

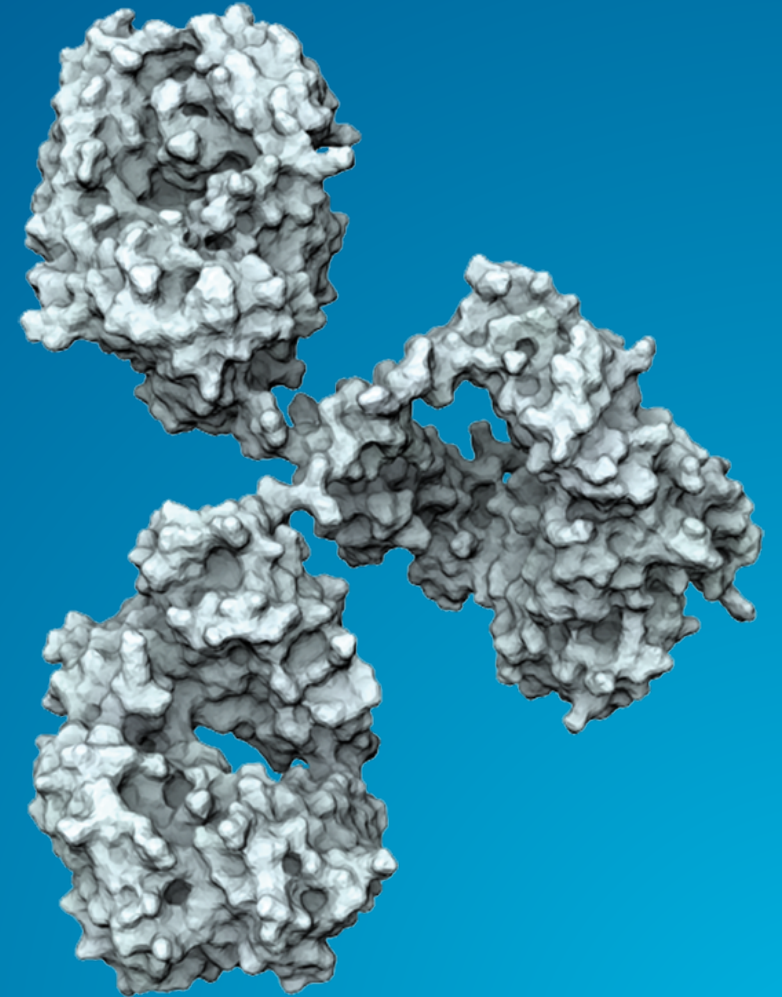


Translating **science** into
global health impact

TB vaccine R&D: An overview

Ben Coates, Advocacy Manager, Europe

TBEC Webinar| 28th September 2020



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And many other generous individuals and partners around the world

As of September 2020

IAVI's Mission

Translating scientific discoveries into affordable, accessible public health solutions to help the people who need them most

What We Do:

Discover new approaches to developing vaccines and other global health tools

Accelerate translational and clinical research through our laboratories in the U.S., India, and the U.K.

Build Capacity in-country for researching vaccine candidates while strengthening local public health and scientific expertise.

Share our resources with other innovators to help the global health community as a whole succeed.

Extend our core capabilities to solving disease prevention and treatment challenges.

An expanded mission

For more than 20 years, IAVI has been a leading force in HIV vaccine research. That mission continues unabated, and now we're also leveraging HIV and TB expertise* to generate innovative solutions to the world's most intractable infectious and neglected diseases by building new partnerships and coalitions.

