Meeting Report

Meeting report: 5th Global Forum on TB Vaccines, 20–23 February 2018, New Delhi India

ABSTRACT

The 5th Global Forum on TB Vaccines was held in New Delhi, India from 20 to 23 February 2018. This was the largest Global Forum on TB Vaccines to date with nearly 350 participants from more than 30 countries. The program included over 60 speakers in 12 special, plenary and breakout sessions and 72 posters. This Global Forum brought a great sense of momentum and excitement to the field. New vaccines are in clinical trials, new routes of delivery are being tested, novel assays and biomarker signatures are being developed, and the results from the first prevention of infection clinical trial with the H4:IC31 vaccine candidate and BCG revaccination were presented. Speakers and participants acknowledged the significant challenges that the TB vaccine R&D field continues to face - including limited funding, and the need for novel effective vaccine candidates and tools such as improved diagnostics and biomarkers to accurately predict protective efficacy. New solutions and approaches to address these challenges were discussed. The following report presents highlights from talks presented at this Global Forum. A full program, abstract book and presentations (where publicly available) from the Forum may be found at tbvaccinesforum.org.

1. Why we need better TB vaccines

In the opening session, Soumya Swaminathan (World Health Organisation, Geneva) noted the commitment and momentum resulting from the 2015 United Nations Sustainable Development Goals (SDGs), the End TB strategy that set targets to reduce the incidence rate of TB by 80% and TB deaths by 90% by 2030 compared to the 2015 figures, and the 2017 WHO Global Ministerial Conference in Moscow. However the burden of TB remains huge, with tuberculosis the 9th leading cause of death globally, and the top infectious disease killer, and an estimated 1.7 billion, 23% of the world’s population, estimated to be infected with Mycobacterium tuberculosis (Mt) [1]. In 2016, approximately 10.4 million new cases of tuberculosis disease (TB) occurred worldwide, of which 90% occurred in adults [2]. The only licensed vaccine to prevent TB, Bacille Calmette Guérin (BCG) is moderately effective in preventing TB in infants and young children, but is unreliable in preventing TB in adolescents and adults and has had no apparent impact on the global TB epidemic. Speakers reiterated forcefully that new, more effective TB vaccines, along with shorter treatment regimens and more accurate diagnostics, will be essential to reach the ambitious targets set forth in the SDGs and the End TB Strategy [3].

The general view at the Forum was that development of a new TB vaccine that is better than BCG is possible and imperative to meet the UN goals. It has been an oft-stated maxim in the field that infection with Mt fails to induce protection, yet 90% of latently infected individuals remain disease-free [4,5]. The results from the H4/BCG revaccination trial (see below) have renewed interest in the effects of BCG vaccination. When BCG gives protective efficacy against mortality, this can persist for far longer than previously thought [6–9], BCG confers non-specific protective efficacy via trained immunity [10], and exposure to non-tuberculous mycobacteria may influence disease and vaccine efficacy [11–13]. There is also increased interest in individuals who resist conversion to positive in an interferon-gamma release assay, or who convert and subsequently revert to negative [14–18].

Barry Bloom (Harvard School of Public Health, USA) gave the introductory keynote address entitled “Why we need a vaccine to control TB and what we need to learn to develop an effective vaccine”. He noted the rationale for vaccines in controlling TB in LMIC eg. patients need to see multiple providers before diagnosis is made, only 40% completion of treatment and non-WHO standard treatments provided in the private sector. He reviewed older studies indicating that healthy nurses who were tuberculin positive and heavily exposed to TB were over 90% protected against disease, and BCG was half as effective as latent TB. He noted that in the South India BCG trial of 260,000 people, which showed no protection against TB in any age group, a subset analysis of those who were skin test negative for both human and non-tuberculous mycobacteria showed significant protection, indicating the need for new vaccines to protect beyond prior exposure to antigens to protect against disease. While a great deal has been learned about immunology of TB from animal studies, for example the essentiality of both CD4 and CD8 cells for protection, multiple immune mechanisms have been found to exist in humans which differ from those in mouse and even non-human primate (NHP) models. It is critically important to identify immune responses that correlate with protection from infection and disease in humans. Probably the best way to do this will be to search for molecular markers of protection in studies in NHPs and from bio-banked samples from human vaccine trials. It is likely that different vaccine concepts, both live attenuated and subunit vaccines will contribute to engendering and understanding protection in humans.

2. Modelling target indications and populations for new TB vaccines

Richard White and Rebecca Harris (London School of Hygiene and Tropical Medicine, UK) presented modelling data on the impacts of potential indications and target populations, demonstrating that...
vaccine impact will vary based on the setting, prevalence of infection, and manifestation (e.g., primary vs reactivation disease). Their modelling shows that in most low and middle-income countries (LMICs) and China, prevention of disease (POD) vaccines may have a faster and greater impact than vaccines developed for prevention of infection (POI), before 2050 [19], [Harris et al. 2018 in press]. In more transmission-driven epidemics (eg, India), efficacy for POI or POD could substantially impact the TB epidemic, assuming that POI leads to POD in those who would normally advance to disease in the absence of vaccination. In aging, reactivation-driven epidemics like in China, post-infection vaccines may have the greatest impact [19].

