Intradermally within 96hrs of birth randomized 3:1 to receive:

ClinicalTrials.gov NCT03536117

- 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)

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 3 NEWBORNS

Phase 3 EFFICACY

EDCTP (European Development Clinical Trials Parnership)

ZENDAL — BIOFABRI

MTBVAC Phase 3 in neonates - RIA2019S-25652

A Phase 3, Randomised, Double blind, Controlled of the Safety, Immunogenicity and Efficacy Evaluation Study in TB-Endemic Regions of Sub-Saharan Africa of MTBVAC in Healthy, BCG Naïve, HIV Unexposed and Exposed, South African newborns

Universidad Zaragoza — TBVI — EPLS — VPD RMPRU — Institut Pasteur de Madagascar — University of KwaZulu-Natal / Yakwazulu-Natali — BIOFABRI

CONSORTIUM - PARTNERSHIP

- Biofabri / Spain / Coordinator
- TuBerculosis Vaccine Initiative (TBVI) / The Netherland
- The University of Zaragoza / Spain
- The University of Cape Town (UCT) / South Africa
- Center de Recherche Biomedicale Espoir Pour La Santé (BRC-EPLS) / Senegal
- Institut Pasteur de Madagascar (IPM) / Madagascar
- The University of Stellenbosch (SUN), Cape Town
- The Respiratory and Meningeal Pathogen Research Unit /RMPRU), Johannesburg, South Africa
- The University of KwaZulu Natal (UKZN), Durban, South Africa

EDCTP — European & Development Countries Clinical Trial Partnership

EDCTP Ref. 11456

EDCTP

Universidad Zaragoza

NON SPECIFIC EFFECTS TB LIVE ATTENUATED VACCINES

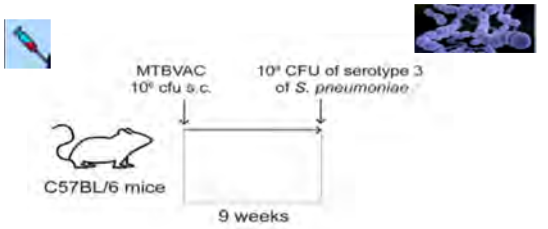
BCG	MTBVAC
• First-line therapy for non–muscle-invasive bladder cancer. Morales *et al* 1976 Journal of Urology.	• Therapeutic efficacy in preclinical model of bladder cancer. Alvarez-Aguedas *et al* 2018 Trans Med.
• Trained immunity in human cells. Kleinnijenhuis *et al* 2012 Proc Natl Acad Sci USA.	• Trained immunity in human cells (epigenetic and metabolic reprogramming of the cells from the innate immune system). Tarancon *et al* 2020 Plos Pathogens.
• Heterologous protection against lethal Candida albicans infection in mice. Kleinnijenhuis Kleinnijenhuis *et al* 2012 Proc Natl Acad Sci USA.	• Heterologous protection against a lethal challenge with *Streptococcus pneumoniae* in an experimental murine model of pneumonia. Tarancon *et al* 2020 Plos Pathogens.
• Therapeutic efficacy against established asthma Tarancon *et al* 2021 Ebiomedicine.	• Therapeutic efficacy against established asthma Tarancon *et al* 2021 Ebiomedicine.
• Beneficial impact on immunization with DTaP vaccine (diphtheria, tetanus, and acellular pertussis). Broset *et al* 2021 Ebiomedicine .	• Beneficial impact on immunization with DTaP vaccine (diphtheria, tetanus, and acellular pertussis). Broset *et al* 2021 Ebiomedicine.

