Progress towards vaccines against TB

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Global HIV Vaccine Enterprise

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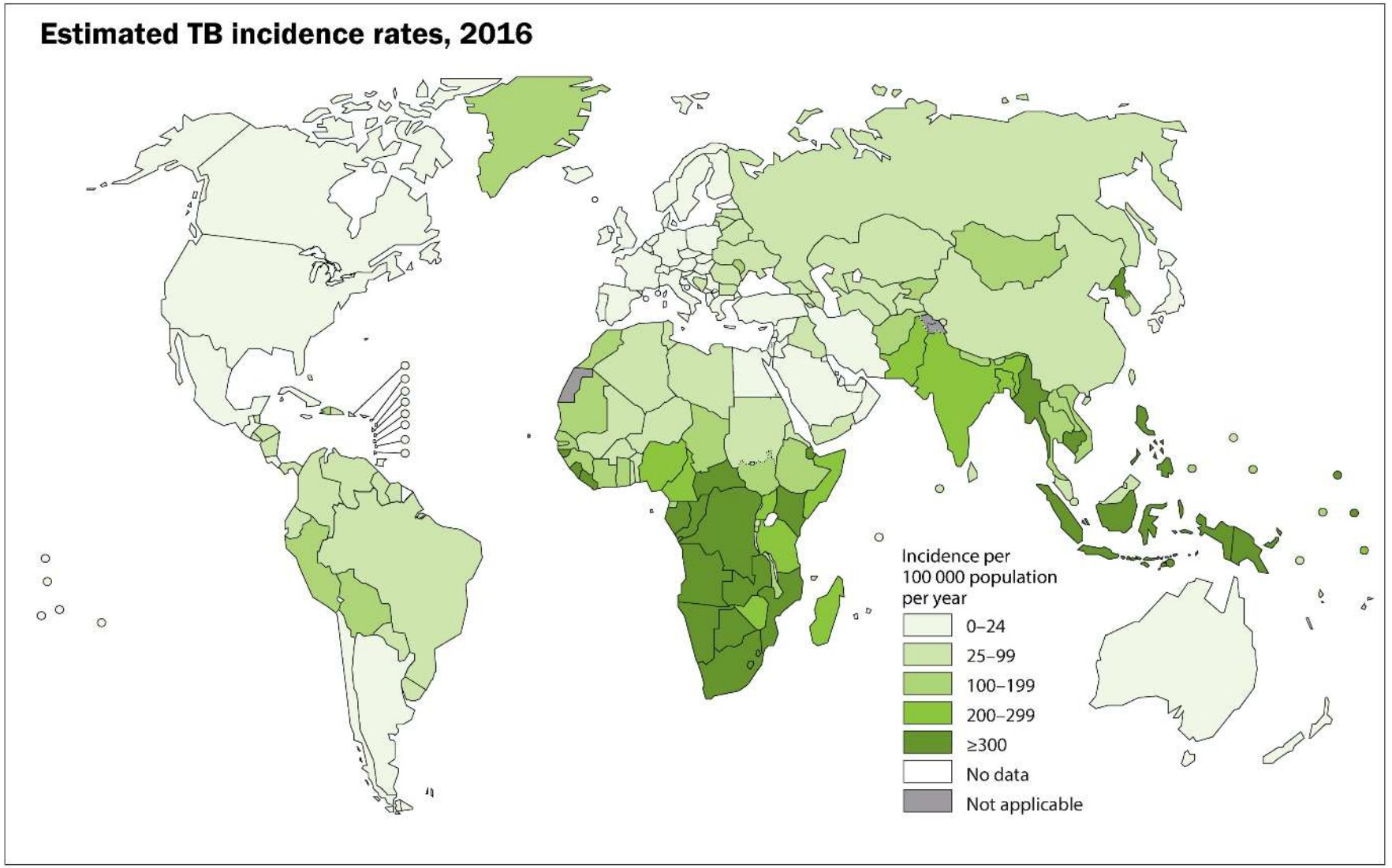
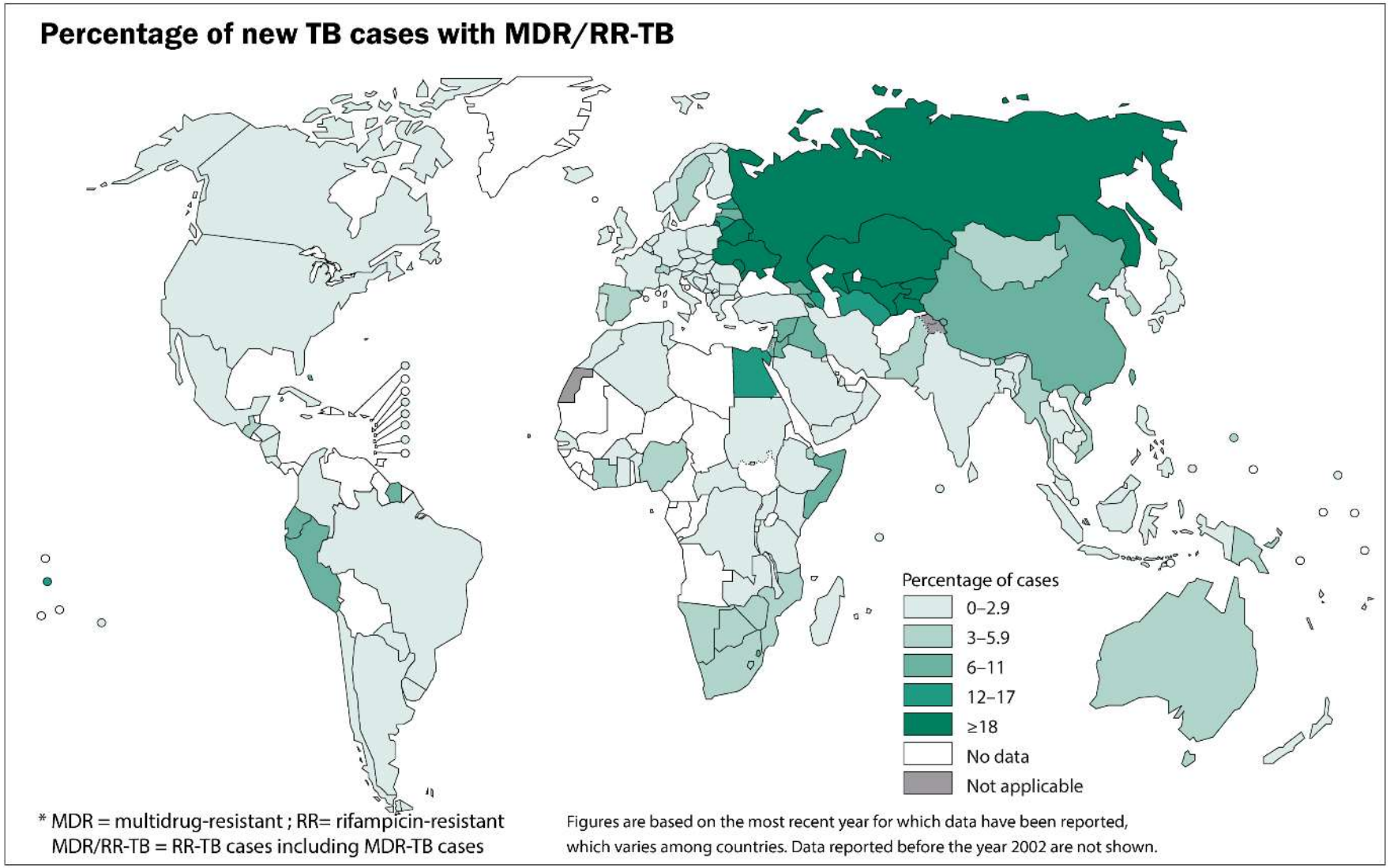
The problem