Vaccines targeted to adolescent/adult populations in LMICs may have a greater and more rapid impact than neonatal vaccination, before 2050, and may be cost effective even at a vaccine efficacy (VE) of 20% for 5 years duration of protection. Furthermore, an appropriate vaccine that targets adults and adolescents may be as or more effective in reducing TB incidence in children below 4 years of age than a childhood vaccine, as preventing TB in adolescents and adults, the main transmitters of TB, would prevent transmission to infants and young children.

3. Vaccine strategies to tackle drug resistant TB

A vaccine to prevent drug-resistant as well as drug-sensitive TB is also a priority. TB accounts for more than one in four of the antimicrobial resistance (AMR) fatalities per year. Although 56 million TB cases have been successfully treated in the last 15 years, only about half of the multi-drug-resistant cases in India, Pakistan and the Russian Federation have a successful treatment outcome. In South Africa, from 2011 to 2014, 74% of XDR-TB patients were deemed programmatically incurable and > 50% of these were discharged home, further spreading the XDR pathogen [20]. Transmission of MDR and XDR strains is a public health problem, and factors such as (i) inadequate treatment, (ii) early discharge of incurable TB patients from hospitals, and (iii) poor adherence to timely treatment due to increased cost and side effects are likely to increase the MDR/XDR-TB burden in the coming years.

Gavin Churchyard (Aurum Institute, South Africa) presented possible vaccination strategies to control the rising burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. Since the molecular changes that result in drug resistance are highly unlikely to alter antigenic proteins, TB vaccine candidates that can target drug susceptible pathogens should be equally efficient against drug resistant organisms. Therapeutic vaccines also have the potential to shorten treatment, reduce treatment failure and ultimately prevent recurrence. Rutili (a vaccine containing cell wall fragments of Mtbc) and M. vaccae have shown some clinical promise, but studies to date have been small and of variable quality [21]. New candidates such as ID93 + GLA-SE [22] and HVJ Envelope/Hsp65 DNA + IL-12 DNA with either Granulysin or Ksp37 [23,24] have shown preclinical therapeutic efficacy, while an Ag85A DNA vaccine gave mixed results [25-27]. Therapeutic value has also been explored for the Ag85B DNA vaccine [28]. Overall, MDR-TB patients may be an ideal group in which to evaluate therapeutic vaccine candidates due to the favourable benefit-risk balance.

4. Novel approaches and strategies to maximize the probability of success

Vaccine development is risky and expensive, and resources are limited. Georges Thiry (Aeras-TBVI Joint Working Group on Stage Gates, France) provided an overview of ‘stage gate criteria’ that have been developed to help promising TB vaccine candidates to advance through the stages of TB vaccine development. These stage gates are part of a portfolio management process intended to reduce risk, increase the overall probability of success, and direct limited resources toward the most promising candidates. Several strategies and approaches are being undertaken to minimize cost and accelerate development of potential candidates. Adaptive trial designs, in combination with other new tools, may act as a proof-of-concept strategy and down-selection tool to triage prevention of disease (POD) vaccine candidates at an early stage, before large, long and expensive efficacy trials are initiated. Several trials, such as the VPM1002 trial in India, the H56:IC31 trial in South Africa and the ID93 + GLA-SE trial in South Africa, are testing the ability of vaccines to prevent recurrent TB disease (POR) in TB patients who have successfully completed treatment for active TB. Still others, including H4:IC31 and DAR-901 are being tested in trials to evaluate whether they can prevent infection (POI) or established latent TB infection (see 3.1 TB vaccines in clinical development).

More work is required to provide improved animal models for down-selection of vaccine candidates and parallel challenge studies, including an urgent need for a human challenge model. So far, every potential TB vaccine candidate has been tested in animal models before progression to humans, but it is unclear whether the currently available preclinical models predict efficacy in humans. A safe human challenge model might greatly accelerate the clinical testing of new TB vaccines, but while an auxotroph might elicit poor immune responses, a persistent strain might be too dangerous to test. To this end, Eric Rubin (Harvard T. H. Chan School of Public Health, USA) and colleagues are exploring ways to modify potential vaccine candidates with (i) inducible killer switches for self-destruction, (ii) requirement of non-canonical amino acids for growth/survival, and (iii) addiction to specific antibiotic(s). Their novel M. smegmatis and tubercumid candidates expressing volatiles such as methyl salicylate and 2-aminoacetophenone might aid in quantitating vaccine presence in the human lung. These approaches will be tested soon in NHPs.

Ann Ginsberg (Aeras, USA) discussed potential options to enrich cohorts for smaller, quicker and more efficient TB vaccine efficacy trials. Phase 3 Prevention of TB Disease efficacy trials could readily require > 10,000 participants to be enrolled with long follow-up periods to obtain a sufficient number of TB cases to power statistical comparisons. While groups such as miners, prisoners, patients with diabetes and people living with HIV are at higher risk for TB disease, and therefore targeted enrolment of such individuals could reduce study sizes, these cohorts represent ethical and/or immunological challenges. In a very feasible approach to reducing sample size and thereby costs, the current M72 Phase IIb study (TB-018) has enrolled only QFT-positive adults to reduce study size, with 3573 participants to be followed for 3 years. Other potentially useful approaches include the preferential enrolment of healthcare workers [29-31] or household contacts of active TB patients [32,33], who are at significantly higher risk of developing disease.

