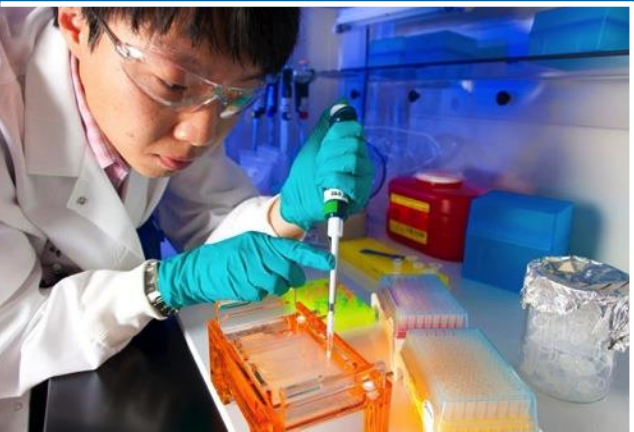
TB Vaccines: state of the art

Ann M. Ginsberg, MD, PhD

IMPAACT Annual Meeting

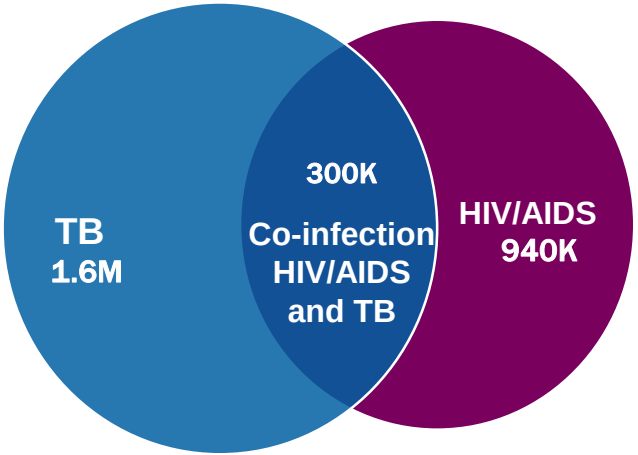
Washington DC

June 11, 2019



“New TB vaccines: a critical, unmet global public health need”*

- **10M new TB cases in 2017**
- **1.6M deaths**
- **>1/4 of all AMR-related deaths**



Deaths in 2017

Source: WHO Global TB Report 2018

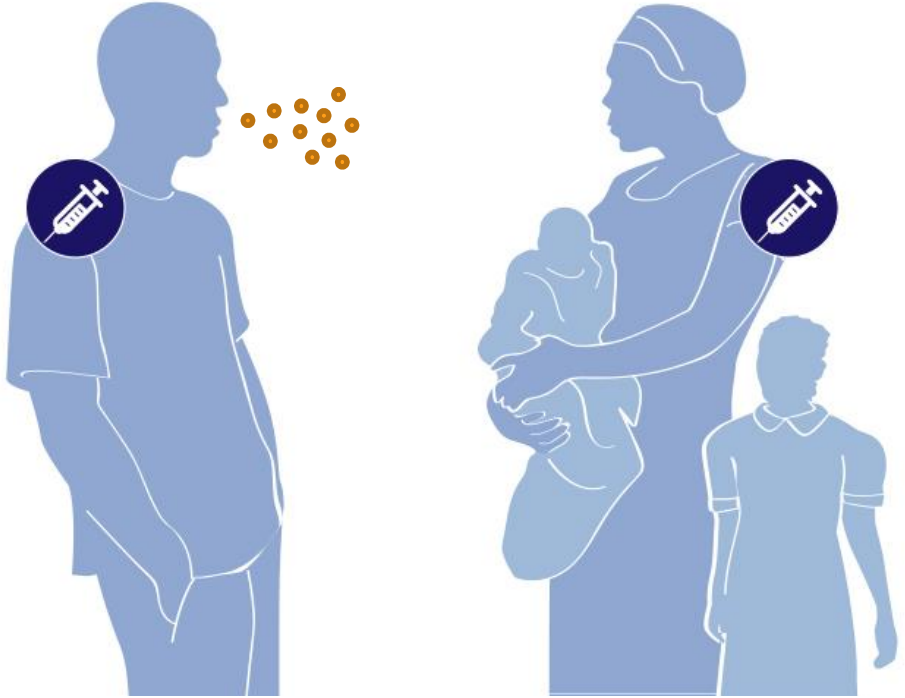
“Development of new, safe and effective TB vaccines would represent a critical tool in halting the spread of both drug-sensitive and drug-resistant-TB.” - *Source: WHO Preferred Product Characteristics for New Tuberculosis Vaccines, 2018

