The Challenges Of Developing New Tuberculosis Vaccines

ABSTRACT The World Health Organization estimates that tuberculosis is causing nearly two million deaths annually, mostly in developing countries. Widespread administration of the current tuberculosis vaccine to newborns is not a reliable route for preventing the disease in adults, the population that drives the epidemic. Several new vaccine candidates are in development, and a few have entered clinical trials. However, the field faces formidable scientific and policy challenges. A collaborative approach to solving scientific, policy, and resource obstacles—as well as new partnerships among emerging economies and vaccine development organizations—will be critical to developing a new tuberculosis vaccine that could achieve its public health potential to save lives and reduce the burden of disease.

The global tuberculosis (TB) epidemic continues to devastate poor and marginalized populations throughout the world. Tuberculosis is second only to HIV/AIDS on the list of infectious disease killers. The World Health Organization estimated that TB took the lives of 1.7 million men, women, and children in 2009. There were an estimated 9.4 million new cases of TB that same year. Most TB cases and deaths occurred in Asia and Africa; the largest number of new cases occurred in India, China, South Africa, Nigeria, and Indonesia.1

Tuberculosis most often occurs in adolescence and adulthood, affecting those in the most productive segments of society and placing a substantial economic burden on national economies.2-3 Ramanan Laxminarayan and colleagues estimate the economic costs of TB in twenty-two high-burden countries to be $3.4 trillion over ten years, and per country costs range from $3.32 billion in Zimbabwe to $1.182 trillion in China.4

Poverty, social disruption, malnutrition, old age, and HIV infection are all risk factors for TB disease. TB/HIV co-infection is a particularly serious problem in Africa, where 80 percent of all TB/HIV co-infection cases in the world are estimated to occur.1

Control of the global TB epidemic is further complicated by the emergence and spread of drug-resistant forms of the disease. Multidrug-resistant TB is resistant to the two most important first-line antibiotics: isoniazid and rifampicin. Extensively drug-resistant TB is resistant to the same two first-line antibiotics plus several second-line antibiotics. Multidrug-resistant TB and extensively drug-resistant TB depend on drugs that are less potent than first-line drugs but are more toxic, are much more expensive, and require longer treatment periods. According to 2008 estimates by the World Health Organization, one-third of the 440,000 cases of multidrug-resistant TB resulted in death.5

New treatment options are needed for people who are infected, but the most effective tool would be a vaccine that prevents infection. Tools for TB control include diagnostics from the late nineteenth century; a vaccine, bacille Calmette-Guérin (BCG), introduced in 1921; and drugs that were developed decades ago.6

The BCG vaccine, when given to newborns, has been associated—in case-control studies—with...
reduced severity of early childhood TB (including meningeal TB, which is nonpulmonary and affects the brain, and miliary TB, which is widely disseminated TB). However, administering the vaccine to newborns does not appear to provide much, if any, protection against adult pulmonary TB, which accounts for most of the transmission and global burden of TB morbidity and mortality. The total burden of TB has remained high in countries where the BCG vaccine is routinely administered to most infants. Thus, the vaccine does not appear to be affecting the global TB epidemic.

In its Global Plan to Stop TB (2006–15), the Stop TB Partnership—an effort sponsored by the World Health Organization—is promoting development and adoption of new TB diagnostic tests, drugs, and vaccines to reach the long-term goal of eliminating the disease.7 Major challenges stand in the way of that goal, but progress is being made. Before 2000 little work was being done on TB vaccines, but now several are under development, and nine are currently in clinical trials, as shown in Exhibit 1.

