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Biotechnology and Vaccines

GLOBAL FORUM ON TB VACCINES

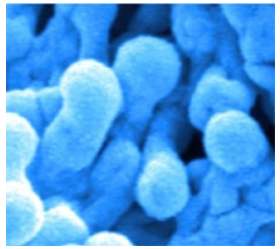
Advancing TB vaccines in the time of COVID-19

MTBVAC an attenuated TB vaccine - Looking towards the efficacy trial

Ingrid Murillo Jelsbak

21st April 2021

A COMPANY OF ZENDAL GROUP



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2 Rhesus Macaques - MTBVAC vaccination. Aerosol with *M. tuberculosis*

3 MTBVAC Phase Phase 3 efficacy trial in newborns - New Challenge

4 Wrap Up

MTBVAC – CLINICAL DEVEL0PMENT OVERVIEW

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2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 - 2028

Phase 1a — *ClinicalTrials.gov: NCT02013245*

36 healthy volunteers

CHUV Centre Hospitalier Universitaire Vaudois

Phase 1b — *ClinicalTrials.gov NCT02729571*

18 adults+36 neonates

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Phase 2a — *ClinicalTrials.gov NCT03536117*

99 neonates

Phase 1b/2a — *ClinicalTrials.gov NCT02933281*

144 adults

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Phase 3

6.500 neonates

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EPLS Centre de Recherche Biomédicale Espoir Pour La Santé

TBVI Tuberculosis Vaccine Initiative

VPD Vaccine Preventable Diseases

RMPRU Respiratory & Meningeal Pathogens Research Unit

Institut Pasteur de Madagascar

UNIVERSITY OF KWAZULU-NATAL INYUVESI YAKWAZULU-NATALI

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MTBVAC Phase 1a in adults – Conclusions

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Phase I Double Blind, Randomized, Controlled, Dose-Escalation Study to Evaluate the Safety and Immunogenicity of MTBVAC in Comparison with BCG in Elispot Tb (ESAT-6, CFP10, PPD)- and HIV-negative volunteers

IP: Dr. François Spertini

Randomized 3:1

MTBVAC ($5x10^3$ CFU) or BCG SSI ($5x10^5$ CFU) (9+3)

MTBVAC ($5x10^4$ CFU) or BCG SSI ($5x10^5$ CFU) (9+3)

MTBVAC ($5x10^5$ CFU) or BCG SSI ($5x10^5$ CFU) (9+3)

- Vaccination with MTBVAC demonstrated an excellent safety profile, comparable to BCG
- Negativity of IGRA tests 7 months after MTBVAC immunization is a key element for progressing MTBVAC to efficacy and prevention of infection trials
- At the same dose level as BCG, the MTBVAC group showed greater frequency of polyfunctional CD4+ central memory T-cells. A transient increase in CFP-10-specific ELISPOT positivity was observed at day 28 in three adult participants who received MTBVAC

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*

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Lancet Respir Med 2015
Published Online November 16, 2015 http://dx.doi.org/10.1016/ S2213-2600(15)00435-X

MTBVAC - Phase 1b. Design

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A randomized, double-blind, dose-escalation clinical trial of the safety, reactogenicity and immunogenicity of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region with a safety arm in adults

IP: Dr. Michele Tameris

MTBVAC IS WELL TOLERATED

18 healthy adults randomized 1:1

- MTBVAC (5 x 105 CFU) or BCG SSI (5 x 105 CFU) (9+9)
- HIV negative, QuantiFERON (QFT) negative, previously BCG-vaccinated

36 healthy, HIV-unexposed, BCG-naïve, newborns randomized 3:1

- MTBVAC (2.5x 103 CFU) or BCG SSI (2.5x105 CFU) (9+3)
- MTBVAC (2.5x104 CFU) or BCG SSI (2.5x105 CFU) (9+3)
- MTBVAC (2.5x105 CFU) or BCG SSI (2.5x105 CFU) (10+2)

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

Lancet Respir Med 2019; 7: 757–70
Published **Online** August 12, 2019 http://dx.doi.org/10.1016/ S2213-2600(19)30251-6

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NORAD DIREKTORATET FOR UTVIKLINGSSAMARBEID NORWEGIAN AGENCY FOR DEVELOPMENT COOPERATION

TBVI Tuberculosis Vaccine Initiative

MTBVAC - Phase 1b in neonates
Kinetics of total CD4+ T-Cell responses induced by vaccination

