Conference report

Meeting report: Virtual Global Forum on Tuberculosis Vaccines, 20–22 April 2021

Sara Suliman [a,b,1], Puck T. Pelzer [a,c,1], Moagi Shaku [a,1], Virginie Rozot [a,d,1], Simon C. Mendelsohn [a,d,*,1]

[a] *Stop TB Partnership Working Group on New TB Vaccines, New York, NY, USA*
[b] *Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[c] *KNCV Tuberculosis Foundation, The Hague, the Netherlands*
[d] *South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, Division of Immunology, Department of Pathology, Wernher and Beit South Building, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa*

A B S T R A C T

The Global Forum on Tuberculosis (TB) Vaccines was held virtually from 20 to 22 April 2021, marking its 20th anniversary. The Global Forum on TB Vaccines is the world's largest gathering of stakeholders striving to develop new vaccines to prevent TB. The program included more than 60 speakers in 11 scientific sessions, panel discussions, and workshops. It provided an overview of the state of the field, and an opportunity to share the latest research findings, as well as new and innovative approaches to TB vaccine research and development (R&D). This year, it was held against the backdrop of the COVID-19 pandemic and convened researchers, developers, funders, and other stakeholders remotely to discuss opportunities and challenges for TB vaccine R&D in these unprecedented times.

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1. Introduction

Tuberculosis (TB) remains a leading cause of mortality from an infectious disease, with 1.4 million deaths in 2019 [1]. After a century, Bacille Calmette-Guérin (BCG), which has limited effectiveness against TB disease, is still the only licensed TB vaccine [2]. This lies in stark contrast to over 100 vaccines for Coronavirus disease of 2019 (COVID-19), which have entered clinical trials, with more than 180 in preclinical stages of development, and at least ten authorized for emergency use [3]. The Virtual Global Forum on TB Vaccines provided an opportunity for stakeholders in TB vaccine research and development (R&D) to come together virtually to discuss the state of the field and how to advance TB vaccine R&D in the time of COVID-19. This report presents highlights from the forum, including updates on TB vaccine clinical research, novel insights and approaches to TB vaccine R&D, and advocacy, policy, access, and funding issues relating to TB vaccines.

1.1. Opening session

In his welcoming remarks, **Nick Drager** (Tuberculosis Vaccine Initiative [TBVI], The Netherlands) looked forward to an exciting conference designed to showcase accelerated development of very promising TB vaccine candidates and continued efforts to innovate and diversify the pipeline of second-generation candidates, whilst highlighting the case for investing in TB vaccine R&D as a key element in the global health agenda. **Mark Feinberg** (IAVI, USA) remarked on the tremendous global public health mobilization efforts as the world faced challenges wrought by the COVID-19 pandemic, urging TB vaccine researchers and developers to take heed of the unprecedented and rapid COVID-19 vaccine advances and accelerate development of new TB vaccine candidates. According to **Lucica Ditiu** (Stop TB Partnership, Switzerland), COVID-19 has set back a decade of progress made against TB, as 1.4 million fewer TB patients received treatment and 500,000 more deaths were recorded in 2020 than 2019 [4]. The Global Forum was opened by **Harsh Vardhan** (Union Minister of Health and Family Welfare, Science and Technology and Earth Sciences, Government of India; Chair, Stop TB Partnership Board), stating that the world must not let the COVID-19 pandemic compromise the progress made in TB, and calling upon the global community to redouble their efforts and ensure adequate funding for TB vaccine research and work towards developing a TB vaccine by 2023. **Helen Rees**

(Wits RHI, University of the Witwatersrand, South Africa) discussed the importance of leveraging research across disciplines for the greater public good, and how repurposing existing technologies, systems and infrastructure can benefit both existing diseases, including TB and HIV, and emerging infectious diseases like COVID-19. Professor Rees emphasized the importance of access, affordability, and delivery of new technologies, and the need for continuous learning and innovation to enable rapid response to future public health challenges.