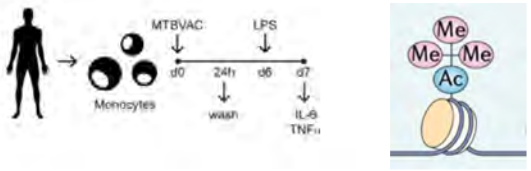
PLOS PATHOGENS

RESEARCH ARTICLE

New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia

Raquel Tarancón[1,2☯], Jorge Domínguez-Andrés[3☯*], Santiago Uranga[1,2], Anaísa V. Ferreira[3,4], Laszlo A. Groh[3], Mirian Domenech[2,5], Fernando González-Camacho[2,5], Niels P. Riksen[3], Nacho Aguilo[1,2], José Yuste[2,5], Carlos Martín[1,2,6‡], Mihai G. Netea[3,7,8‡]

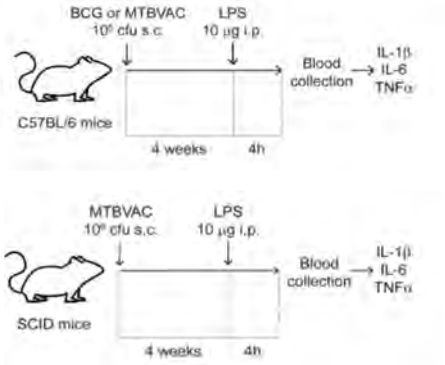




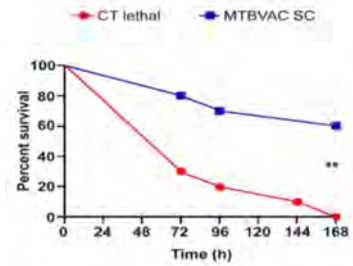
MTBVAC induces epigenetic reprograming in human PBMCs

Induction of glycolysis and glutaminolysis and the accumulation of histone methylation marks at the promoters of proinflammatory

Genes: TNFα, IL6



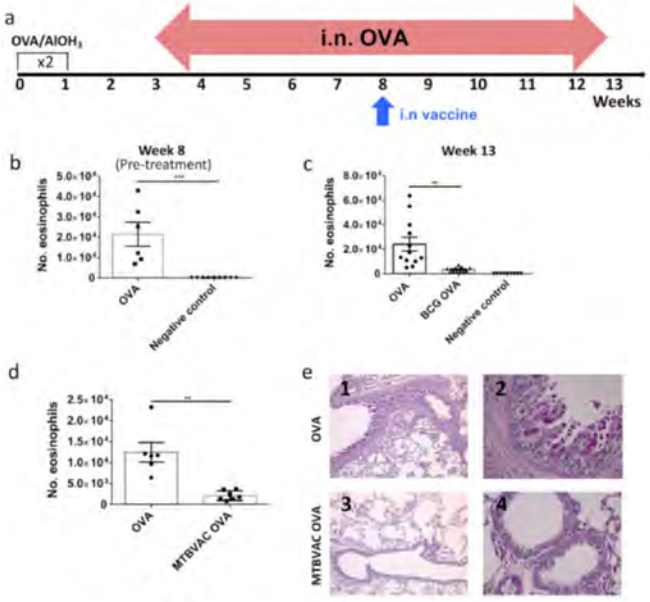
MTBVAC induces trained immunity *in vivo* in mice: Immunocompetent and SCID

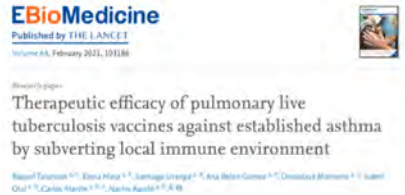


MTBVAC protect *in vivo* in mice against *S. pneumoniae* infection Heterologous protection against a lethal challenge with *S. pneumoniae* in an experimental murine model of pneumonia.