- Estimated 1/3 of world population infected
- 10 % will develop TB
- 10.4 million cases and 1.4 million deaths in 2016
- WHO End TB strategy: 90% reduction in incidence by 2035



TB and AMR

- Better TB drugs becoming available
- Correlation between antibiotic use and resistance
- Vaccines reduce antibiotic use, reduce AMR
- Need for a TB vaccine as part of the global emergency response to AMR



BCG, the world's most widely used vaccine

- Used in many national immunization programs with high coverage
- Different strains used for routine vaccination
- Efficacious against disseminated TB in children
- Estimated 117,132 deaths prevented per birth cohort during first 15 years of life
- Protection against leprosy
- Other non-specific (immuno-modulatory) effects suspected

- Variable protection from infection or pulmonary TB
- Inconsistent protection in adolescence
- Safety considerations in HIV-infected infants and children

- **The BCG vaccine has not stopped the epidemic**

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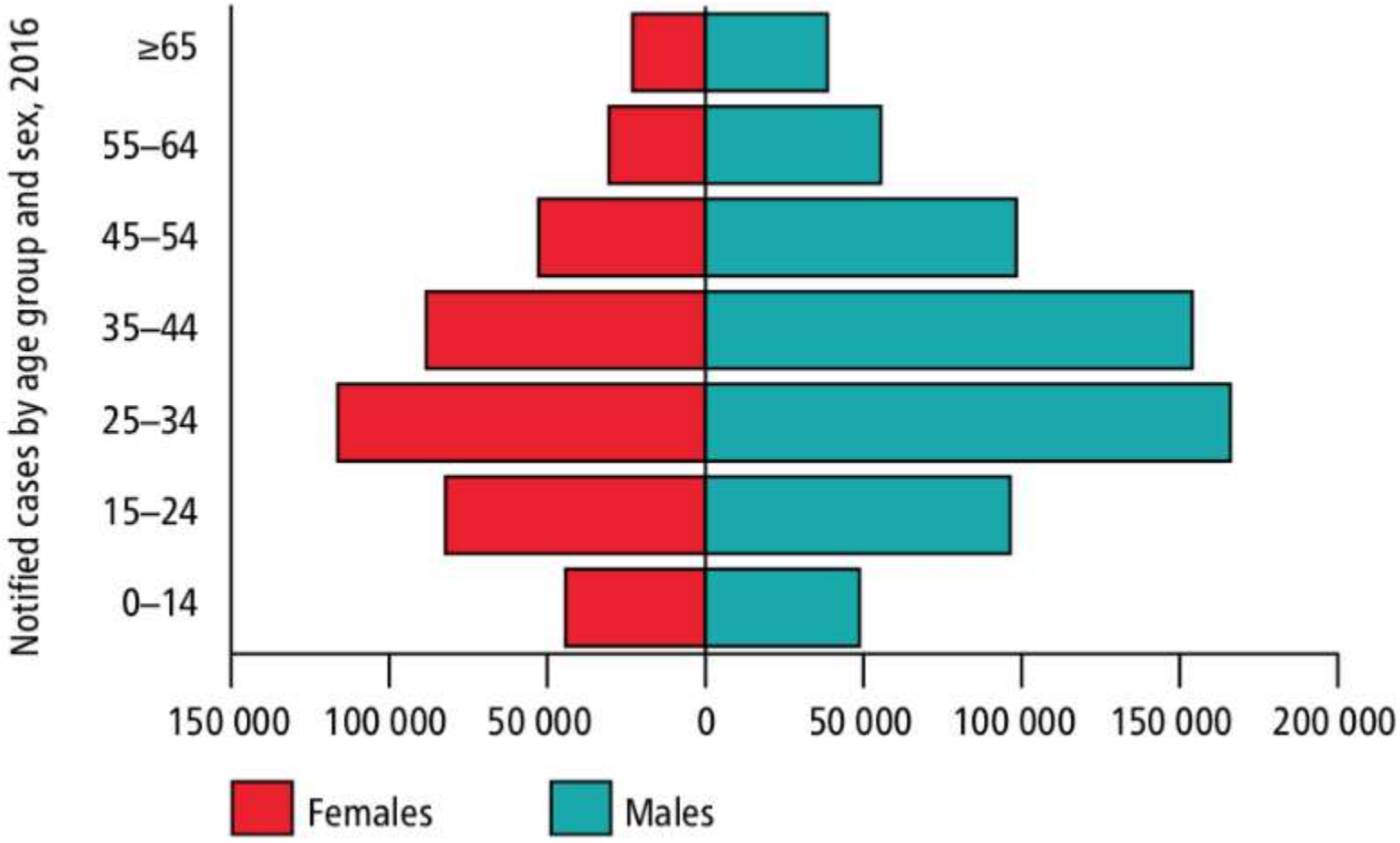
Tb incidence per age group



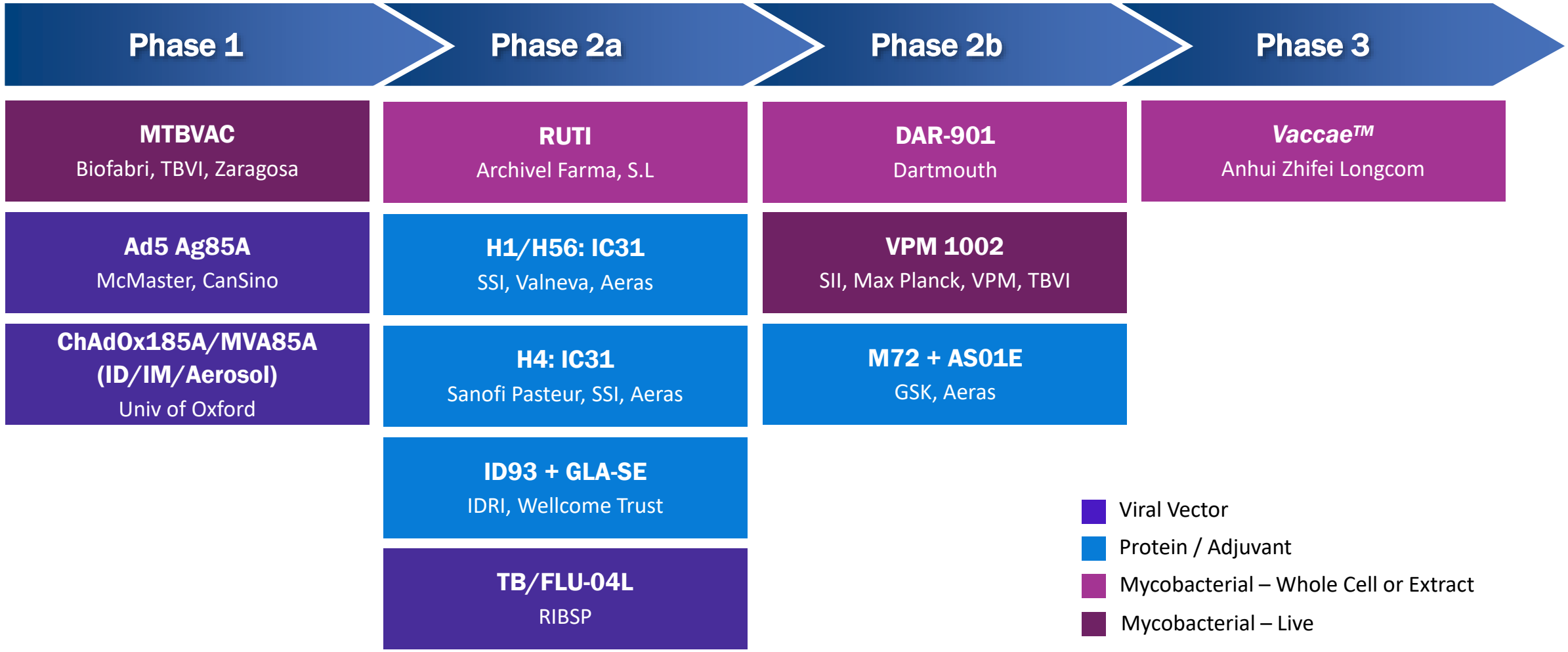
- WHO Global tuberculosis report 2017, African region 2016