Emilio Emini (Bill & Melinda Gates Foundation, USA) noted the impact that COVID-19 has had on TB services and R&D, but also recognized the opportunities that have arisen from the global response to the pandemic as we renew collective focus on TB, such as translating the novel technologies and approaches used in the development of COVID-19 vaccines to accelerate TB vaccine development. **Emily Erbelding** (NIAID Division of Microbiology and Infectious Diseases, USA) highlighted the importance of focused multi-disciplinary teams of scientists with sufficient resources working collaboratively to accelerate progress in COVID-19 research and applying it to other global public health threats, such as TB. **Michael Makanga** (European & Developing Countries Clinical Trials Partnership [EDCTP], Netherlands) introduced the new global TB vaccine roadmap, an initiative funded by EDCTP with support from WHO. He highlighted the roadmap's three mandates: To (I) diversify the vaccine pipeline, (II) accelerate vaccine development by optimizing animal models, defining correlates of vaccine efficacy, harmonizing standard protocols, and exploring innovative trial designs to study vaccine efficacy, and (III) ensure that public health impact of novel TB vaccines is increased.

2. Novel insights and approaches to TB vaccine R&D

Development of effective TB vaccines requires innovative approaches and insights into biological mechanisms that confer protection and/or lead to disease. **Michael Gerner** (University of Washington, USA) presented insights from the ultra-low dose aerosol *Mycobacterium tuberculosis* (*Mtb*) infection model in mice [5], which recapitulates human lung granuloma composition better than mice infected with a conventional high dose. Using this model coupled with multiplex confocal imaging and quantitative spatial analysis with histo-cytometry and CytoMAP, his group showed that Transforming Growth Factor β (TGF-β) signaling restricted *Mtb*-specific T cell responses in the lung parenchyma resulting in impaired *Mtb* containment in the murine granuloma [6]. However, whether decreased long-term TGF-β signaling may be associated with lung pathology during infection remains to be explored. **Hannah Gideon** (University of Pittsburgh, USA) showed the heterogeneity and immune correlates of bacterial control in TB granulomas in the non-human primate model by co-registering longitudinal PET-CT imaging, single-cell RNA-sequencing and measures of bacterial clearance. She showed that granulomas that appear late in infection were better at restricting *Mtb* growth and were characterized by higher proportion of hybrid type 1/17 T cells, cytotoxic functional programs, and stem like memory phenotype than early granulomas [7] and these findings can be leveraged for new vaccine development. **Andrea Cooper** (University of Leicester, UK) reviewed the desired immunological characteristics of a successful vaccine. She showed that blocking IL27R signaling in T cells enhanced their entry, persistence, and fitness in *Mtb*-infected lesions in murine lung parenchyma revealing that IL27R expression specifically on T cells limits protection during *Mtb* infection [8]. **Lenette Lu** (UT Southwestern, USA) presented how post-translational modifications of the constant (Fc) region of *Mtb*-specific antibodies can classify different TB disease states [9,10]. These Fc modifications can also distinguish household con-

tacts of TB cases that convert their tuberculin skin test (TST) from those that remain TST-negative, also known as "resisters" [11]. Finally, **Mustafa Diken** (BioNTech, Germany) presented the benefits of the mRNA vaccine technology used for COVID-19 [12], and how it can be tailored for TB vaccinology using additional strategies such as self-amplifying RNA molecules [13]. Overall, the session presented novel immunological mechanisms that could be incorporated to improve efficacy of candidate TB vaccines.