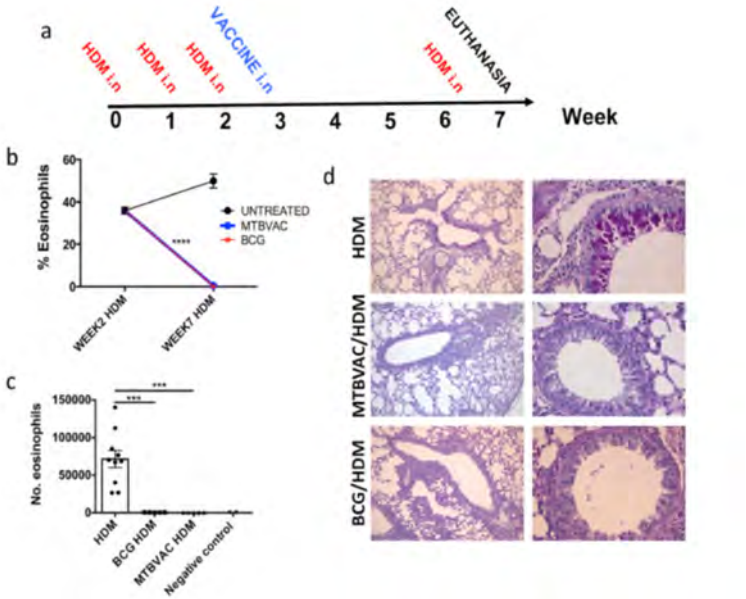
THERAPEUTIC EFFICACY MTBVAC AGAINST ESTABLISHED ASTHMA

BCG and MTBVAC intranasal revert established allergic airway responsiveness in an OVA-driven chronic model.

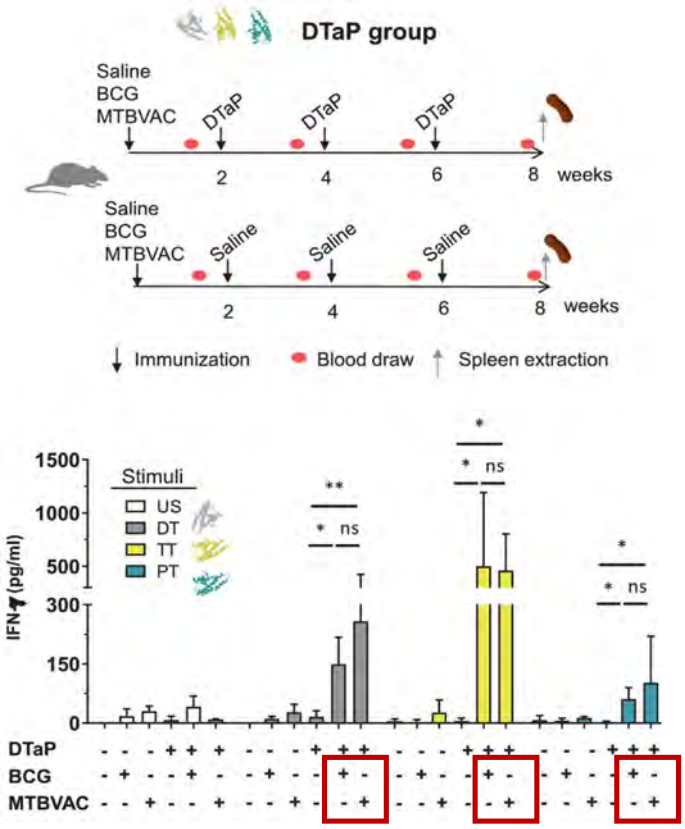




BCG and MTBVAC intranasal vaccination reverts established allergic airway responsiveness induced by the relevant house dust mite allergen HDM.

