The Tuberculosis Vaccines Pipeline

Back to basic science

By Mike Frick

The last year in tuberculosis (TB) vaccine research has demonstrated how setbacks can sometimes produce the potential for unexpected progress. Dominant hypotheses have yielded to new investigative directions, and unresolved questions have returned to center focus in the wake of disappointing results from the first efficacy trial of a TB vaccine since 1968. The announcement in February 2013 that TB vaccine candidate MVA85A did not confer significant added protection against TB to infants vaccinated with the existing TB vaccine, bacille Calmette-Guérin (BCG), delivered unwelcome news in a field eager for success.¹ One month after the publication of these results, TB vaccine researchers gathered in Cape Town, South Africa, at the Third Global Forum on TB Vaccines, where conversation focused on the lessons the historic MVA85A trial holds for future vaccine discovery efforts.

Discussions in Cape Town and during the following year have led researchers to revisit topics ranging from the predictive value of animal models used in preclinical development to the tradeoffs of different clinical trial endpoints to the complex contextual factors that affect risk of Mycobacterium tuberculosis (MTB) infection and TB disease. Driving these intersecting lines of inquiry is the urgent need to better understand host–pathogen interaction, or the interplay between MTB and the human immune system.

Answering these questions will require embracing new approaches in preclinical and clinical research as well as forging stronger connections between clinical research and development (R&D) and laboratory advances in basic science. Over the past year, developers have introduced new study designs in phase II trials, although not every TB vaccine candidate is taking advantage of these innovations. Findings from basic research have cast doubt on the core assumptions that steered TB vaccine R&D from its revitalization in 2000, when the pipeline sat empty,² to the present day, when the pipeline now has 16 candidates or vaccine combinations under active clinical development.
Table 1. Vaccine Candidates under Active Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Strategy</th>
<th>Type</th>
<th>Sponsor(s)</th>
<th>Status</th>
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<tr>
<td>M. indicus pranii</td>
<td>Immunotherapeutic</td>
<td>Whole-cell M. indicus pranii</td>
<td>Ministry of Science and Technology (Government of India), Cadilla Pharmaceuticals</td>
<td>Phase III</td>
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<td>Viral vector</td>
<td>Oxford University, Aeras, European &amp; Developing Countries Clinical Trials Partnership (EDCTP)</td>
<td>Phase IIb</td>
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<td>M72 + AS01</td>
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<td>Protein/adjuvant</td>
<td>GlaxoSmithKline, Aeras</td>
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<tr>
<td>VPM1002</td>
<td>Prime</td>
<td>Live recombinant rBCG</td>
<td>Vakzine Projekt Management GmbH, Max Planck Institute for Infection Biology, Tuberculosis Vaccine Initiative (TBVI), Serum Institute of India</td>
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<td>Crucell, Aeras</td>
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<td>Prime-boost</td>
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<td>Statens Serum Institut (SSI), TBVI, EDCTP, Valneva</td>
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<td>SSI, Sanofi, Institut Pasteur, Aeras</td>
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<td>SSI, Valneva, Aeras</td>
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<td>Live genetically attenuated MTB</td>
<td>University of Zaragoza, Biofabri, TBVI</td>
<td>Phase I</td>
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The composition of the TB vaccine pipeline remains virtually unchanged from the picture presented in TAG’s 2013 Pipeline Report. The pipeline includes vaccines designed to replace BCG (prime vaccines), improve the limited immunity conferred by BCG (prime-boost vaccines), and shorten TB chemotherapy (immunotherapeutic vaccines). Candidates under the prime strategy seek to either modify BCG or genetically attenuate MTB itself to produce a safer, more effective vaccine that could replace BCG altogether. Within the prime-boost strategy, viral-vectored and adjuvanted subunit vaccines aim to augment the limited immunity conferred by BCG. Viral-vectored vaccines use weakened, nonreplicating viruses to transport MTB DNA into human cells, where it is transcribed into antigens (proteins that provoke an immune response). Adjuvanted subunit vaccines combine different MTB antigens with adjuvants that boost the body’s natural immunity. The pipeline also contains several whole-cell vaccines constructed from inactivated mycobacteria related to MTB such as *Mycobacterium vaccae*.

**OLD QUESTIONS IN BASIC SCIENCE**

The lack of biomarkers that correlate with protective immunity against TB disease or MTB infection remains the central challenge of TB vaccine R&D. The word biomarker refers to genes, biological processes, or clinical phenotypes that act as precursors or signals of a particular disease or response to immunization or treatment. Biomarkers can help researchers improve the selection of candidates to advance to late-phase trials by giving glimpses of efficacy earlier in a vaccine’s development. The term is so frequently invoked as a stand-in for the many unanswered questions in TB immunology that it has become a too-convenient shorthand conflating distinct immunological questions that will not be solved by easy, unitary solutions. Context matters: researchers will need to identify unique markers for different stages of infection and disease, or define “biosignatures” comprising markers associated with both host and pathogen response.