3. Accelerating TB vaccine research and development: Launch of a global roadmap

A special session organized by EDCTP and the Amsterdam Institute for Global Health and Development (AIGHD) launched the "Global roadmap for R&D of TB vaccines" [14], collaboratively developed by AIGHD, EDCTP, and WHO through a consultative process. **Frank Cobelens** (AIGHD, Netherlands) provided an overview of the roadmap, which defines key actionable priorities and short, medium, and long- term objectives across the R&D continuum to speed up the development and deployment of new TB vaccines that will be affordable and accessible in low-to-middle income countries (LMICs). **Willem Hanekom** (Africa Health Research Institute, South Africa) stressed the need to develop an implementation strategy for the roadmap and demonstrating how TB research can advance research in other diseases. He also emphasized the importance of learning from the COVID-19 vaccine experience through increased collaboration and early communication of results. **Videlis Nduba** (Kenya Medical Research Institute [KEMRI], Kenya), **Ann Ginsberg** (Bill & Melinda Gates Foundation, USA), **Birgitte Giersing** (WHO, Switzerland), **Rajinder Suri** (Developing Countries Vaccine Manufacturers Network, Switzerland) and **Agnes Saint-Raymond** (European Medicines Agency, EU) discussed how the roadmap could be used by different stakeholder groups and implementation strategies to realize the goals set out in the roadmap from the perspectives of the research community, funders, policymakers, manufacturers, and regulatory agencies.

4. Clinical research for TB vaccines

Despite slow progress since BCG vaccination was first introduced in humans in 1921, there have been some exciting clinical trial results in recent years. BCG revaccination was found to reduce sustained QuantiFERON conversion in *Mtb*-uninfected adolescents by 45.4% (95% confidence interval [CI], 6.4–68.1) in a prevention of infection trial first reported in 2018, providing hope for a promising new application of an old vaccine [15]. In 2019, the phase 2b M72/AS01E vaccine trial demonstrated 49.7% (95% CI, 2.1–74.2) protection against TB disease in IFN-γ release assay (IGRA)-positive adults [16,17]. **Ann Ginsberg** highlighted the positive impact of these results on the TB vaccine field, providing convincing evidence that improved TB vaccines are within reach. Even though the number of new candidates has not drastically increased in recent years, the TB vaccine pipeline has evolved with candidates progressing to later trial phases [18]. Novel trial designs, such as prevention of *Mtb* infection and prevention of TB recurrence following completion of treatment, have also emerged, but prevention of disease trials evaluate the most impactful endpoint and remain the gold standard. This session provided updates on other advanced key TB vaccine candidates in the pipeline.

Alexander Schmidt (Bill & Melinda Gates Medical Research Institute, USA) presented recent developments and plans for the investigational M72/AS01E vaccine. Together with academic stakeholders, efforts are being directed at identifying candidate correlates of protection from the previous phase 2b study [17] that could be validated in the planned clinical endpoint phase 3 trial.

An observer-blinded, randomized, placebo-controlled safety and immunogenicity phase 2 trial to support inclusion of people living with HIV in Phase 3 is currently ongoing across six sites in South Africa [NCT04556981]. A large clinical endpoint trial in high TB incidence settings is needed to confirm vaccine efficacy in both IGRA-positive and IGRA-negative participants in diverse communities and geographic settings. To prepare for this phase 3 trial, a large epidemiological study enrolling 8,000 participants at 50 sites in Africa, Asia, and South America will be conducted to build capacity for phase 3 trials and determine IGRA-positivity by age at site level. To accelerate potential public health impact for this investigational vaccine, it is important that antigen manufacturing is scaled up and refined prior to phase 3, evidence needs for policy recommendations defined, phase 3 design agreed upon by stakeholders and regulators, and financing discussed posthaste.

C. Fordham von Reyn (Dartmouth Geisel School of Medicine, USA) presented results from the phase 2b 1:1 randomized, placebo controlled trial of DAR-901 [NCT02712424], an inactivated *M. obuense* (non-tuberculous mycobacterium), for prevention of infection in 650 BCG vaccinated, IGRA-negative Tanzanian adolescents [19]. Participants were followed over three years with five IGRA tests, and the primary endpoint was defined as IGRA conversion. The vaccine was safe and well tolerated, but did not prevent IGRA conversion (a marker for infection), despite evidence that the original SRL-172 strain of the vaccine prevented TB disease [NCT00052195] [20]. A possible explanation for these results might be the low vaccine dose. Hence, a dose escalation trial is planned for 2022 before the expected start of a phase 3 study trial aiming at assessing prevention of TB disease in 2023.