Goals And Approach
The Global Plan to Stop TB states that the introduction of new, effective TB vaccines will be an essential component of a strategy to eliminate the disease by 2050; elimination is defined as less than one case per million population.7

In 2006 the Stop TB Partnership’s working group on new TB vaccines set an ambitious objective of identifying a safe, effective, licensed vaccine that would be available at a reasonable cost by 2015. The target year was later revised to 2020. Modeling research has shown that a new vaccine that has only modest efficacy, but that is more effective than the current BCG vaccine in protecting against adult pulmonary TB, has the potential to greatly reduce both the health impact and the economic burden of the disease.8–10 Although the initial 2015 objective for introducing a new TB vaccine is unlikely to be met, there is reason to be optimistic regarding the eventual success of new TB vaccines. The fact that the normal immune response of healthy people to Mycobacterium tuberculosis, the pathogen that causes tuberculosis, protects approximately 90 percent of infected people against TB disease demonstrates that a vaccine is possible. These people develop latent TB infection characterized by a positive tuberculin skin test without progression to active disease.11 However, both reactivation of latent TB infection to produce TB disease and reinfection with M. tuberculosis after successful treatment of the disease suggest that the immune response to the pathogen is complex and that multiple vaccines may need to be developed for different patient populations.

### Exhibit 1
New Tuberculosis Vaccines In Clinical Development

<table>
<thead>
<tr>
<th>Vaccine (source, sponsor)</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCG REPLACEMENT OR PRIMING VACCINE CANDIDATES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rBCG30 (UCLA, Aeras)</td>
<td>Recombinant BCG overexpressing Ag85B</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>rBCG+UreaC.Hly; VPM-1002 (Max Planck Institute, VPM)</td>
<td>Recombinant BCG that perforates the endosome to enhance immunogenicity</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>AERAS-422 rBCG (Aeras)</td>
<td>Recombinant BCG that perforates the endosome and overexpresses Ag85A, Ag85B, and Rv3407</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>BOOSTING VACCINE CANDIDATES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M72 + AS01 (GSK, Aeras)</td>
<td>Fusion protein, Mtb 39 + Mtb 32, plus AS01 adjuvant</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>MVAB5A (Oxford, Emergent Biosolutions, Wellcome Trust, Aeras)</td>
<td>Nonreplicating vaccinia vector expressing Ag85A</td>
<td>Phase IIB</td>
</tr>
<tr>
<td>AERAS-402/Ad35 (Crucell, Aeras)</td>
<td>Replication-deficient adenovirus vector expressing Ag85A, 85B, and 10.4</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Ad Ag85A (McMaster University)</td>
<td>Adenovirus vector expressing Ag85A</td>
<td>Phase I</td>
</tr>
<tr>
<td>Hybrid-1 + IC31 (Staten Serum Institut, Intercell)</td>
<td>Recombinant fusion protein Ag85B+ESAT-6 plus IC31 adjuvant</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Hybrid-1 + CAF01 (Staten Serum Institut)</td>
<td>Recombinant fusion protein Ag85B+ESAT-6 plus CAF01 adjuvant</td>
<td>Phase I</td>
</tr>
<tr>
<td>Hybrid-4/AERAS-404 + IC31 (Staten Serum Institut, Sanofi-Pasteur, Intercell, Aeras)</td>
<td>Recombinant fusion protein Ag85B+TB10.4 plus IC31 adjuvant</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Source: Stop TB Partnership Working Group on New TB Vaccines. Tuberculosis vaccine candidates—2009 [Internet]. Geneva: Stop TB Partnership; [cited 2011 May 26]. Available from: http://www.stoptb.org/wg/new_vaccines/assets/documents/TB%20Vaccine%20Pipeline%202009.pdf. A 2010 update is forthcoming. Notes: In addition to the ten vaccine candidates in this exhibit, two vaccines made from inactivated environmental mycobacteria, Mw and M vaccae, and one vaccine made from disrupted M tuberculosis, RUTI, are in clinical development, especially for postinfection immunotherapy indications. Also, more than twenty candidates for BCG replacement and priming and for boosting are in various stages of preclinical development.
A formidable scientific obstacle is a lack of understanding or definition of the components of the protective immune response to *M. tuberculosis* infection or to a TB vaccine that are predictive or correlate with protection. There are clues that one type of the body’s immune cells, CD4 T cells, which can target *M. tuberculosis* specifically and produce multiple types of cellular signaling molecules to control the pathogen, may be important in protection. There is also suggestive evidence from animal studies that other types of white blood cells, called CD8 and Th17 T cells, may be important for protection.

