POLICY

Tuberculosis vaccines: Time for a global strategy

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We need a global strategy for the development of better tuberculosis vaccines.

More than 130 years after identification of its infectious etiology, 120 years after the first vaccine trial, and 94 years after the Bacille Calmette-Guérin (BCG) vaccine was introduced into clinical use, tuberculosis (TB) remains a global health threat according to the World Health Organization. Although TB incidence is on a slow decline, multidrug-resistant strains of the bacterium *Mycobacterium tuberculosis* (*Mtb*) continue to emerge. Furthermore, BCG does not reliably protect against pulmonary TB, the disease manifestation that leads to transmission. As we commemorate World TB Day on 24 March 2015, we can celebrate having accomplished the modest Millennium Development Goal 6: halting and reversing TB incidence by 2015. However, we have not met the more ambitious 2015 Stop TB Partnership target of a 50% global decline in mortality and prevalence, especially in Africa and Europe. The post-2015 strategy of the Stop TB Partnership, which was approved by the World Health Assembly in 2014, aims for a 95% reduction in TB mortality and a 90% reduction in TB incidence by 2035. But the only realistic chance of meeting this goal requires the introduction of new and more efficacious interventions, such as vaccines. At this time, we have to acknowledge that current efforts at turning the TB tide remain insufficient.

Infants are highly susceptible to TB and thus receive BCG immediately after birth, before potential infection with *Mtb*. Vaccine candidates to replace BCG in newborns would have to be safer than BCG and afford protection against pulmonary TB that lasts into late adolescence. In endemic areas, adolescents and adults are often infected with *Mtb* without displaying clinical disease—so-called latent TB infection (LTBI). Booster candidates that are effective before and after exposure to *Mtb*, by modulating immunity afforded by neonatal vaccination or other mycobacterial exposure, are needed. TB vaccination should ultimately cover all age groups; however, modeling studies suggest that targeting adolescents and adults for vaccine-induced prevention of pulmonary TB would provide the greatest impact on a population level (*1*).

After a hiatus of more than 80 years, the 21st century has witnessed important advances in TB vaccine development. More than a dozen new preventive vaccine candidates are now progressing through the vaccine-development pipeline (*2*). Yet, the first and only new candidate evaluated in a clinical end point trial recently failed (*3*).

FINANCIAL CONSTRAINTS

With an increasing number of candidates, new financial, infrastructural, and scientific challenges arise. Considering a financial investment of U.S. $2000 to $10,000 per study participant, phase 2b clinical trials for preliminary proof of efficacy using disease end points will cost more than U.S. $20 million, whereas a phase 3 trial for ultimate safety and efficacy determination would