Another vaccine in advanced stages of clinical development is MTBVAC, a live attenuated *Mtb* strain hypothesized to provide better protection against TB infection by inducing a broader *Mtb*-specific immune response than BCG [21]. **Ingrid Murillo Jelsbak** (Biofabri, Zendal Group, Spain) presented the progress of MTBVAC, from a phase 1a trial in healthy European adults [NCT02013245] to a phase 1b trial in South African healthy newborns to assess the safety and immunogenicity of three escalating dose levels of MTBVAC [NCT02729571]. The phase 1b dose escalation trial showed that a single dose of MTBVAC induced substantial cytokine (IFN-γ, IL-2, or TNF-α) -expressing antigen-specific CD4+ T cell responses that persisted for one year. Parallel randomized controlled dose-defining trials of the safety and immunogenicity of MTBVAC in healthy HIV-unexposed, South African newborns (phase 2a) [NCT03536117] and adults (phase 1b/2a) [NCT02933281] are ongoing. A phase 3 efficacy study in nearly 7,000 newborns across six sites in Africa is expected to follow thereafter. Recruitment for these two clinical trials was delayed due to the COVID-19 pandemic with knock-on effects for the phase 3 study in African newborns, which was due to start in 2021, but is now planned to start enrolling in February 2022 and complete follow-up by 2028.

The H56:IC31 subunit protein vaccine (Ag85B, ESAT-6, and Rv2660c in IC31 adjuvant) has been tested in five safety and immunogenicity trials in *Mtb*-exposed and -unexposed adolescent and adult populations [22,23,24], as well as at different time points after TB treatment initiation [NCT03512249]. H56:IC31 has been shown to be safe and well tolerated, inducing a long-lived polyfunctional CD4+ T cell response over a year post vaccination. **Álvaro Borges** (Staten Serum Institut, Denmark) presented prevention of recurrence trials. While demonstration of efficacy against TB disease requires large numbers of participants and long duration of follow-up, targeting individuals on TB treatment, with up to 8% risk of TB recurrence within one year following treatment completion, allows for a more cost-effective trial design with smaller sample size and shorter follow-up. An ongoing phase 2 randomized, placebo-controlled trial to evaluate the safety and efficacy of H56:IC31 in reducing the rate of TB recurrence in HIV-uninfected adults successfully treated for drug-susceptible pulmonary TB is currently enrolling 900 participants in South Africa and Tanzania [NCT03512249]. Mycobacterial genome sequencing will be performed to identify if TB recurrence is due to the original organisms (i.e. relapse) or new infection. The results of the trial are anticipated in 2024.

Sajjad Desai (Serum Institute of India, India) provided an update of trial results for VPM1002, a recombinant BCG vaccine designed to enhance immune activation and cross-presentation to CD8+ T cells [25]. Thus far, the vaccine has been shown to be safe, less reactogenic than BCG, and immunogenic after a single dose in adults with and without previous BCG vaccination, as well as in HIV-unexposed newborn infants [26,27]. A randomized, single administration phase 3 trial is currently enrolling 6,940 newborn infants in five African countries with the primary objective of showing non-inferiority of VPM1002 to BCG vaccination in preventing TB infection [NCT04351685]. An ongoing phase 2/3 trial in 2,000 adult volunteers in India and Bangladesh is evaluating whether VPM1002 prevents recurrence of TB after successful treatment completion within one year of follow-up [NCT03152903]. Another household contact trial in India is examining whether VPM1002 or *Mycobacterium indicus pranii* (Immuvac) [28] prevents disease in healthy household contacts of TB patients [CTRI/2019/01/017026]. Thus far, no safety concerns are reported. The efficacy of VPM1002 in reducing severe respiratory infections, the incidence or severity of SARS-CoV-2 infection, and hospital admissions due to COVID-19 is currently being assessed in two ongoing phase 3 trials in elderly individuals in Germany [NCT04435379] and in health care workers in India [CTRI/2020/04/024749]. VPM1002 will also be evaluated for safety and efficacy in a phase 3 trial of prevention of *Mtb* infection in health care workers in India, planned to start in late 2021. Similar to BCG, preliminary data also support that VPM1002 could be effective in treating bladder cancer [NCT02371447].

