UPDATE ON PROGRESS IN TB VACCINE DEVELOPMENT

GVIRF
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INTRODUCTION -

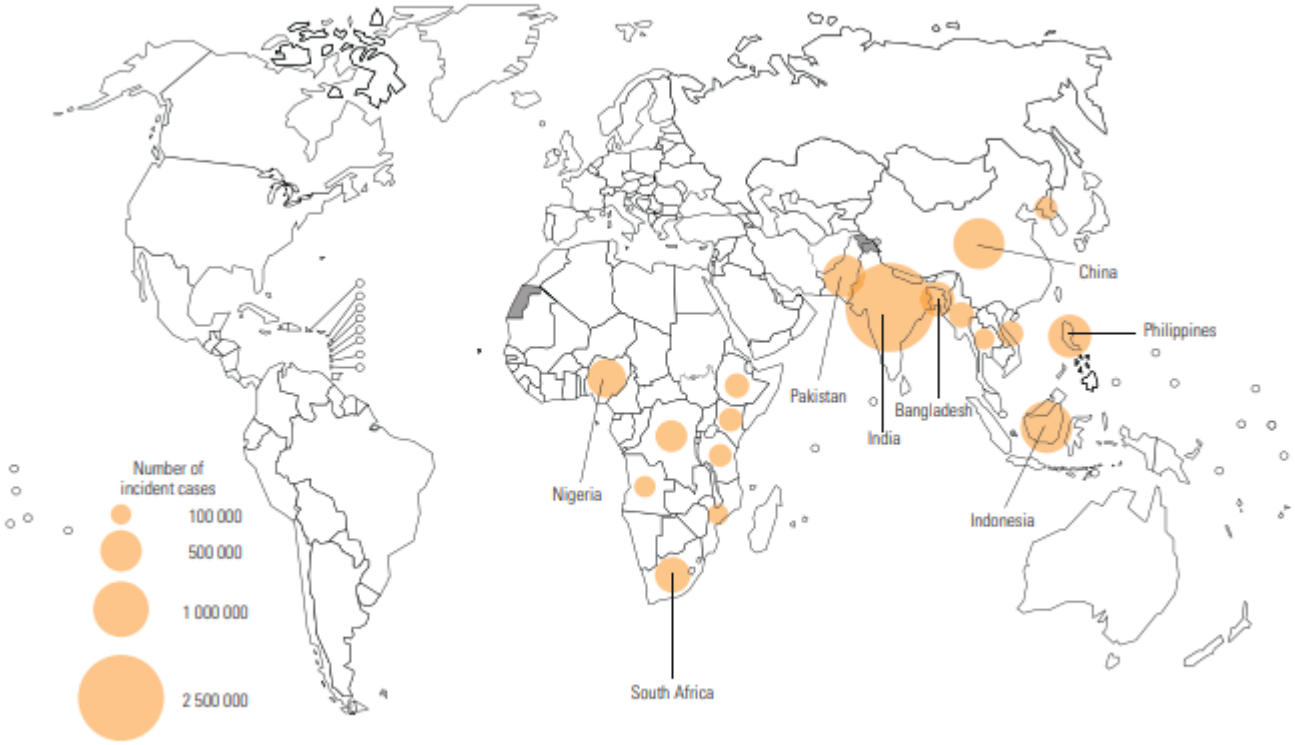
THE URGENT NEED FOR BETTER TB VACCINES

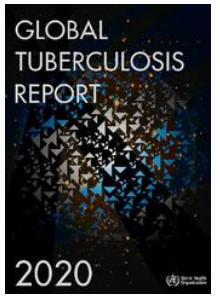
LEADING INFECTIOUS KILLER AND KEY DRIVER OF ANTIMICROBIAL RESISTANCE

In 2019, globally there were:

- **10 million new cases** of TB
  - 56% men
  - 32% women
  - 12% children
- **1.4 million deaths**
- Persons living with HIV, accounted for 8% of the cases and 14% of the deaths
- Almost **500,000** of the cases **were drug-resistant**

Estimated TB incidence in 2019, for countries with at least 100 000 incident cases





https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

IMPACT OF TB ON COVID-19 AND COVID-19 ON TB

Previous/current TB increases risk of COVID-19 mortality

- ~1.4/2.5X in Western Cape, South Africa^

TB testing decreased ~50% in South Africa during Level 5 COVID-19 lockdown

Globally, a 3-month lockdown and a protracted 10-month restoration could lead to an **additional 6.3 million cases of TB between 2020 and 2025, and an additional 1.4 million TB deaths** during this time.*

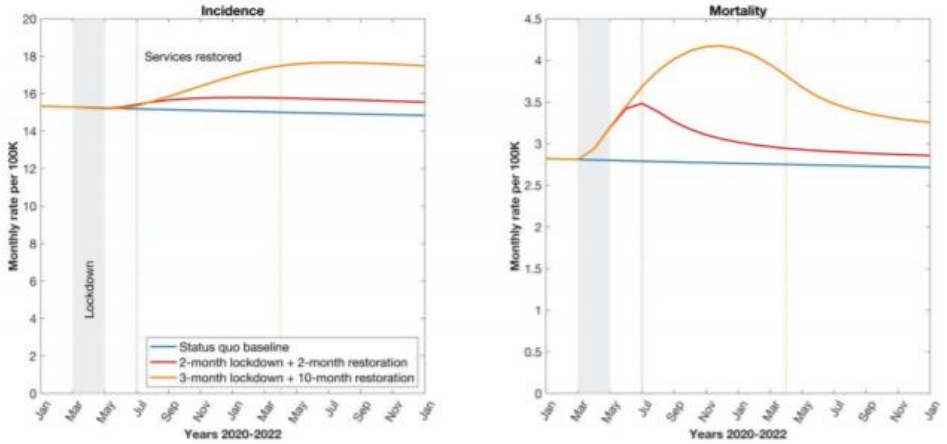


Figure 1. Dynamics of TB incidence and mortality following a COVID-19 lockdown, in the illustrative example of India. The grey shaded area shows the duration of the lockdown, while the vertical dashed line shows the point at which normal TB services are restored. Overall impacts in cumulative TB burden, from 2020 to 2025, are summarised in table 1 for each country.

