Update on Research and Development Pipeline: Tuberculosis Vaccines

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Current tuberculosis (TB)—control methods, which do not include an adequate vaccine, do not effectively block transmission of TB. Modeling studies show that mass vaccination campaigns using new vaccines could prevent 85.9 million new cases and 14.5 million deaths from 2015 through 2050 in southern Asia alone. After a dearth of many years, the development pipeline now includes 7 vaccine candidates that are being tested in humans. Two nonreplicating viral vectored vaccines have very recently entered the first phase IIb efficacy trial in infants (the first such trial in 80 years) and in human immunodeficiency virus–infected adults. Science is moving forward, but the scientific advancements need to be accompanied by political mobilization to ensure that the resources are available to develop, manufacture, and distribute the new vaccines and, thus, save millions of lives.

The World Health Organization (WHO) aims to eradicate tuberculosis (TB) as a public health problem by 2050 [1]. This is an ambitious plan to reduce the number of cases to <1 per million population, because globally, 1 of 3 persons is estimated to be infected with the causative agent Mycobacterium tuberculosis.

Eradication will be impossible without an effective vaccine. Although TB is curable, it has been estimated that an individual with active TB infects ≧3 other individuals before receiving a diagnosis and treatment. It is therefore impossible to lower the reproductive rate of the disease to <1, despite treating millions of persons.

The WHO estimated that there were 10.4 million cases of TB in 2007 [2], of which 9.27 million were new episodes of disease. Modeling studies estimate that, without new vaccines or other new tools, there will be 101.7 million new cases and 17.9 million TB-related deaths in southern Asia alone from 2015 through 2050 [3]. These same modeling studies show that, if properly deployed with mass vaccination, these new pre- and postexposure TB vaccines could prevent 85.9 million (84%) of these cases and 14.5 million (81%) of these deaths [3].

A vaccine will also help against the spread of drug-resistant TB. The new generation of vaccines being developed will protect against drug-resistant forms of the disease, because they are directed against antigens that are not modified by resistance to antibiotics. Of the estimated global total of TB disease cases, an estimated 4.9% cases involve multidrug-resistant (MDR) TB [2]. Ominously, of the 0.5 million cases of MDR-TB worldwide, it is estimated that the majority (0.3 million) occurred in persons not previously treated for TB.

The majority of humans infected with TB control but do not eliminate the pathogen, therefore creating a vast reservoir of latent TB infection. Such latent TB reactivates when the immune system weakens—most notably, in individuals with HIV infection. In 2007, the WHO estimated that ∼1.4 million individuals were jointly infected with TB and HIV, and 456,000 of these coinfected individuals died [2].

Extensive work in a community showed that the incidence of active TB was 5% per year among HIV-infected individuals with CD4 T cell counts of 450–1000 cells/mm³. Incidence increased to 30% when CD4 T cell counts decreased to <25 cells/mm³ but decreased to ∼5% when CD4 T cell counts were restored with antiretroviral therapy [4, 5]. Although most of this incident TB was reactivated TB, molecular techniques
showed that ∼30% of cases were probably attributable to new infections [6]. This inverse relationship between CD4 T cell counts and incidence of TB suggests that vaccines capable of inducing a vigorous durable T cell response of the proper type should be able to protect against TB. Data reported recently on 2 of the new vaccine candidates revealed strong antigen-specific T cell responses in HIV-infected individuals with CD4 T cell counts as low as 200 cells/mm³ [5, 7], suggesting that even immunosuppressed HIV-infected individuals could be protected.

TB VACCINES

Bacille Calmette-Guérin (BCG) Vaccine

The only currently licensed vaccine against TB is BCG vaccine, of which >100 million doses are given each year. It is accepted that BCG vaccine protects young children (age, <5 years) against more dangerous extrapulmonary forms of TB [8] and, thus, is given as a routine vaccination in many countries, as recommended by the WHO.

However, the efficacy of BCG vaccine against pulmonary TB is doubtful. Some studies have shown that BCG vaccine has a protective effect against pulmonary TB, and others have failed to show such benefits; in 2 studies, the vaccine appeared to enhance the risk of *M. tuberculosis* infection [5, 9, 10]. A trial involving >10,000 infants that was performed by the South African TB Vaccine Initiative in the Western Cape province of South Africa found a 4.5% incidence of disease over 18 months, despite routine BCG vaccination [11].