5. Advocacy for TB vaccines

This session highlighted the importance of collaboration amongst global health stakeholders to respond to public health threats, exemplified by the response to COVID-19. Session chairs **Rhea Lobo** (Bolo Didi, Denmark) and **Uvistra Naidoo** (Red Cross Children's Hospital, South Africa) called on TB researchers to be vocal advocates for TB vaccine R&D. The goal of this session was to help provide some of the tools they may need. Reflecting on the lessons learned from the HIV/AIDS advocacy community in driving development of new antiretroviral drugs, **David Lewinsohn** (Stop TB Partnership Working Group on New TB Vaccines [WGNV], Oregon Health & Science University, USA) suggested that TB vaccine researchers should also advocate for the development of new tools to combat TB. **Nandita Venkatesan** (University of Oxford, England) emphasized the need for researchers to acquire advocacy skills to be able to champion new policy and funding to governments. She suggested that one key strategy is to refute the myth that TB is a disease of the past and highlight the existing desperate need for a new TB vaccine. **Evaline Kibuchi** (Global TB Caucus African Region, Stop TB Partnership, Kenya) recommended that sensitizing governments and communities to new TB vaccines should start immediately to prepare for their implementation. **Agustin Martin** (Deutsche Stiftung Weltbevölkerung, Germany) outlined an approach to preparing advocacy campaigns: (I) Identifying priorities and resources needed (e.g. policies, laws, and budgets), (II) mapping and engaging with key stakeholders, and (III) understanding decision making processes. **Rosa Herrera** (Global TB CAB, TB Proof, Mexico) shared the importance of advocating

to affected communities and civil society organizations to increase knowledge and interest in TB vaccine R&D, emphasizing the important role of TB survivors, and the need to diversify advocacy approaches. **Anastasia Koch** and **Cheleka Mpande** (Eh!woza, University of Cape Town, South Africa) encouraged TB scientists to apply their academic research skills (communication, collaboration, grant writing, critical thinking, and problem solving) to TB advocacy. Community engagement such as the Eh!woza initiative enables the translation of scientific findings into meaningful benefits for affected communities, which helps to build trust. **Laia Ruiz Mingote** (Communications Consultant/Advocate, Spain) shared key principles for better communication, including providing simple packets of information and clear, short, and direct messages. Finally, **Rabita Aziz** (Infectious Diseases Society of America, USA) introduced tools to increase the reach and effectiveness of TB-scientist advocates, which includes preparing policy briefs, meetings with legislators, testifying in front of lawmakers, starting petitions, public awareness campaigns through demonstrations or media advertisements, and a social media presence.

6. BCG 100 years later

On July 18th, 2021, BCG will celebrate its 100th birthday. Although over 100 million doses are administered annually [29], **Helen McShane** (The Jenner Institute, University of Oxford, UK) highlighted that there are still large gaps in our knowledge about how BCG works and why it has limited efficacy. Recent studies have shown that BCG protects against other non-mycobacterial infections in Ugandan neonates [30]. **Simone Joosten** (Leiden University Medical Center, Netherlands) expounded on the concept of BCG-induced trained immunity, which is a potential mechanism behind this non-specific protection [31,32], where BCG induces epigenetic changes in innate cells that are associated with protection against heterologous infections including experimental viral infections [33]. It has been proposed that "training" of long-lived hematopoietic stem cells results in altered macrophages that provide better protection against *Mtb* infection than naïve macrophages [34]. **Nigel Curtis** (Murdoch Children's Research Institute and University of Melbourne, Australia) elaborated on the non-specific (or 'off-target') effects of BCG, suggesting that vaccination could offer protection against COVID-19 [35]. The BRACE trial [NCT04327206], amongst many others, is currently investigating this hypothesis. The non-specific protective effects of BCG, induced by trained immunity [36] are mostly seen in those recently vaccinated; BCG given many years prior is unlikely to be beneficial against COVID-19 [37].