TB Vaccine Development: Multiple Target Populations

- Infants/children
- Adolescents/Adults
- TB patients – during or post-cure

Stopping the cycle of transmission in adolescents and adults will prevent the spread of TB to children

To reduce TB in 0-4 year olds, vaccination of adolescents/adults appears more effective than vaccinating neonates under most scenarios.
(Knight et al, unpublished)



Therapeutic Indications

- Prevention of TB disease
  - BCG replacement
  - BCG boost (proximal)
  - BCG boost (distal)
- Prevention of recurrent TB
- TB treatment shortening +/or increased cure rates (adjunct to treatment)

Potential Phase 3 Trial Endpoints

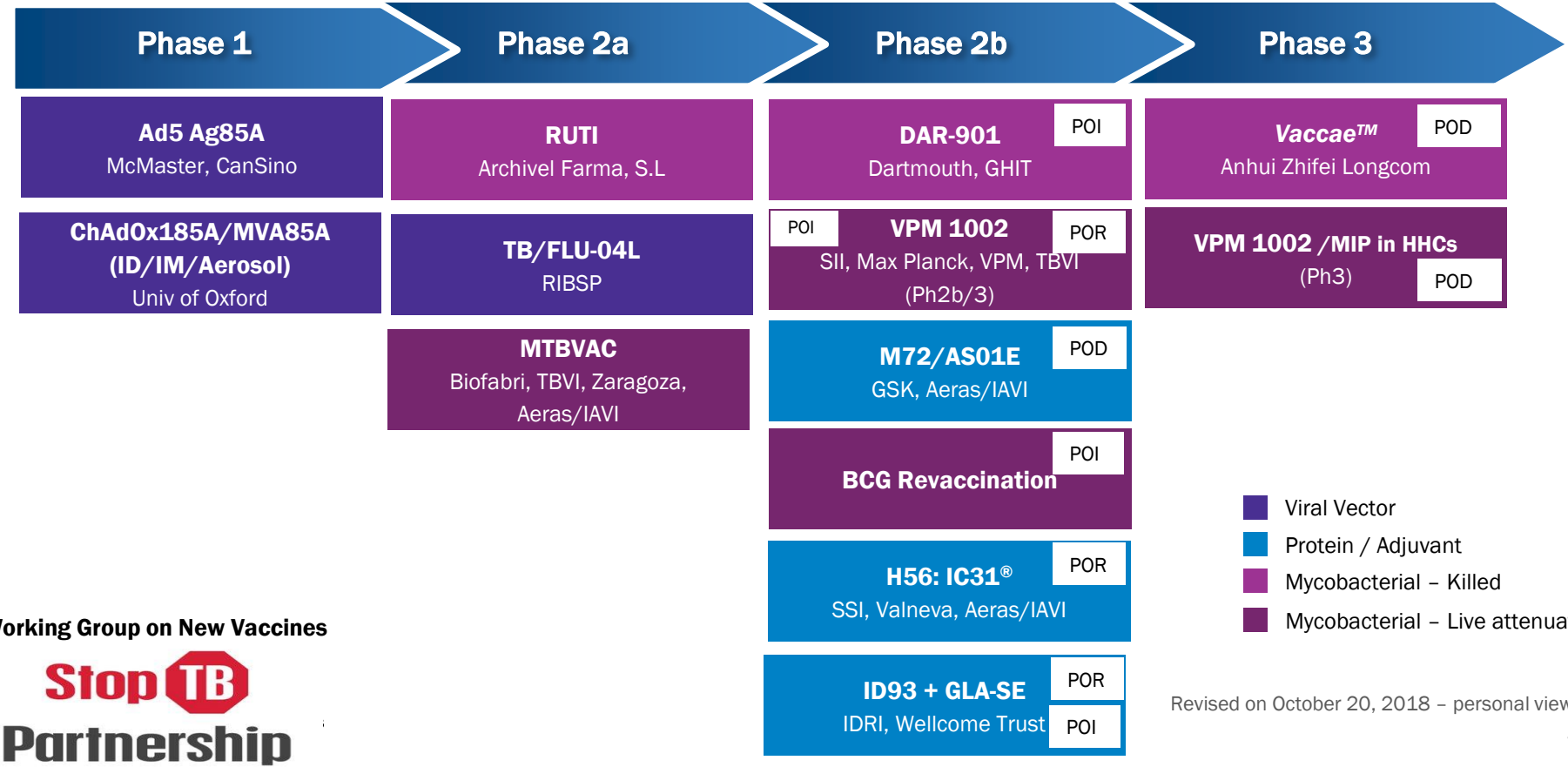
Choice based on desired target indication for licensure