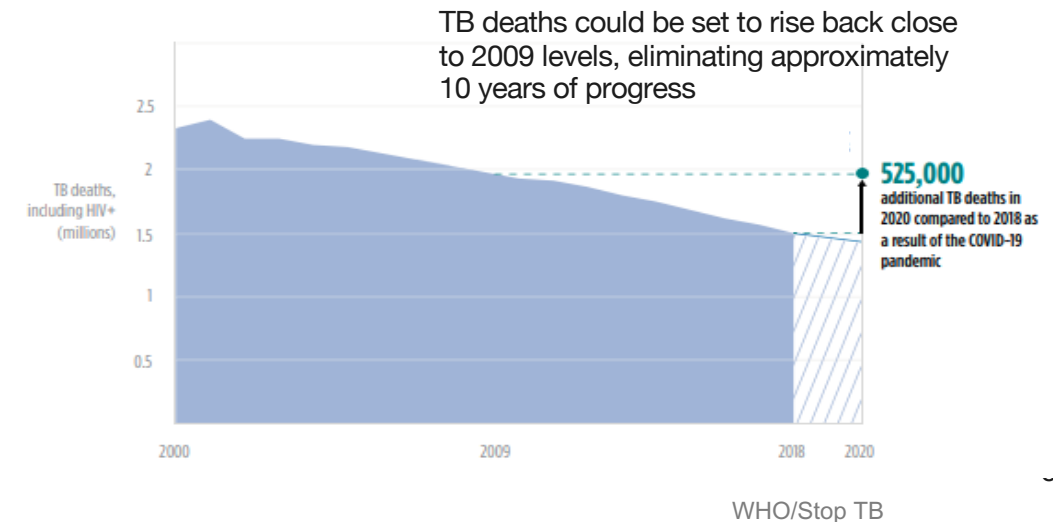
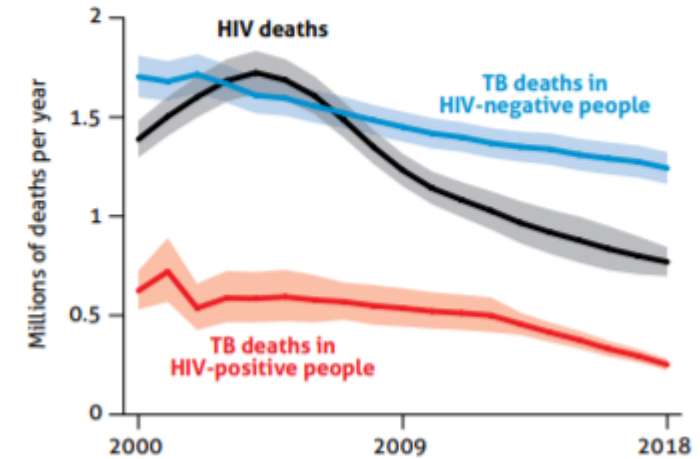
*In October 2018, IAVI acquired tuberculosis vaccine clinical research programs and assets, including clinical staff, from Aeras, the product development nonprofit focused on TB vaccines.



TB is still a major threat to global health

- In 2018, an estimated 10 million people fell ill with TB and at least 1.2 million people died – the equivalent of over three thousand lives lost every single day.
- According to the WHO, “TB is ... a major cause of ill health, one of the top ten causes of death worldwide and the leading cause of death from a single infectious agent, ranking above HIV/AIDS”.
- In 2018, the 30 high TB burden countries accounted for 87% of new TB cases. Eight countries (including India, China and Indonesia) account for two thirds of the total.
- MDR-TB is a growing problem. In 2018, there were about half a million new cases of rifampicin-resistant TB, of which nearly four hundred thousand involved multidrug-resistant TB.
- COVID-19 risks making things far worse: Stop TB estimates between 2020 - 2025 an additional 1.4 million TB deaths could be registered as a result of the pandemic

Global trends in the estimated number of deaths caused by TB and HIV, 2000–2018.^{a,b} Shaded areas represent uncertainty intervals.