Gavin Churchyard (Aurum Institute, South Africa) discussed prevention of infection and prevention of disease endpoints for TB vaccine trials, and their policy implications. TB vaccines intended for *Mtb*-uninfected individuals are classified as pre-exposure vaccines, and vaccines for *Mtb*-infected individuals, those with TB disease, or following treatment are deemed post-exposure vaccines. BCG can prevent *Mtb* infection and TB disease if administered pre-infection, while it provides limited protection against disease in infected persons [38]. Efficacy can also vary by non-tuberculous mycobacteria (NTM) exposure and latitude [39,40]. Earlier studies using tuberculin skin testing for *Mtb* sensitization were unable to differentiate infection with *Mtb* from BCG or NTMs. IGRA, which can be used to distinguish *Mtb* from NTM infection, and sustained from cleared infection, provides more evidence for BCG protection against *Mtb* infection [15,41]. Pre-exposure BCG vaccination of adolescents and adults may be a cost-effective strategy to curb transmission, reduce the reservoir of *Mtb* infection, and prevent TB disease.

Richard White (London School of Hygiene and Tropical Medicine, UK) provided mathematical modelling estimates of the impact of COVID-19 disruptions on global BCG coverage, and on pediatric TB mortality. Through epidemiological models, he demonstrated that delayed or missed BCG vaccination is very likely to increase the future burden of pediatric TB mortality [47]. Global action is urgently required to support countries in large and rapid catch-up campaigns, and resuming BCG vaccination programs as soon as possible, to minimize excess deaths.

7. Leveraging COVID-19 to advance TB vaccine R&D

It has taken an unprecedented effort with colossal investment and collaboration from governmental, private-sector, and academic institutions drawing on extraordinary resources to develop, test, and roll out multiple COVID-19 vaccine candidates within a year. Session co-chairs **Gerald Voss** (TBVI, Belgium) and **Julio Croda** (Oswaldo Cruz Foundation; Federal University of Mato Grosso do Sul, Brazil) opened this session by remarking on the importance of learning from this rapid progress and exploring how these advances could be exploited for TB vaccine R&D, which was a major theme at the Virtual Global Forum and the subject of this panel discussion.

In recent times, the importance of leveraging existing delivery platforms such as mRNA [42] and viral-vectored [43] vaccines to tackle emerging infectious diseases for accelerated vaccine development has become self-evident, with Ebola vaccines reaching market within six years [44], and COVID-19 vaccines within a year. **Valerie Oriol Mathieu** (Janssen Infectious Diseases and Vaccines, Netherlands) attributed the success of this platform-based approach to the accumulation of data across a spectrum of infectious diseases through more than a decade of development. The pre-existing production capacity and supply chains have made rapid, at-scale manufacturing possible.

Another factor contributing to the rapid licensure of COVID-19 vaccines was utilization of existing clinical trial infrastructures. **Jim Kublin** (HIV Vaccine Trials Network [HVTN]; Fred Hutchinson Cancer Research Center, USA) described how the COVID-19 Prevention Network, established on the foundations of HVTN, was able to leverage resources and expertise of over 200 trial sites, with years of accumulated trial experience and local community engagement structures already in-place, to rapidly pivot and support late-phase COVID-19 vaccine efficacy trials. The new COVID-19 vaccine delivery platforms with expanded manufacturing capabilities, and coordinated trial networks, could be harnessed to accelerate TB vaccine development, testing, and licensure.

COVID-19 has presented innumerable obstacles to conducting quality laboratory research: from lockdowns to shortages of reagents, and long consumable lead times. **Erica Andersen-Nissen** (Cape Town HVTN Immunology Laboratory, South Africa) argued that despite these challenges, the pace of scientific progress during the epidemic has accelerated. This can be attributed to the culture of openness in which research has been conducted: increased goodwill and collaboration, and sharing of knowledge, experience, data, and samples. This is most evident in the increase in open access and pre-print publications, as well as public virtual scientific meetings, which has allowed rapid sharing of cutting-edge research. **Andersen-Nissen** emphasized that the pandemic has provided leadership opportunities for early career investigators that would not have otherwise been possible.

