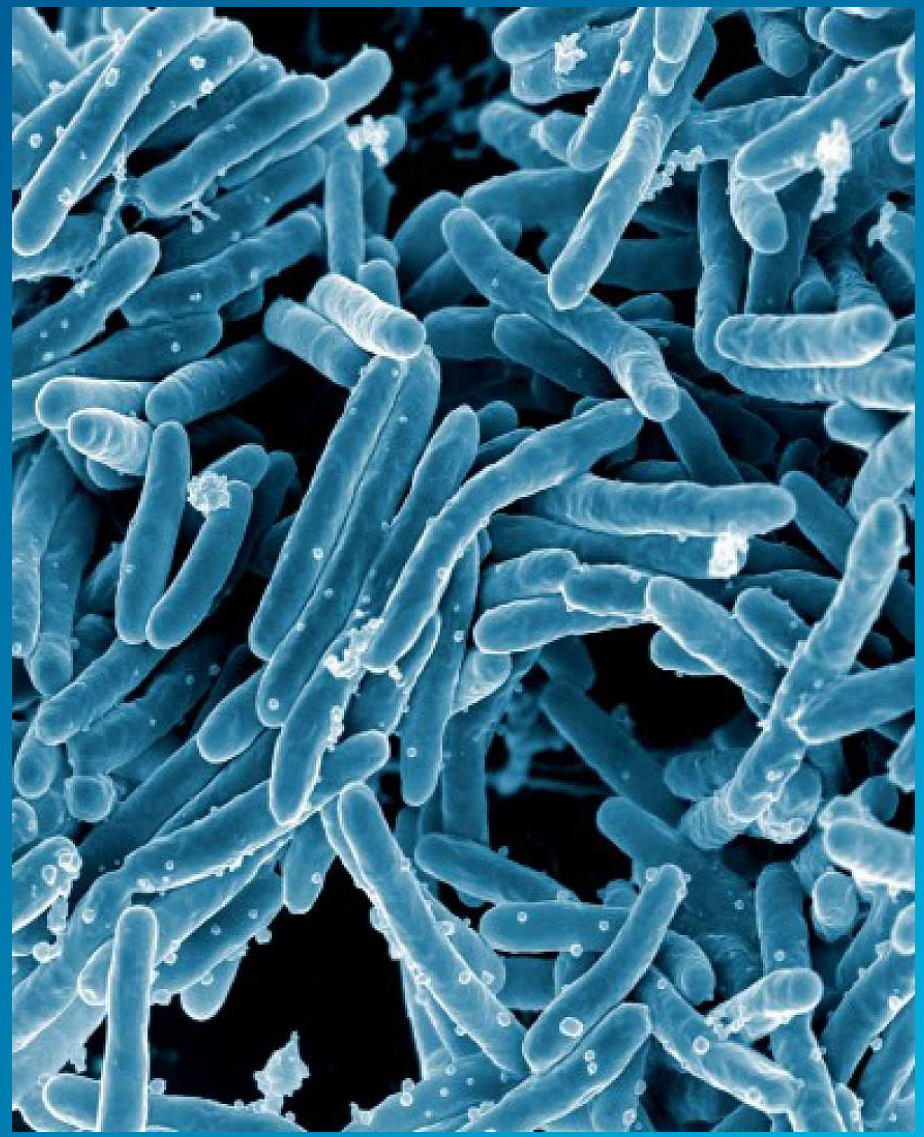
Translating **science** into **global** health impact