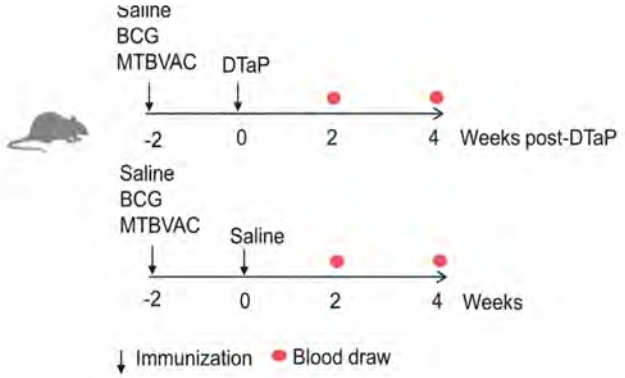


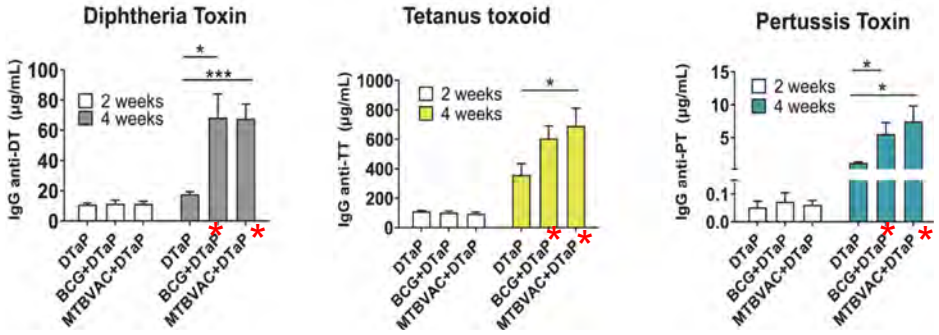
BENEFICIAL IMPACT ON IMMUNIZATION WITH DTaP VACCINE (DIPHTHERIA, TETANUS, AND ACELLULAR PERTUSSIS)



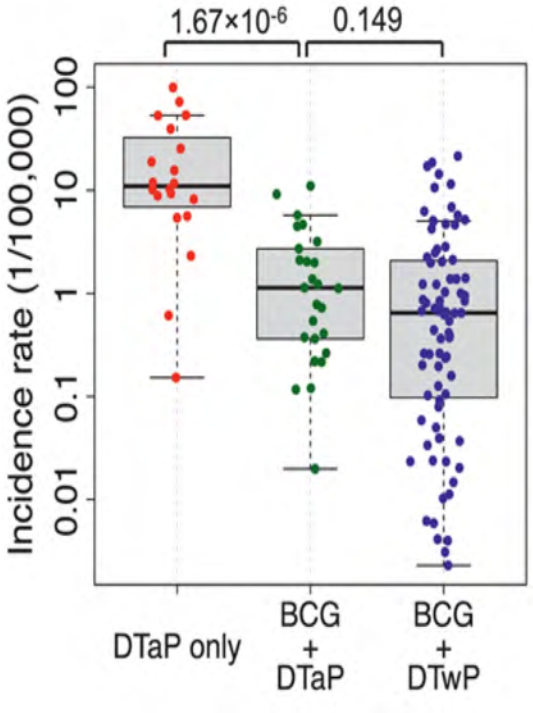
Immunization with DTaP alone failed to trigger a Th1response, as measured by the production of IFN-γ. Both BCG and MTBVAC when administered before DTaP, triggered Th1 immune responses against diphtheria, tetanus, and pertussis in mice.

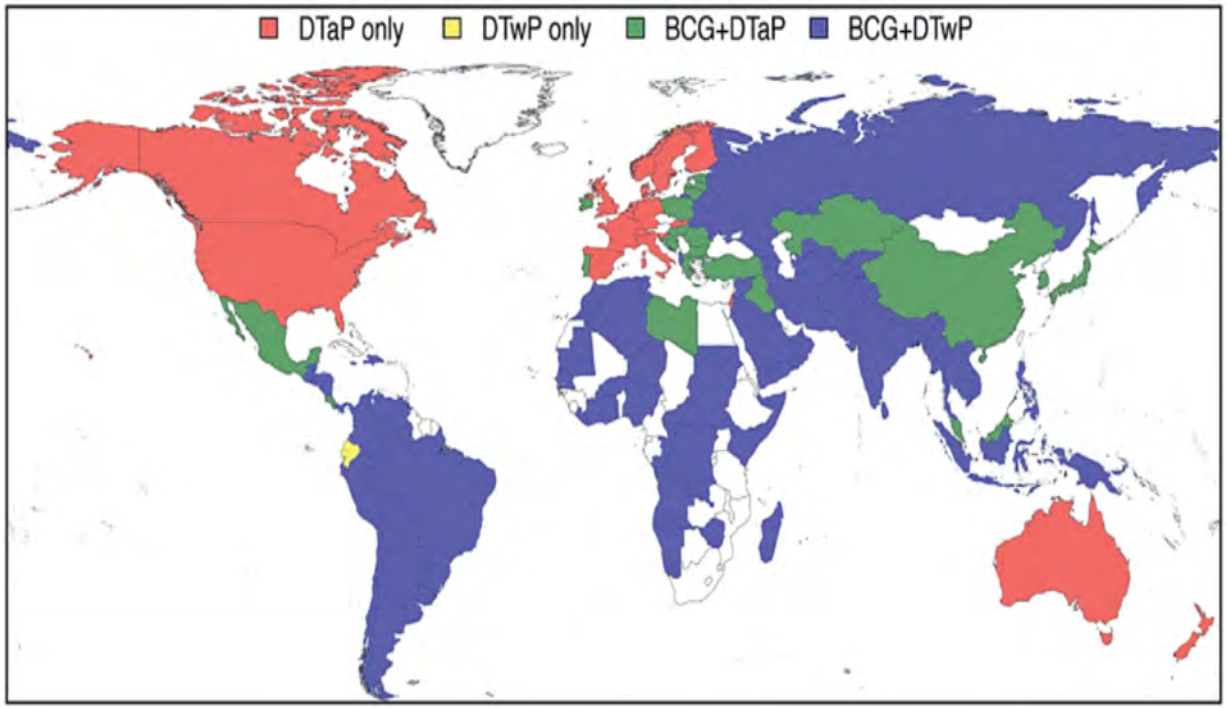
HUMORAL RESPONSES AGAINST DTaP ANTIGENS WERE ALSO ENHANCED BY PREVIOUS IMMUNIZATION WITH BCG OR MTBVAC