New TB vaccines are needed



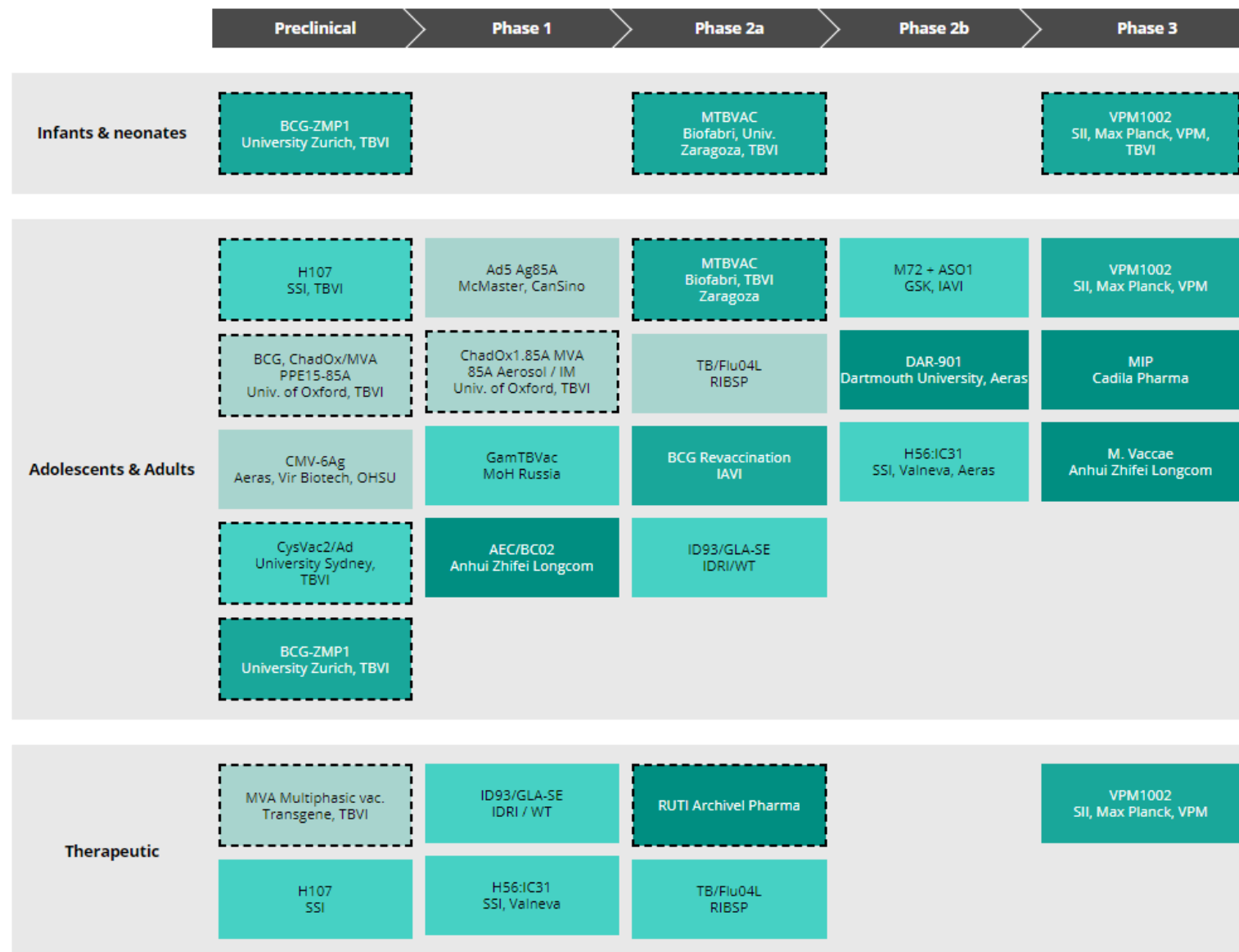
- The only existing TB vaccine, BCG, was first used around 100 years ago, and while partially effective in preventing severe forms of TB in infants and young children, does not adequately prevent pulmonary TB in adolescents and adults. If you get vaccinated against TB today, the doctor will be using a vaccine which is roughly the same age as the Model T Ford.
- We don't have new TB vaccines partly because developing them is difficult, but mostly because their development hasn't been prioritized. In 2018, the world spent a total of around \$750 million on R&D for new HIV/AIDS vaccines and around \$160 million on malaria vaccines – but only about \$65 million on developing TB vaccines.
- One study estimated that only 1.1 percent of new drugs approved between 1975 and 1999 were for poverty-related and neglected diseases, despite them represented 12 percent of the global disease burden.

Exciting advances



- The last few years have seen some genuine breakthroughs in the development of TB vaccines, with numerous candidates advancing through the pipeline.
- In late 2019 GSK and IAVI reported that the **M72/AS01_E candidate vaccine** was significantly protective against pulmonary TB in HIV-negative adults with latent TB infection.
 - The trial was conducted in TB-endemic regions (Kenya, South Africa and Zambia) and involved about 3,500 people, who were given either the M72 vaccine or a placebo. 13 people who got the vaccine went on to develop active pulmonary TB, compared to 26 in the placebo group – meaning the overall vaccine efficacy was 50%, with an immune response sustained for three years. This represents the first time in almost a century that a new vaccine has been shown to help provide protection against TB disease
- Separately, another trial found that revaccination with the **BCG vaccine** could help significantly reduce sustained TB infections in adolescents.
- Research into the use of TB vaccines to treat and prevent Covid-19 is also underway.
- Several other candidates are also moving through clinical trials – we are arguably closer than ever to having a new vaccine