Components of the early or innate immune response cells, which do not target *M. tuberculosis* specifically but have evolved to attack all invading pathogens, may be important in driving the initial infection in the direction of long-term containment of a latent TB infection. Antibodies may play a role in protecting against TB transmission and infection. However, the preponderance of evidence suggests that the action of CD4 and CD8 T cells provides the primary mechanism of protection against *M. tuberculosis.*

The likelihood seems low that one day there will be a single vaccine that works against all forms of TB in all age groups, or a single immune response marker that serves as a surrogate for protection, akin to antibodies in the case of currently licensed vaccines against viruses and bacteria. The lack of both a correlate of protective immunity—a marker that might predict efficacy—and an animal model that is known to predict efficacy of vaccine candidates in humans poses substantial technical challenges. These challenges force the TB vaccine research and development effort to depend heavily on large efficacy trials of promising candidates in humans—candidates that have plausible rationales but that lack a known mechanism or biomarker of protection.

**Strategy And Development**

A widely pursued approach to developing new TB vaccines is called a heterologous prime-boost strategy, in which a person receives two different vaccines to protect against the target disease. The first component of this strategy—the “prime” aspect—is to continue early infant primary immunization with the BCG vaccine to prevent severe early childhood TB disease. The second component of the heterologous prime-boost strategy is to administer a second—different—TB vaccine as a boost to the primary BCG vaccine, which will broaden and prolong the protection that vaccine provided. Boosting can be done during infancy or childhood and again later in adolescence or young adulthood. For adolescents or adults who are latently infected, prime boosting may extend the duration of protection and prevent reactivation of TB disease or reinfection with *M. tuberculosis.*

An important goal for new TB vaccines is to be safe and effective as preventive vaccines to administer to healthy infants. The World Health Organization currently recommends not giving BCG vaccine to HIV-infected infants because of evidence that they are at increased risk of serious BCG disease caused by the live vaccine. This problem has created interest in vaccines that are safer as well as more effective than the current BCG vaccine.

Before 2000 there was almost no clinical development work being done with new TB vaccines. During the period 2001–10 three candidates to replace BCG vaccine, made by genetic modification using recombinant DNA technology, entered small-scale, first-time testing (Phase I), the initial stage of clinical testing to evaluate the safety of a candidate vaccine in humans (Exhibit 1). In preclinical animal studies of these candidates, there is evidence of greater safety, immunogenicity, priming for boosting, and protection against *M. tuberculosis.* During this period, a number of candidates for boosting BCG entered clinical development. These boosting candidates use parts of the *M. tuberculosis* microbe delivered by various methods to induce appropriate immune responses.

To date, all of the new TB vaccine candidates in early clinical development have acceptable safety profiles (no serious side effects)—including in HIV-infected people for several of the live vaccine candidates—and have stimulated the kind of immune responses that may be associated with protection.

In 2009 one of the boosting candidates, a modified vaccinia virus Ankara (MVA85A) that expresses an *M. tuberculosis* antigen, 85A, entered a Phase IIb proof-of-concept trial in more than 2,700 infants in South Africa. This type of trial is designed for preliminary efficacy evaluation and to further test the safety of the vaccine in a larger group than Phase I trials, before moving into still larger-scale Phase III efficacy testing. The vaccine is being evaluated as a booster vaccine in infants who received the BCG vaccine at birth. Preliminary results from the trial are expected in 2012.

Another candidate (AERAS-402/Ad35), an adenovirus that expresses 85A and two other *M. tuberculosis* antigens, has also advanced into Phase II proof-of-concept testing in Africa.

Eventually, there will be a need for field trial sites capable of doing large efficacy trials in hu-
mans of the most promising new investigational TB vaccines or, quite likely, prime-boost combinations of vaccines. These trials will require further site preparation and funding well beyond that currently available for preclinical and early clinical development of candidates. Although Africa has been the main host of early and mid-stage trials, emerging economies in which TB is endemic may be positioned to play a greater role in the future.