Country	Excess TB cases from 2020 - 2025		Excess TB deaths from 2020 - 2025	
	For every month of lockdown	For every month of restoration	For every month of lockdown	For every month of restoration
India	232,665	144,795	71,290	40,685
Kenya	3,980	3,133	1,747	1,157
Ukraine	1,058	625	270	137
Global	**608,400**	**420,400**	**126,100**	**83,200**

Table 2. Estimates for incremental impact on TB burden by each additional month of lockdown or restoration

* *Developed by Stop TB Partnership in collaboration with Imperial College, Avenir Health, Johns Hopkins University and USAID.*

^ Western Cape Government

NEW VACCINES ARE KEY TO BLOCKING TRANSMISSION AND ENDING THE EPIDEMIC

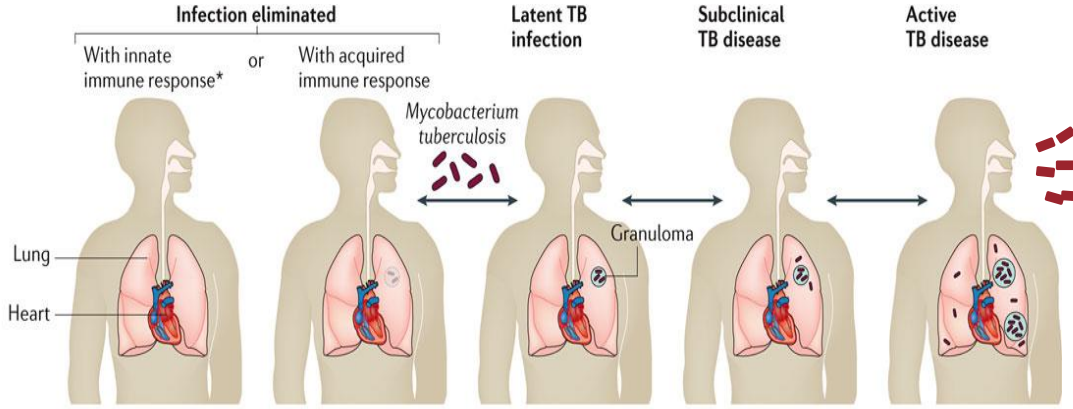
Natural history includes a spectrum: from exposure and clearance to initial infection to “latent TB infection (LTBI)” to subclinical TB to active TB disease

Transmission is mainly by adolescents and adults with active pulmonary TB; role of subclinical TB in transmission only beginning to be explored

Only globally licensed vaccine, BCG, has been in use since 1921; delivered, primarily to infants in high burden countries

Infant BCG does not effectively protect adolescents and adults from developing active disease and transmitting to others

The Spectrum of TB

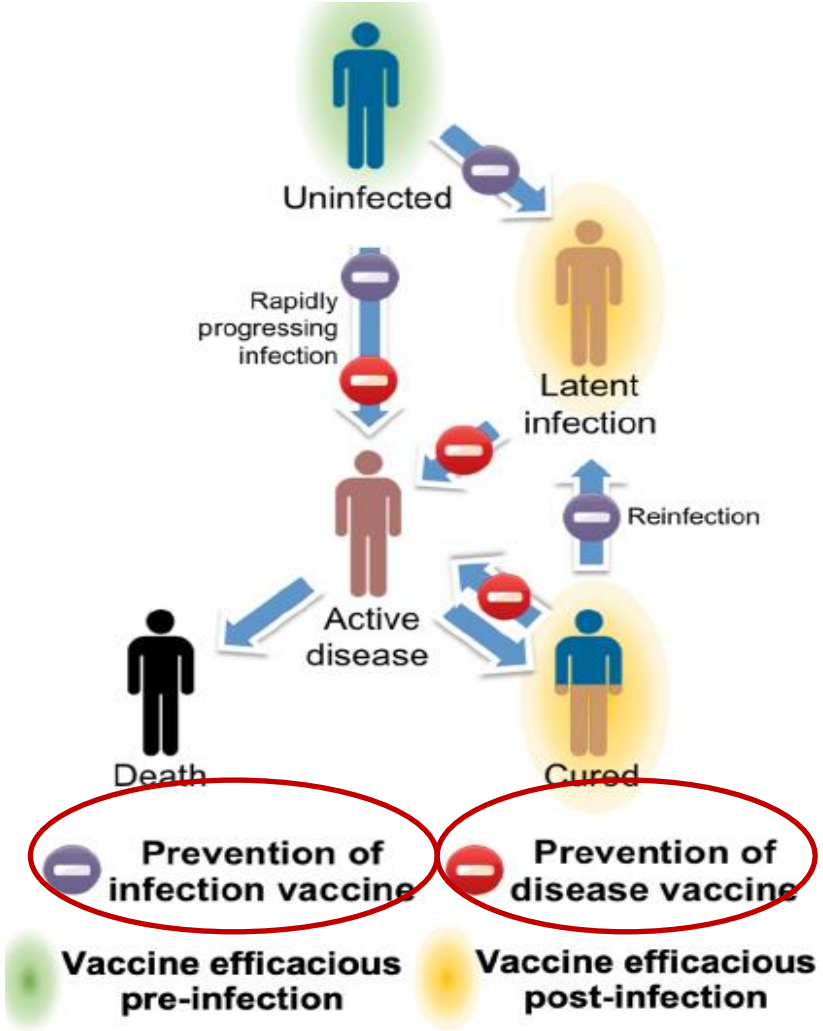


TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews | Disease Primers

Pai, M. *et al.* (2016) Tuberculosis. The*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