# TB Vaccine Development: Progress, Challenges and Lessons from the COVID-19 Pandemic

**Lewis Schrager, Senior Leader, TB Impact Area**
**IAVI**

NYC World TB Day Conference
18 March 2022



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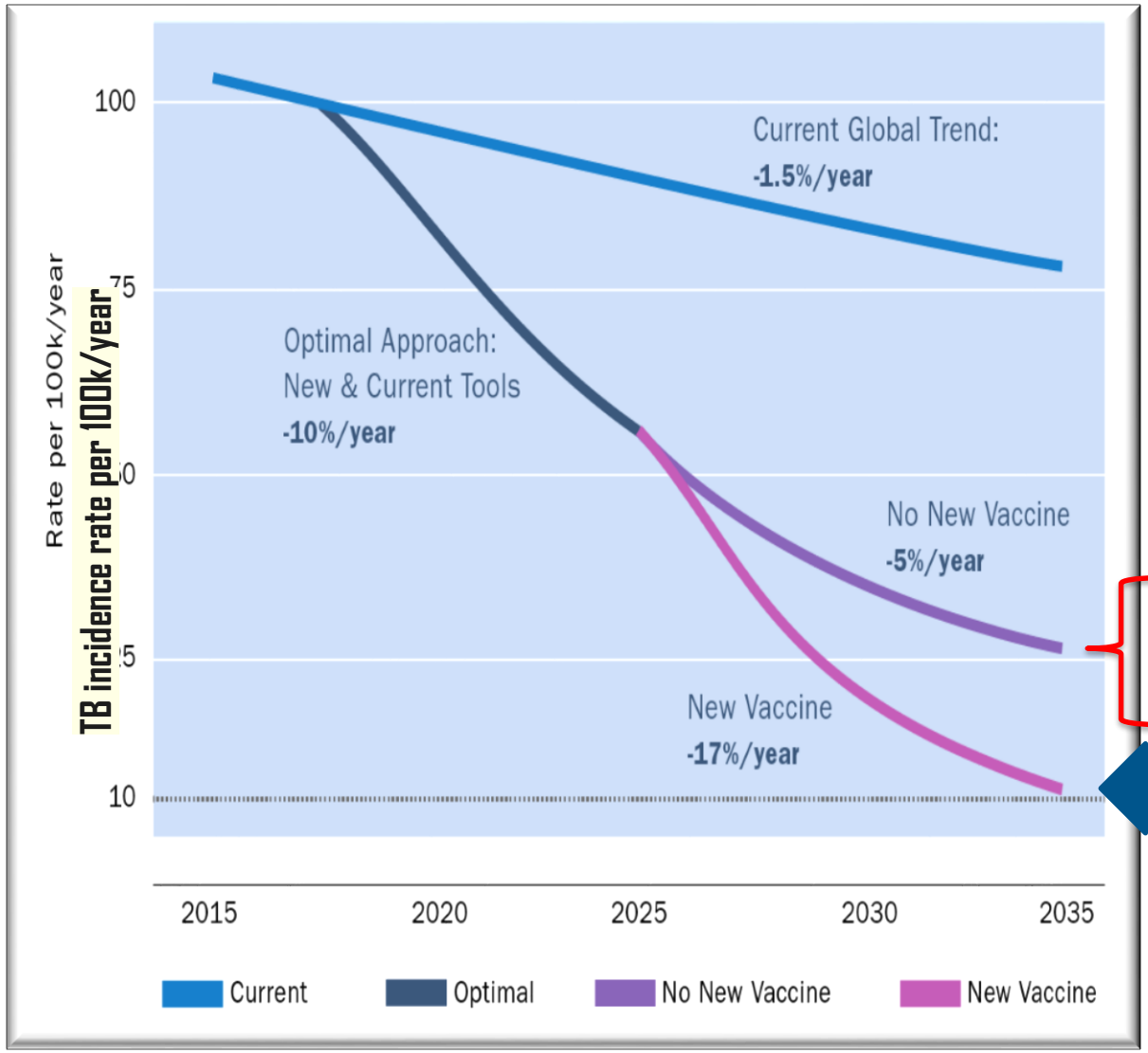
As of October 2021

# Agenda

- Importance of developing new vaccines to ending the spread of TB
- Progress in developing new TB vaccines
- Lessons from the COVID-19 response: requirements to facilitate TB vaccine development