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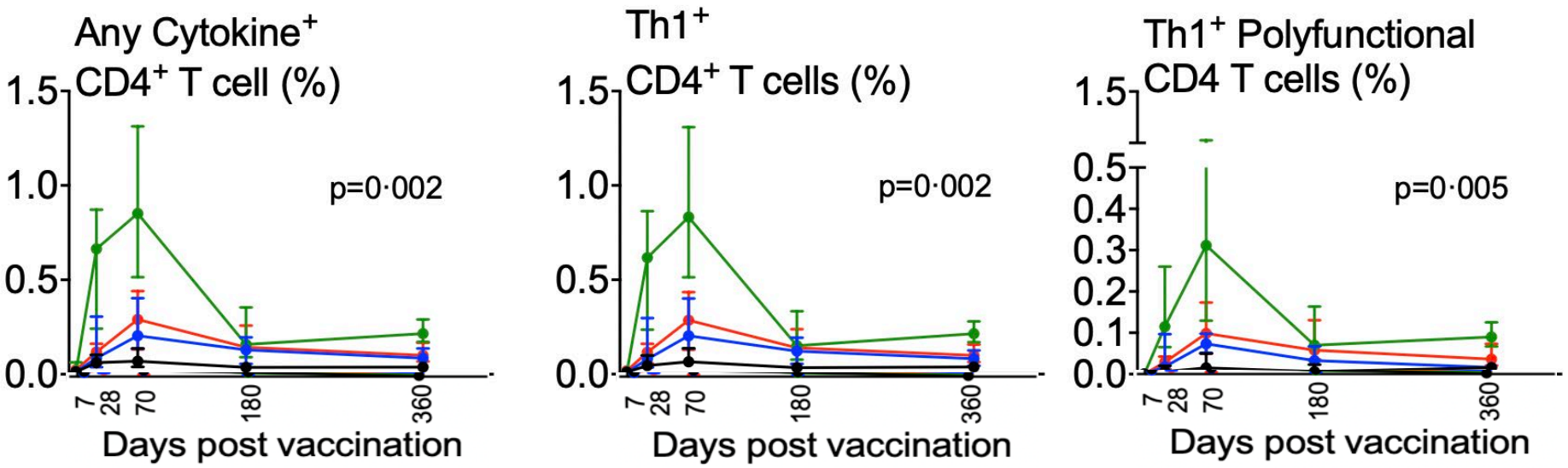
Longitudinal kinetics of antigen-specific CD4 T cells expressing the indicated cytokine responses in participants after vaccination and measured by whole blood intracellular cytokine staining assay



BCG 2,5x10^5 CFU | MTBVAC 2,5x10^3 CFU | MTBVAC 2,5x10^4 CFU | MTBVAC 2,5x10^5 CFU

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

MTBVAC - Phase 1b. Summary conclusions

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- MTBVAC in infants appears to be as, and more, safe than 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 in 80% in infants at M6 with MTBVAC highest dose reverting to less than 50% in M12 (QFT lower than 4IU/ml !)
- Based on these immunogenicity results, the low MTBVAC dose could be omitted from future studies

PHASE 1B IN NEWBORNS, SA - MTBVAC QFT CONVERSION		
GROUP	D180 QFT +	
MTBVAC - Cohort 1 $2.5X10^3$ N=9	3 of 8	37,50%
MTBVAC - Cohort 2 $2.5X10^4$ N=9	6 of 8	75%
MTBVAC - Cohort 3 $2.5X10^5$ N=10	7 of 9	77,78%
BCG SSI $2.5X10^5$ N=8	0 of 7	0%

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MTBVAC - Phase 2a in neonates RIA2019V-1637

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Dose-Defining Safety and Immunogenicity Study and Capacity Building to Support Vaccine Efficacy Trials in TB-Endemic Regions of Sub-Saharan Africa

IP: Dr. Michele Tameris

Selection dose, Safety, Reactogenicity and Immunogenicity

99 healthy, HIV-unexposed, BCG-naïve, newborns randomized 3:1

- MTBVAC ($2.5x10^4$ CFU) or BCG (2.5x105 CFU) (25+8)
- MTBVAC ($2.5x10^5$ CFU) or BCG (2.5x105 CFU) (25+8)
- MTBVAC ($2.5x10^6$ CFU) or BCG ($2.5x10^5$ CFU) (25+8)

Enrolment completed **FUP – 12 months** ***LPLV March 2022***

Lowest dose level desestimated

COVID 19

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European & Development Countries Clinical Trial Partnership

RIA2019V-1637

PARTNERSHIP

Biofabri / Spain / Coordinator
Stichting TuBerculosis Vaccine Initiative (TBVI) / The Netherland
University of Zaragoza / Spain
University of Cape Town (UCT) / South Africa
Center de Recherche Biomedicale Espoir Pour La Santé (BRC-EPLS) / Senegal
Institut Pasteur de Madagascar (IPM) / Madagascar

