Status of Vaccine Research and Development of Vaccines for Tuberculosis
Prepared for WHO PD-VAC

I. About the Disease and Pathogen

Basic information on pathogen, including transmission, estimated global disease burden for those at risk, for morbidity and for mortality, including uncertainties/data gaps, geographical distribution, economic burden if available, age groups affected and target groups for vaccination. Existing preventive, diagnostic and treatment measures and their limitations.

In March 1993, the World Health Organization (WHO) designated tuberculosis (TB), a disease caused by Mycobacterium tuberculosis (Mtb), a global public health emergency. Currently, TB is a leading cause of mortality world-wide in HIV-infected individuals and in women of childbearing age. There are more than 1.3 million deaths from TB each year, making it the number nine overall cause of mortality worldwide. Nearly 1 billion people have died of TB over the past few centuries, an astounding number. Ninety-nine per cent of the TB deaths and 95% of the over 8 million new cases each year occur in the low and middle-income countries that comprise 85% of the world’s population. The epidemic of TB in sub-Saharan Africa has been fueled by HIV disease, and the increasing incidence of diabetes in Asia further threatens attempts at control.

One of the highest priorities of TB research is to develop vaccines that are more efficacious for preventing TB than Mycobacterium bovis bacillus Calmette-Guérin (BCG), the only vaccine available to protect against TB. Better control of TB than that provided by BCG could be achieved by vaccines that protect individuals from initial infection with Mycobacterium tuberculosis (Mtb), prevent those infected from progressing to active disease, or decrease the capacity for transmission by those with active disease. Different vaccines may be required to induce immune responses in diverse populations, such as infants, young adults, those already latently infected with Mtb, and those co-infected with Mtb and HIV. Experts in TB prevention and control mostly agree that the largest vaccine impact would be to mass vaccinate all adolescents/young adults in high burden countries, regardless of their infection status, even with a vaccine that is only 50-60% efficacious. Such a vaccine could prevent an estimated 30 to 80 percent of incident TB cases in high-burden settings during the first 35 years after its introduction, depending on the type of protection the vaccine affords. This impact would save millions of lives and billions of dollars in treatment and control costs.

II. Overview of Current Efforts

A. Vaccines currently available and their limitations

Include perceived limitations with available vaccines for low and middle-income country markets (LMIC). These could include safety, effectiveness, serotype/strain coverage, supply, affordability, financing, number of WHO prequalified vaccines, WHO policy recommendations for available vaccines, perceived lack of priority from endemic country authorities.

Where there are no vaccines available, this section should focus on the evidence that vaccine development is biologically feasible including from development of naturally acquired immunity, from vaccine development for related pathogens, from animal models or in vitro data

The human immune system can contain tuberculosis infection in the majority of cases following infection, and a partially effective vaccine for infants exists. These data, as well as evidence that prior Mtb infection may protect against later disease, paint an optimistic picture for the development of a vaccine. On the other hand, because Mtb has co-evolved with humans over many years and may use the
human immune system to maintain its propagation,\textsuperscript{4} and because prior active pulmonary tuberculosis does not protect and may actually be a risk factor for reinfection and disease, some scientific skepticism has arisen concerning the prospect for developing an effective vaccine.

BCG is a live, attenuated vaccine that is widely administered to infants in most areas endemic for TB. BCG has been shown to be effective for the prevention of more serious extrapulmonary tuberculosis in young children, such as tuberculous meningitis and miliary tuberculosis.\textsuperscript{5} A meta-analysis of prospective trials and case-control studies concluded efficacy against pulmonary TB in infants and adolescents to be approximately 50\%, with a range from a low of zero to a high of eighty percent.\textsuperscript{6} When delivered to newborns, however, BCG is not fully effective in preventing adult pulmonary TB, which constitutes the bulk of the global morbidity and mortality disease burden.