Experience with field trials to date has made clear the challenges in detecting and accurately diagnosing TB in early childhood—an important target population. This is less likely to be an obstacle in adolescents and adults, age groups in which much TB morbidity and mortality occurs. All of these groups—infants, children, and adults—are important target populations for new TB vaccines.

**PROSPECTS FOR ADOPTING NEW TB VACCINES**

In 2010 Aeras, a nonprofit product-development partnership dedicated to the development of new TB vaccines, commissioned a study to gain greater understanding of potential drivers of and barriers to future adoption of new TB vaccines in endemic countries. Eighty-six public health policy and decision makers in eight “high-burden” countries heavily affected by TB were asked questions on a range of topics, such as perceived national health care priorities, the magnitude and management of tuberculosis in their countries, the adoption of potential new TB vaccines, and funding for these vaccines.

In particular, participants were presented with a number of scenarios describing potential new vaccines. Scenario 1 described a BCG replacement vaccine that would be available in 2016; that would be safer in HIV-infected infants; that would be priced at the level of current BCG vaccines; and that would be designed to work with a second, different vaccine available later than 2016. Scenario 2 described an inexpensive booster vaccine that would be available in 2016; that would be administered to infants and again in adolescence; and that would result in reductions of symptomatic disease by at least 60 percent, fewer new infections than BCG alone, and 50 percent lower TB incidence by 2050.

In response to Scenario 1, twenty-five respondents (29 percent) expressed the viewpoint that their country would be likely to adopt the vaccine within three years of its first licensure, and ten respondents (12 percent) stated that adoption was unlikely. Another thirty respondents (35 percent) stated that adoption would depend on proof of efficacy and cost efficiency. Twenty-four percent of the participants (twenty-one of eighty-six) did not respond to this question.

A lack of political will may impede the introduction of new TB vaccines.

In response to Scenario 2, thirty-three respondents (39 percent) expressed the view that the vaccine was likely to be adopted in their country; only eight respondents (9 percent) stated that adoption was unlikely. Twenty-five respondents (29 percent) stated that adoption would depend upon scientific proof of safety and efficacy, the ease of implementing a booster shot, and cost. Again, fewer than a quarter of participants (twenty of eighty-six, 23 percent) did not provide a response. Overall, the survey results demonstrated that there is considerable demand for using a partially effective vaccine against TB that improves upon BCG.

However, respondents also anticipated a number of barriers to the adoption of new TB vaccines in endemic countries. Respondents most frequently mentioned compliance with regulatory requirements, including proof of efficacy and safety, as potential challenges. Respondents in all countries except Brazil and South Africa noted the need for supportive results from local clinical trials. In order of decreasing frequency, respondents also mentioned the need for training to deliver prime-boost vaccines, cost of a new vaccine, and infrastructure such as cold-chain capabilities to maintain vaccines at the necessary temperatures in distribution.

A common theme in response to many of the questions was the notion that political will would be a key factor in successful adoption. Commenting on Scenario 1, one respondent noted: “[My country] has a planned vaccination programme. Those planned vaccines are free. If the new vaccine is not planned, it is on people’s own expense. TB mainly threatens poverty-stricken people in rural areas. These patients are very poor and can’t afford the vaccine. They will have problems getting inoculated.”

TB is primarily a disease of poverty, and consequently those most directly affected are also those who may have the least ability to advocate for their own needs. Respondents noted that TB needed more attention in their countries but that it was often overshadowed by other public health issues. With competing public health and other priorities, and the recognition that benefits of
new, more effective vaccines may take many years to be realized, a lack of political will may impede the introduction of new TB vaccines.

Overall, results from the study suggested that (1) there was a great deal of heterogeneity among decision makers; (2) strong efficacy data, including in-country data, will be an important success factor for adoption decisions; (3) cost, if kept low, is not likely to be a major obstacle; and (4) although education and preparation will be necessary, raising expectations too high needs to be avoided.