Despite the rapid development of COVID-19 vaccines, access and implementation has been challenging in many parts of the world. **Gordon Dougan** (Wellcome Trust, UK) highlighted the lack of manufacturing, supply chain, and research capacity (specifically the lack of young investigators) in LMICs, which requires substan-

tial investment. The Wellcome Trust has recently updated its strategy, focusing on infectious diseases, specifically those that have potential to escape antimicrobial therapy, such as TB. They are currently assessing how to invest in a TB vaccine program. However, he emphasized that new large-scale platforms for TB vaccine delivery will need to be affordable and accessible in settings with limited resources.

Hassan Mahomed (Western Cape Department of Health and Stellenbosch University, South Africa) explained that deployment of COVID-19 vaccines has proved challenging in many LMICs due to a paucity of adult immunization programs—an important consideration for TB vaccines. During the pandemic, trial design and reporting have had a strong influence on policy and attitudes. Therefore, vaccine roll-out needs to be considered during the design phase to provide clear data for policy makers. Misinformation, particularly on social media platforms, has further obfuscated the mixed messages promulgated by politicians, fueling vaccine hesitancy. Vaccine hesitancy needs to be carefully addressed through public engagement before we have a TB vaccine ready for distribution.

Nicole Lurie (Coalition for Epidemic Preparedness Innovations, USA) set an ambitious target of developing a vaccine within 100 days for future pandemics. To achieve this, every section of the vaccine pipeline needs to be fine-tuned and pre-deployed: the delivery systems need to be refined (e.g. improve temperature stability of mRNA vaccines), manufacturing capacity bolstered, fast-track regulatory pathways developed, young investigators cultivated, and centers of research excellence with broader focus on applying platforms across diverse infectious diseases developed.

8. Policy and access issues relating to TB vaccines

A rapid roll-out of new TB vaccines will require political commitment, funding, mobilization of resources, and multi-sectoral collaboration. **Stephanie Seydoux** (French Ambassador for Global Health, France) called for a strong common will for achieving the WHO Sustainable Development Goals and deployment of multilateral mechanisms in order to overcome practical and legal obstacles hindering TB vaccine R&D. Similar mechanisms applied to COVID-19 could be used for TB, including leveraging public research funding, sharing data and knowledge, promoting technology transfer, supporting and strengthening health systems, increasing multilateral funding, and promoting vaccine equity. Session co-chair **Shelly Malhotra** (IAVI, USA) noted that introduction of new vaccines has historically been significantly delayed in countries where the need is the greatest, thus widening global disparities in public health. Panelist **Luciana Leite** (Instituto Butantan, Brazil) suggested that we should learn from the COVID-19 vaccine trial innovations, including expediting regulatory pathways for vaccine development by performing different phases of TB vaccine trials in parallel. **Cherise Scott** (Unitaid, Switzerland) commented on the RTS,S malaria vaccine experience and how this can inform TB vaccine roll-out, and the importance of harnessing lessons from pilots to inform scaled-up vaccine delivery. **Evaline Kibuchi** (Stop TB Partnership, Kenya) addressed obstacles to vaccine roll-out in LMICs; the lack of manufacturing capacity in LMICs for local production hinders rapid distribution of TB vaccines. Access to funding also remains a major barrier, Kibuchi suggested that governments should be involved in R&D early in the development process. Another hurdle is the low demand for vaccines in affected communities. Dr. **Jeremiah Chakaya** (Liverpool School of Tropical Medicine, UK) highlighted the need to prepare delivery pathways for immunization in adolescents and adults, noting the potential to leverage existing service delivery channels.