\textbf{B. General approaches to vaccine development for this disease for low and middle income country markets}

\textit{What are the scientific approaches and indications and target/age/geographic groups being pursued? What public health needs will these vaccines meet if successfully developed? Where there are several different possible indications/target groups, how much consensus is there as to prioritization between these for vaccine development in LMIC.}

Most successful, licensed vaccines available today induce neutralizing antibodies that provide protective immunity. Animal and human studies of TB, however, suggest that a robust cellular immune response is required for protection against Mtb infection and disease.\textsuperscript{7,8} For this reason, the majority of current clinical TB vaccine candidates are based on a variety of vectors, adjuvants and antigens that induce classical TH1 cytokines such as IFN-\(\gamma\) or TNF-\(\alpha\) from either CD4\(^+\) or CD8\(^+\) T cells.

These clinical candidates are based on a variety of vaccine approaches, such as inactivated whole cell or whole cell extracts (\textit{M. indicus pranii}, \textit{M. vaccae}, \textit{M. obuense}, RUTI and \textit{M. smegmatis}), viral-vectorized candidates (vaccinia based MVA85A, influenza, and human adenovirus 5 and 35 constructs), fusion protein subunits with TH1-inducing adjuvants (M72/AS01, Hybrid 1/CAF01, Hybrid 1/IC31, H4/IC31, H56/IC31 and ID93/GLA-SE), and live recombinant BCG or attenuated TB vaccines (VPM 1002, Aeras 422, rBCG30, and MTBVAC). DNA vaccines are being developed in different countries, notably emerging economies, but have not yet entered into human clinical trials. To date, clinical trials characterizing these candidate vaccines have included studies of safety and immunogenicity in diverse populations, including healthy, TB-naïve adults and infants, latently infected adolescents and adults, HIV-infected adults, as well as patients undergoing drug treatment for TB.

BCG vaccine is the most widely administered neonatal vaccine worldwide. Due to the short-term protectiveness of BCG, and its nearly universal use in TB-endemic countries, new candidate vaccines are being studied as boosters in adolescents and adults who received BCG as infants. Recombinant BCG vaccines are also being studied as replacements for BCG to improve safety in HIV-exposed infants and to induce better efficacy as well as better priming. Attenuated live Mtb strains, which have shown acceptable safety in immune suppressed animal models, are also in early clinical development.

An initial Phase IIB proof-of-concept (PoC) efficacy trial in 2,797 BCG-vaccinated infants boosted at 4 to 6 months of age with a viral-vectorized vaccine containing one antigen (MVA85A) showed no efficacy against TB disease or infection.\textsuperscript{5} Whether this disappointing outcome was due to the magnitude of the immunologic response, the single Ag85A antigen studied, the population vaccinated, or an incorrect immunologic hypothesis is not clear. A large, Phase IIB trial in 3600 HIV-uninfected, adults latently infected with Mtb is about to begin in three African countries using the GSK M72 adjuvanted fusion protein vaccine. This study should further our understanding of potential correlates of protection, as well
as the role of TH-1 induced immunological responses in preventing the development of disease in latently infected individuals.

In addition to these large-scale PoC trials, a new set of human studies are under way, based on the use of innovative trials designs intended to show the biologic activity of vaccine candidates using more focused populations specifically selected to reduce sample size. The first of these new trial designs is testing whether a novel vaccine (H4/IC31) or the use of BCG re-vaccination can prevent infection by Mtb (as opposed to disease). The trial uses novel blood tests in which BCG vaccination does not interfere with the test result – a common obstacle with the longtime, standard diagnostic, the tuberculin skin test. The study is enrolling adolescents in South Africa with a high rate of incident Mtb infection, thereby requiring only 330 subjects per arm rather than the two thousand or more needed in the classic PoC trials. The second innovative trial design is to study the ability of a vaccine to prevent the 4-6% relapse and/or reinfection rate typically observed following successful treatment of active TB. A “Prevention of Recurrence” trial using both the ID93 and H56 candidates will begin shortly and require approximately 450 subjects per arm.

III. Technical and Regulatory Assessment

Highlight perceived positive/negative aspects in clinical/regulatory pathways e.g. well established product development and regulatory pathway to licensure, accepted immune correlates and/or functional assays, accepted surrogate efficacy endpoints, existence of well accepted animal or challenge models, agreed trial designs and endpoints. Possibilities to develop case for correlates/surrogates should be included.