THE FUTURE OF VACCINE DEVELOPMENT Speaking at the National Institutes of Health in early 2011, the administrator of the US Agency for International Development, Rajiv Shah, made a strong statement about the promise of vaccines and the need to fight TB:

“TB has always been the signature disease of the urban poor. In a world that is urbanizing at a rate of 200,000 [people] every day, we must fight TB now before it becomes an unparalleled global killer.... The evidence is clear: Vaccines are the best public health investment we can make. Our best hope of sustainably eliminating malaria, TB, and closing the chapter on HIV/AIDS will, in fact, depend on their development and widespread use.”

Although there is considerable momentum in the development of new TB vaccines, the field is faced with tremendous scientific challenges coupled with large funding needs. In its revised Global Plan to Stop TB (2011–2015), the Stop TB Partnership estimates that $1.9 billion is required over the next five years to meet targets for the development of new and better TB vaccines. 17

The majority of funding for TB vaccine research and development today is provided by two major funders: the Bill & Melinda Gates Foundation (44 percent) and the National Institute for Allergy and Infectious Diseases at the National Institutes of Health (18 percent). The remaining 38 percent of funds come from governments, research institutes, foundations, and other organizations. 18 An independent study provided similar findings. 19 Regarding costs of development, clinical trials will represent the largest cost over time. Exhibit 2 shows a breakdown of costs associated with key TB vaccine research and development areas: Clinical trials represent a majority share in 2014 and 2015.

There are a number of approaches to take in meeting the financial and scientific challenges ahead. Expanded partnerships to address the scientific complexities and clinical trial needs will be critical to successful TB vaccine development. There is a growing role for greater involvement in all phases of TB vaccine research and development by emerging economies where TB is endemic. Additionally, to balance the concerns of both public health officials and private-sector investors, policies such as tiered pricing may need to be instituted to ensure that new vaccines are provided at affordable prices to those regions where they are most needed, and to ensure an acceptable return on investment for developers. 9

With the spread of multidrug-resistant and extensively drug-resistant TB, coincidence with HIV, and escalating urbanization—especially in China, India, Latin America, and much of Africa—the threat of TB is growing for populations across the world. Although it is recognized that new TB vaccines will be pivotal in efforts to eliminate the disease, the lack of a known correlate of protection or animal model known to predict protection, the need for large clinical trials, a considerable funding gap, and multiple barriers to adoption of new vaccines will need to be overcome for the tremendous public health benefits to be realized.

Greater collaboration between groups already involved with TB vaccine development globally—and increased partnerships among researchers and policy makers in emerging economies—will be critical in addressing the scientific, resource, and policy challenges to TB vaccine development and adoption.
Survey research presented in this article was supported with funding from the Bill & Melinda Gates Foundation. The authors also acknowledge Jamie Rosen for her assistance with editing.

NOTES

6 There are several BCG strains that vary in genetic makeup due to continuous subculture across laboratory locations since BCG was first developed. For the purposes of this paper, we refer to a singular BCG vaccine.
13 Boosting BCG with BCG does not appear to provide improved protection. Although revaccination with BCG has been practiced in some countries in the past, it is not recommended by the World Health Organization.
ABOUT THE AUTHORS: LEWELLYS F. BARKER, ANNMARIE E. LEADMAN & BARTHOLT CLAGETT

In this article in Health Affairs, Lewellys Barker and his colleagues survey the activities, challenges, and opportunities for new tuberculosis (TB) vaccines. As TB has spread and new drug-resistant forms of the disease have emerged, few advances have been made against the disease in the past forty years. Now Barker and colleagues report that multiple vaccines are in development, and a few have entered clinical trials—“although we do not have a good basis for predicting how well they will work,” he cautions.

Barker is senior medical adviser for Aeras, a nonprofit product-development partnership in Rockville, Maryland, that conducts research and development on new TB vaccines. He served in the Public Health Service, at the National Institutes of Health, and at the Food and Drug Administration. His major career focus has included preclinical and clinical work on viral diseases such as hepatitis, HIV, and smallpox; rickettsial and bacterial vaccines; immune globulins; and diagnostics for the detection, treatment, and prevention of infectious diseases.

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