# Delivering a new vaccine for TB is a global health imperative

- Tuberculosis has caused more deaths globally than any other single infection over the past decade
- A new TB vaccine is required to reach the WHO End TB Strategy targets of 95% reduction in TB mortality and 90% reduction in TB incidence by 2035
- Vaccines offer the best chance to contain the accelerating spread of multi-drug resistant tuberculosis




Sources: O'Neill Review, 2016 and WHO Global TB Report 2016, WHO Health Assembly 2014, Abu-Raddad LJ, et al., 2009; Dye, 2013, Lietman, et al, 2000, Ziv, 2004; WHO's End TB Strategy/UN Sustainable Development goals.

# Bacille de Calmette et Guerin (BCG): The Only Licensed Vaccine Against TB

*M. bovis*-derived; 230 passages over 13 years (1908-1921, Lille, France)

Given at or close to birth

>3 billion doses administered; safe

**60-80% efficacy vs. severe TB disease (meningitis, miliary TB) in children**

Variable protection vs. primary infection in children (0% - 74% risk reduction)

Unreliable protection vs. adult pulmonary TB (newborn injection)

First human administration of BCG to a newborn infant – Paris, 1921

# BCG is insufficient to end the TB epidemic

**Despite near universal infant BCG vaccination** in TB-endemic countries:

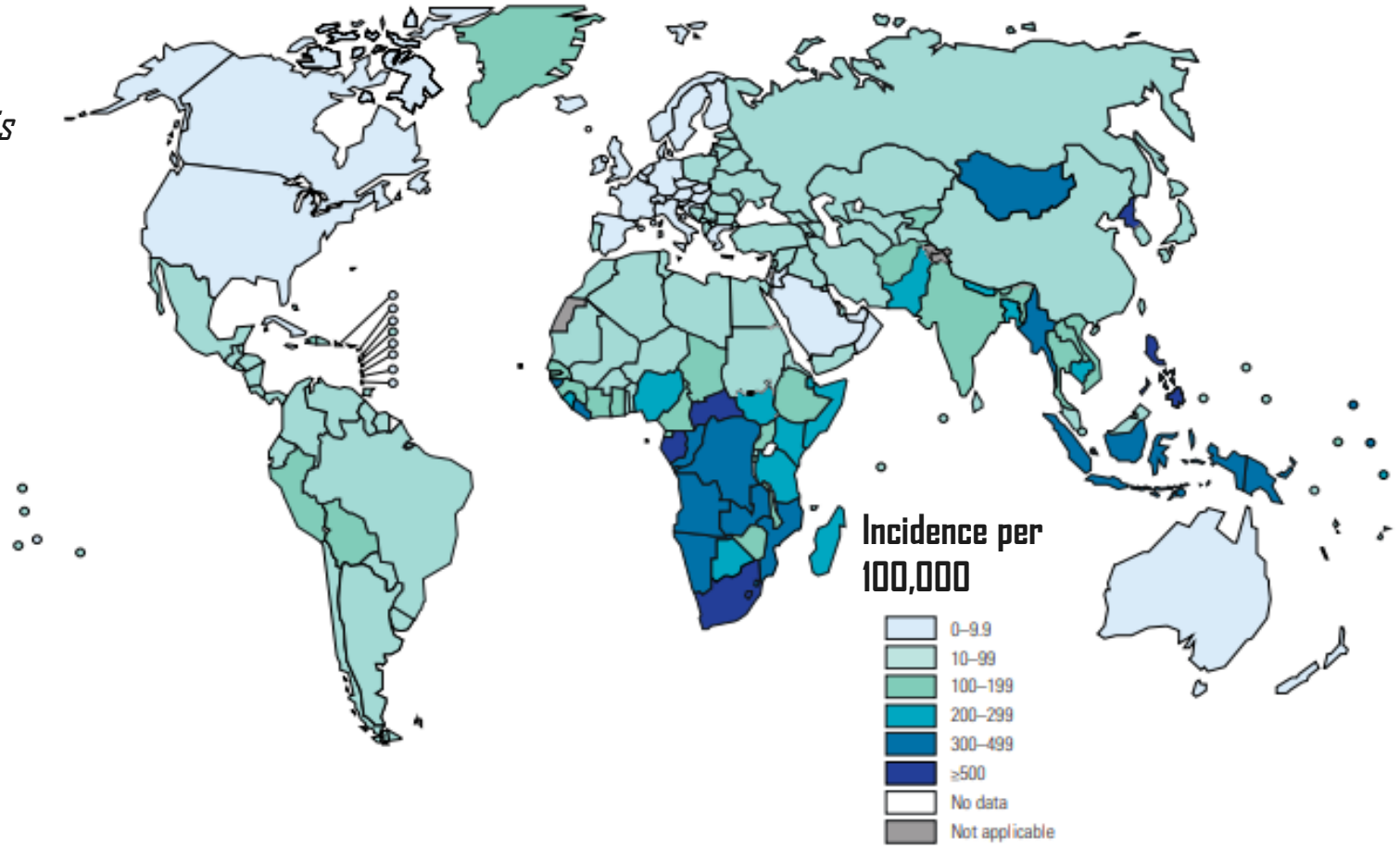
- **25%** of people are infected with *Mycobacterium tuberculosis* (Mtb)
- **10 million** people developed active TB & **1.5 million** people died of TB in 2020