The spread of HIV infection, which is heavily concentrated in areas with a high TB burden, has added an additional risk when BCG vaccine is given to HIV-infected children. Despite being a greatly attenuated live vaccine, BCG vaccine can cause disseminated disease (“BCG-osis”) in HIV-infected children at rates as high as 1%. For this reason, the WHO has recommended that the vaccine not be given to HIV-infected children. However, because most infants are not tested for HIV infection, this presents policy makers with a dilemma: vaccinate and risk causing disease in children who may be HIV infected or do not vaccinate and risk dangerous forms of TB disease to which HIV-infected infants are particularly susceptible [12]. This combination of ineffectiveness and risks of adverse events demands that better vaccines be developed to protect everyone.

TB Vaccine Development

The 88 years since the Messieurs Calmette and Guérin released their vaccine included a period of complacency during which lack of TB in the developed world, coupled with the use of BCG vaccine, led to a dearth of research on vaccines, treatment, and diagnostics. Recognition that HIV infection was fueling a resurgent TB epidemic led to a drive to develop new vaccines. In 2009, there were more vaccines in the development pipeline than ever in history (Figure 1). Vaccines can potentially interrupt TB at several stages: they can block initial infection, prevent early disease, prevent latent infection, or prevent reactivation of latent disease.

The widespread use of BCG vaccine in areas where the burden of TB is high has led to a focus on a prime-boost strategy. Newborns first have their immune systems primed with either a standard form of BCG vaccine or a newer-generation genetically engineered recombinant BCG vaccine and are then given the new TB vaccine as a booster. We and others [13, 14] have found in humans that BCG priming enhances the immune responses to a variety of TB “booster vaccines,” such as recombinant proteins plus adjuvants or viral vectors. It has been...
shown in animals, including nonhuman primates, that such prime-boost responses are even further enhanced if recombinant BCG–overexpressing TB antigens are used as the prime instead of BCG [15–17].

Although research has focused on injectable vaccines, aerosolized vaccines that are delivered to the deep lung and mimic the natural route of *M. tuberculosis* infection are also being developed, as are oral vaccines (S Rao, K Song, DL Bolton, RL Wilson, JJ Mattapallil, C Andrews, J Sadoff, J Goudsmit, MG Pau, R Seder, PA Kozlowski, GJ Nabel, M Roederer, unpublished data) [5]. Both approaches would have the advantage of being inexpensive and easily administered.

**TB Vaccine Pipeline**

**Recombinant BCG vaccines.** The first new recombinant BCG TB vaccine to be tested in humans [18, 19] was rBCG30 (developed by Dr. Horowitz’s group at University of California, Los Angeles). This organism induced higher levels of antigen-specific CD4 and CD8 T cells through overexpression of antigen 85B; however, it contained the antibiotic-resistant marker hygromycin and could not be developed further [20], because use of antibiotic markers is opposed by regulatory authorities for fear that it will increase spread of drug resistance. The next recombinant BCG vaccine to be tested was VPM1002 (developed by Dr. Kaufman’s group at the Max Planck Institute, Berlin, Germany). This vaccine had improved safety in immunosuppressed animals and increased potency through perturbation of the endosomal membrane [21] but also contains antibiotic-resistance markers. One of the 4 recombinant BCG vaccines developed by the Aeras Global TB Vaccine Foundation should enter human clinical testing in early 2010 [5]. Two of these antibiotic marker–free strains are nonreplicating and should be safe in HIV-infected infants. Many other recombinant BCG vaccines and recombinant nonreplicating and attenuated TB organisms are in preclinical development [22–25].

**Booster vaccines for BCG- or recombinant BCG-primed infants and for adolescents and adults.** Two recombinant proteins combined with advanced adjuvants have been tested in phase I trials in Europe and are currently being tested in studies in Africa. The GSK M72 Aeras-sponsored vaccine is a recombinant fusion protein that has induced protection in long-term nonhuman primate challenge studies [26] and high levels of CD4 T cells in BCG-primed individuals, including HIV-infected individuals with CD4 T cell counts as low as 200 cells/mm³ [7]. This vaccine is scheduled for phase Ib efficacy studies in 2010. Two recombinant fusion proteins developed by the Statens Serum Institut, Hybrid-1 and HYVAC4/AERAS-404 (with Sanofi-Pasteur), induce protection in mice and guinea pigs and also induce antigen-specific CD4 T cell responses in humans.

Two recombinant nonreplicating viral-vec-orted TB vaccines have undergone extensive clinical studies and have entered phase Ib proof-of-principle safety and efficacy studies. One of these vaccines, MVA8A/AERAS-485 (Emergent Biosolutions), was developed by Dr. McShane’s group at Oxford University (London, United Kingdom). It is a highly attenuated vaccinia virus that has been tested for safety and immunogenicity in infants, adults with and without latent TB, and HIV-infected adults. After a BCG prime, it induces mostly polyfunctional CD4 T cells that can be induced to proliferate and persist at fairly high levels in a dose-dependent manner [13, 27–29].