Target populations and goals

- WHO draft Preferred Product Characteristics (soon final)
- Prevention of active pulmonary disease in adolescents and adults
  - Individual benefit
  - Reduction in transmission
- Prevention of TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children
  - Maintain and expand benefits of BCG (replace or boost)

http://www.who.int/immunization/research/ppc-tpp/WHO_new_TB_vaccine_PPC_20180116.pdf?ua=1

Global Clinical Pipeline of TB Vaccine Candidates



Revised on July 19, 2017

Please note: Information is self-reported by vaccine sponsors

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Phase 2 Prevention of Infection Trial

Overview

- Developed to de-risk candidates earlier, at lower cost, and with fewer subjects than classical Prevention of Disease trials - for up/down candidate selection

Proof of Concept trial:

Phase 2 POI trial to evaluate safety, efficacy and immunogenicity

Design:

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

Study Size:

N=990 (330/arm)

Study Arms:

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

Population:

- QFT*-negative, HIV-negative, adolescents (aged 12–17)
- High risk of infection (~10% per year)
- Western Cape, South Africa (SATVI; DTHF)

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

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Prevention of Infection Study Objectives

- Primary
  - Evaluate safety profile of H4:IC31 and BCG re-vaccination
  - Evaluate prevention of *Mtb* infection, measured by initial QFT conversion (H4:IC31 vs. placebo; BCG vs. placebo)
- Secondary
  - Evaluate prevention of sustained *Mtb* infection, measured by sustained* QFT conversion (H4:IC31 vs. placebo; BCG vs. placebo)
  - Evaluate immunogenicity in HIV-uninfected, remotely BCG vaccinated adolescents
- Exploratory
  - Initial and sustained infection using various more stringent QFT conversion thresholds
  - Rate of reversion or sustained conversion through end of study
  - Exploratory immune assays

* Sustained conversion defined as QFT-positivity maintained for at least six months post-initial conversion

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POI Trial Results and Conclusions

- Neither vaccine showed statistical significance in preventing initial infection
- BCG revaccination: statistically significant prevention of sustained QFT conversion (increased clearance or control of infection; VE-45.4%; p=0.01)
  - ➢ Warrants evaluation of BCG revac in Prevention of TB Disease trial (in similar populations)
- H4:IC31: modest signal in prevention of sustained QFT conversion
  - Not statistically significant at 95% confidence level (VE=30.5%; p=0.08)
  - ➢ First indication by a subunit vaccine of any protection against TB infection or disease in humans; suggests benefit of studying other subunit vaccines (e.g., M72/AS01E, H56:IC31)
- Both appeared safe and immunogenic in adolescents studied

➢ POI trial design is feasible and may be useful tool for decision-making

Key areas of focus and opportunities

- Rational investment decisions and portfolio management
  - Stage gating criteria

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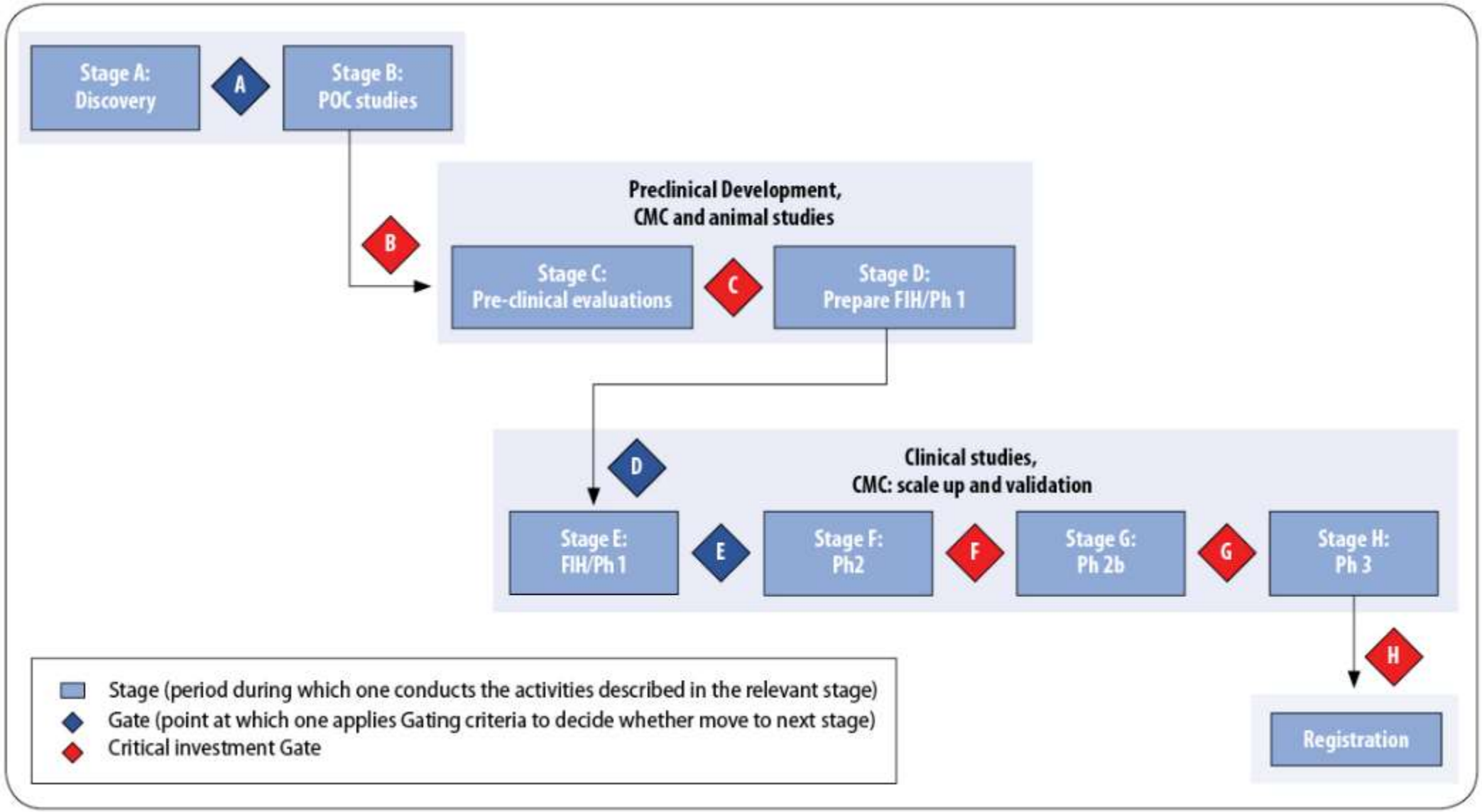
Stages and Gates for a TB vaccine