**Infant BCG vaccination offers little or no protection against transmission**:

- **Infants** & younger children **are not a significant source of transmission**
- **BCG-induced protection wanes** to zero 10–15 years after vaccination, around the time **when transmission increases**.

FIG. 4.4

**Estimated TB incidence rates, 2019**




Sources: Starke, J. Transmission of mycobacterium tuberculosis to and from children and adolescents, Seminars in Pediatric Infectious Disease, Volume 12, Issue 2, April 2001, Pages 115-123; WHO, Global TB report, 2021; Abubakar et al., 2013; Sterne et al.,1998; Mangtani et al., 2014; Sterne et al., 1998,

# Major TB vaccine progress, to date

- **1921** – First use of BCG in an infant

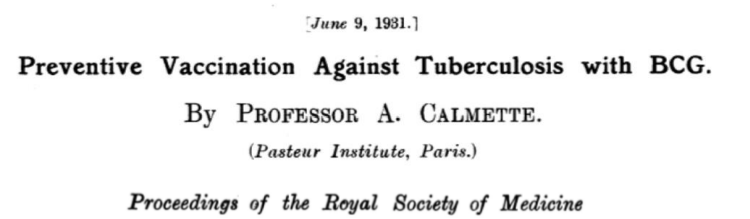
  *Proc R Soc Med* 1931:241(11);1481-90.

- **2018** – BCG revaccination results in 45% reduction in sustained interferon-gamma release assay (IGRA) conversion (vs. placebo) in Mtb-uninfected adolescents

  *N Engl J Med* 2018;379:138-49. DOI:10.1056/NEJMoa1714021

- **2019** – M72/AS01$_E$ vaccine phase 2B study for protection against TB disease in adults who are HIV-negative, IGRA+: 50% protection

  *N Engl J Med* 2019;381:2429-39. DOI:10.1056/NEJMoa1909953



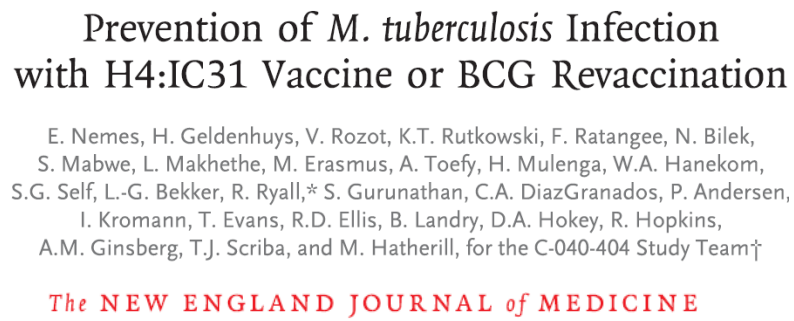
[June 9, 1931.]