Sriram Selvaraju (National Institute for Research in Tuberculosis, India) reported that in this Indian setting, excluding co-incident cases diagnosed in the first month after recruitment, 16/1385 healthy household contacts developed TB disease, with most diagnosed in the first 6–12 months of follow-up. Medical and nursing trainees in Indian hospitals are also at high risk of developing TB. Aarti Avinash Kinikar (Bryamjee Jeejeebhay Government Medical College, Pune, India) showed that medical residents had a relative risk of infection of 2 and that over one third of trainees developing incident TB reported TB exposure within the hospital setting; thus this group would really benefit from a preventive TB vaccine.

5. Clinical development of new TB vaccines

5.1. TB vaccines in clinical development

Ann Ginsberg (Aeras, USA), provided an overview of TB vaccines in clinical development, noting that we stand at a critical juncture in TB vaccine development. At the time of the 5th Global Forum, there were 13 candidates in the clinical vaccine development pipeline (see Fig. 1), including the M72/AS01e candidate from GlaxoSmithKline (GSK) for
which efficacy results from the multinational Phase Ib POD study are expected in mid-2018 and five additional vaccine candidates whose developers have recently reported or are expected to report efficacy results in POD, POR or POI trials in the next two to three years (H4:IC31, BCG revaccination, VPM1002, M. vaccae and DAR-901). Yet there is a relative lack of diversity in the pipeline with respect to types of immune responses being generated by design, and future vaccine candidates may require new antigens, new modes of delivery or different hypothesized mechanisms of immune protection.

Mark Hatherill (South African Tuberculosis Vaccine Initiative (SATVI), South Africa) presented exciting efficacy results on the first POI study, which took place in South Africa, sponsored by Aeras (NCT02075203). Nine-hundred and ninety QFT-negative adolescents who had undergone neonatal BCG vaccination were enrolled and randomised equally into each of three study arms and received the H4:IC31 candidate vaccine, BCG revaccination or saline. The research team showed that BCG revaccination, and to a lesser extent the H4:IC31 subunit vaccine, prevented sustained conversion of the Interferon-Gamma Release Assay (IGRA) (positive being defined as > 0.35 IU/ml of IFNγ in the QuantiFERON-TB (QFT) Gold Test sustained for at least 6 months), compared to saline placebo administration to QFT-negative adolescents [34]. The team demonstrated that BCG provided 45.4% vaccine efficacy (95% confidence interval 6.4–68.1), and H4:IC31 provided 30.5% vaccine efficacy (80% confidence interval 3.0–50.2) with no statistical significance at the 95% confidence interval level [34]. This finding is a momentous achievement for the field and opens the doors for future studies of correlates of protection from Mtb infection.

Sustained QFT-conversion was the secondary endpoint of this study, whereas there was not statistically significant efficacy against the primary endpoint of initial QFT-conversion. The authors observed a number of QFT-converters who initially converted but then later reverted, highlighting the “zone of uncertainty” regarding repeat measures of QFT values between 0.2 and 0.75 IU/ml as presented by Elisa Nemes (SATVI, South Africa) [34]. This trial highlights the importance of standardising laboratory assays and storing samples from all vaccine clinical efficacy trials for future possible correlates research. These encouraging results now need to be repeated in other populations and demographic settings. First results from another POI study, using DAR-901, are expected later in Q4 2019 [35] (see below).

Prasad Kulkarni (Serum Institute of India, India) presented progress with VPM1002, a recombinant BCG designed to be both safer and more immunogenic than parental BCG, which is being tested in a Phase III post-exposure study in India to prevent recurrent TB disease in adults who have completed successful TB treatment (NCT03152903). VPM1002 is also being progressed to a Phase III prime study in HIV-negative and -positive infants in Africa (NCT02391415) [36]. These trials build on successful Phase I trials in Germany and South Africa and a Phase IIa trial and Phase II trial in newborn infants in South Africa [37,38]. Kavita Singh (Multi Vaccines Development Program, India) discussed the potential of TB vaccines to prevent disease in the healthy household contacts of TB patients. A Phase III trial of VPM1002 (single vaccination) and heat-killed Mycobacterium indicus pranii (MIP; two vaccinations four weeks apart) compared to placebo is being planned, which would have 4000 participants per arm. Incident cases will be captured between 2 and 38 months after screening, and immunogenicity assessed in some of the participants. The MIP vaccine was safe when used as a therapeutic vaccine in combination with drug treatment in sputum-smear positive pulmonary TB patients [39].

Pere-Joan Cardona (Institut d’Investigació en Ciències de la Salut German Trias i Pujol, Spain) presented data on the development pathway of oral delivery of M. manresensis, a water-borne mycobacterium related to M. fortuitum [40], to prevent TB disease. The underlying hypothesis is that a PPD-specific regulatory T cell response reduces IL-17 production to limit neutrophil infiltration into the lungs, preventing the immunopathology associated with active TB disease. A Phase I study has demonstrated an acceptable safety profile and induction of an antigen-specific regulatory T cell profile in adults [41]. The candidate, classified as a probiotic food supplement, is now being tested in Phase II efficacy studies to prevent active TB disease in adults

Global Clinical Pipeline

![Global Clinical Pipeline](image_url)

Fig. 1. Global clinical pipeline of TB vaccine candidates. Information on candidates in clinical development is self-reported by vaccine sponsors, coordinated by the Working Group on TB Vaccines and was updated in September 2017 by Aeras. Image courtesy of Aeras.
in Georgia (NCT02897180).