The pipeline



Live
 Wholecell
 Subunit
 Vector

TBVI

Challenges remain

- TB vaccine development is at a critical juncture. In order to bring game-changing new vaccines to market, we need to conduct late stage efficacy trials for the M72 candidate, prepare for licensure and use of a new TB vaccine, build understanding the epidemiology of TB, and continue advancing a diverse portfolio of vaccine candidates.
- Some of the scientific obstacles are complex, but one of the biggest barriers is funding – later-stage clinical trials can run to hundreds of millions of dollars.
- Globally, R&D funding is concentrated on a few large donors - the NIH, the Gates Foundation and a few pharmaceutical firms collectively provide nearly three-quarters of TB vaccine R&D funding
- There's also a problem of the pipeline drying up –after decades of underinvestment, if current leading candidates fail, we don't have a large number of alternatives in advanced development.
- We need to advance TB vaccine candidates in late stage efficacy trials and prepare for TB vaccine implementation – but also develop next generation candidates to address current and future unmet needs and facilitate human correlate identification to streamline TB vaccine development.
- Sustained investment in R&D is therefore essential.

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The Broad Benefits of TB Vaccine Research

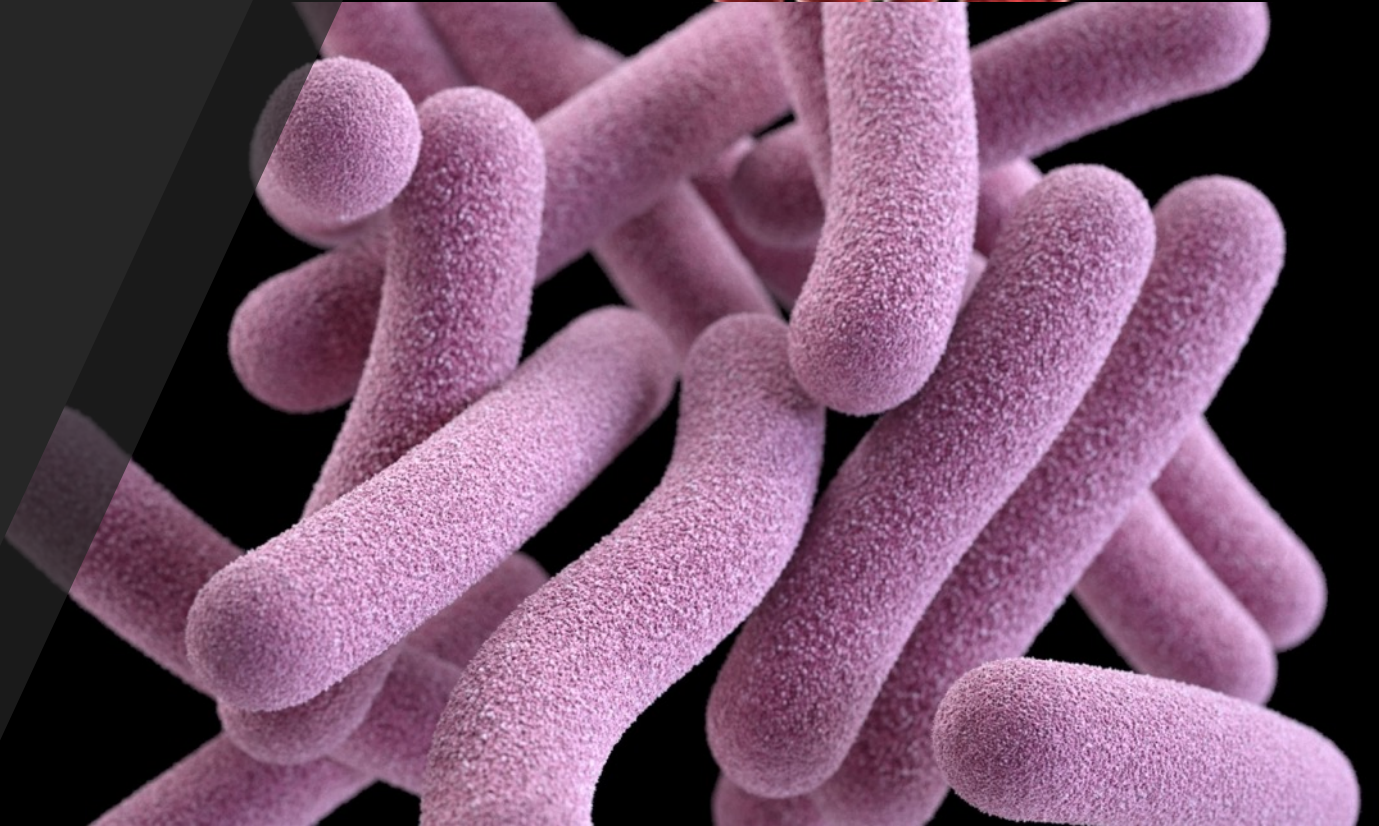
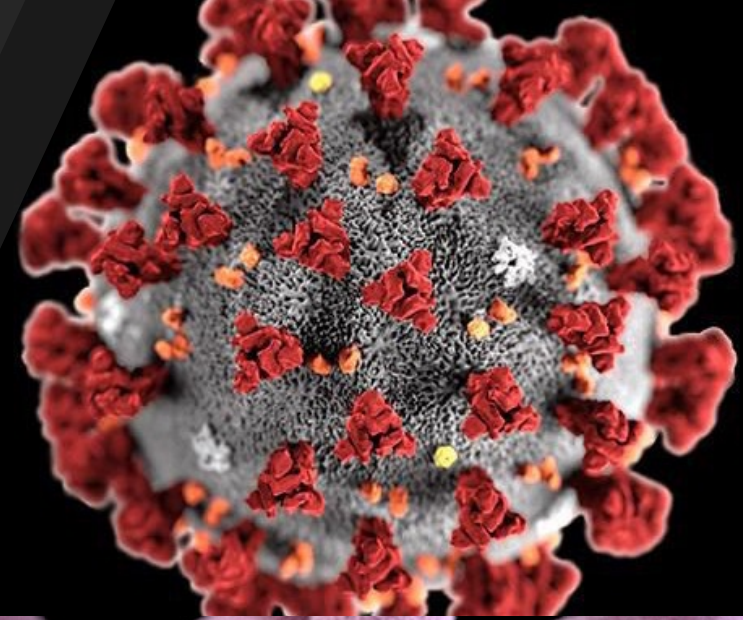
The Impact of **COVID-19** on Research and Development for TB Vaccines