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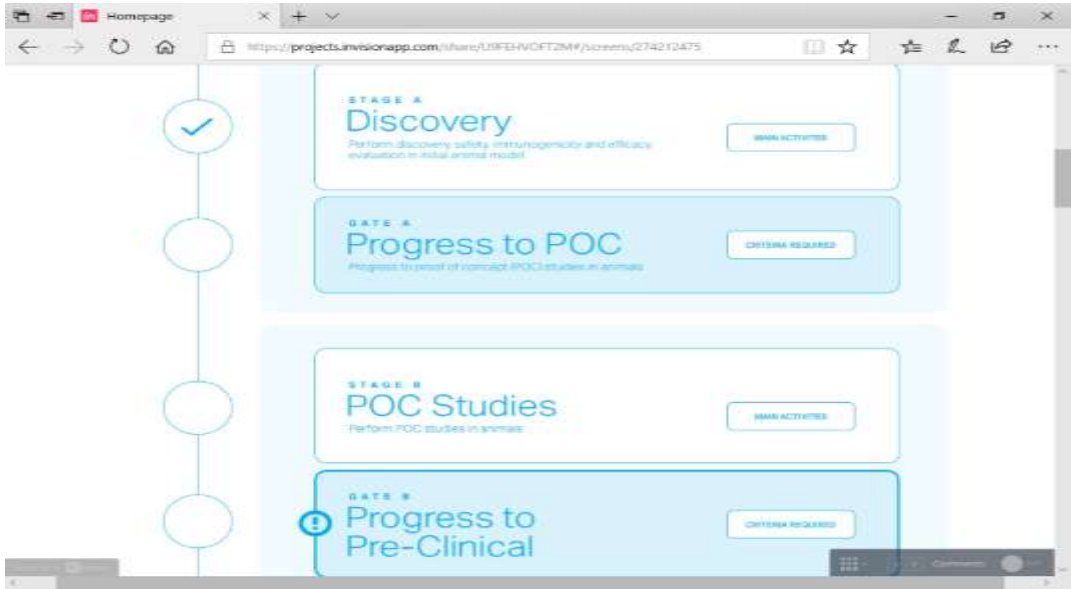
Stage gate process

- Criteria were initially defined in 2012 and now revised by Aeras and TBVI and validated through broad external stakeholder consultations
- Stage Gates are a versatile tool to accelerate TB vaccine candidates development
- Facilitate global TB vaccine portfolio management
- An offer to researchers, developers, funders and other decision-makers
- Will go online in summer of 2018