Aldar Bourinbaiar (Immunitor LLC, Mongolia) presented data from a Phase III study of oral administration of heat-killed M. vaccae (formulated as an oral tablet) as an adjunct to conventional TB therapy to treat active TB disease (NCT01977768). Two Phase II trials have shown therapeutic potential alongside conventional TB therapy in adults [42,43]. Interim results from the randomised (2:1) Phase III trial of 100 patients receiving the V7 M. vaccae vaccine and 52 who were given placebo showed that after just one month 68% of those receiving V7 had mycobacterial clearance in sputum smears compared to 23.1% of the placebo group, regardless of whether they had drug-sensitive or drug-resistant TB. The full Phase III results and the associated mechanisms of action will be of interest to the community as a whole.

There is a lot of interest in the clinical development of MTBVAC, the first attenuated live Mtbc vaccine in clinical trials. Carlos Martin (University of Zaragoza, Spain) discussed the mechanism of attenuation and protection by MTBVAC, a Mtbc devoid of fad26 (leads to loss of PDIM) and phoP, a transcription factor regulating major Mtbc virulence genes (preventing ESAT6 secretion). MTBVAC induced immunogenic responses in animal models, with improved protective efficacy relative to BCG [44,45], and was tested for safety and reactinogenicity in Lausanne, Switzerland [46], Michele Tameris (South African Tuberculosis Vaccine Initiative, South Africa) presented results from a Phase I study of MTBVAC with a safety run-in in adults [46], and safety and immunogenicity results from a dose-escalation in infants vaccinated at birth (NCT02729571). MTBVAC was well tolerated in all dose groups and induced specific vaccine dose-dependent immune responses. Interestingly, up to 78% of vaccinated infants converted to a positive QFT at 6 months post vaccination, in a dose-dependent manner. This is likely due to administration of MTBVAC rather than natural infection, as MTBVAC still secretes CFP-10 into culture filtrate [47]. However, as protocol and South African guidelines dictate, children under 5 years of age who were QFT-positive were provided IPT. At 12 months post vaccination, > 60% of QFT-converters had reverted. This vaccine candidate is scheduled to advance into both adult and infant clinical trials in 2018, in which QFT conversions will be further investigated.

Tracey Day (Infectious Disease Research Institute, USA), presented data on the clinical development of the recombinant protein antigen ID93 combined with the TLR-4 agonist adjuvant GLA-SE, a glycopyranosyl lipid A stable nano-emulsion. A Phase Ia clinical trial in adults in the US demonstrated an acceptable safety profile and induction of both antigen-specific CD4+ T cell responses and multi-functional antibody responses capable of antibody-dependent cellular phagocytosis (NCT01599897). A Phase Ib study in Mtbc-infected and uninfected adults in Cape Town, South Africa, demonstrated safety and robust antigen-specific CD4+ T cell and antibody responses (NCT01927159) [48]. Interestingly, CD4+ T cell responses to each of the four ID93 subunit proteins showed diverse functionality profiles, as measured by cytokine expression profiles, suggesting that each of the four antigens may be expressed at different stages of the Mtbc life-cycle, which induce immune responses with corresponding stages of T cell differentiation [48]. The authors suggest this breadth of T cell differentiation to antigens may be important in expanding the diversity of the current TB vaccine pipeline. Finally, Day presented preliminary immunogenicity data on the use of ID93 + GLA-SE in a Phase Ia study evaluating a prevention of recurrence vaccination strategy in South African adults who had successfully completed treatment for active TB (NCT02465216). Vaccination of this group was well-tolerated, and induced antigen-specific, multifunctional CD4+ T cell and humoral responses. Safety and immunogenicity results from this study are expected to be published later in 2018. Ongoing trials are also evaluating liposomal and lyophilized adjuvant formulations. Planned studies will assess safety, immunogenicity, and efficacy for prevention of infection, prevention of recurrence, and immunotherapeutic strategies.

New viral vectors may have promise for delivery of TB antigens. Marina Stukova (Research Institute of Influenza, St. Petersburg, Russia), presented results of a Phase I study of vaccination with TB/FLU-01L, a replication-deficient influenza A virus vector expressing ESAT-6, in QFT-negative, previously BCG-vaccinated adults (NCT02501421). Two doses, delivered 21 days apart by either intranasal or sublingual routes, were well-tolerated, and induced both CD4+ and CD8+ T cell responses, with no viral shedding detected after vaccination. A Phase IIa trial in QFT-positive individuals is ongoing. Another viral vector, the adenovirus-based TB vaccine candidate expressing Ag85A (Ad5Ag85A) developed by McMaster University, has entered into a Phase I clinical trial testing aerosol administration (NCT02337270).

DAR-901, consisting of inactivated M. obuense (a non-tuberculous mycobacterium), was discussed by Ford von Reyn (Dartmouth, USA). Pre-clinical studies have demonstrated safety and superior protective ability over BCG as a boost to BCG in animal models [49]. A Phase I trial in BCG-vaccinated adults demonstrated safety and immunogenicity in HIV-negative, HIV-positive, IGRA-negative and IGRA-positive individuals [35]. Results from a Phase Ib POI randomised controlled trial in 650 IGRA-negative Tanzanian adolescents will be available in Q4 2019 (NCT02721424), and DAR-901 is expected to advance to a Phase III POD trial in 2020.