TBEC Webinar Series

Mike Frick

Treatment Action Group

September 2020



Two things are true:

1. COVID-19 has disrupted TB research.
2. TB research has contributed to COVID-19 R&D.
The most obvious area of crossover is TB vaccines.

TREATMENT ACTION GROUP POLICY BRIEF

August 2020

TAG

Treatment Action Group
www.treatmentactiongroup.org

TB Research Investments Provide Returns in Combating Both TB and COVID-19:

Sustained and Expanded Financing Is Needed to Safeguard Tuberculosis
Research Against COVID-19-Related Disruptions and Improve Global
Epidemic Preparedness

By Catherine Tomlinson

Edited by Mike Frick, Lindsay McKenna, Suraj Madoori

1

COVID-19 has disrupted TB research in myriad ways.

- Participant enrollment
- Participant monitoring and support
- Supply chain disruption
- Sample collection
- Sample export
- Laboratory capacity
- Community engagement

“TB clinical trials carry inherent challenges at the best of times. Locations with the highest TB burden often have less resilient regulatory infrastructure, complex operational environments, and more limited clinical trial experience. During an unexpected and large-scale disruption like COVID-19, the impact of these weaknesses becomes more magnified.”

—ID Rusen, Trop Med Infect Dis, June 2020

Covid-19 research in Europe needs coordination, but we must not stop European research investments in poverty related diseases

August 24, 2020

- “We must remain aware of the danger of an excess of COVID-19 exceptionalism in the planning of future research funding that would come at the expense of other urgent global health needs. Tuberculosis, malaria, and HIV have well documented research needs and any redirection of funding from these poverty-related diseases to covid-19 would be highly deleterious to global public health.”
- “The reduction of research funds to support improved TB research and control will not only ruin earlier investments made in the past decade, but also have direct consequences on the quality of programme management and the availability of better diagnostics and treatments in the near future.”

Pletschette M, et al. [BMJ Opinion](#). August 2020.

2

TB research strengthens more than the movement to end TB. Investments in TB research yield broad benefits.

Cross-disease benefits for COVID-19 from TB R&D include:

- Transmission and aerobiology research
- Artificial intelligence
- Diagnostic tools (Xpert)
- **Vaccine platforms (BCG and others)**
- Research infrastructure and capacity
- Laboratory biosafety
- Implementation research (on e.g., contact tracing)

Shoring up global investments in TB R&D may deliver not only new tools to end TB in our lifetimes but also cross-disease benefits that may be leveraged in combating COVID-19 and future pandemic threats.