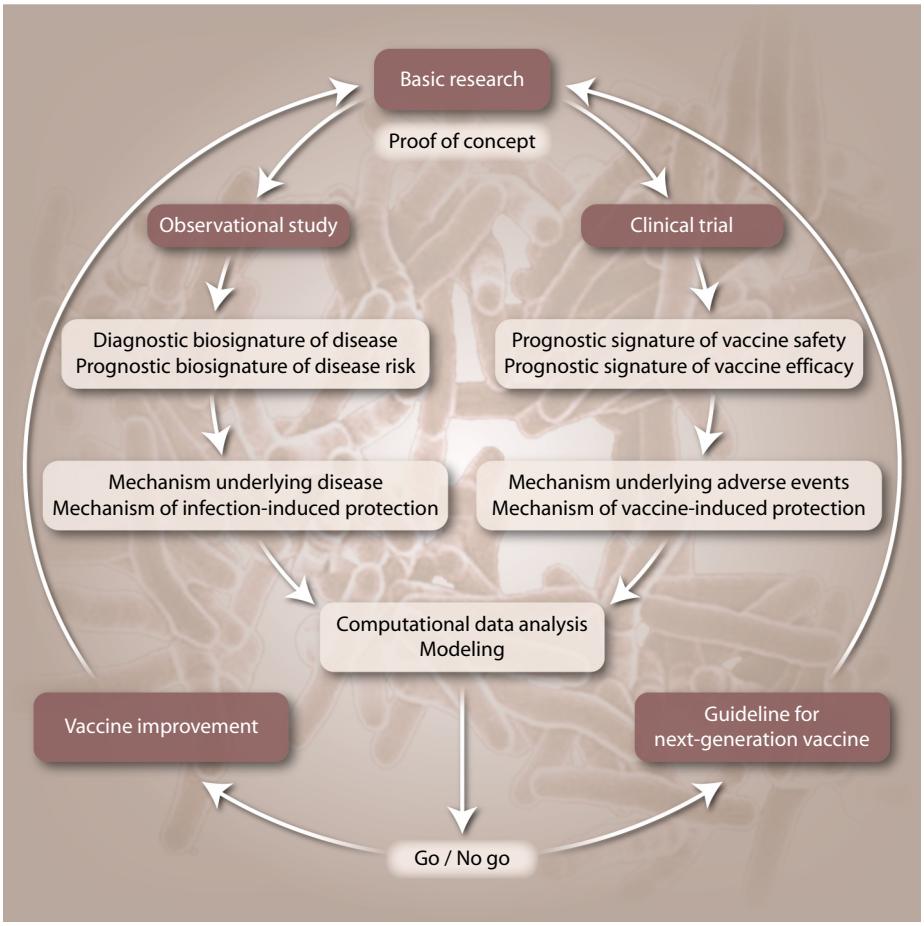

Fig. 1. New knowledge drives acceleration. Current clinical trials are restricted to analyzing canonical measures considered relevant to safety and efficacy. Because of the lack of correlates of protection for TB, researchers need new information that likely can be provided by global omics profiling. Data are generated from observational studies that analyze disease severity and disease risk in naturally *Mtb*-infected individuals and from vaccine clinical trials that focus on signatures of safety and efficacy. Through computational data analysis and modeling, new information can be harnessed to improve vaccine candidates entering the clinical trial pipeline and to design new vaccination strategies.

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likely cost U.S. $100 million or more. An enormous financial investment by industry, academia, governments, and intergovernmental and nongovernmental organizations would be required for the completion of such trials. Ongoing support for complementary activities in TB vaccine research and development (R&D) would need to continue in parallel. The current U.S. $250 million spent on TB vaccine R&D is at the low end, at one-third of the amount spent on AIDS vaccines. Incentives for private industry engagement are limited because TB vaccine development is viewed as a high-risk endeavor (*4*) (www.policycures.org/downloads/GF_report13_all_web.pdf).

GLOBAL PORTFOLIO MANAGEMENT

Obviously, the most suitable vaccine candidates must be selected for further development as early in the process as possible. One potentially productive path forward involves the establishment of global portfolio-management structures for TB vaccine candidates. Discussions toward such structures involve multiple stakeholders. In Europe, the Tuberculosis Vaccine Initiative (TBVI; www.tbvi.eu) has been central in this process and uses a bottom-up approach by facilitating collaborations among numerous European academic research laboratories with support from the European Commission (EC) and other funders. The product development partnership Aeras (www.aeras.org) in the United States, South Africa, and China uses an industry-modeled portfolio-management approach in its focus on TB vaccine development, with substantial support from the Bill & Melinda Gates Foundation. TBVI, Aeras, the European and Developing Countries Trials Partnership (EDCTP), the EC, and the European Investment Bank (EIB) have deliberated on the formation of a so-called global TB vaccine partnership. Recently, representatives from endemic-country funders, such as those from the BRICS nations (that is, Brazil, Russia, India, China, and South Africa), also have been approached. Partnership activities could include setting priorities for targeted populations, defining clinical end points, harmonizing clinical trial design, promoting head-to-head assessment of vaccines (including prime-boost combinations), defining go/no-go criteria, and characterizing correlates of protection. Recommendations from a qualified and broad representation of stakeholders could help to determine which candidates will progress through the clinical trial pipeline. These activities could lead to profound savings and an increased probability of success. Further leverage could be achieved by harmonizing clinical trial efforts with those used for testing TB drugs and HIV vaccines.

CURTAILING COSTS

Accelerating trials. Community-wide clinical trials for TB vaccine efficacy require large numbers of study participants who must be followed up for a long time period. Thus, any reduction in trial size or duration will alleviate required investments. Reduction could be achieved by conducting, before larger community-wide trials, so-called plausibility-of-efficacy phase 2b trials, which target individuals at particularly high risk of developing TB disease. Newborns, even when vaccinated with BCG, are susceptible to pulmonary TB, and a recent efficacy trial (*3*) revealed an incidence rate of ~1.5%, which is twice that of adolescents or young adults in the same geographical area. Household contacts of newly diagnosed TB cases in endemic areas, health care workers entering into TB settings, and miners can be considered as high-risk adult populations. Another potential target population is individuals in whom TB disease recurs after successful completion of chemotherapy; rates of recurrent TB disease, composed of relapse or reinfection, exceed 4% in some settings.