Prevention of TB disease (POD)

Prevention of (established) Mtb infection (POI)

Prevention of TB disease recurrence (POR)

Global Clinical Pipeline of TB Vaccine Candidates

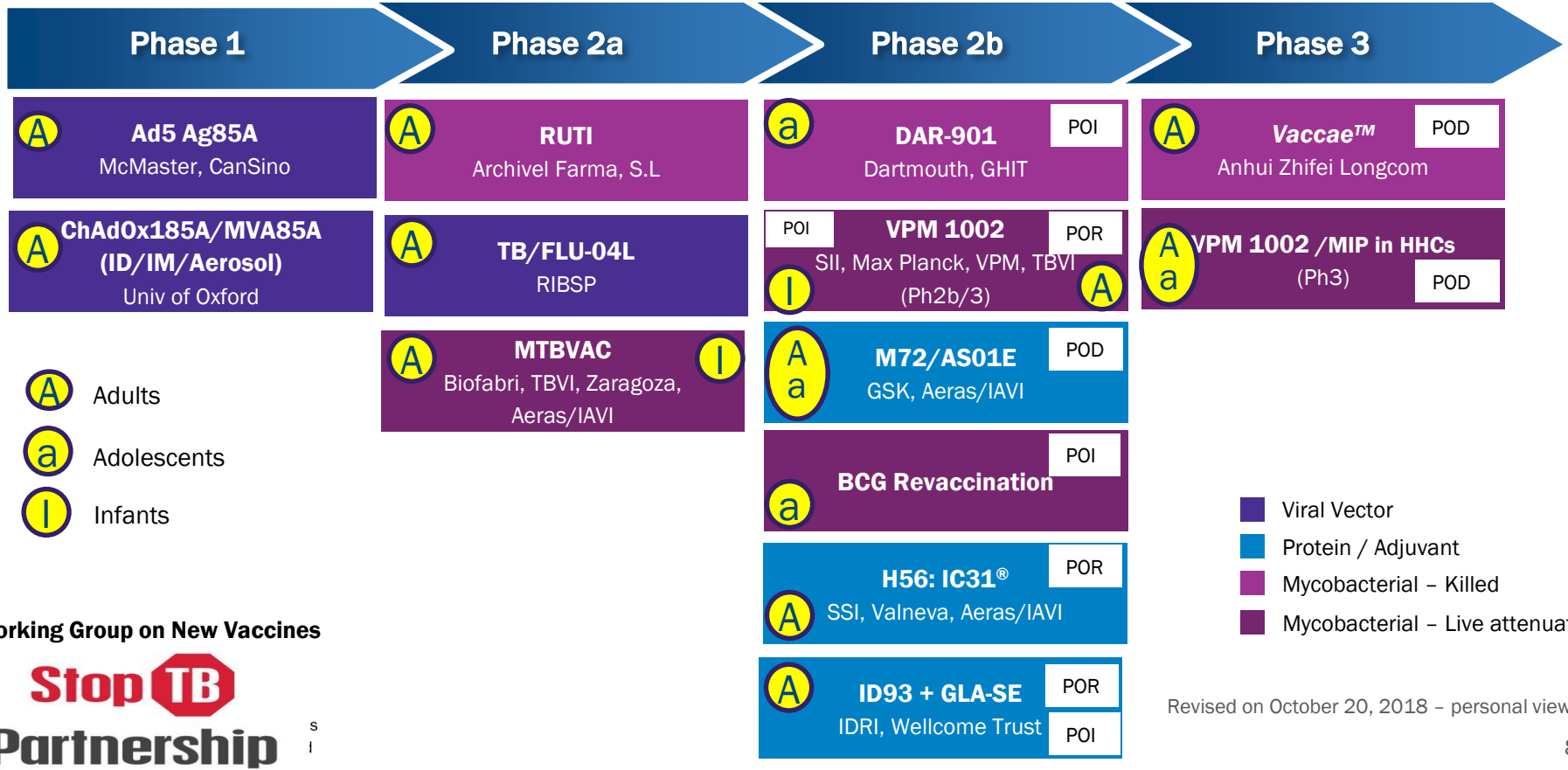


Working Group on New Vaccines

Stop TB Partnership

Revised on October 20, 2018 – personal view!