MORE EFFECTIVE TB VACCINES COULD SAVE MILLIONS OF LIVES



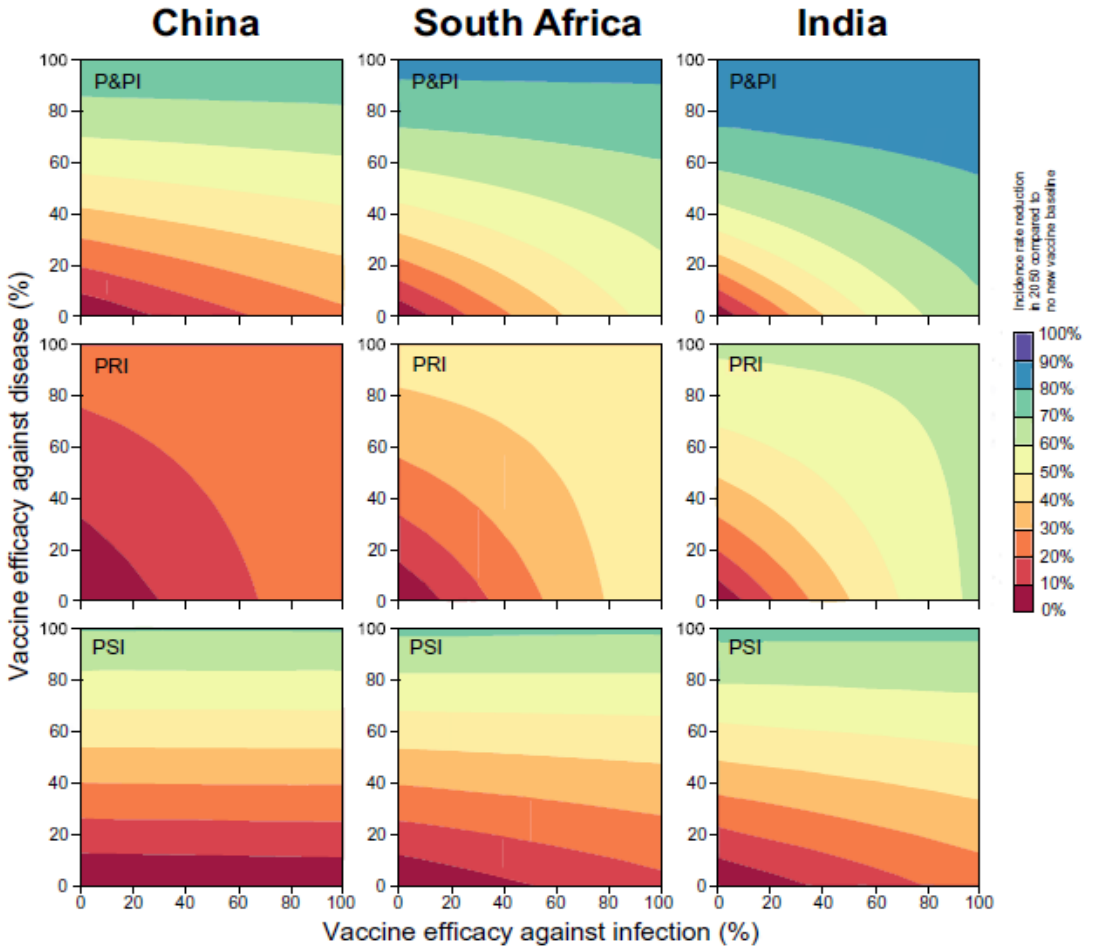


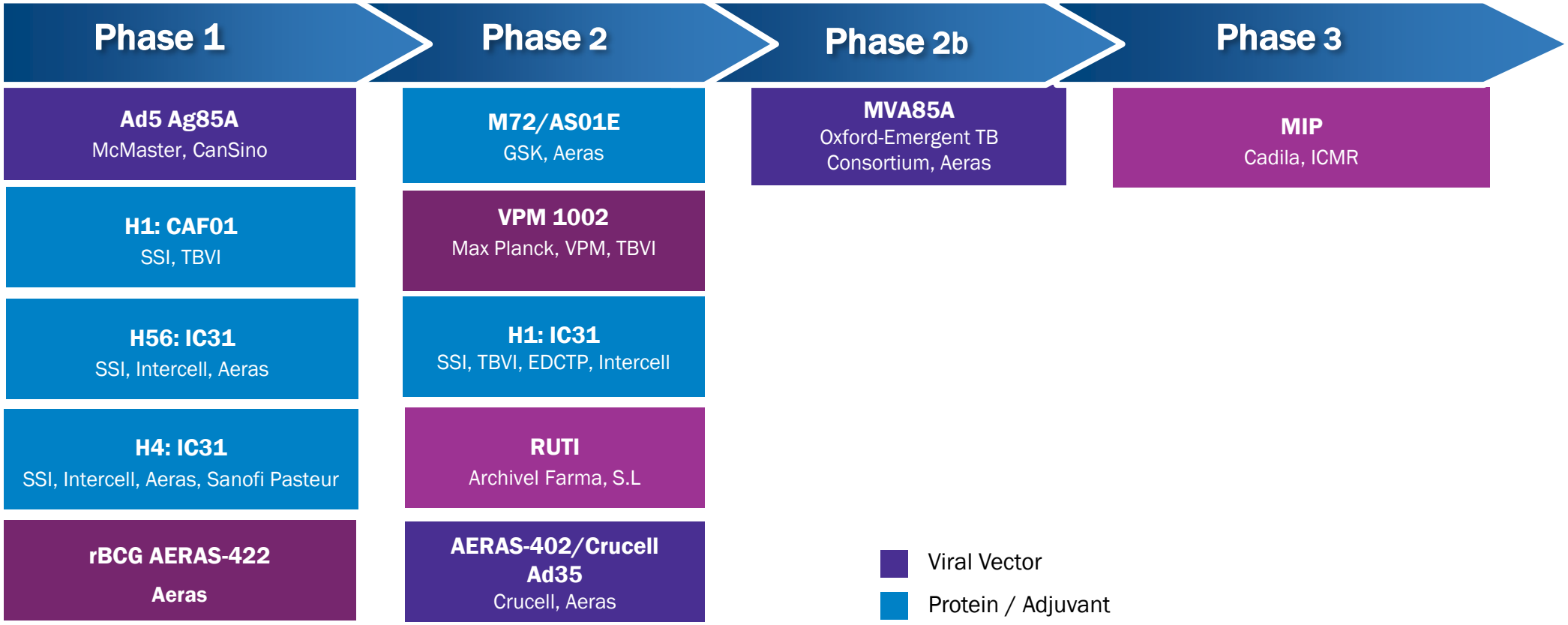
Fig. 3. Vaccine impact by prevention of infection and prevention of disease efficacy. IRR in 2050 by country from a vaccine with 10-year duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (P&PI; top row), pre-infection populations (PRI; middle row), or post-infection populations (PSI; bottom row), assumed safe and efficacious in HIV-positive populations, delivered from 2025 as routine vaccination of 9 year olds and as 10-yearly mass campaigns in China, South Africa, and India.

PROGRESS IN TB VACCINE R&D -

- From 2011 to now

GLOBAL CLINICAL PIPELINE (2011)

12 candidates – most in early development; 2 in efficacy trials (1 preventive, 1 therapeutic)