On 15 July 2009, a girl became the first infant to receive a new TB vaccine being studied for efficacy in >80 years. In total, 2800 infants in the trial will receive the BCG vaccine at or near birth and a booster at 14–16 weeks of age with either MVA85A/AERAS-485 or placebo. This study has 90% power to detect a 60% decrease in the incidence of clinical TB, compared with placebo. The same vaccine is scheduled to be tested for efficacy in HIV-infected adults with CD4 T cell counts >350 cells/mm³ in 2010.

The second clinically advanced TB vaccine is AERAS-402/Ad35 (Crucell), a nonreplicating Ad35-vectored vaccine that [15, 16] has shown protection in nonhuman primate challenge models as a boost to recombinant BCG vaccine. When delivered to the lung of nonhuman primates as an aerosol, AERAS-402 induced high levels of antigen-specific CD4 T cells and CD8 T cells in bronchoaveolar lavage cells [17]. This vaccine induced antigen-specific polyfunctional CD4 T cells and very high levels of antigen-specific CD8 T cells in South African adult volunteers who had received BCG vaccine at birth [14]. Phase Ib efficacy studies of AERAS402/Cruckell Ad35 as a booster to BCG vaccine in infants should begin in 2010 in several African countries.

In July 2009, it was announced that AERAS402/Cruckell Ad35 would be tested for safety and efficacy by Aeras and the Aurum Institute (South Africa) in HIV-infected adults who have latent TB infection, have CD4 cell counts >350 cells/mm³, and are not receiving highly active antiretroviral therapy. This proof-of-principle study will not only help determine whether the vaccine can benefit HIV-infected individuals but also indicate whether it can prevent reactivation from latency and new infections [5]. Another promising adenovirus-based vaccine using the Ad5 vector recently entered clinical phase I trials [30, 31].

An efficacy trial of an inactivated *Mycobacterium vaccae* vaccine tested in 2000 HIV-infected adults in Tanzania reported 33 TB cases in the control group and 52 cases in the placebo group (efficacy, 37%; *P = .027*) among individuals with culture-proven cases. There was no significant protection in individuals with probable TB. The study will need to be repeated with current good manufacturing practice–manufactured vaccine but provides some promise that HIV-infected individuals can be protected [32].
A variety of other vaccines are in preclinical development. AERAS-405 is based on the nucleocapsids of bacterial phages and, therefore, is extremely inexpensive to produce and can be delivered as an aerosol to the lung or by oral administration through shigellosis to the gut [5]. Capsular polysaccharides are being explored [33], as is the heparin-binding hemagglutinin mycobacterial adhesion protein, which has been associated with dissemination of *M. tuberculosis* from lung to extrapulmonary tissues [34–37] and may play a role in reactivation and dissemination.

**CHALLENGES OF TB VACCINE DEVELOPMENT**

**Gaps in scientific knowledge.** Developing a vaccine against TB requires overcoming several problems that were not significant obstacles in the development of most of the most widely used vaccines against other diseases. There are major gaps in our knowledge. For example, it is unclear why 70% of individuals exposed to TB by infected household contacts do not even allow the organism to replicate enough to convert their tuberculin skin tests and never develop active TB. Furthermore, more needs to be learned about the nature of latency, which genes the organism expresses during the latent state, and which immunologic and local environmental factors specifically lead to reactivation. Understanding these issues in more depth will help in design of vaccines that can prevent actual productive infection, latency, or reactivation.

Another mysterious finding is that, in contrast to most organisms (except possibly typhoid), *M. tuberculosis* does not vary the amino acid sequences of the epitopes that the cellular immune system recognizes but actually purifies them and keeps them very constant. It is as if there were some advantage to the organism to be recognized by the human immune system rather than mutating away from that recognition, as HIV so successfully accomplishes [38]. This finding may imply that the organism can distort the human immune system for its own purposes to eventually evade and later spread.

A central problem in TB vaccine development is that the lung is a privileged site and the organism has evolved for hundreds of thousands of years to live in that site in balance with an immune system that cannot make too vigorous a response without killing the host. Vaccines must induce the amount, type, and location of cellular and, possibly, humoral responses that protect against the organism and do not accelerate disease. The downfall of Dr. Koch’s attempts against the disease may have, in part, been attributable to the fact that his treatment for TB (the heat-inactivated filtrate of TB cultures) possibly accelerated disease in some cases [39].