**Preventive Vaccination Against Tuberculosis with BCG.**

By PROFESSOR A. CALMETTE.

(*Pasteur Institute, Paris.*)

*Proceedings of the Royal Society of Medicine*



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†

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Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

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# Current Strategies for TB Vaccine Development

## Target Indications


**Pre-infection: Prevention of Infection (PoI)**

**Post-infection: Prevent of Disease (PoD)**

- After initial infection
- Reactivation from latency
- Most important strategy to meet END TB 2035 goals (95% reduction in TB deaths, 90% reduction in TB incidence, compared to 2015)

**Prevention of Recurrence (PoR)**

- Prevent recurrent TB following completion of drug treatment

## Target populations

Infants

**Adolescents/Adults**

TB patients

# WHO Preferred Product Characteristics: TB Vaccines Key Parameters

- Indication: Immunization for **prevention of active pulmonary TB disease**
- Target population**: Adolescents and adults**
- Outcome measure and efficacy: **50% or greater** efficacy; protective in persons **with and without latent Mtb infection**
- Safety: **Favorable in particular risk groups, such as individuals with HIV/AIDS and other immunodeficiencies, the elderly, pregnant and lactating women**
- Schedule: A **minimal number of doses (<3) and boosters** required
- Programmatic suitability and prequalification: **The vaccine should be prequalified to support purchasing by United Nations agencies**
- Value proposition: **Favorable cost-effectiveness should be established; price should not be a barrier to access, including in low- and middle-income countries**

# Global Clinical Pipeline of TB Vaccine Candidates

| *Phase 1* | *Phase 2a* | *Phase 2b* | *Phase 3* |
|---|---|---|---|
| **AdHu5Ag85A**<br>McMaster, CanSino | **RUTI**<br>Archivel Farma, S.L. | **DAR-901**<br>Dartmouth, GHIT (POI) | **VPM1002***<br>SIIPL, VPM (POI; POD ) |
| **AEC/BC02**<br>Anhul Zhifel Longcom | **TB/FLU-04L**<br>RIBSP | **M72/AS01$_E$**<br>GSK, Gates MRI (POD) | **Immuvac**<br>Cadila, ICMR (POD) |
| | **MTBVAC***<br>Biofabri, TBVI, Zaragoza | **BCG revaccination**<br>Gates MRI (POI) | |
| | **ChAdOx185A/MVA85A**<br>Univ. of Oxford (ID/IM/Aerosol) | **H56:IC31**<br>SSI, Valneva, (POR) | |
| | | **ID93+ GLA-SE**<br>IDRI, Wellcome Trust, Quartis (POR, POI) | |
| | | **GamTBvac**<br>MoH Russia | |

**POD** = Prevention of Disease
**POI** = Prevention of Infection
**POR** = Prevention of Recurrence

Viral Vector | Protein Adjuvant | Mycobacterial – Killed or Lysate | Mycobacterial – Live attenuated

* Infant/ neonate and adolescent/ adult trials.

# Critical Needs for Developing Successful TB Vaccines

- Identification of correlates of immune protection
  - >4,000 antigens expressed at different times in Mtb life cycle (“stage-specific” antigens)
  - Protective immune response not yet identified
- Development of an animal challenge model reliably predictive of vaccine efficacy in humans
- Funding necessary to develop and test new TB vaccines