Global Clinical Pipeline of TB Vaccine Candidates



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Candidates in Mid- or Late-stage Evaluation in Infants and Adolescents

Infants

- VPM1002
- MTBVAC

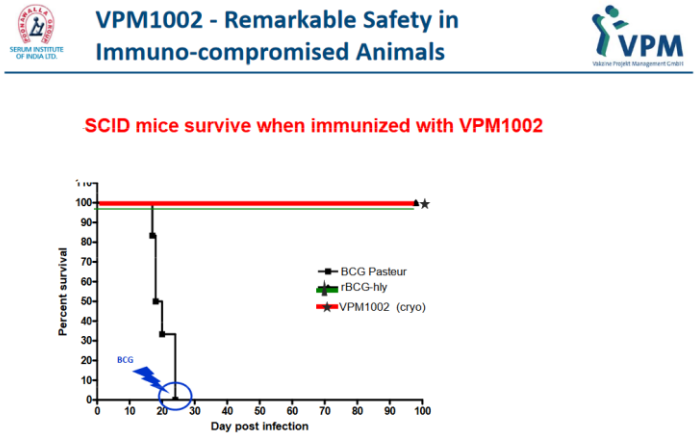
Adolescents

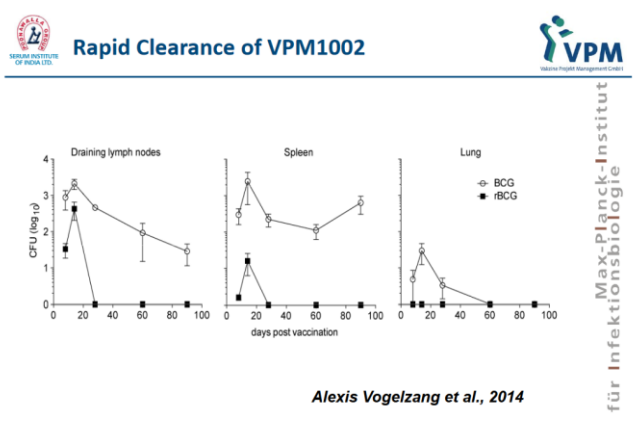
- BCG revacc
- DAR-901
- M72/AS01E

VPM1002

VPM1002: BCG replacement in infants

- recombinant BCG: rBCGΔureC::hly
- Target Product Profile
  - No interference with TB diagnostics (IGRA; novel skin test)
  - Induction of CD4+ and CD8+ immune response
  - Induction of multifunctional T-cells (IL-2;IFN-γ;TNF-α)
  - Safer than BCG in immunocompromised vaccinees