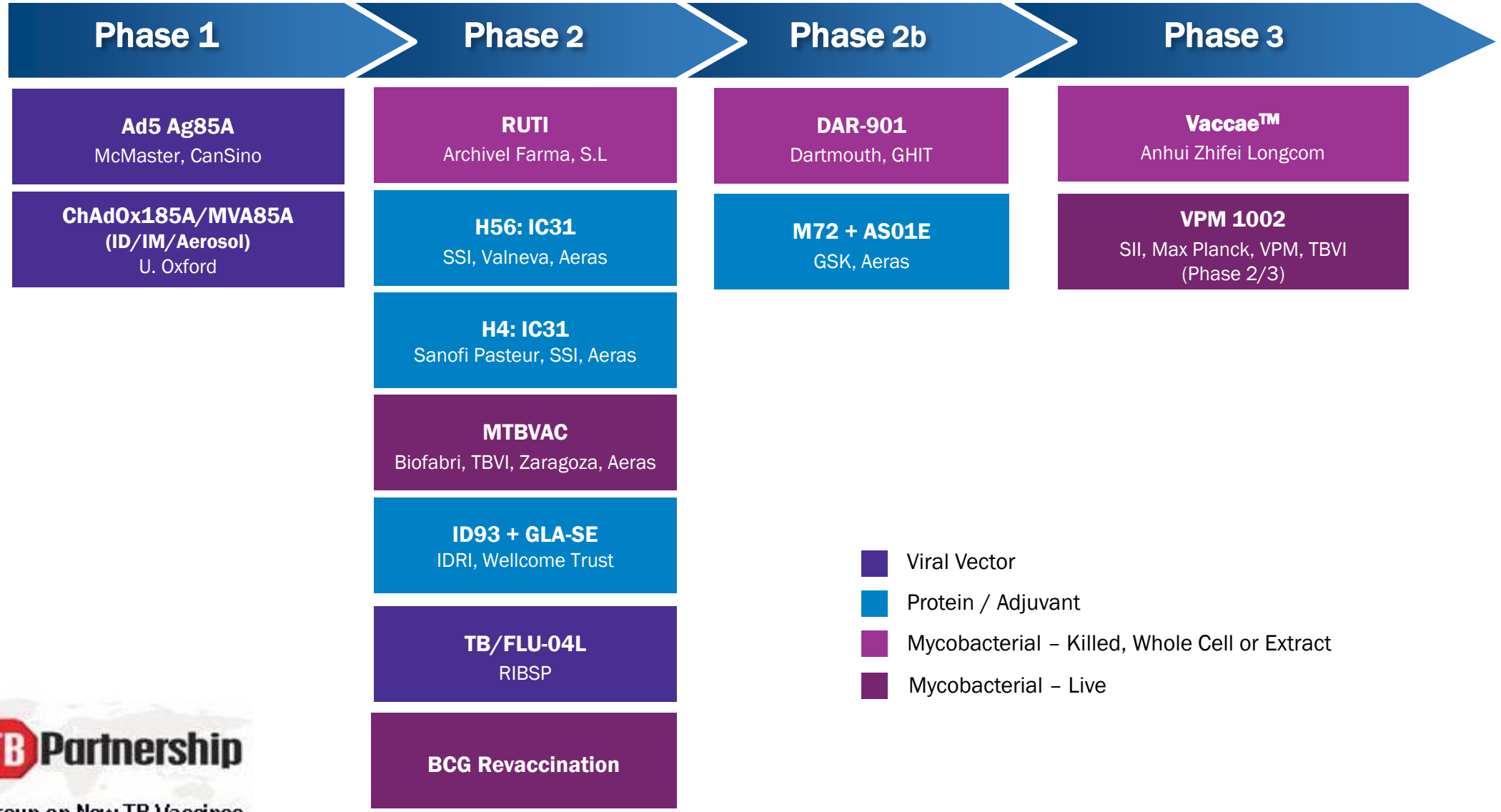
TB Vaccine Types
Viral-vectored: MVA85A, AERAS-402, AdAg85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56
rBCG: VPM 1002, AERAS-422
Killed WC or Extract: Mw, RUTI

Source: Tuberculosis Vaccine Candidates – 2011

Stop TB Partnership
Working Group on New TB Vaccines

Global Clinical Pipeline (2018)

14 candidates – more in early Phase 2; 4 candidates in efficacy trials (all preventive)



Stop TB Partnership
Working Group on New TB Vaccines

GLOBAL CLINICAL PIPELINE (2020)

14 candidates – some new, majority in efficacy trials (all preventive); variety of endpoints and populations

Phase 1	Phase 2	Phase 2b	Phase 3
AdHu5Ag85A McMaster, CanSino	**RUTI** Archivel Farma, S.L	**DAR-901** Dartmouth, GHIT	**VPM 1002** SIIPL/VPM
AEC/BC02 **Anhui Zhifei Longcom**	**TB/FLU-04L** RIBSP	**M72/AS01E** GSK, IAVI	**Immuvac** Cadila, ICMR
	MTBVAC Biofabri, TBVI, Zaragoza, Aeras/IAVI	**BCG Revaccination** Gates MRI	
	ChAdOx185A/MVA85A (ID/IM/Aerosol) Univ of Oxford	**H56: IC31®** SSI, Valneva, IAVI	
		ID93 + GLA-SE IDRI, Wellcome Trust	
		GamTBvac **MoH Russia**	

POI = Prevention of Infection;
POD=Prevention of Disease;
POR = Prevention of Recurrence;
HHC = household contact(s)
LTBI+ = TST+ or IGRA+

- Viral Vector
- Protein / Adjuvant
- Mycobacterial – Killed, Whole Cell or Extract
- Mycobacterial – Live

Stop TB Partnership
Working Group on New Vaccines

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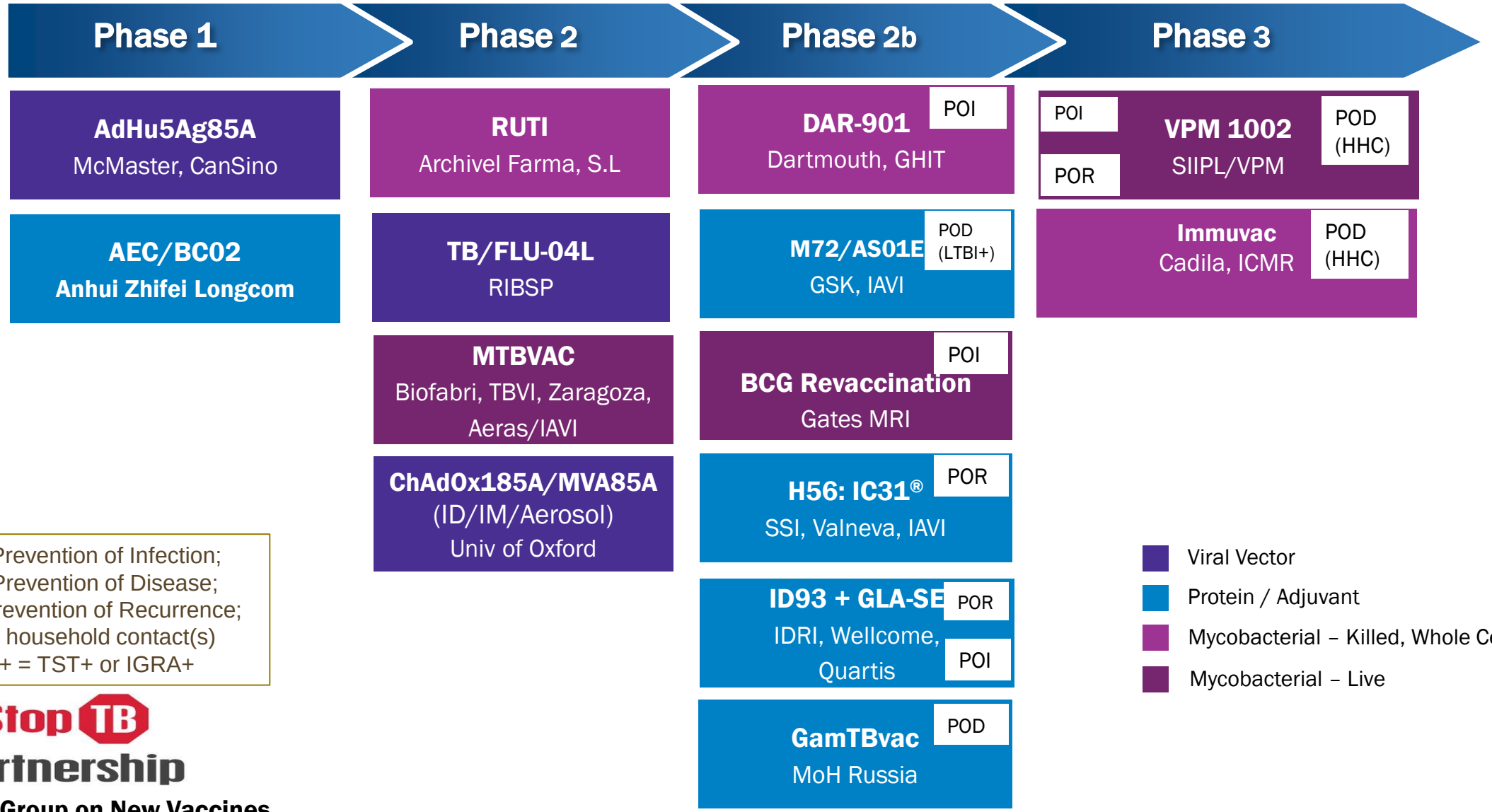