At present there are no accepted correlates of protection that, unto themselves, could support a decision to license a TB vaccine. It is presumed that prevention of actual disease will continue to be the primary endpoint of Phase 2b or 3 trials. However, whether regulators will accept stringent definitions based on clinical outcomes and supporting evidence for a licensure decision without a direct culture of Mtb is not yet clear. Whether regulators would accept data from the nucleic acid-detecting GeneXpert, infection-based endpoints rather than endpoints based on overt disease, or data obtained from population-based cohort studies as evidence of vaccine efficacy, rather than large double-blind randomized studies, remain open issues. Attempts are underway to engage the TB community, along with the regulatory experts, to begin discussions concerning these and other licensure issues.  

We have no clear models upon which to identify the “best” vaccine Mtb antigens, as many TB vaccine animal challenge models have a narrow dynamic range of responses that do not allow for easy differentiation among candidates. This limitation is being addressed by refinement of the mouse, guinea pig and macaque models to better approximate natural infection by Mtb and better mimic human disease. The use of low dose challenge, sophisticated imaging techniques, and novel vaccine candidates (such as H56, Cytomegalovirus (CMV) approaches, and aerosolized adenovirus vaccines) have recently shown that the macaque model may potentially be useful to delineate correlates of vaccine-induced protection.

In human biomarker studies, gene expression patterns of inflammatory biosignatures have correlated with risk for TB disease progression, and with the extent of radiographic involvement in both active and latent TB cases. In response to these data, TB vaccine developers are pursuing a systems immunology approach in which gene expression signatures are compared in samples from various time points. These signatures are then correlated to either specific measures of immunogenicity, or to protection in efficacy studies. This method allows for a broader unbiased net to be cast in assessing immune responses, and in searching for a correlate of vaccine-induced protection.
IV. Status of Vaccine R&D Activities

Summarize status of vaccine design, pre-clinical and clinical trial activity, including platforms, vectors, and adjuvants. Note academic, government, biotech and industry entities engaged. Summarize antigenic targets (if subunit approaches). Section on major advances in last 3-5 years, including key opportunities highlighted by recent science developments in the area.

Sixteen candidate vaccines have moved forward into clinical studies in the last 10 years. A dozen candidates currently are under active clinical study, summarized in Table 1. These studies are supported by a combination of multinational pharmaceutical companies (GSK, Crucell, Sanofi-Pasteur), smaller vaccine developers (Serum Staten Institut, Infectious Disease Research Institute, Vakzine Projekt Management, BioFabri, and others), academics (MPIIIB, US and European Universities), and TB vaccine-focused non-profits (Aeras and TBVI). Support has primarily been through the Bill & Melinda Gates Foundation, governmental organizations such as the EC, DGIS, DIFD, and the NIH, and through direct investments of companies. The business case for TB vaccines, as recently developed by a working group of Aeras, TBVI, EC, EIB, and BMGF, is compelling, with potential returns on investment that range into the billions of dollars. Due to the perceived scientific risks, however, it has been difficult to engage industry, whether large or small, from entering into this field without substantial early subsidization from granting organizations.

Early signals of potential efficacy may be obtained from the three large trials mentioned above over the next three years: prevention of disease by vaccination with the GSK product; prevention of infection through use of the Sanofi and the Serum Staten Institut candidates; and prevention of recurrence using the IDRI and Serum Staten Institut candidates. If any of these prove promising, there will be considerable momentum to carry one or more of these into larger efficacy studies. The use of a live, attenuated TB vaccine, and the exploration of whole cell vaccines, will continue with a focus on better defining an immune response surrogate.

Other innovative leads that will be aggressively pursued over the next 5 years will include the use of aerosolized adeno vectors for vaccination followed by modified vaccinia Ankara has been especially promising in both preclinical models and in early human trials. CMV candidates will move forward in both the TB and HIV area, as they induce prolonged and high levels of effector T cells in the mucosal location where the pathogen first encounters the human host. Other promising leads include intranasal attenuated parainfluenza viruses for induction of mucosal immunity, self-replicating RNA candidates, and electroporated DNA vaccines. The value of a number of novel BCG replacement strategies will also become clearer. Systematic study of heterologous platform combinations using common antigen sets is now underway for many of these approaches.