5.2. Community engagement in vaccine trials

To carry out such vaccine trials in the community requires more than good vaccine trial design. Moses Zimba (Centre for Infectious Disease Research, Zambia) discussed the importance of Good Participatory Practice (GPP) in trial participant retention, reducing stigma and misconceptions, educating communities and generating advocacy. GPP Guidelines for TB Vaccine Research have been developed in part by Aeras, and remind researchers of the importance of coordinating retention events for participants, scheduled home visits, regular visit reminders, after-hours visit options and provision of other health care related services at the same facility (e.g., family planning clinic and social care services). The benefits and impact from community engagement activities is clear. At the site where Zimba works, the study retention rate was 97.2%, only 2% of study visits were missed, and issues with stigma and discrimination were quickly resolved.

6. Improving the effectiveness of new vaccines

BCG given by the intradermal (ID) route demonstrates protective efficacy against systemic TB infection during infancy/early childhood, but fails to provide consistent, high-level protection against pulmonary TB in adolescents and adults [50]. One possible explanation is that the ID route does not induce sustained T cell responses in the lung that may be critical for pulmonary TB [51]. Robert Seder (National Institute of Allergy and Infectious Diseases and National Institute of Health, USA) and his collaborators assessed how the route and dose of BCG influenced T cell responses in the lungs of NHP. NHP were immunized by the standard ID route or intravenous (IV), aerosol (AE) or a combination of ID/AE routes. AE and IV administration increased the frequencies of multi-functional (IFNγ, TNFα, IL-2 and IL-17) PPD-specific CD4+ T cells by 10–100 fold respectively in bronchoalveolar lavage (BAL) compared to BCG ID. Moreover, IV immunization also induced a higher frequency of CD8+ T cells that were sustained for at least 4 months after IV immunization. Further, BCG administered IV induced a profound change in the ratio of macrophages and T cells in BAL. These data establish how the magnitude, quality, breadth and durability of T cell responses in the lung can be strikingly increased by BCG administered by the IV route. 

Coupled with the results of ID BCG revaccination as part of the H4:IC31 POI trial, there may be further interest in delivering BCG by alternative routes. Frank Verreck (Biomedical Primate Research Centre, The Netherlands) discussed work extending his earlier demonstration of superior protection in NHPs to Mtbc challenge if BCG were administered via the pulmonary mucosal (PM) route as compared to ID [51]. Post
infection, IGRA conversion in NHPs vaccinated via the PM route was delayed compared to the ID route. The PM route also resulted in reduced lung pathology and draining hilar lymph node involvement. This route of delivery improved protection from both high-dose and repeated ultra-low dose Mtb challenges in NHPs.

Tom Scriba (SATVI, South Africa) discussed vaccination following mycobacterial exposure, which is likely to be of greater importance if new TB vaccines are administered to adolescents or adults. Earlier studies of the protection induced by BCG showed greatest protection in those children who were tuberculin skin test (TST) negative [52]. Exposure to non-pathogenic mycobacteria in the environment could induce a protective response not improved with vaccination (“masking”) or stop the replication of BCG so that it cannot induce protection (“blocking”) [53]. Natural immunity can be induced by exposure to Mtb, and the challenge is to improve on this by vaccination. BCG re-vaccination is well-tolerated [54] but it is clear that prior mycobacterial sensitisation by BCG or by infection with Mtb can have marked effects on the immunogenicity of new TB vaccines [55]. As up to 50% adolescents in some countries have latent TB infection (LTBI) [56], and on the immunogenicity of new TB vaccines [55]. As up to 50% adolescents in some countries have latent TB infection (LTBI) [56], and on the immunogenicity of new TB vaccines [55].

7.3. Attenuated vaccines

As discussed above, MTBVAC, a live, attenuated Mtb strain, is in clinical trials, but other live attenuated Mtb vaccines are in preclinical development. Deepak Kaushal (Tulane National Primate Research Center, USA) discussed the improved protection obtained using stress-response deficient attenuated Mtb compared to BCG with enhanced recruitment of proliferating CD4+ and CD8+ T cells to the lymphoid follicles and lungs. Bacterial burdens were three logs lower in NHPs vaccinated with MtbΔsigH compared with BCG [60]. Such animals also showed diminished granulomatous pathology. No pulmonary TB-like symptoms were seen among the NHPs vaccinated with MtbΔsigH [61], although these animals did develop HIV-like symptoms when infected with SIVmac239.

7.4. Viral and nucleic acid-based vaccines

Viral vectors promote efficient gene transduction and intracellular antigen presentation [62]. Aurelio Bonavia (Vir Biotech, USA) presented preclinical data obtained with VIR-2020, a novel, human attenuated CMV prophylactic vaccine candidate. Compared to controls, the rhesus CMV ortholog vaccine showed an overall 70% reduction in TB infections/disease (lung and extra-pulmonary disease) in NHPs. There was no disease in 41% of animals by CT scan and necropsy [63]. Stephane Leung-Theung-Long (Transgene SA, France) showed that the efficacy of chemotherapy against Mtb in a murine model was significantly improved by co-administration of the MVA-based MVATG18598 therapeutic vaccine carrying 10 antigens spanning active, latent and resuscitation phases of Mtb infection [64]. Mice subcutaneously vaccinated with MVATG18598 showed both Th1-associated T-cell responses and cytolytic activity against all 10 Mtb antigens. In combination with chemotherapy in chronic post-exposure murine models, this vaccine helped reduce bacterial burden significantly in the lungs. Concomitantly, an increase of the frequency of IFNγ-producing T-cells and production of specific antibodies were observed. It also reduced disease relapse by 30–40%, which is another important clinical goal for a therapeutic vaccine.