Crossroads: TB Vaccine Pipeline and **COVID-19**

Phase 1	Phase 2a	Phase 2b	Phase 3
AEC/BC02 Anhui Zhifei Longcom	RUTI Archivel Farma, S.L	DAR-901 Dartmouth, GHIT	Vaccae™ Anhui Zhifei Longcom
Ad5Ag85A McMaster, CanSino	MTBVAC Biofabri, TBVI, Zaragosa	M72/AS01E GSK	VPM1002 SII, Max Planck, VPM, TBVI (Phase 2/3)
ChAdOx1 85A/MVA85A (ID/IM/Aerosol) Univ of Oxford	ID93 + GLA-SE IDRI, Wellcome Trust, Quratis	H56:IC31 SSI, IAVI, EDCTP, Valneva	Immuvac ICMR, Cadila Pharmaceuticals
	TB/FLU-04L RIBSP	BCG Revaccination Gates Medical Research Institute (GMRI)	

Vaccine construct also being
studied against COVID-19

BCG and COVID-19 Trials

HCWs = healthcare workers

Registry number + Sponsor	Intervention (BCG strain)	Primary endpoint	Study population	Study locations	Date of last data collection
<u>NCT04327206</u> (BRACE) Murdoch Childrens Research Institute	BCG (Danish 1331)	Incidence of COVID-19 disease and severe disease	10,078 HCWS	Australia, Netherlands, Spain	June 2021
<u>NCT04328441</u> (BCG-CORONA) UMC Utrecht	BCG (Danish 1331)	Unplanned absenteeism from work (for any reason)	1500 HCWS	Netherlands	March 2021
<u>NCT04348370</u> (BADAS) Texas A&M University	BCG (Tice strain)	Incidence of COVID 19 infection	1800 HCWS	USA	May 2021
<u>NCT04379336</u> TASK Applied Science	BCG (Danish 1331)	Incidence of HCWs hospitalized due to COVID-19	500 HCWS	South Africa	April 2021
<u>NCT04475302</u> ICMR	BCG (NA)	Mortality due to COVID-19 disease	2175 elderly	India	Jan. 2021
<u>NCT04384549</u> Assistance Publique - Hôpitaux de Paris	BCG (Danish 1331)	Incidence of documented COVID-19	1120 HCWS	France	Feb 2021
<u>EUCTR2020-002111-22-PL</u> University of Rzeszów	BCG (Moreau)	Death or life-threatening health impairment	1000 HCWS	Poland	NA
<u>EUCTR2020-001783-28-HU</u> National Korányi Institute of Pulmonology	BCG (Danish 1331)	Unplanned absenteeism from work (due to documented COVID-19 infection)	1000 HCWS	Hungary	NA

+ about a dozen more similar trials

Adapted from WHO Compendium of research projects at the interface of TB and COVID-19

VPM1002 and COVID-19 Trials

Registry number + Sponsor	Primary endpoint	Study population	Study locations	Date of last data collect.
NCT04387409 Vakzine Projekt Management	Number of days absent from work due to respiratory disease (with or without documented SARS-CoV-2 infection)	1200 healthcare workers	Germany	June 2021
NCT04435379 Vakzine Projekt Management GmbH	Number of days with severe respiratory disease at hospital and/or at home	2028 elderly individuals	Germany	May 2021
NCT04439045 University Health Network, Toronto	Self-reported incidence of SARS-CoV-2 infection (confirmed by positive test)	2626 frontline workers	Canada	July 2021
ACTRN12620000707965 Accelagen Pty Ltd, Serum Institute of India	incidence of lab-confirmed SARS CoV-2/COVID-19 infection with severe, critical or life-threatening disease severity based on medical records	3468 healthcare workers or individuals with high-risk of infection (>65 or < 18 with comorbidities)	Australia	March 2021

Adapted from WHO *Compendium of research projects at the interface of TB and COVID-19*

COVID-19 and TB vaccines: other areas of overlap

- **BCG:CoVac**: novel BCG-based COVID-19 vaccine candidate developed in Australia using earlier TB vaccine discovery work.
- **MTBVAC**: live, attenuated form of genetically weakened *M. tuberculosis*. Being studied as a TB vaccine candidate and, possibly, against COVID-19 based on mouse data that MTBVAC protects against challenge by lethal pneumonia.
- **RUTI**: TB vaccine candidate made of fragmented *M. tuberculosis*. Undergoing a clinical trial of protection from COVID-19 in healthcare workers.
- **MIP**: TB vaccine candidate consisting of whole-cell *M. indicus pranii* (sometimes called *Mycobacterium W*) and being studied in critically ill COVID-19 patients in India
- Efforts to develop COVID-19 **human challenge models** have benefitted from techniques and facilities used to develop a TB challenge model using aerosol BCG (Oxford), which have demonstrated the feasibility of aerosol pathogen challenge and built experience with monitoring immune responses in the lungs and blood.