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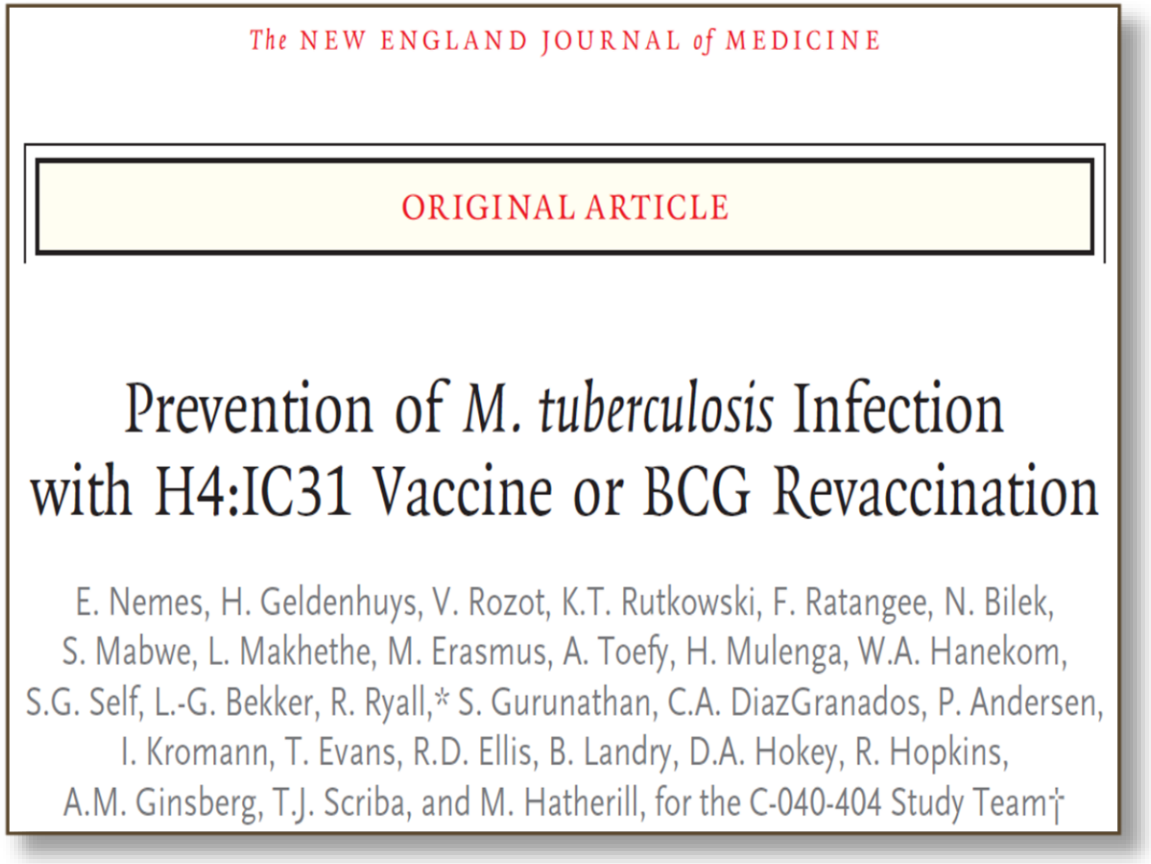
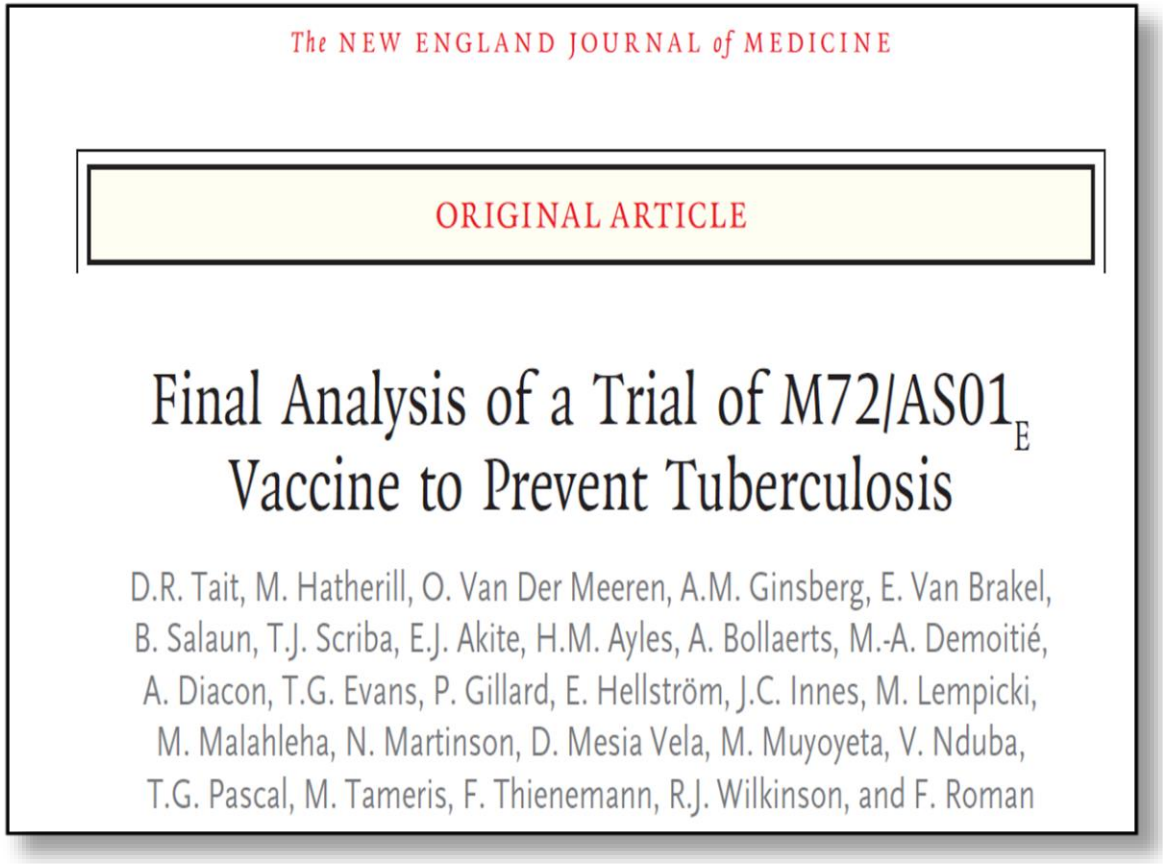
Stop TB Partnership
Working Group on New Vaccines

PROGRESS - TWO POSITIVE EFFICACY TRIALS!