There is no known surrogate immunologic marker that predicts vaccine-induced immunity in humans. Furthermore, animal models do not exactly reflect human pathology or pathogenesis. To date, vaccinated nonhuman primates have been challenged with doses (generally 200–2000 colony-forming units) that cause 100% of the animals to develop active disease. This is in contrast to low disease rates among humans after exposure, indicating the need for more natural nonhuman primate models of infection. Protected and nonprotected subjects need to be examined with intense immunological and microarray analysis to discover immunologic surrogates of immunity.

**Policy and political challenges.** Scientific research and development is a necessary but insufficient factor in the eradication of TB. Equally important is ensuring that any products can be swiftly registered for human use and rapidly prequalified by the WHO (as are HIV drugs; MM Lumpkin, personal communication) and that the vaccines are affordable and available in areas where they are most needed. This will involve some form of international mechanism to facilitate the delivery of future vaccines to impoverished areas and will require the same level of dedication and determination seen in the campaign to eradicate polio. One of the motivations should be the financial burden of TB; the global cost of the disease was estimated to be $47 billion in 2007 [40].

Both preexposure prophylaxis for infants and adults and postexposure prevention of the reactivation of latent disease are important points to stop TB transmission. Whether or not this dual approach is feasible in first-generation vaccines, quantitatively, the biggest impact on TB transmission will come through mass vaccination campaigns, rather than just through the vaccination of neonates. A model by Abu-Raddad et al [3] found that vaccination of neonates with a vaccine that is 60% effective before exposure to TB would lead to a 39% reduction in the incidence of TB by 2050 in southern Asia alone. Mass vaccination with such a preexposure vaccine would lead to an ∼80% decrease in incidence by 2050. A policy of mass vaccination, especially if combined with aggressive case finding and treatment, would, however, require sustained commitment from national and international bodies and significant financial resources.

**Funding challenges.** TB research, particularly TB vaccine work, is underfunded. TB vaccine research is underfunded by ∼$1 billion, according to the Treatment Action Group [41]. The contrast between HIV infection and TB is stark. The Office of AIDS Research at the National Institutes of Health reported that 10% of the total budget for 2007 was spent on research on HIV infection and AIDS, of which 21% ($596,775,342) was spent on vaccines. In contrast, TB-specific research at the National Institutes of Health in 2007 was 0.6% of the total budget ($160 million), of which only 10% ($15,689,367) was spent on vaccine research. According to the Treatment Action Group, this expenditure on TB-specific research fares particularly badly when compared with the $122 million spent on smallpox, a disease that was eradicated 3 decades ago [42].

Overall, over the past 25 years, there has been a significant
increase in funding for TB research, including increasing dominance of donor organizations, such as the Bill & Melinda Gates Foundation, the Wellcome Trust, and the Dutch, British, Norwegian, and other European governments. With TB vaccines moving toward or into phase II trials, a looming issue is the cost of such large-scale efficacy trials. It is estimated that the costs of phase III trials for a single candidate in infants (14,000 participants) and in adolescent and adults (25,000 participants), in addition to manufacturing costs, will be ~$180 million. Even the Bill & Melinda Gates Foundation may not be able to support such trials without a multinational effort, including creative financing by industry, the World Bank, the International Finance Facility, and even private equity.

CONCLUSIONS

A reinvigorated—although still underfunded—research campaign is leading to the development of new vaccines against TB that are entering advanced clinical trials. However, the science alone is not enough. An effective vaccine needs to be accompanied by strong political will, clear policy objectives, a facilitative regulatory environment, and sufficient funding, to substantially reduce the spread and extent of the disease. Mass vaccination campaigns would save millions of individuals from TB-related morbidity and mortality and would have economic benefits that would flow from individuals, households, and communities up to country level; would lead to economic development; and would boost human capital potential. Researchers and policy makers need to start planning how to best produce and use an effective vaccine when it becomes available. TB has been described as a disease older than history; it is time for humanity to curb or even eradicate this ancient pandemic.

Acknowledgments


Potential conflicts of interest. B.B. and J.C.S are employees of the Aeras Global TB Vaccine Foundation, which sponsors some of the vaccines identified in this paper.

Supplement sponsorship. This article is part of a supplement entitled “Synergistic Pandemics: Confronting the Global HIV and Tuberculosis Epidemics,” which was sponsored by the Center for Global Health Policy, a project of the Infectious Diseases Society of America and the HIV Medicine Association, through a grant from the Bill & Melinda Gates Foundation.

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