# Lessons Learned from SARS-CoV-2 Vaccine Development

- Vaccines = the foundation of effective public health campaigns against infectious (especially respiratory) pathogens
- Historically rapid development of SARS-CoV-2 vaccines
  - 11 Jan 2020: release of SARS-CoV-2 sequence
  - 14 Jan 2020: NIH VRC and Moderna collaborate on COVID-19 vaccine design
    - VRC pre-fusion spike protein sequence also shared with other vaccine manufacturers (e.g., Pfizer/BioNTech, Janssen)
  - 16 March 2020: 1st phase 1 trial begins (Moderna mRNA)
  - 9 November 2020: Pfizer/BioNTech mRNA phase 3 results – 95% efficacy
  - 16 November 2020: Moderna mRNA phase 3 results – 94% efficacy
- FDA Emergency Use Authorizations
  - 11 December 2020 (Pfizer/BioNTech)
  - 18 December 2020 (Moderna)

# Lessons Learned from SARS-CoV-2 Vaccine Development (2)

- Historically rapid SARS-CoV-2 vaccine development *"due to more than a decade of basic research, planning and preparation for a betacoronavirus emergence motivated by the episodes of SARS-CoV-1 and MERS-CoV."* [1]
- Preceded by decades of investment in research and development along two tracks
  - Immunogen development (advances in immunology, structural biology)
    - >20 years studying and creating stabilized, pre-fusion spike proteins; targets for virus neutralizing antibodies
      - HIV-1 Env trimer[2]
      - RSV preF trimer[3]
      - Coronaviruses (SARS-CoV ⟶ MERS-CoV ⟶ SARS-CoV-2) spike protein[2]
  - Development of immunogen delivery strategies, novel vaccine platforms
    - mRNA vaccines: Required years of persistence and financial support despite skepticism[4]


[1]Graham BS. Rapid COVID-19 Vaccine Development. Science 2020;368:945-946.
[2]Sanders RW, Moore JP. Virus vaccines: proteins prefer prolines. Cell Host Microbe 2021:29;327-333. doi:10.1016/j.chom.2021.02.002
[3]McClellan JS, et al. Structure-based design of a fusion glycoprotein vaccine for RSV. Science 2013:342;592-8.
[4]Dolgin E. The Tangled History of mRNA Vaccines. Nature 14 Sept 2021

# Lessons Learned from SARS-CoV-2 Vaccine Development (3)

- *"The full development pathway for an effective vaccine for SARS-CoV-2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths."*[1]
  - Operation Warp Speed (OWS): Integrated program comprising HHS components (ASPR, BARDA, NIH, CDC) + DoD to advance medical research, logistics, and down-select vaccine candidates
- Partnerships between governments, academia, pharmaceutical and biotech companies critical to rapid, efficient SARS-CoV-2 vaccine development
  - Researchers at publicly funded universities, national research centers (e.g., J. McClellan, U. Texas; B. Graham, VRC/NIAID) solved pre-fusion spike protein structure, optimized expression levels
  - SARS-CoV-2 pre-fusion spike protein sequences provided to vaccine manufacturers
    - Moderna mRNA (OWS funding)
    - Pfizer/BioNTech mRNA (German government funding)
    - Janssen adenovirus-vectored vaccine (OWS funding)

[1]Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. Science 2020:368;948-50