2018

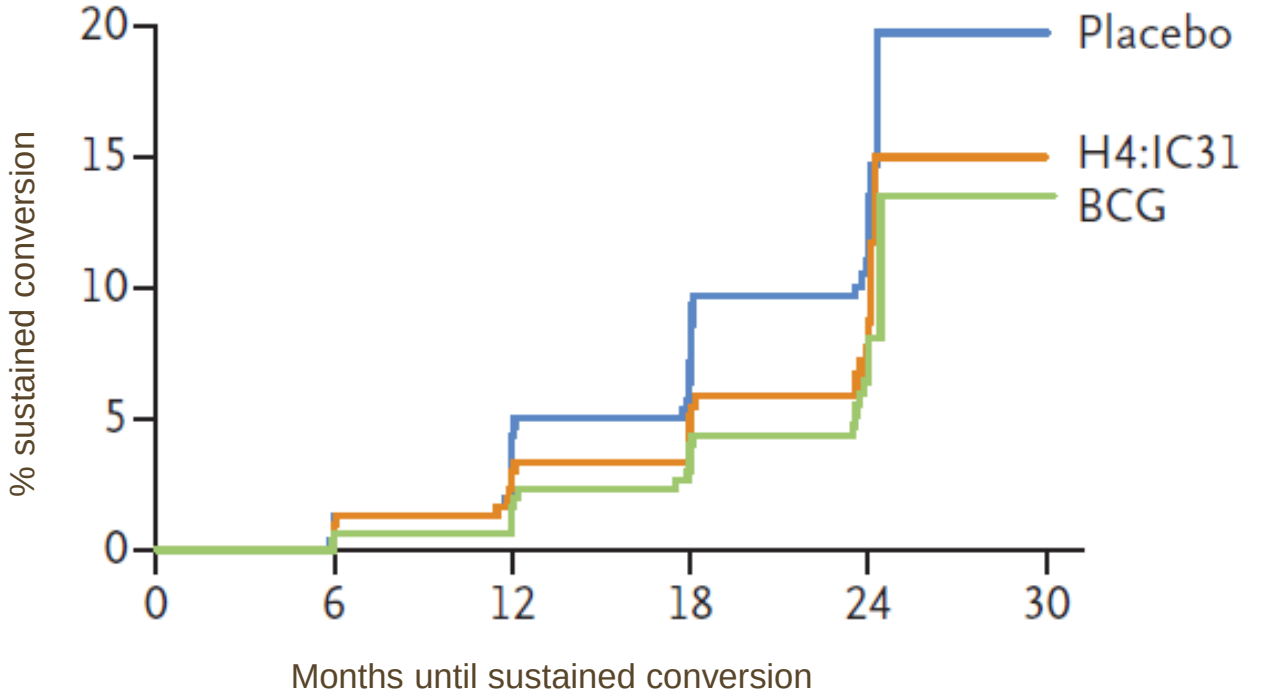


2019

BCG REVACCINATION PHASE 2 TRIAL IN *M.tb*-UNINFECTED POPULATION (POI TRIAL)

N=990 QFT-negative, HIV-negative adolescents in South Africa, randomized 1:1:1, partially blinded; primary endpoint: initial QFT conversion, secondary endpoint: sustained QFT conversion

BCG: 45% (95%CI 6.4-68.1%) vaccine efficacy for sustained QFT conversion



QFT = QuantiFERON-TB Gold In-tube assay

DOI: 10.1056/NEJMoa1714021

BCG REVACCINATION – NEXT STEPS

Larger, confirmatory Phase 2b trial ongoing in South Africa (NCT04152161)

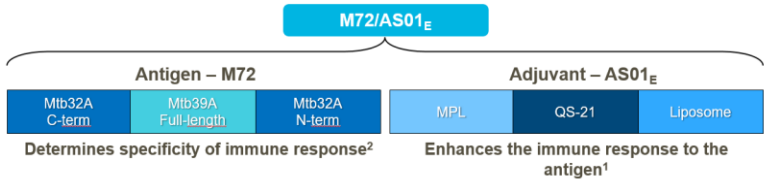
- Randomized (1:1), placebo-controlled, observer blind; 2 arms - BCG vs. saline placebo; single intradermal injection
- 1800 QFT-negative 10 to18 year-olds
- ~50% enrolled
- Primary endpoint: sustained QFT conversion (from negative to positive, lasting at least six months)
- Exploratory endpoints: to define Correlates of Protection
- Trial Sponsor: Gates Medical Research Institute