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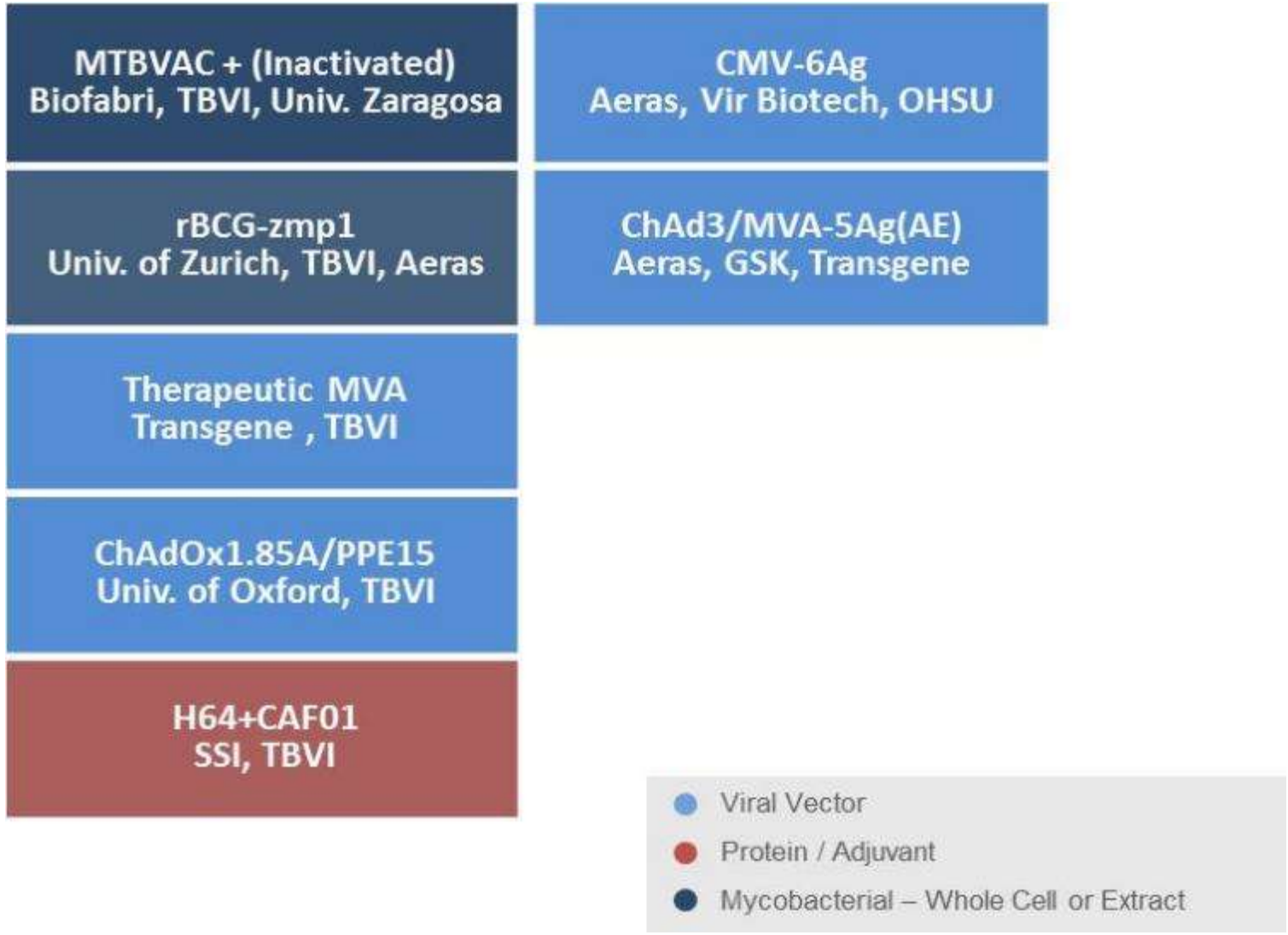
Pre-Clinical TB Vaccine Pipeline



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Key areas of focus and opportunities

- Rational investment decisions and pipeline management
  - Stage gating criteria
- Discovery research to feed the early pipeline
  - Technology platforms and antigens
  - Host-directed therapies
  - Alternative immunization routes
- Preclinical models to prioritize candidates
  - Pertinent models to answer scientific questions (i.v. BCG)
  - Supportive evidence for evaluation of novel candidates in clinical trials
  - Ultimate validation from a clinical efficacy signal
- Immune correlates and biomarkers to predict vaccine efficacy
  - Exploit the signal from BCG revaccination
  - Biobanks from clinical trials
  - Novel assays (microbial growth inhibition)

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  - Experimental medicine (aerosol) and controlled human challenge model
  - Alternative clinical endpoints