COVID-19 and TB Vaccine Funding Disparities

USG funding for COVID-19 vaccines:

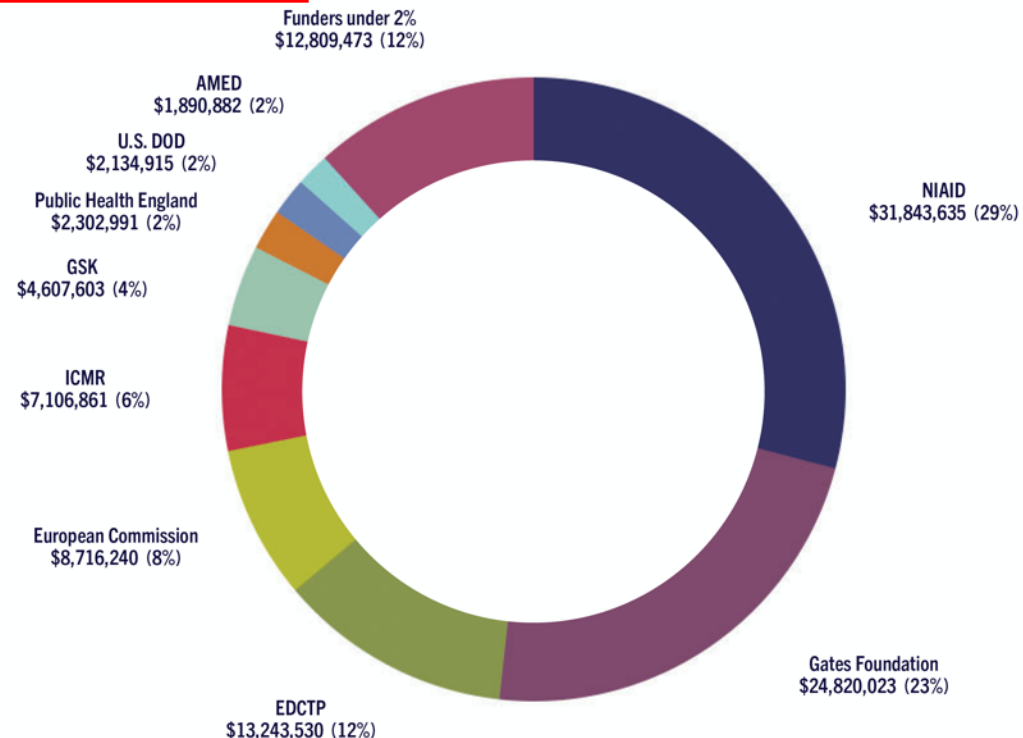
- \$1.525 billion to Moderna*
- \$1.001 billion to Janssen
- \$2.042 billion to Sanofi and GSK
- \$1.950 billion to Pfizer/BioNTech
- \$1.600 billion to Novovax
- \$1.200 billion to AstraZeneca
- \$38 million to Merck and IAVI

* Source: BARDA [COVID-19 Medical Countermeasure Portfolio](#)

** TAG and Stop TB [Report on TB Research Funding Trends](#)

TB vaccine funding 2019**

Vaccines: \$109,476,154



Longstanding issues in TB vaccine R&D

- Lack of biomarkers or correlates of protection that could act as surrogate markers in clinical trials.
- Inclusion of PLHIV and children in the TB vaccine R&D agenda.
- Need to develop better animal models to inform human trials.
- Mechanisms for regular community engagement and protocol review.
- Chronic underfunding.
- Small advocacy community.

Year	TB Vaccine R&D Funding
2018	USD\$109,476,154
2017	\$100,338,945
2016	\$95,394,136
2015	\$80,736,948
2014	\$111,340,797
2013	\$92,373,647
2012	\$92,049,229
2011	\$99,183,567
2010	\$81,280,821
2009	\$115,741,957

Emerging issues in TB vaccine R&D

- Provision of TB preventive therapy (TPT) as part of TB vaccine trials as an ethical imperative.
- Inclusion of pregnant women in TB vaccine trials.
- Trial site capacity to enable multiple large efficacy trials.
- Attention to access and benefit sharing (and understanding access as something to address at earlier stages of R&D).
- Development of human challenge models.
- **Introduction of next-generation vaccine candidates (e.g., mRNA).**
- Funding for experimental medicine, biomarker investigations, and research on stored samples from clinical trials.
- **Intersection of TB vaccine R&D and COVID-19 vaccine R&D.**