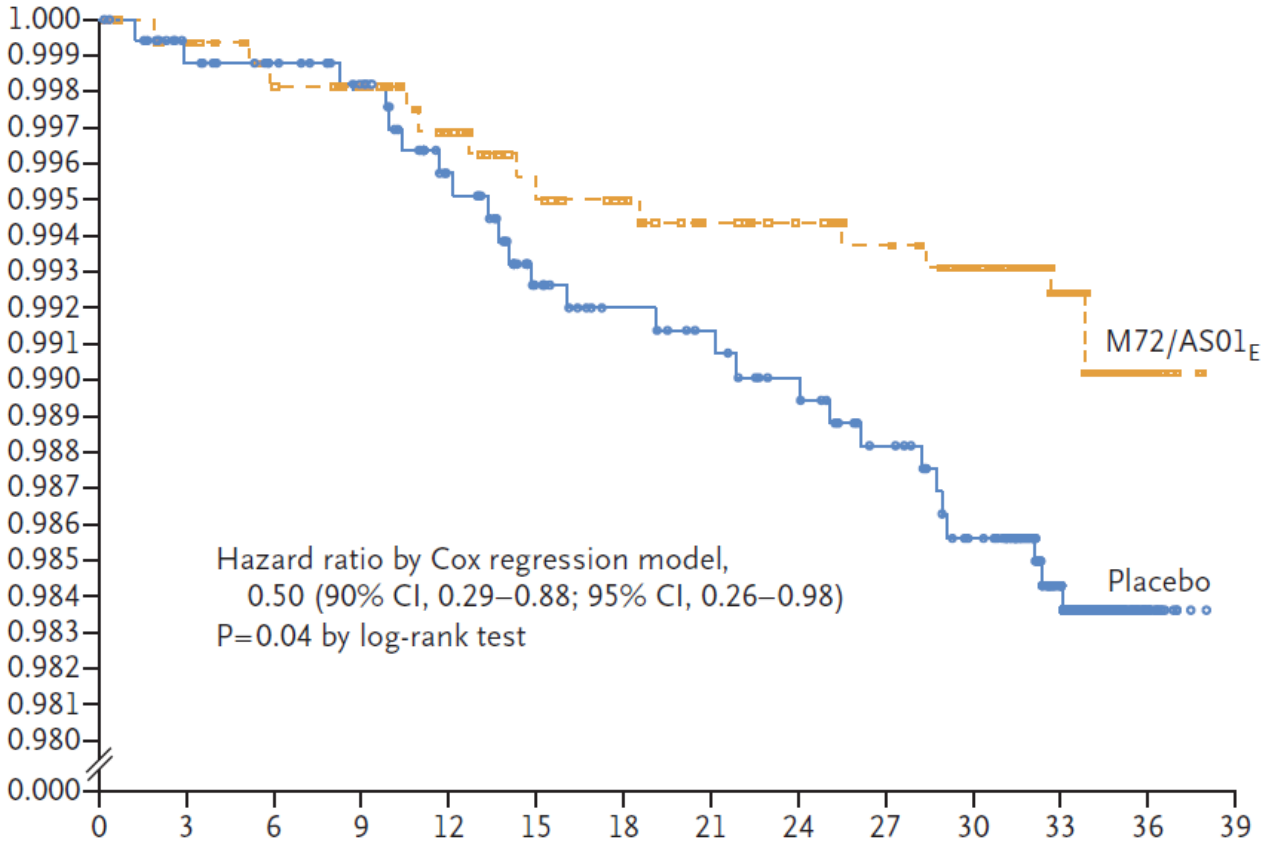
Potential policy change to be evaluated based on results

M72/AS01$_E$ PHASE 2B TRIAL PROOF-OF-CONCEPT IN LTBI+ AFRICAN ADULTS

Vaccine efficacy: 49.7% (95% CI 2.1 to 74.2%)

Acceptable safety profile





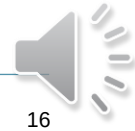
References: DOI: 10.1056/NEJMoa1803484 and DOI: 10.1056/NEJMoa1909953

1. Skeiky et al. J Immunol 2004;172:7618–28; 2. Mortier et al. BMC Immunol 2015;16:63; **3.** Leroux-Roels et al. Hum Vacc Immunother 2014;10:2211–9.

M72/AS01$_E$ – NEXT STEPS

Consistent with WHO PPC for Adolescent/Adult Vaccine to Prevent TB Disease

- GSK licensed M72 to Gates Medical Research Institute for use in most Lower/Middle Income Countries (LMICs); AS01$_E$ to be supplied by GSK
- Correlates of Protection discovery project underway
- Phase 2 safety trial in Persons Living with HIV (PLHIV) - enrolling in South Africa
- Phase 3 development in planning
  - Scale-up CMC process and manufacturing
  - Site feasibility assessment and capacity-building for Phase 3 trial(s), including epidemiology study at ~50 sites and multiple continents



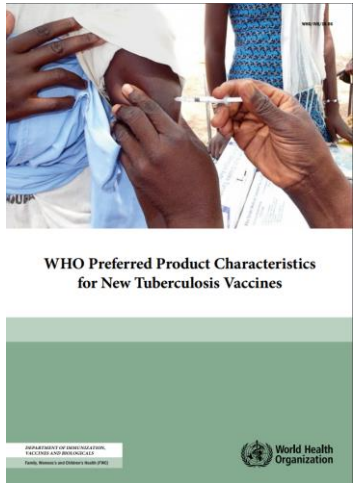
PROGRESS IN PRECLINICAL AND TRANSLATIONAL SCIENCE

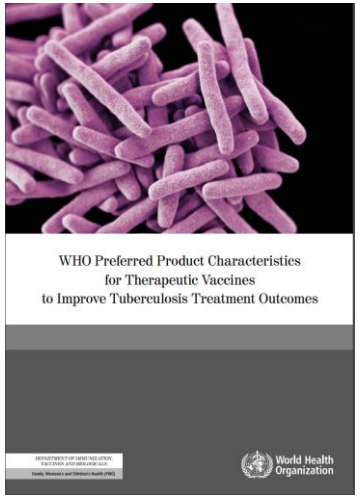
- Alternate Routes of Administration
  - iv BCG in mice[1] and NHP[2] – high levels of protection and evidence of role for trained innate immunity[3]
  - Phase 1 studies of aerosol delivery in humans[4]
- Unprecedented levels of protection in NHP models – CMV-TB[5], iv BCG[8]
- Novel preclinical candidates/vectors: e.g., CMV-TB[5], mRNA
- New tools available or under development – examples:
  - Bar-coded *M. tuberculosis* strains[6]
  - Controlled human infection models[7]
  - Biorepositories to support correlates discovery
  - Single cell TCR sequencing to inform antigen selection
- Exploration of more diverse vaccine-induced immune responses

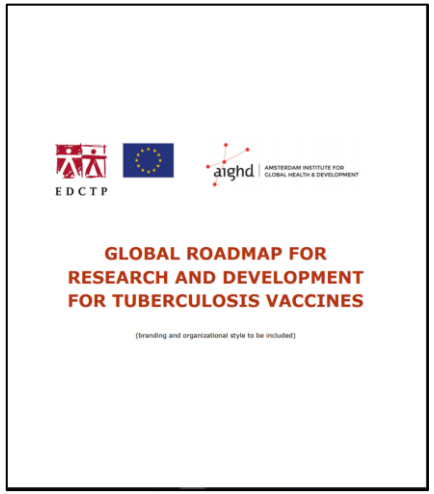
[1]Kaufmann E et al, Cell. 2018 Jan 11;172(1-2):176-190.e19. doi: 10.1016/j.Cell.2017.12.031. [2]Sharpe S et al, Tuberculosis (Edinburgh) 2016 Dec; 101: 174–190. [3]Cell Rep. 2016 Dec 6;17(10):2562-2571. doi: 10.1016/j.celrep.2016.11.011. [4]Manjaly TZR, PLoS Med. 2019 Apr 30;16(4):e1002790. doi: 10.1371/journal.pmed.1002790. eCollection 2019 Apr. 5Hansen SG et al, Nat Med. 2018 Feb;24(2):130-143. doi: 10.1038/nm.4473. Epub 2018 Jan 15. [6]Martin CJ et al, Mbio. 2017 May 9;8(3). pii: e00312-17. doi: 10.1128/mBio.00312-17. [7]Minhinnick A et al, J Infect Dis. 2016 Mar 1;213(5):824-30. doi: 10.1093/infdis/jiv482. Epub 2015 Oct 8; [8]Darrahet al Nature 2020 doi: 10.1038/s41586-019-1817-8; [9]Hansen et al Nat Med 2018 doi: 10.1038/nm.4473.