Agnès L. Chenine (Aeras, USA) discussed the immunogenicity and efficacy conferred by ChAd3-5Ag + MVA-5Ag prime-boost regimens in NHPs challenged with virulent Mtb 12 weeks after the final vaccination. Different routes of delivery were evaluated, including aerosol, parenteral, and heterologous parenteral prime-aerosol boost regimens. NHPs vaccinated parenterally showed the highest T cell response in blood (PBMCs) while animals vaccinated via aerosol showed the highest response in BAL. Gross pathology, bacterial burden, and PET/CT were evaluated as efficacy endpoints. Despite the induction of a robust T cell response, no significant protection was observed in any of the vaccinated groups.

Conventional and self-amplifying mRNA-based vaccines have been tested in various preclinical animal models, including NHPs, and Jeffrey Ulmer (GSK Vaccines, USA) discussed results showing their ability to elicit potent T-cell and antibody-based immune responses. Several mRNA-based vaccine candidates are currently being evaluated in human clinical trials.

8. Biomarkers and correlates

The lack of a validated biomarker or correlate of protection from TB remains a major impediment to the development of an effective vaccine. Biomarkers would be invaluable in demonstrating relevant immunogenicity, down-selecting vaccine candidates, and thereby contributing to stage gates, reducing the time-scale of clinical trials and optimising vaccine dose. However, the field is fraught with challenges including the rarity of head-to-head testing which is mainly limited to animal models, that biomarkers may be vaccine-specific, and the circular issue of the need for biomarkers to design rationally rather than empirically a protective vaccine, but the need for a protective vaccine to identify biomarkers. Hazel Dockrell (London School of Hygiene and Tropical Medicine, UK) outlined ways in which we can learn in the interim through the study of: a) individuals who do and do not develop disease in vaccine trials, b) exposed contacts who do and do not develop disease, c) individuals with active disease compared to latent infection, d) latently infected individuals with long-term non-progression, e) TB cases before and after treatment and f) treated TB cases who do and do not relapse.

Biomarker research conducted by the TBVAC2020 consortium includes identifying, testing, evaluating and prioritising the most
promising human biomarkers, but also bridging with animal models [65]. Key samples and assays include (i) peripheral blood mononuclear cells (PBMC) for flow cytometry, intracellular cytokine staining (ICS), ELISpot and the functional mycobacterial growth inhibition assay (MGIAs); (ii) serum for antibody ELISAs and multiplex cytokine/chemokine assays; and (iii) RNA analyses. IFN-γ ELISpot responses and Ag85A-specific antibody responses were recently identified as correlates of reduced risk of disease in BCG vaccinated South African infants, and activated HLA-DR+ T cells as a correlate of increased risk of disease [66]. Such findings now require replication. Interestingly, a follow-up study from the same cohort presented by Iman Satti (University of Oxford, UK) found that these immune parameters did not correlate with risk of infection, as defined by QFT conversion in the absence of disease. MGIAs have the potential to provide the best insight into biosignatures. Although they can be technically complex [67,68], improved control of mycobacterial growth was detected following BCG vaccination in both UK infants [69] and historically vaccinated adults using the direct PBMC MGIAs, consistent with the findings of Fletcher et al. [70].

Stefan H.E. Kaufmann (Max Planck Institute for Infection Biology, Germany) spoke on the identification of predictive biosignatures to improve TB vaccine development, with a focus on whole blood transcriptomic signatures, the most advanced area of TB biomarker research. Such signatures can be applied to stratify individuals at high risk of progression to disease (which may represent those with incipient subclinical TB), significantly reducing the size, duration and cost of clinical vaccine trials. Zak et al. recently described a 16-gene signature able to predict progression from LTBI to active disease with 66% sensitivity and 81% specificity within a year of TB diagnosis, which was validated in independent cohorts of South African and Gambian progressors and controls from a GC6 household contact study [71]. This signature may be further minimised by introducing pair ratios to just 2 genes; such a signature has been applied to the GC6 and adolescent cohorts with a specificity of 70–80% [72]. The transcript and a metabolite-based signature developed as part of the GC6 initiative were both able to predict progression to active TB in household contacts up to 12 months prior to the onset of clinical disease. These bio-signatures may be useful for stratification of study participants for clinical trials and may be harnessed for the targeting of preventative therapy before the development of clinical disease and subsequent transmission. The Correlate of Risk Targeted Intervention Study (CORTIS) in South Africa led by the South African TB Vaccine Initiative (SATVI) aims to test the prognostic performance of these signatures in healthy individuals, as well as the efficacy of targeted preventive therapy on development of TB disease [73].