A variety of highly novel vaccine candidates are being developed by academia, industry, and expert consortia, utilizing a number of innovative and diverse approaches. There is renewed emphasis on prevention of infection through antibody-mediated or other immunologic mechanisms; in addition, optimal glycolipid constructs and adjuvants that induce responses via the CD1 system are being explored. Both approaches are high risk/high reward investigations that expand the immunologic response space being probed by TB vaccine candidates. Testing of these novel candidates is being facilitated by the concurrent development of new animal models of natural transmission. The models include human- or primate-to-guinea pig transmission, as well as novel macaque-to-macque transmission in an environment controlled setting. While these programs progress, significant attempts will be undertaken to build a safe mycobacterial construct that can be used in a human TB challenge model, which would open wide the field of early clinical vaccine assessment. The strain of Mtb used will need to exhibit some degree of low level replication, a failsafe kill switch and a second attenuation mechanism to help ensure safety. The strain must be modified such that the bacterial burden can be easily measured in
the challenged subject through the imaging of a luminescent marker or by measuring a soluble, secreted marker in blood or urine.

There is also an important need to use a more rational approach for selection of TB vaccine candidates for future studies. First, there is a need to ensure that each vaccine carried forward into efficacy studies addresses a new hypothesis, rather than pursuing a vaccine approach that has already failed. It will be critical to then choose only the best vaccine candidate among those that are likely to induce a similar magnitude and phenotype of immune responses. From candidates that have similar target profiles, head to head comparisons of candidates in animal and early human studies would be optimal, and mechanisms and incentives (such as support from funding agencies) to do such comparisons are needed. This approach also implies the need for a diverse and robust pipeline of candidates representing not just a set of minor improvements but truly novel approaches that test different immunologic hypotheses.

**Table 1. Development Status of Current Vaccine Candidates**

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Type</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad5 Ag85A [McMaster University, CanSino]</td>
<td>human Adenovirus 5 1 antigen</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>MTBVAC [TBVI, Zaragoza, Biofabri]</td>
<td>Live attenuated TB</td>
<td>X</td>
<td></td>
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<tr>
<td>DAR-901 [Dartmouth, Aeras]</td>
<td>Heat-killed NTM</td>
<td>X</td>
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<tr>
<td>Combination Crucell Ad35/MVA85A [Crucell, Oxford University, Aeras]</td>
<td>hAdenovirus35 (3 antigen) followed by MVA (1 antigen)</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>ID93 + GLA-SE [IDRI, Aeras]</td>
<td>4 Ag adjuvanted fusion protein</td>
<td>X</td>
<td></td>
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<tr>
<td>VPM 1002 [Max Planck, VPM, TBVI, Serum Institute of India]</td>
<td>Modified recombinant BCG</td>
<td>X</td>
<td></td>
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<tr>
<td>H1 + IC31 [Statens Serum Institut (SSI), TBVI, EDCTP]</td>
<td>2 Ag adjuvanted fusion protein</td>
<td>X</td>
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<tr>
<td>RUTI [Archivel Farma, S.L]</td>
<td>Lysate of Mtb</td>
<td>X</td>
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<tr>
<td>H4/Aeras-404 + IC31 [SSI, Sanofi-Pasteur, Aeras, Intercell]</td>
<td>2 Ag adjuvanted fusion protein</td>
<td>X</td>
<td></td>
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<tr>
<td>H56/Aeras-456 + IC31 [SSI, Aeras, Intercell]</td>
<td>3 Ag adjuvanted fusion protein</td>
<td>X</td>
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<tr>
<td>Crucell Ad35/Aeras-402 [Crucell, Aeras]</td>
<td>h Adenovirus 35 3 antigen</td>
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<tr>
<td>MVA85A/Aeras-485 [Oxford University, Aeras]</td>
<td>Modified vaccinia Ankara; 1 Ag</td>
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<tr>
<td>M72 + AS01E [GlaxoSmithKline, Aeras]</td>
<td>2 Ag adjuvanted fusion protein</td>
<td>X</td>
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References