INFORMING “NEXT-GEN” CANDIDATES

- WHO issued **Preferred Product Characteristics**
- Draft **TB Vaccine R&D Roadmap** published (led by AIGHD with funding from EDCTP and participation from WHO and many stakeholders)
  - in final comment period
- **Full Public Health Value Proposition** being developed (WHO, LSHTM)







SUMMARY

RECENT RESULTS ARE GAME-CHANGING

Proof of concept that a subunit vaccine can protect against TB disease (POD)

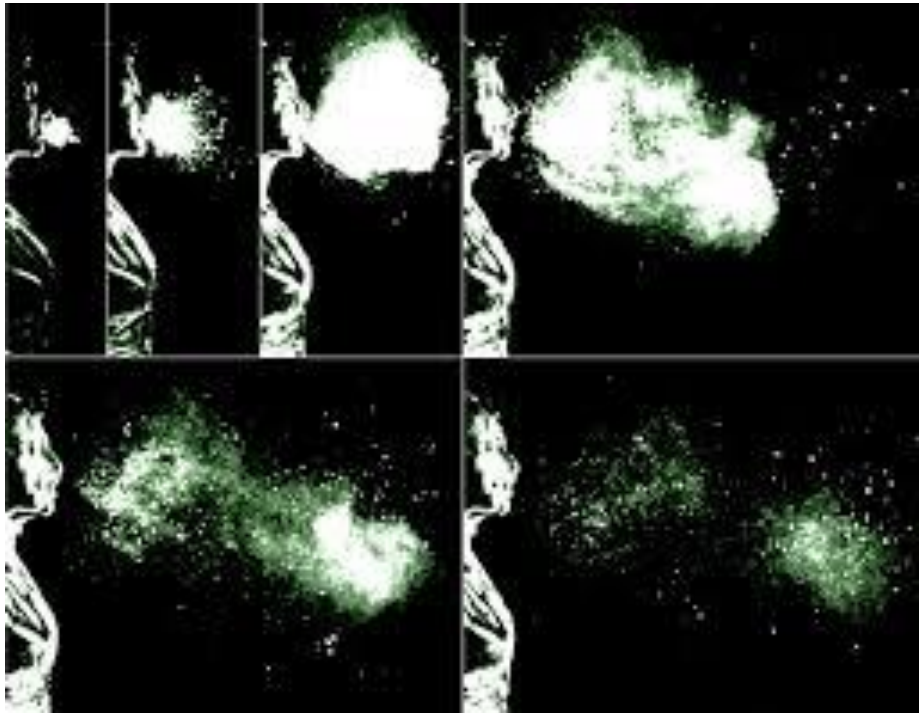
First demonstration that a vaccine can protect M.tb-infected adults from developing TB disease

- *Could be transformational for TB prevention*

Enhanced use of BCG – to protect high risk, uninfected populations from Mtb infection with BCG revaccination

Opportunity to discover correlates of protection and increase understanding of protective human immune responses

Human and preclinical testing should proceed in parallel across a portfolio - human efficacy data informs optimization and use of preclinical models, while preclinical findings inform human TB vaccinology

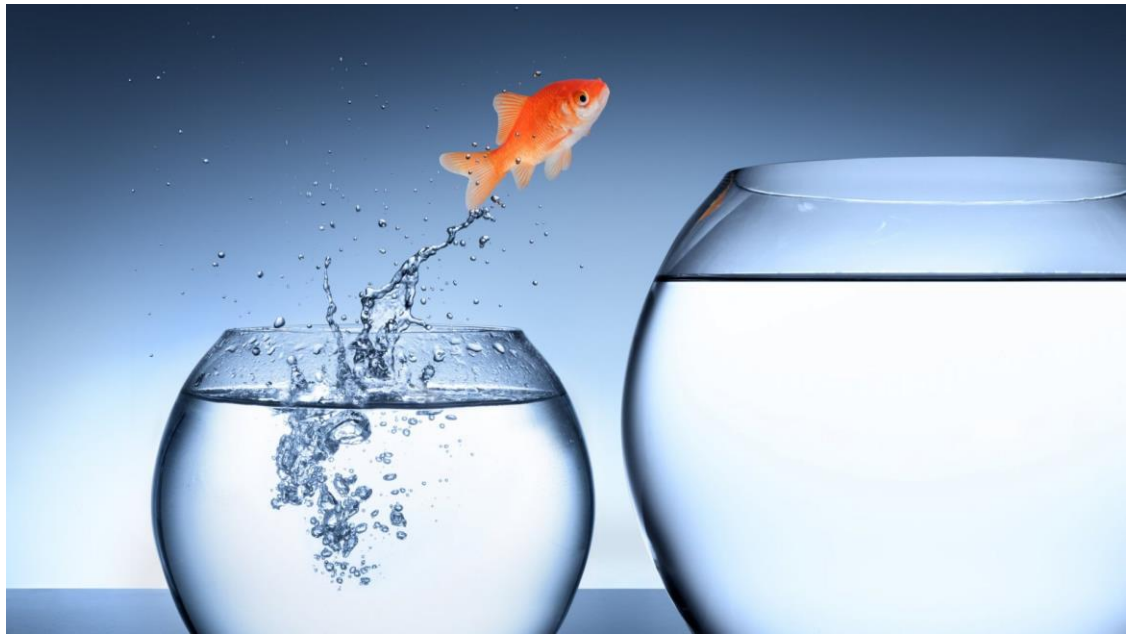


Stopping the cycle of transmission in adolescents and adults will prevent the spread of TB to all age groups

KEY CHALLENGES

What is still needed?

- Validated, vaccine-induced Correlate(s) of Protection
- Predictive animal model(s)
- Further elucidation of human protective immune responses
- More robust and diverse preclinical pipeline
- Knowledge of effects of HIV status, QFT/TST status, age and geography on vaccine efficacy
- Preparation for access, adoption and delivery to end users



KEY OPPORTUNITIES

- Correlate(s) of Protection analyses underway from M72 and BCG revax Ph2B trials
- More physiologic small animal model(s) being developed (e.g., ultra-low dose mouse)
- Application of state-of-the art single cell and –omics technologies
- Leveraging from COVID-19 vaccine R&D - examples:
  - New vaccine platforms (e.g., mRNA)
  - Streamlined regulatory pathways and harmonization
  - Collaboration models
  - Financing mechanisms

➢ How can TB vaccine R&D best leverage learnings and infrastructure from COVID-19 vaccine R&D to accelerate progress and ensure success?

THANK YOU

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www.impatientoptimists.org