9. Impact of TB preventive treatment as standard of care on TB vaccine development

Updated guidelines for TB preventive treatment (TPT) were issued by the WHO in 2020 providing recommendations for individuals at high risk of infection. This session, organized by FHI Clinical, explored the impact of widespread TPT use on TB vaccine development. **Ghiorghis Belai** (FHI Clinical, Kenya) highlighted the importance of identifying populations at high risk of *Mtb* infection that might be targeted for TPT, as this would affect vaccine efficacy assessment. **Carole D. Mitnick** (Harvard Medical School, USA) and **Ben Woods** (FHI Clinical, USA) discussed the use of TPT as an inclusion or exclusion criterion for TB vaccine trial design and how this would impact trial results. Measured vaccine efficacy would likely be reduced by the use of TPT in trial participants. This will require increased trial sample sizes and could affect vaccine policy development. **Falgunee K. Parekh** (EpiPointe, USA) recommended that ongoing TB surveillance, particularly in high TB incidence countries, is required to track changes in TB prevalence as a result of TPT roll-out. Parekh also recommended leveraging TPT contact tracing efforts to identify high risk individuals for TB vaccine trial participation.

10. Closing the financing gap for TB vaccine R&D

In addition to the scientific challenges of developing new TB vaccines, the lack of sufficient funding is a major barrier to progress. In comparison to the $28 billion pledged to date for COVID-19 diagnostics, therapeutics, and vaccine R&D [45], only $116 million was invested in TB vaccines in 2019 [46], despite TB remaining a leading infectious cause of death globally over many decades [1]. Session co-chair **Mike Frick** (Treatment Action Group, USA) reflected that this continued paucity of TB research funding is alarming given the United Nations (UN) member states' pledge of $2 billion annual TB research funding at the 2018 United Nations High-Level Meeting on TB. This highlighted the unmet commitments by the UN member states to end TB. Session co-chair **Glaudina Loots** (Department of Science and Innovation, South Africa), reiterated the need for global public health organizations, including the WHO and vaccine developers to work together to produce a TB vaccine in a short time, as exemplified by the COVID-19 vaccine effort. **Lucica Ditiu** explained how the continued lack of TB R&D funding is emblematic of the inequalities of TB disease, which predominantly affects LMICs and not high-income countries. She recommended that TB advocates need to be united and vocal. Furthermore, she advised that there needs to be significant financial investment in TB vaccine advocacy. **Manjula Singh** (Indian Council on Medical Research, India) discussed how TB vaccine researchers need to come together to develop a research agenda and a detailed plan of action to present to governments in high-TB burden countries for sanction of budgets for TB vaccine R&D. **Nick Menzies** (Harvard University, USA) highlighted the importance of adequately communicating the urgency, and enumerating the global health and economic value propositions, of new TB vaccines. **Shiva Dustdar** (European Investment Bank) encouraged bolder action for development of new TB vaccines, commenting on the lack of clearly articulated narratives advocating for TB vaccines, such as exemplified by the COVID-19 or HIV pandemics.

Closing Session

David Lewinsohn (WGNV, USA) opened the session by thanking the speakers, chairs, participants, Organizing Committee, Planning Committee and sponsors for their contributions to the Virtual Global Forum. **Eric Goosby** (UCSF-Gladstone Centre for AIDS Research and former UN Secretary-General's Special Envoy for Tuberculosis, USA), remarked on the barriers COVID-19 has pre-

sented to progress in meeting global health needs and highlighted that TB advocates must clearly articulate the urgent need for a TB vaccine to governments and funding organizations. **Soumya Swaminathan** (WHO, Switzerland) reflected on the role of the WHO to help facilitate TB vaccine R&D to achieve the 2030 end TB targets of 90% reduction in TB related deaths, 80% reduction in TB incidence, and eliminating all catastrophic disease burden and expenses caused by TB. **Olivier Véran** (Minister of Solidarity and Health, France) closed the meeting, acknowledging the importance of new vaccines in global efforts to end TB and that sufficient investment in research will be essential to achieving results. He recognized the commitment of the TB vaccine R&D community to developing better vaccines, and reiterated France's commitment to the fight against TB and to support for R&D of new TB vaccines as a global public good. Mr. Véran expressed France's honor to host the 6th Global Forum on TB Vaccines in Toulouse from 22 to 24 February 2022 under the high patronage of President Emmanuel Macron.

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