MTBVAC Phase 1b/2a in adults and adolescents

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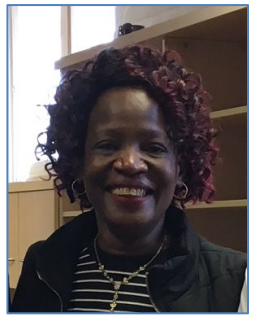
Phase 1b/2a Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults with and without Latent Tuberculosis Infection in South Africa



IP: Dr. Angelique Luabeya

NIH National Institutes of Health

CDMRP

Trial Population – 144 (96 +48)

QFT negative individuals:

- Cohort 1: n =12 MTBVAC (5 x 103 CFU) and n=6 BCG
- Cohort 2: n= 12 MTBVAC (5 x 104 CFU) and n=6 BCG
- Cohort 3: n= 12 MTBVAC (5 x 105 CFU) and n=6 BCG
- Cohort 4: n= 12 MTBVAC (5 x 106 CFU) and n=6 BCG

QFT positive individuals:

- Cohort 5: n =12 MTBVAC (5 x 103 CFU) and n=6 BCG
- Cohort 6: n= 12 MTBVAC (5 x 104 CFU) and n=6 BCG
- Cohort 7: n= 12 MTBVAC (5 x 105 CFU) and n=6 BCG
- Cohort 8: n= 12 MTBVAC (5 x 106 CFU) and n=6 BCG

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Enrolment completed **FUP – 12 months** ***LPLV September 2021***

TBVI Tuberculosis Vaccine Initiative

iavi International AIDS Vaccine Initiative

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

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COVID 19

Rhesus Macaques - MTBVAC vaccination.
Aerosol with M. tuberculosis

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npj | Vaccines

www.nature.com/npjvaccines

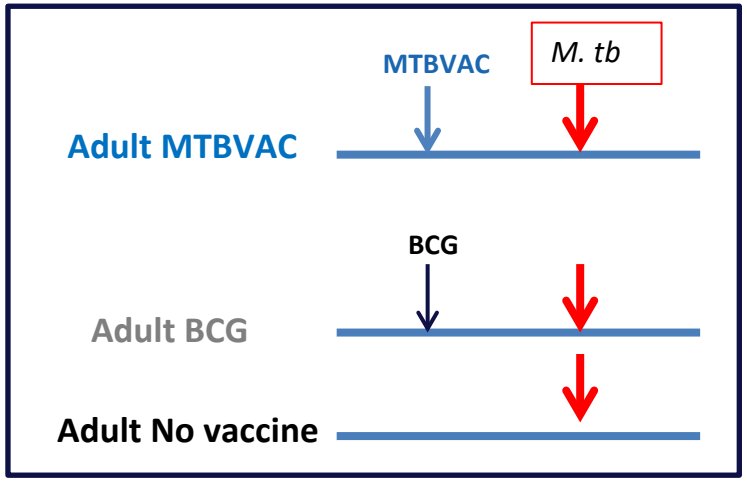
4th January 2021

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]



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.

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

Rhesus Macaques - MTBVAC vaccination.
Aerosol with M. tuberculosis

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- **A single intradermal vaccination with MTBVAC given to adult rhesus macaques was well tolerated and conferred a significant improvement in outcome following aerosol exposure to M.tuberculosis compared to by a single BCGvaccination**

- **Vaccination with MTBVAC resulted in a significant reduction in M. tuberculosis infection-induced disease pathology following challenge:**

  - In vivo medical imaging
  - Gross pathology lesion counts
  - Pathology scores recorded at necropsy
  - Frequency and severity of pulmonary granulomas
  - Frequency of recovery of viable M. tuberculosis from extrapulmonary tissues

Concordance between immune profiles measured in clinical trials and a macaque pre-clinical study demonstrating significantly improved outcome after M. tuberculosis challenge as evidence to support the continued development of MTBVAC as an effective prophylactic vaccine for TB vaccination campaigns.

npj | Vaccines

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

MTBVAC - Phase 3 Efficacy trial in neonates

MTBVAC Phase 3 in neonates - RIA2019S-25652

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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

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TBVI TuBerculosis Vaccine Initiative

University of Cape Town · iYunivesithi yaseKapa · Universiteit van Kaapstad

EPLS Centre de Recherche Biomédicale Espoir Pour La Santé

Institut Pasteur de Madagascar

VPD Vaccine Preventable Diseases RMPRU Respiratory & Meningeal Pathogens Research Unit

