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Status of vaccine research and development of vaccines for tuberculosis

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ABSTRACT

TB is now the single pathogen that causes the greatest mortality in the world, at over 1.6 million deaths each year. The widely used the 90 year old BCG vaccine appears to have minimal impact on the world-wide incidence despite some efficacy in infants. Novel vaccine development has accelerated in the past 15 years, with 15 candidates entering human trials; two vaccines are now in large-scale efficacy studies. Modeling by three groups has consistently shown that mass vaccination that includes activity in the latently infected population, especially adolescents and young adults, will likely have the largest impact on new disease transmission. At present the field requires better validated animal models, better understanding of a correlate of immunity, new cost-effective approaches to Proof of Concept trials, and increased appreciation of the public health and scientific community for the size of the problem and the need for a vaccine. Such a vaccine is likely to also play a role in the era of increasing antibiotic resistance. Ongoing efforts and studies are working to implement these needs over the next 5 years, which will lead to an understanding that will increase the likelihood of a successful TB vaccine.

1. The disease and pathogen

Q5 In March 1993, the World Health Organization (WHO) designated tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis* (Mtb), a global public health emergency. Since 1993 there are more than 1.5 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, and TB is a leading cause of mortality in HIV-infected individuals and in women of childbearing age. Ninety-nine per cent of the TB deaths and 95% of the over 9.5 million new cases each year occur in the low and middle-income countries that comprise 85% of the world's population. One-third of the world's population is estimated to be latently infected and 5–10% of these people may go on to develop active TB disease; however, the risk is considerably higher in the presence of predisposing factors. As such, in part 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 (partially) protect against TB disease [1]. Research and development is one of the three pillars of the WHO TB strategy, and will play a crucial role in accelerating the reductions in TB incidence and mortality required to reach global TB targets to reduce TB deaths by 95% and to reduce new infections by 90% between 2015 and 2035. Better control of TB than that provided by BCG could be achieved by vaccines that protect individuals from initial infection with *M. 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 result from mass vaccination of all adolescents/young adults in high burden countries, regardless of their infection status, even with a vaccine that is only 50–60% efficacious over a 10 year duration. Such an initial vaccine strategy could prevent up to 50 million cases of incident TB cases in high-burden settings during the first 35 years after its introduction, and would be effective in preventing infant disease as well [2]. This impact would likely save millions of lives and billions of dollars in treatment and control costs. It

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is also important to note that strains of Mtb that are resistant to standard anti-tuberculous drugs, including multiply drug resistant (MDR) and extensively drug-resistant (XDR) strains are becoming more common. While Mtb is likely to continue to evolve resistance against drugs develop to combat it, it is highly unlikely that such resistance would result in a concomitant development of resistance against otherwise effective TB vaccines.

2. Overview of current efforts

2.1. Vaccines currently available and their limitations

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 [3], 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 [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 [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 per cent [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.

2.2. General approaches to vaccine development for this disease for low and middle income country markets

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 [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-γ or TNF-α 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 (*Mycobacterium indicus pranii*, *Mycobacterium vaccae*, DAR-901 (*Mycobacterium obuense*), RUTI and *Mycobacterium smegmatis*), viral-vectored candidates (vaccinia based MVA85A, influenza, and human adenovirus 5 and 35 and chimpanzee adenovirus), 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.

An initial Phase IIB proof-of-concept (PoC) efficacy trial in 2797 BCG-vaccinated infants boosted at 4–6 months of age with a viral-vectored vaccine containing one antigen (MVA85A) showed no efficacy against TB disease or infection [9]. Whether this disappointing outcome was due to the magnitude of the immunologic response, the single dose of 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 under way in three African countries (South Africa, Kenya, Zambia) 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. Data are expected in 2018.

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 sustained 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 the ID93 candidate will likely begin shortly and require approximately 450 subjects per arm. All of these trials represent an attempt to make decisions earlier in development (a “shift to the left”), including the initial attempts to coordinate a more globally focused preclinical consortium effort, given the 20–50 million dollar cost needed to conduct classical efficacy disease endpoint studies. Of note, a 10,000-person Phase 3 study is underway in Guanxi province to test the efficacy of a killed *M. vaccae* lysate vaccine to prevent TB in adults with latent disease.

3. Technical and regulatory assessment

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, or infection-based endpoints (such as IGRA tests) rather than endpoints based on overt clinical or culture-positive disease remain open issues. Similarly, discussions concerning the use of population or community randomized study designs rather than large double-blind individual randomized studies are ongoing. There is clearly a need to engage the TB community, along with the regulatory experts, to begin discussions concerning these and other licensure issues [10].

We have no clear preclinical 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 PET/CT 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.

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