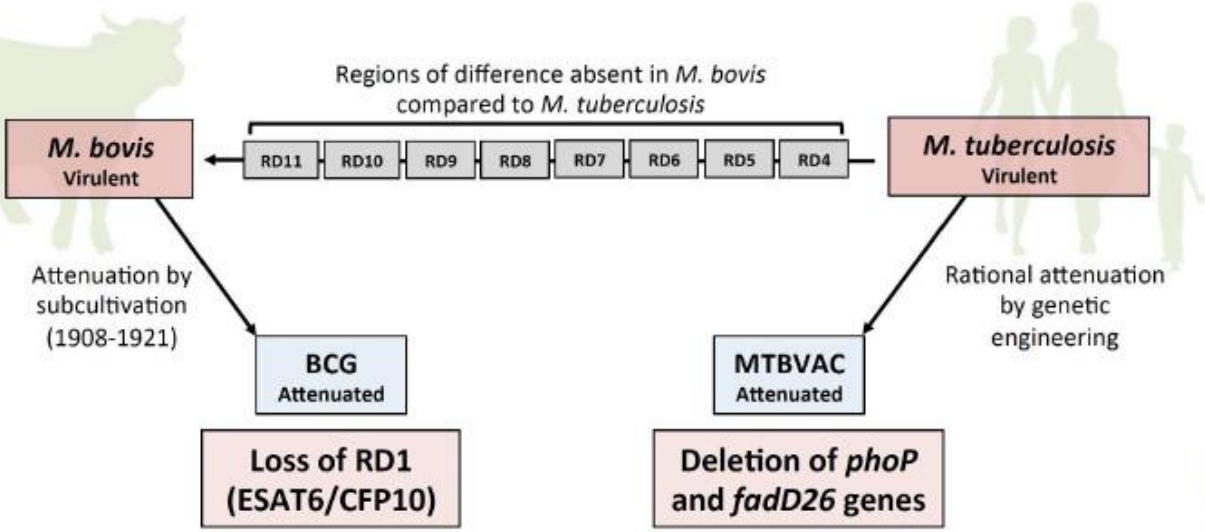
VPM1002: Current Status

- Infant indication
  - Phase 2 Safety and Immunogenicity of VPM1002 Compared With BCG in HIV-exposed and HIV-unexposed, BCG-naive Newborn Infants in South Africa (completed, final analysis underway); *NCT02391415*
  - Phase 3 newborn efficacy trial in Africa in preparation – initiation anticipated 4Q2019; SII is trial sponsor

- Adult TB indications
  - Phase 2/3 Efficacy and Safety Trial of Recombinant BCG Vaccine in **Prevention of TB Recurrence** in India: n=2000; *NCT03152903;* SII is trial sponsor
  - Phase 3 **Prevention of TB Disease** trial in household contacts (age 6-99yrs) in India - ongoing; n=12,000; *CTRI/2019/01/017026;* ICMR is trial sponsor

MTBVAC

MTBVAC A new live attenuated TB vaccine



BCG →
1084 epitopes

MTBVAC →
1603 epitopes

A total of 433 T cell-epitopes present in RD regions absent in BCG

Gonzalo- Asensio et al Frontiers in Immunology 15 Dec 2017

MTBVAC: Current Status

- Infant indication
  - Phase 1b/2a safety, immunogenicity and dose-finding in South Africa (SATVI); *NCT03536117;* Biofabri is trial sponsor

- Adolescent/Adult indication
  - Phase 1b/2a safety, immunogenicity and dose-finding in Mtb-infected and –uninfected adults in South Africa (SATVI); *NCT02933281;* IAVI is trial sponsor

BCG Revaccination

ORIGINAL ARTICLE

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

Elisa Nemes, Ph.D., Hennie Geldenhuys, M.B., Ch.B., Virginie Rozot, Ph.D., Kathryn T. Rutkowski, M.Sc., Frances Ratangee, B.N., Nicole Bilek, Ph.D., Simbarashe Mabwe, M.Sc., Lebohang Makhethe, B.Sc., Mzwandile Erasmus, B.Sc., Asma Toefy, B.Sc., Humphrey Mulenga, M.P.H., Willem A. Hanekom, M.B., Ch.B., et al., for the C-040-404 Study Team†

N Engl J Med 2018; 379:138-149

C-040 POI Trial Results and Conclusions

Trial: NCT02075203

- Both H4:IC31® and BCG revaccination appeared safe and immunogenic
- Neither vaccine showed statistical significance in preventing initial infection (initial QFT conversion)
- BCG revaccination demonstrated statistically significant prevention of sustained infection (sustained QFT conversion): VE: 45.4%; p=0.01
- H4:IC31did not demonstrate statistically significant prevention of sustained QFT conversion: VE: 30.5%; p=0.08; not being further developed
- Biobank created and analysis plan being developed for discovery of candidate correlates of risk and/or protection against sustained infection

BCG Revaccination: Current Status

- Adolescent indication:
  - Gates MRI planning a repeat Phase 2b **Prevention of Infection** trial in high risk of Mtb infection adolescents in Africa

DAR-901

DAR-901

- Whole cell, inactivated non-tuberculous mycobacterium (*M.obuense*) booster vaccine; vaccine sponsor = Dartmouth

Current status:

- Phase 2 **Prevention of Infection** Trial in adolescents (13-15 year olds) in Tanzania; n=650; estimated completion Dec. 2019; *NCT02712424;* Dartmouth is trial sponsor