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CONSORTIUM - PARTNERSHIP

6 Participant sites

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- 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

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European & Development Countries Clinical Trial Partnership

MTBVAC Phase 3 in neonates - Timelines

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Phase 3 Safety, Immunogenicity and Efficacy in neonates
6 African sites

Protocol Submission May 2021
Pre-dose definition

Protocol Submission Sep 2021
Definitive Dose

Protocol Approval Jan 2022

First vaccination Feb 2022

Study duration
From 2022 to 2028

COVID 19

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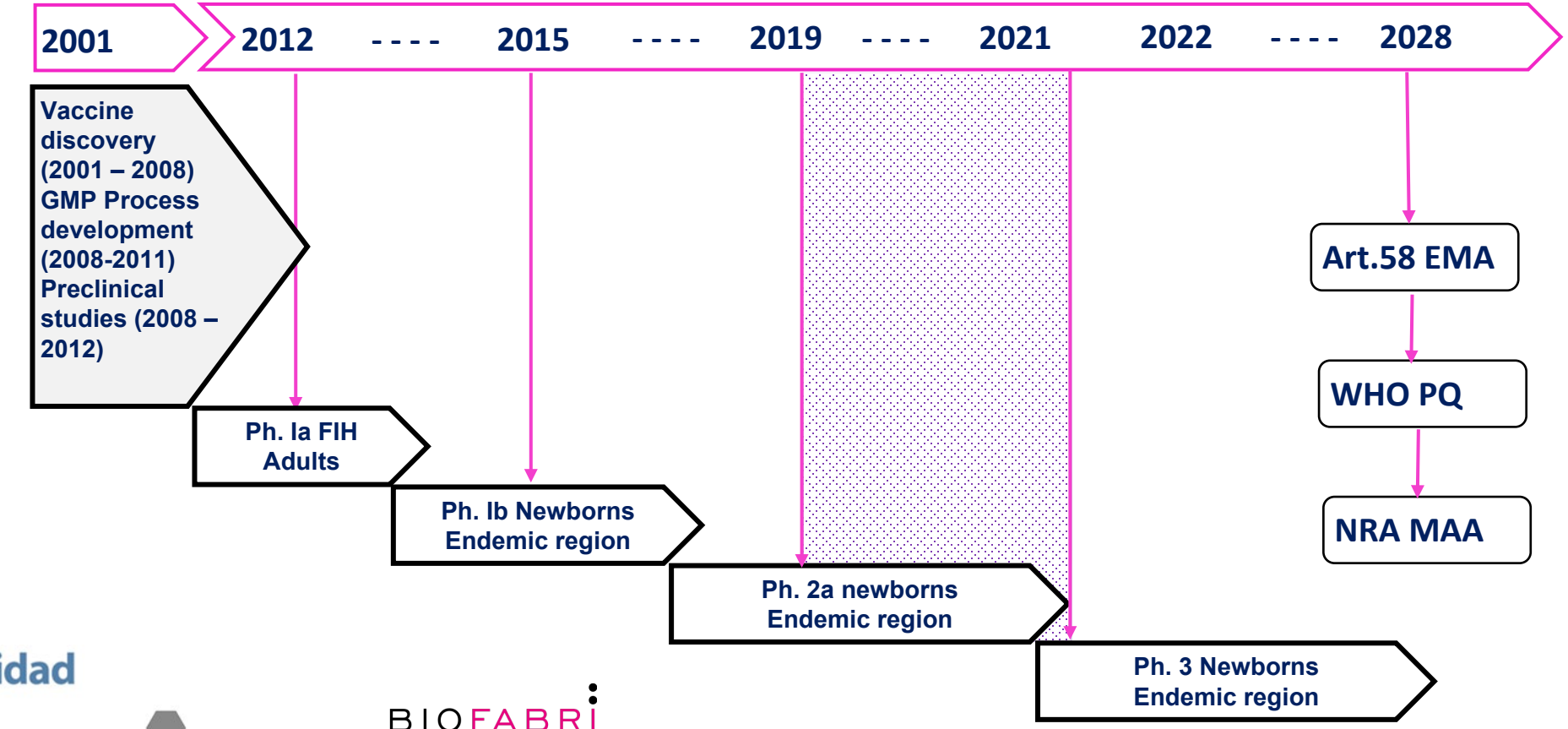
MTBVAC for Neonates – Wrap up



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MAA – Marketing Authorisation Application; NRA – National Regulatory Authority; PQ- Prequalification

Thank you

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