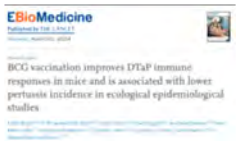




HUMAN EPIDEMIOLOGICAL DATA SHOWED THAT PERTUSSIS INCIDENCE WAS10-FOLD LOWER IN COUNTRIES THAT USE DTaP and BCG COMPARED TO COUNTRIES THAT USE ONLY DTaP



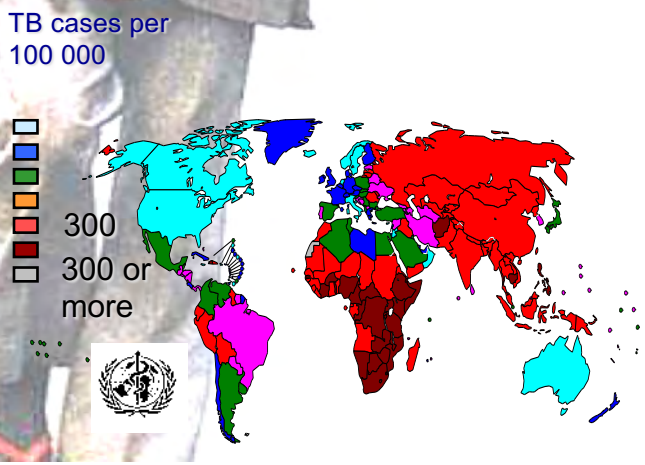




TUBERCULOSIS Vaccines:

LIVE VACCINES

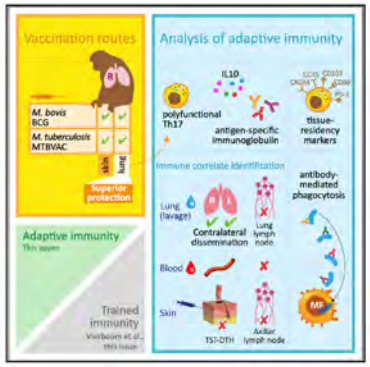
Protection Pulmonary TB
Better than BCG + same nonspecific effects



Years of effort and billions of dollars have driven polio to just a few impoverished corners of the world. The campaign is intensifying, but the virus is tenaciously resisting

Polio: The Final Assault?

RESEARCH ON NEW ROUTES OF ADMINISTRATION: RESPIRATORY ROUTE

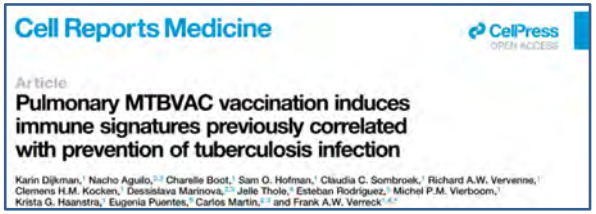


Cell Reports Medicine

Article

Pulmonary MTBVAC vaccination induces immune signatures previously correlated with prevention of tuberculosis infection