Another cost-saving clinical trial approach would be to test the ability of vaccines to prevent infection by targeting uninfected persons who test negative in an interferon-γ (IFN-γ) release assay or tuberculin skin test. These tests indicate productive infection with *Mtb* in individuals with LTBI or TB disease by measuring an antigen-specific immune response. Clinical trials that test a vaccine's ability to prevent *Mtb* infection using such measures require smaller sample sizes than those aimed at preventing full-blown TB disease. Although prevention of infection by itself is a vaccination goal, results could guide application for true disease prevention, assuming that the mechanisms of protection overlap in the studied cohorts.

Biosignatures. Alternatively, clinical trial sizes and costs can be reduced with the use of a molecular test (using blood or other biological samples) that identifies *Mtb*-infected individuals who are at elevated risk for developing TB disease—so-called risk biosignatures (*5*, *6*) based, for example, on global gene expression profiles and antigen-specific immune responses. Such a biosignature is emerging as a result of (i) a prospective cohort study of adolescents [National Institutes of Health (NIH) 5R01AI087915-05] and (ii) the multi-African-country Grand Challenge 6 household contact study (www.biomarkers-for-tb.net/consortium/the-consortium).

Biomarker discovery is increasingly recognized as an important component of future TB vaccine R&D. Indeed, correlates of efficacy for new vaccine candidates would be game-changing for the TB vaccine field. Yet, correlates of vaccine protection can only be described in the setting of a successful placebo-controlled efficacy trial, as has occurred in the HIV field. For example, in the Thai RV144 HIV vaccine efficacy trial, immunization induced protection in 31% of participants; this margin was too low to advance development of the tested vaccine but did allow the identification and characterization of markers that can discriminate between protected and unprotected study participants—and have informed further vaccine development (*7*).

Until a successful TB efficacy trial has been completed, researchers must rely on studies of correlates of TB disease risk to guide our understanding of protective efficacy against full-blown TB disease (Fig. 1). Such biosignatures are expected from the prospective adolescent trial and the Grand Challenge 6 study mentioned above. Another study has compared immune responses in infants who developed TB after BCG vaccination with infants who remained healthy for the first 2 years of life (*8*). Although markers of TB disease risk could not be identified, the study provided compelling evidence against IFN-γ and other type 1 cytokines as correlates of risk in this test population.

Adaptive trial design. Most recently, adaptive trial designs, which modify ongoing trials in response to interim results and plan accordingly, have been proposed for accelerated clinical development. Adaptive vaccine trials could deliver safety and efficacy data more rapidly by allowing iterative modifications after participant enrollment in response to interim safety or efficacy signals (*9*). For example, participant numbers could be increased or decreased and duration of follow-up modified on the basis of new disease incidence data, prognostic clinical surrogate end points, or interven-

tion regimens. End point–driven clinical trial designs also ensure that trials have the requisite power to answer the hypothesis at hand. Careful and transparent decision-making processes are imperative. Ideally, adaptive clinical trial designs would be complemented by transparent regulatory and licensure processes that incorporate global and regional input for expedited approval (*10*).

Biorepositories. In all phases of clinical trials, a detailed assessment of the host response would facilitate the iterative learning necessary for the design of adaptive or future trials (Fig. 1). At the very least, quality biological samples should be collected, stored, and made available to the research community at large; data generated by using biological samples also should be shared in a transparent manner. Analyses of biological samples from a given clinical trial not only would help to assess the vaccine tested in that trial but also could provide data to guide the next generation of vaccines and clinical trials. The additional burden of sample collection, storage, and analysis might not be attractive to sponsors, but the knowledge gained is critical for advancing the TB vaccine field. This approach emphasizes the importance of iterations from basic vaccine research to vaccine development to clinical trials and back, using state-of-the-art analytical tools in the wet laboratory, strong computational capacities, and attentive clinical observation (*5*, *6*, *10*).

NEED FOR NEW KNOWLEDGE

Last, almost all current vaccine candidates—although they may appear diverse at first sight—build on a single paradigm—namely, containment of *Mtb* immunity mediated by conventional T cells. Hence, all share an inherent risk of failure. The concept of a "black swan" as an unpredictable event with ground-breaking consequences has been propagated in economics by N. N. Taleb. TB vaccine research needs to keep an eye on unconventional approaches that could bring about a "pink swan" by harnessing hitherto unknown mechanisms of protection for designing more efficacious and safer vaccines. Any new paradigm in basic or clinical research should be aggressively pursued in search of the key elements to eliminate one of the world's most persistent and deadly pathogens.

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