M72/AS01$_E$

ORIGINAL ARTICLE

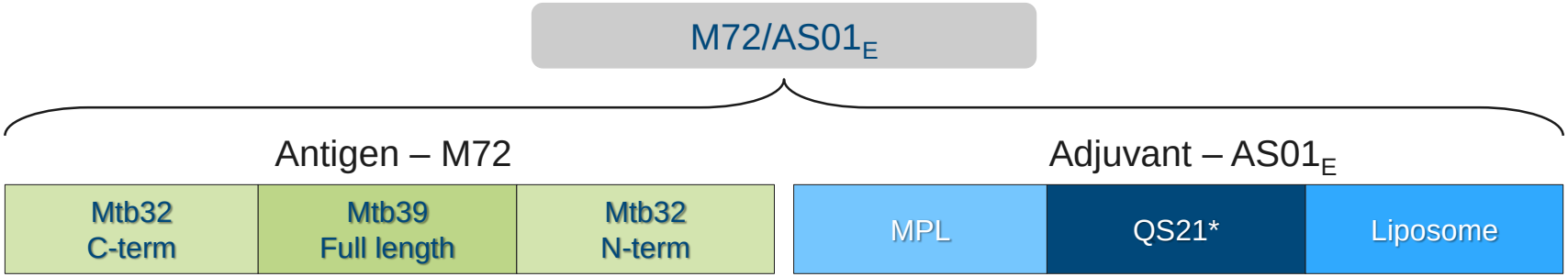
Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

Olivier Van Der Meeren, M.D., Mark Hatherill, M.D., Videlis Nduba, M.B., Ch.B., M.P.H., Robert J. Wilkinson, F.Med.Sci., Monde Muyoyeta, M.B., Ch.B., Ph.D., Elana Van Brakel, M.B., Ch.B., Helen M. Ayles, M.B., B.S., Ph.D., German Henostroza, M.D., Friedrich Thienemann, M.D., Thomas J. Scriba, Ph.D., Andreas Diacon, M.D., Ph.D., Gretta L. Blatner, M.S., M.P.H., et al.

Van Der Meeren et al., NEJM, 2018

M72/AS01$_E$ Candidate Vaccine

M72 antigens were initially identified in the context of controlled human infection



Determines specificity of the immune response[1]

- Recombinant protein comprising **full length Mtb39A** flanked by **inverted halves of Mtb32A**[1,2]
- Mtb 32A and 39A are highly immunogenic[2]
  - Genes present in virulent and avirulent strains of Mtb complex and in BCG[1]

Enhances the immune response to the antigen[2]

- Immunostimulants (MPL and QS21) in a liposome formulation[3]

1. BMC Immunol 2015;16:63; 2. J Immunol 2004;172:7618–28; 3. Hum Vacc Immunother 2014;10:2211–9.
*AS01$_E$, Adjuvant System containing 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL [25 µg], produced by GSK), *Quillaja saponaria* Molina, fraction 21 (QS-21 [25 µg], licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome.

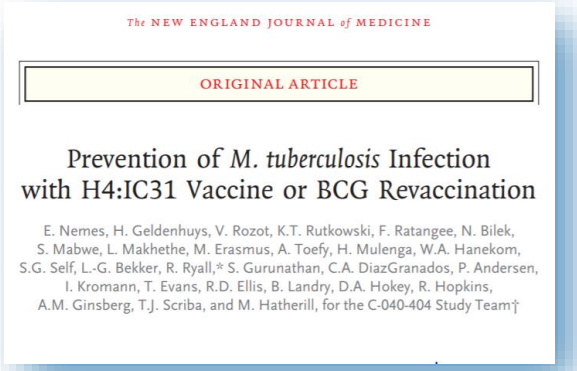
Phase 2b Prevention of Disease Trial in QFT+ 18-50 Year Old Adults: Primary Analysis Results Summary