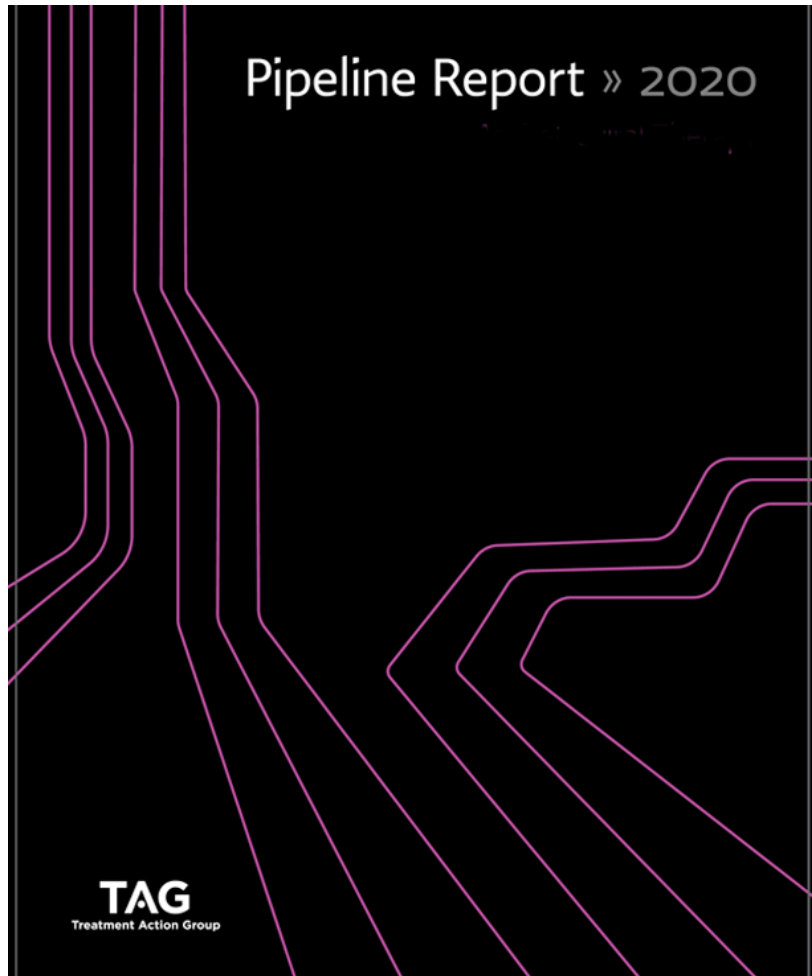
Closer look: **BioNTech**

- German biotech company developing mRNA vaccines.
- Partnering with Pfizer on a COVID-19 mRNA vaccine (BNT162b2).
- Newly working with Gates Foundation to develop mRNA vaccines for HIV and TB:
 - 2019: Gates Foundation makes \$55 million equity investment in BioNTech to develop HIV and TB mRNA vaccines (with the potential to receive up to \$100 million from the Gates Foundation via future grant funding to support clinical evaluations of the resulting candidates).
 - Under the agreement, BioNTech “will retain rights for commercialization of the vaccine candidates in the developed world, while providing affordable access to the candidates in developing countries.”

European support is essential for the future of TB vaccine research: then (BCG) / and now (below)

Phase 1	Phase 2a	Phase 2b	Phase 3
AEC/BC02 Anhui Zhifei Longcom	RUTI Archivel Farma, S.L	DAR-901 Dartmouth, GHIT	Vaccae™ Anhui Zhifei Longcom
Ad5Ag85A McMaster, CanSino	MTBVAC Biofabri, TBVI, Zaragosa	M72/AS01E GSK	VPM1002 SII, Max Planck, VPM, TBVI (Phase 2/3)
ChAdOx1 85A/MVA85A (ID/IM/Aerosol) Univ of Oxford	ID93 + GLA-SE IDRI, Wellcome Trust, Quratis	H56:IC31 SSI, IAVI, EDCTP, Valneva	Immuvac ICMR, Cadila Pharmaceuticals
	TB/FLU-04L RIBSP	BCG Revaccination Gates Medical Research Institute (GMRI)	

Vaccine developed by
European/Central Asian
institution



Thank you!

← coming soon: overview of TB vaccine clinical development