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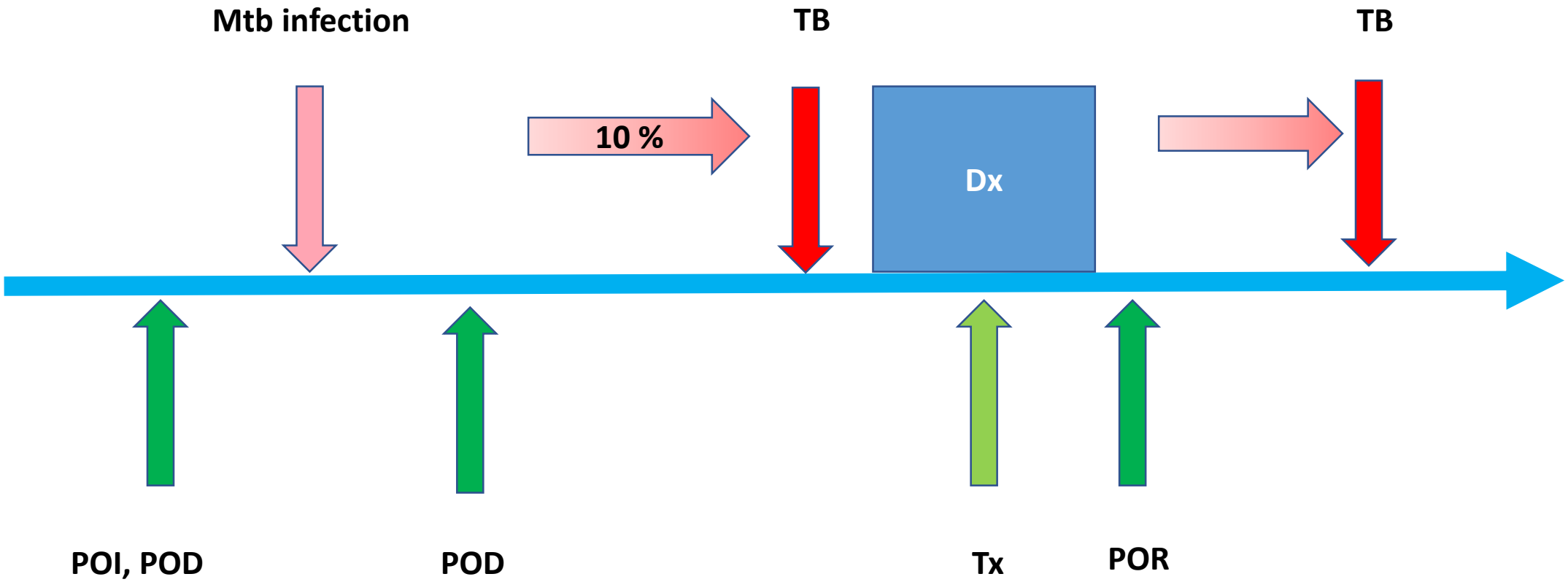
Clinical efficacy trial endpoints



- Prevention of Infection (POI), Disease (POD), Recurrence/re-infection (POR)

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  - Alternative clinical endpoints
  - Late stage trials

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How to do TB vaccine efficacy trials

Tuberculosis 93 (2013) 143–149

Contents lists available at SciVerse ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

Lessons learnt from the first efficacy trial of a new infant tuberculosis vaccine since BCG

Michele Tameris[a,*], Helen McShane[b], J. Bruce McClain[c], Bernard Landry[c], Stephen Lockhart[d], Angelique K.K. Luabeya[a], Hennie Geldenhuys[a], Jacqui Shea[d], Gregory Hussey[e], Linda van der Merwe[a], Marwou de Kock[a], Thomas Scriba[a], Robert Walker[c], Willem Hanekom[a], Mark Hatherill[a], Hassan Mahomed[a]

- Diagnostics and treatment insights
- Normal lab ranges in African infants
- Immunological mechanisms and correlates

Immune correlates of risk analysis – MVA85A efficacy trial

Blood samples collected from healthy infants up to 3 years before they developed TB disease

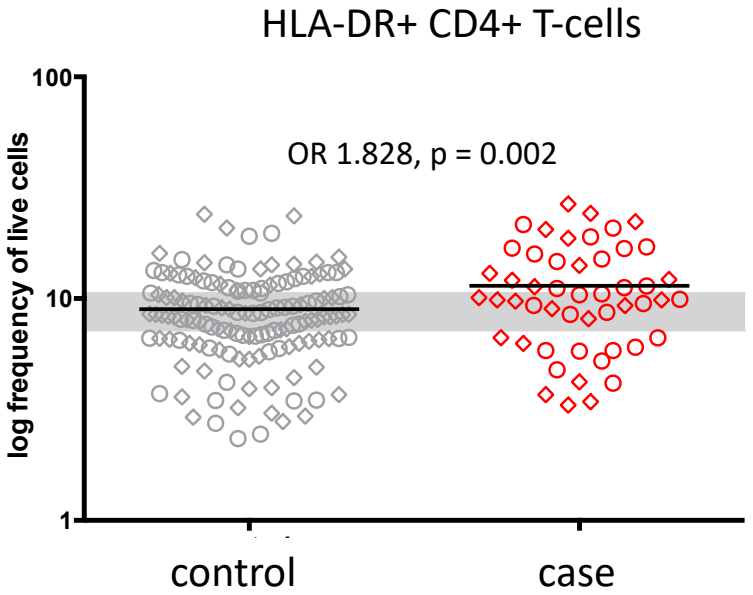
ARTICLE

Received 21 Dec 2015 | Accepted 22 Feb 2016 | Published 12 Apr 2016 | Updated 6 May 2016