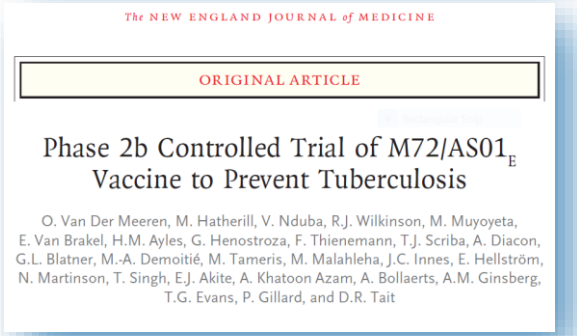
- M72/AS01$_E$ prevented TB disease in Mtb-infected adults
  - Efficacy of 54% [CI90% 14-75%, p=0.04] - primary endpoint met
  - Efficacy of 58% [p=0.05] - secondary endpoint met
  - Acceptable safety profile
- Final Analysis underway (3 years post-vaccination follow-up)
- Correlates analysis in planning
- Next steps under discussion with stakeholders and funders
  - Interest in extending target ages (infants; younger adolescents; elderly)

Van Der Meeren et al., NEJM, 2018

2018 – a Year of Unprecedented Progress

- New use for 98 year old current vaccine - protect high risk, uninfected populations from Mtb infection with BCG revaccination
- First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease
- Proof of concept that a subunit vaccine (2 Mtb antigens plus adjuvant) can protect against TB disease
- First opportunity to discover correlates of protection and increase understanding of protective human immune responses





International AIDS Vaccine Initiative

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USAID FROM THE AMERICAN PEOPLE

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BILL & MELINDA GATES foundation

THE WORLD BANK

Funded by the European Union

UKaid from the British people

CEPI New vaccines for a safer world

JAPAN Official Development Assistance

Ministry of Foreign Affairs of the Netherlands

MINISTRY OF FOREIGN AFFAIRS OF DENMARK DANIDA INTERNATIONAL DEVELOPMENT COOPERATION

Irish Aid An Roinn Gnóthaí Eachtracha agus Trádála Department of Foreign Affairs and Trade

सत्यमेव जयते Ministry of Science & Technology Government of India

amfAR, The Foundation for AIDS Research | Bill & Melinda Gates Foundation | The Buimerc Group | Broadway Cares/Equity Fights AIDS | The City of New York, Economic Development Corporation | Coalition for Epidemic Preparedness Innovations | European Union | Foundation for the National Institutes of Health | GlaxoSmithKline | Government of Japan | The Hearst Foundations | Irish Aid, Department of Foreign Affairs and Trade | Ministry of Foreign Affairs of Denmark | Ministry of Foreign Affairs of The Netherlands | Ministry of Science & Technology, Government of India | National Institute of Allergy and Infectious Diseases | Norwegian Ministry of Foreign Affairs | U.K. Department for International Development | The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development | The World Bank

And many other generous individuals and partners around the world

As of May 2018

Thank you

email: aginsberg@iavi.org

ANNEX

Overview – First TB Vaccine POI Trial

Trial: NCT02075203

Objectives:

Phase 2 Proof of Concept Prevention of Infection study to evaluate safety, efficacy and immunogenicity

3 Study Arms:

- H4:IC31 (IM, 2 doses, 56 days apart)
- BCG revaccination (ID, 1 dose; SSI BCG)
- Placebo (saline; IM, 2 doses, 56 days apart)

Population:

- QFT*-negative adolescents (12–17y.o.)
- Western Cape, South Africa
- High risk of infection (~10% per year)

Design:

- Randomized (1:1:1)
- Placebo-controlled
- Partially blinded

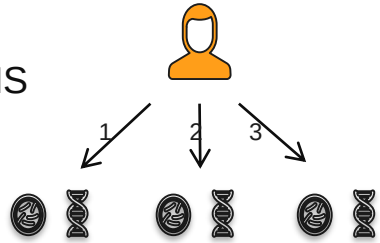
Study Size:

N=990 (330/arm)

*QFT = QuantiFERON Gold In-Tube interferon gamma release assay

Phase IIb Study design

- Subjects
  - HIV negative healthy adults (18 - 50 years)
  - Negative sputum by PCR (Xpert MTB/RIF)
  - Mtb-infected : positive by QuantiFERON
- Design
  - Double-blind, randomized (1:1)
  - M72/AS01$_E$ or Placebo
  - 2 doses 1 month apart
- TB cases determination by
  - Active follow-up every 2 months either by calls, home visits or SMS
  - TB symptoms and bacteriological confirmation
    - By PCR and/or MGIT culture
- 3 years follow up
  - Primary analysis at year 2
  - LSLV November 2018



Van Der Meeren et al., NEJM, 2018