A key theme emerging from the biomarkers and correlates sessions was the need for testing in cohorts that reflect real-world variability within and between populations. In addition to the differences in how European and African infants respond following BCG vaccination described by Dockrell, Jeffrey A Tornheim (Johns Hopkins University School of Medicine, USA) described how gene expression profiles of European and African infants respond following BCG vaccination in both UK infants [69] and historically vaccinated adults using the direct PBMC MGIAs, consistent with the findings of Fletcher et al. [70].

Basic research is fundamental to progress in the TB vaccine field and needed to identify new vaccine candidates. Understanding the biology of Mtb such as the biochemical pathways critical for its survival and pathogenesis, the host immune response, and the host-pathogen interaction are essential in identifying novel targets for both therapeutic and vaccine interventions. One major theme of the basic research presented at the 5th Global Forum was the mechanisms by which Mtb manipulates the host cellular response through immune evasion or modulation. For example, Ekanish Mittal (Washington University School of Medicine, USA) discussed how the Mtb secreted virulence factor EssH (TB10.4) impedes antigen presentation and transfer to bystander cells by altering exosomes, thus impairing the ability of CD4+ T cells to recognise infected macrophages.

Buka Samten (University of Texas Health Science Center, USA) presented data showing significantly higher levels of cyclic AMP (cAMP) in PBMC from TB patients compared with latently infected individuals. Elevated cAMP was associated with inhibition of IFN-γ production by T cells through the protein kinase A (PKA) type I pathway via suppression of transcription factors that regulate IFN-γ [80]. A further protein kinase, PknG, was shown to mediate persistence under latency-like conditions in vitro via phosphorylation of the metabolic regulator GarA, and contributed to stable granuloma formation in a guinea pig model as presented by Mehal Zahoor Khan (National Institute of Immunology, India) [81]. Another approach reported by Dipendra Mitra, All India Institute of Medical Sciences, is to target the checkpoint inhibitor PD-1 to enhance the efficacy of therapeutic TB vaccines. Both the regulatory T cell and the PD-1 axes are involved in actively suppressing T cell responses in tuberculosis, and blocking PD-1 restores IFNγ and TNFα production. Giving anti-PD-1 antibodies can reduce the bacterial burden in Mtb infected mice, particularly if this is combined with drug therapy, offering the prospect of a novel host-directed therapy.

An improved understanding of the immune response to Mtb infection is also critical to inform vaccine strategies. Cheleka Mpande (University of Cape Town, South Africa) presented the kinetics of Mtb-specific CD4+ T cells in a longitudinal cohort of recent QFT converters, revealing highly activated specific CD4+ T cells during acute infection followed by an increase in resting Mtb-specific central memory T cells (TCM) during established infection. Mtb-specific stem cell-like memory (Tscm) CD4+ T cells were also induced during primary infection, and displayed chemokine receptor profiles consistent with memory Th1/Th17 cells and expressed cytotoxic effector functions during established infection [82]. Polymorphisms in TLR genes have recently been associated with susceptibility to TB and idiopathic pulmonary fibrosis. Javed Ali Shah (University of Washington, USA) described how the Toll interacting protein (TOLLIP) deficiency allele, rs5743854, is associated with decreased expression of long non-coding RNA (IncRNA) TOLLIP-AS1 expression, BCG-specific memory phenotypes and increased TB susceptibility [83–85].

David Lewinsohn (Oregon Health & Science University, USA) spoke on immune responses generated via the ‘non-classical’ presentation of antigens through receptors that are highly conserved in humans. In some cases these antigens are non-protein antigens. Donor-unrestricted T cells (DURTs) include HLA-E- or CD1-restricted T cells, Mucosal Associated Invariant T (MAIT) cells, natural-killer T-cells (NKT cells) and γδ T cells [86]. The diversity of MHC class I and II alleles and the TCR means that conventional T cells of each host may recognise different peptides, and that the immunodominant T cell antigens for any
infection cannot be generalised between individuals. Furthermore, there is an inherent risk of pathogen escape by antigenic variation. DURTs, however, recognise their antigens through highly-conserved molecules present among all humans, offering attractive candidates for vaccine targeting [86]. Although this is a relatively new field, there is already evidence accumulating for enrichment of MAITs and CD1-restricted T cells in the lung during Mtb infection and of DURTs facilitating control of Mtb via polyclotoxic functions [87,88]. Knock-out and adoptive transfer studies indicate that DURTs can be protective in mice [89,90], and there have been two preclinical vaccine studies demonstrating modest levels of protection [91]. Ongoing studies are investigating whether DURTs are induced following BCG vaccination and whether they have memory.

Interest in vaccine-induced memory has expanded beyond T cells. Maziar Divangahi (McGill University, Canada) discussed how we can harness the power of innate immunity in vaccines against TB via the reprogramming of haematopoietic stem cells (HSCs) [92]. He examined how BCG-IV vaccination ‘educates’ HSCs via epigenetic reprogramming that can be transmitted to myeloid-committed progenitors to generate ‘trained immunity’ with sustainable protective capacity against TB. He also discussed how identifying the protective signature of trained immunity will lead to a novel roadmap for developing TB vaccines. Chang Ook Park (Yonsei University, South Korea) talked about tissue resident memory T cells (TRM), cells that have also become of increasing interest to immunologists over the last few years. Skin TRM cells that localise with dendritic cells rapidly produce effector cytokines protecting against infection, as shown in a model of skin infection with Candida. Mucosal vaccination with BCG also generates TRM in the lungs of mice, which protect against TB [93].