# Lessons Learned from SARS-CoV-2 Vaccine Development (4)

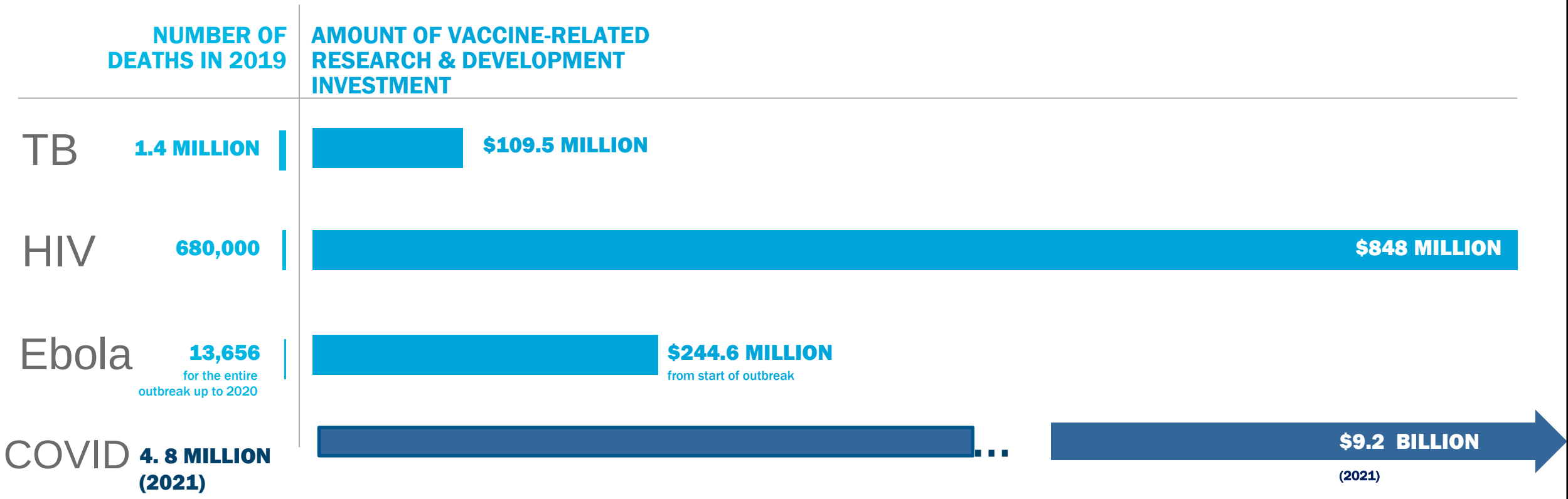
- OWS: established a paradigm for independent but harmonized phase 3 vaccine trials[1]
  - Closely-aligned primary endpoints (prevention of symptomatic COVID-19)
  - Powered to establish VE >50% (LB of 95% CI >30%)
  - Common DSMB established by NIH
  - Core set of validated assays established to measure vaccine-induced binding and neutralizing antibody responses
    - Common set of immune measurements from which to assess potential immune correlates of protection established for each trial
  - NIAID merged existing DAIDS/DMID clinical research networks + DoD sites + VA clinical network into a combined COVID-19 Prevention Network (CoVPN)
- Early involvement of regulatory agencies speeded vaccine assessment, authorization for use
- CAUTION: Vaccine hesitancy, politization of vaccination efforts, lack of access (low-income countries; impoverished populations) impeded the effect of COVID vaccinations to stem the pandemic

[1]Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons and prospects. Immunity 2021:54;1636-51. doi.org/10.1016/j.immune.2021.07.017

# Lessons Learned from SARS-CoV-2 Vaccine Development : Requirements to Facilitate TB Vaccine Development

- Commitment to robust and reliable support for basic mycobacteriology/mycobacterial immunology research
- Commitment to robust and reliable support for development of novel Mtb immunogens/immunogen delivery strategies
- '*Industry, government, and academia collaborate in* (previously) *unprecedented ways, each adding their individual strengths'*
  - **An *Operation Warp Speed* for TB vaccine development?**
    - Support government/academia/industry partnerships in TB vaccine R&D
    - Foster independent but harmonized phase 3 vaccine trials
- Early involvement of regulatory agencies in TB vaccine clinical development plans
- Engage in efforts to overcome vaccine hesitancy, avoid politization of vaccination efforts, ensure vaccine access
- **Increase in funding to drive the full spectrum of R&D needed for TB vaccine development**

# Global TB vaccine research is severely underfunded





**Sources:**

http://www.who.int/mediacentre/factsheets/fs104/en/
http://www.who.int/gho/hiv/en/
https://exlibrisgroup.com/blog/covid-19-funding-trends-and-impacts/
https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2019/
https://www.hivresourcetracking.org/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5112007/
https://www.unaids.org/en/resources/fact-sheet
https://www.cdc.gov/vhf/ebola/history/chronology.html
https://www.tballiance.org/

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