Biomedical Primate Research Centre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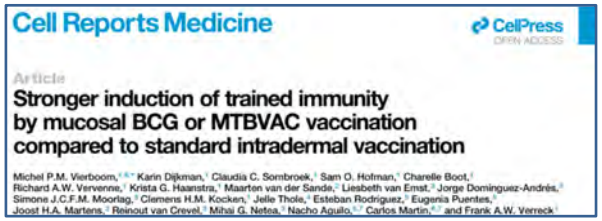
Article

Pulmonary MTBVAC vaccination induces immune signatures previously correlated with prevention of tuberculosis infection

Karin Dijkman,[1] Nacho Aguilo,[2,7] Charelle Boot,[1] Sam O. Hofman,[1] Claudia C. Sombroek,[1] Richard A.W. Vervenne,[1] Clemens H.M. Kocken,[1] Dessislava Marinova,[2,5] Jelle Thole,[3] Esteban Rodriguez,[3] Michel P.M. Vierboom,[1] Krista G. Haanstra,[1] Eugenia Puentes,[3] Carlos Martin,[2,7] and Frank A.W. Verreck[1,4,7]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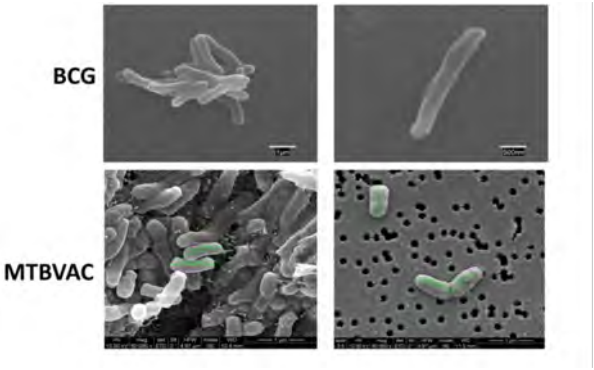
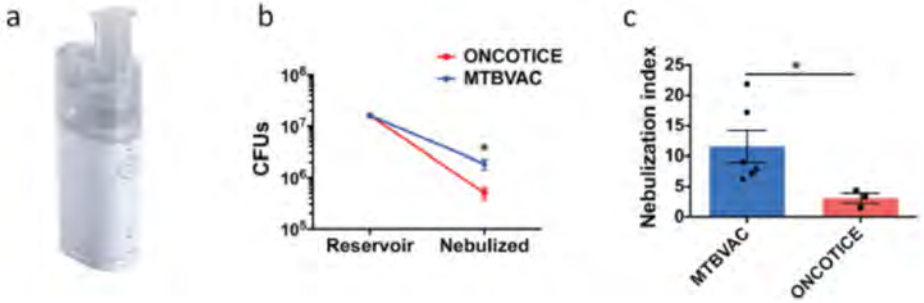
Article

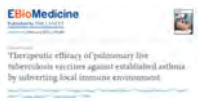
Stronger induction of trained immunity by mucosal BCG or MTBVAC vaccination compared to standard intradermal vaccination

Michel P.M. Vierboom,[1,6,*] Karin Dijkman,[1] Claudia C. Sombroek,[1] Sam O. Hofman,[1] Charelle Boot,[1] Richard A.W. Vervenne,[1] Krista G. Haanstra,[1] Maarten van der Sande,[2] Liesbeth van Emst,[3] Jorge Dominguez-Andrés,[3] Simone J.C.F.M. Moorlag,[3] Clemens H.M. Kocken,[1] Jelle Thole,[3] Esteban Rodriguez,[3] Eugenia Puentes,[3] Joost H.A. Martens,[3] Reinout van Crevel,[3] Mihai G. Netea,[3] Nacho Aguilo,[2,7] Carlos Martin,[2,7] and Frank A.W. Verreck[1]





Aerosol delivery for administration for live TB vaccines into the lung compartment. Efficacy of nebulization *in vitro* of two clinical formulations of MTBVAC and BCG in a standard commercial nebulizer, demonstrating the feasibility of reaching therapeutic bacterial doses using standard nebulization devices.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