10. The importance of political commitment, partnerships and resources in vaccine development

The presentations at the 5th Global Forum on TB Vaccines demonstrated the significant scientific progress being made, and there was a sense of excitement and optimism, as new data was announced and new, transformative approaches to R&D were presented and discussed. But it was also recognized that political commitment, financial resources, and partnerships and collaborations will be essential to sustain and build on this momentum. During the Opening Session and Inaugural Ceremony, Sunil Khaparde (Deputy Director General of TB, Ministry of Health & Family Welfare, India), Preeti Sudan, (Secretary, Department of Health and Family Welfare and Department of Health Research, and Director General, Indian Council of Medical Research, Ministry of Health & Family Welfare, India) and Anupriya Patel (Honourable Minister of State, Ministry of Health & Family Welfare, India), expressed the commitment of the Government of India to addressing the TB epidemic through a comprehensive approach that includes new approaches to improve services and care to those impacted by TB, and investing in R&D for new TB vaccines. Renu Swarup (Senior Advisor, Department of Biotechnology, Ministry of Science and Technology, India) and Ashutosh Sharma, (Secretary, Department of Science & Technology and Department of Biotechnology, Ministry of Science and Technology, India), reiterated India's commitment to ending TB, reviewed India's investment in R&D infrastructure and human resource capacity, and discussed the importance of partnerships and collaboration across sectors, noting that the public sector, private sector, academics and civil society all have important roles in the research and development of new TB vaccines. Soumya Swaminathan (Deputy Director General, WHO, Switzerland), and Poonam Khetrapal Singh (WHO Regional Director for South-East Asia, India) discussed the importance of new TB vaccines to “bend the curve” and achieve the declines in incidence and mortality that will be necessary to meet the time-bound global targets to end TB. Mona Balani (Touched by TB Coalition, India) reminded the audience of the devastating impact of TB on individuals, families and communities, and that prevention of TB should be a priority, and Blessina Kumar (Global Coalition of TB Activists, India) emphasized that new TB vaccines must be affordable and accessible to those who most need them, and the importance of engaging affected communities and civil society in TB vaccine research. Henk Bekedam (WHO Representative to India, WHO Country Office for India) made a strong case for investment in TB vaccines as a global public health good as it would help in accelerating the much needed “bending of the curve”, and also stressed the need for effective community engagement. The speakers in these sessions noted that collaborations within and across countries, such as the newly formed BRICS TB Research Network, the India TB Research Consortium, and the RePORT (Regional Prospective Observational Research on Tuberculosis) Consortium, can provide new opportunities to share and leverage knowledge, resources, and learnings to accelerate and advance TB vaccine R&D; and emphasized the need for increased investment in and support for TB vaccine R&D.

Fareed Abdullah (Medical Research Council, South Africa), Shelly Batra (Operation ASHA, India), Michel Kazatchkine (Global Health Centre, Graduate Institute for International and Development Studies, Switzerland), Rajiv Modi (Cadila Pharmaceuticals, India), and Jacqueline Shea (Aeras, USA) contributed to a roundtable discussion during the final plenary session, providing perspectives on key challenges, issues and strategies in TB vaccine R&D. They agreed that developing new TB vaccines is scientifically feasible. It will, however, require a significant increase in investment and a broader and more diverse funding base, recognizing that TB is a public health emergency that requires new models of financing and collective action at a global level towards which all governments and all sectors must contribute, and that new TB vaccines must be affordable and accessible. The panelists also discussed the centrality of new TB vaccines to meeting global targets to end the TB epidemic, that TB and new TB vaccines must be placed on the forefront of the global health agenda, and that we must be stronger and bolder in our advocacy and communications around TB vaccine R&D.

Lucica Ditiu (Stop TB Partnership, Switzerland), provided the closing address for the 5th Global Forum on TB Vaccines, noting that this is a unique and momentous time for TB, with the recent WHO Ministerial Conference on TB in November 2017 and the upcoming UN High Level Meeting on TB in September 2018, and she challenged participants to become advocates, to hold global leaders accountable to their commitments, and to speak with a united voice to ensure that we have the financial resources needed to deliver a new and effective TB vaccine by 2025.

11. Conclusions

The TB vaccine field still has much to do to deliver TB vaccines that would prevent TB infection and/or disease, as well as accelerate TB treatment and prevent TB relapse, hopefully also helping to control drug-resistant tuberculosis. Overall the conclusion of the Forum was upbeat. Old vaccines are being tested via new routes, such as giving BCG intravenously; old and new vaccines may be able to prevent infection as well as disease with the first human data being shown indicating that a subunit vaccine expressing just a small number of Mtb antigens may be able to have protective efficacy; and gene expression analysis and improved assays measuring mycobacterial growth inhibition are bringing new insights. It is likely that there will be more focus in the coming period on progression from infection to disease, and on how to assess IGRA conversion and reversion.

The next few years will see the results of more TB vaccine clinical efficacy trials. We hope that at least some of these will induce protective efficacy, although others will not. Certainly, all will help us better understand TB; as Barry Bloom (Harvard T. H. Chan School of Public Health, USA) stated in his Keynote address, “the only vaccine studies which fail are those from which we fail to learn”. Although the TB vaccine field receives a fraction of the funds that would be...
commensurate with TB’s global disease burden, it is making remarkable progress.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tube.2018.08.013.

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