DOI: 10.1038/ncomms11290 OPEN

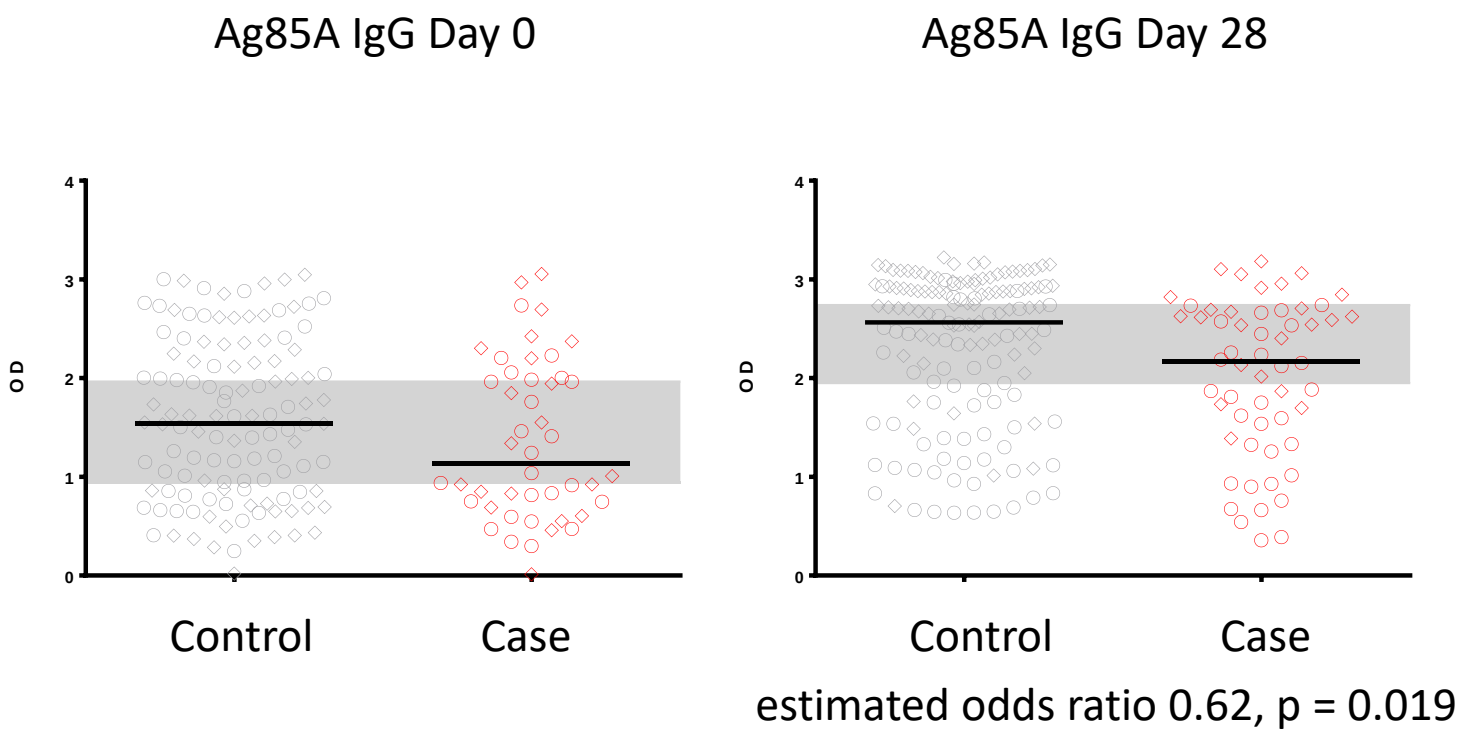
T-cell activation is an immune correlate of risk in BCG vaccinated infants

Helen A. Fletcher[1,2], Margaret A. Snowden[3], Bernard Landry[3], Wasima Rida[4], Iman Satti[1], Stephanie A. Harris[1], Magali Matsumiya[1], Rachel Tanner[1], Matthew K. O'Shea[1], Veerabadran Dheenadhayalan[3], Leah Bogardus[3], Lisa Stockdale[1,2], Leanne Marsay[5], Agnieszka Chomka[6], Rachel Harrington-Kandt[1], Zita-Rose Manjaly-Thomas[1], Vivek Naranbhai[7], Elena Stylianou[1], Fatoumatta Darboe[8], Adam Penn-Nicholson[8], Elisa Nemes[8], Mark Hatherill[8], Gregory Hussey[8], Hassan Mahomed[8], Michele Tameris[8], J Bruce McClain[3], Thomas G. Evans[3], Willem A. Hanekom[8], Thomas J. Scriba[8] & Helen McShane[1]



Result significant if Conditional Logistic Regression P<0.05 and FDR<2
Shaded bar indicates medium third of immune response level

Antibodies correlate with reduced risk of TB disease



Are they directly involved in protection or correlating with another immune parameter?

Fletcher HA *et al* Nature Communications, 2016

Priority areas and recommendations

- Maintain a healthy pipeline from discovery to late stage to launch and invest wisely
- Sustain discovery research
  - Novel antigens and technology platforms
  - Immune mechanisms of pathogenesis
  - Alternative delivery routes
- Continue to identify correlates of vaccine protection (and TB risk)
  - Novel in vitro assays
  - Relevant animal models
  - Controlled human challenge model
  - Learnings from late stage trials and cohort studies
- De-risk clinical development
  - Correlates of protection
  - Controlled human challenge model
  - Experimental medicine studies
  - Alternative clinical endpoints (infection, recurrence)
- Conduct late stage clinical trials

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Acknowledgements and references

- Progress and challenges in TB vaccine development
  - https://f1000research.com/articles/7-199/v1
- Global report on tuberculosis vaccines 2018
  - http://www.tbvi.eu/wp-content/uploads/2018/02/Summary-SWRTV_Finalproof.pdf
- Invaluable suggestions, contributions (and slides) from colleagues at:

  - Aeras
  - NIAID
  - WHO
  - BMGF
  - U. Oxford
  - LSHTM
  - TBVI