Ultimately, biomarkers are tools that may be helpful in selecting better candidates and designing shorter, faster trials, but whose identification will depend on answering lingering questions about the dynamics of host–pathogen interaction. Even when found, potential biomarkers will not shorten the clinical pipeline overnight, as any markers of immunity will require the clinical validation that hinges on confirming vaccine efficacy in large phase III
trials. In the meantime, much work remains unfinished on the basic-science front, beginning with improving our understanding of BCG, the TB vaccine we already have.

**BCG: the old friend we barely know**

First introduced in 1921 and now the most widely given vaccine in the world, BCG protects infants and children from tuberculous meningitis and severe forms of disseminated TB. The protection afforded by BCG declines in adolescence, although the biological mechanisms behind this waning remain unknown—a mystery revisited in multiple publications in the past year. A systematic review of 21 randomized controlled trials comparing BCG with placebo (all of them conducted decades ago) reinforces several earlier suspicions about BCG’s adolescent disappearing act and variable protection. The review found that BCG conferred greater protection in northern latitudes, where vaccine recipients face less exposure to non-MTB mycobacteria (NTM), which are commonly found in the soil in equatorial regions. The average protection conferred by BCG also appeared greatest in trials that enrolled MTB-naive subjects (either neonates or school-aged children with negative MTB skin tests). Notably, the strain of BCG used in different trials did not appear to explain variability in BCG efficacy.

Understanding the nuances of BCG is essential given the pipeline’s preponderance of candidates designed to boost BCG. An old question in TB vaccine R&D asks whether prior exposure to NTM masks or blocks the efficacy of BCG. The “masking” hypothesis speculates that exposure to mycobacteria confers some level of protection against TB, and so BCG vaccination offers limited additional protective effect. In contrast, the “blocking” hypothesis proposes that exposure to NTM produces antigens that block the replication of BCG (as a live attenuated vaccine, BCG must replicate to be effective). Clarifying the effects of NTM exposure on BCG efficacy may help researchers predict whether candidate vaccines will be similarly compromised. One approach would be to explicitly model NTM exposure in preclinical animal studies. Another strategy would be to take NTM exposure as a given and, rather than try to predict its effects preclinically, treat it and BCG as “background noise” on top of which developers prime and boost with new candidates.
The role of NTM exposure has raised questions since the earliest days of the World Health Organization (WHO)’s BCG vaccination program in 1948, and is unlikely to yield to simple answers. Solidifying consensus that NTM exposure underlies part of BCG’s variable performance does, however, open the door to related questions that may be easier to answer. For one, the optimal times to administer and boost BCG remain unclear. One study suggests that the immune response to BCG in infants peaks at 10 weeks after vaccination. Consequently, the best time to boost BCG may come 14 weeks after vaccination, when the body has had time to develop greater cellular memory of BCG, and the effector CD4 and CD8 T cells provoked by BCG are no longer in a state of peak activity. One tension underlying this and related work is that most studies of BCG are conducted in infants, while most vaccines in the pipeline are being developed with adolescents in mind. BGC dynamics in infants might differ from the immune responses required to boost BCG in more immunologically mature young adults. Research on BCG and trials of candidate vaccines are focusing on different age cohorts, with unknown consequences for new product development.

Dangerous liaisons: host–pathogen interaction and the missing markers of immune response

Work to understand BCG might also bring the misunderstood interplay between human host and MTB pathogen into sharper focus. TB vaccine R&D has focused on achieving cell-mediated immunity by triggering Th1 cytokines (e.g., IFNγ, TNFα, and IL-2) produced by either CD4 or CD8 T cells. These cytokines are small proteins that act as signaling molecules that help direct the body’s immune response by changing the behavior of other cells. The emphasis on inducing Th1 immunity draws from both animal-model data suggesting a connection between T-cell expression of IFNγ, TNFα, and IL-2 and protection against TB disease, as well as observations that CD4 T-cell depletion places people with HIV at a higher risk of developing TB. Yet mounting evidence suggests that invoking a strong Th1 response alone is not sufficient for a new vaccine to outperform BCG; researchers will need to look beyond IFNγ and its cytokine cousins when evaluating the immunogenicity of candidate vaccines.

An elegant study in South Africa measured the BCG-specific CD4 and CD8 T-cell response in nearly 6,000 infants. The authors found no correlation between the magnitude of expression of Th1 cytokines and protection against
TB disease. These results echo earlier concerns about the poor predictive value of IFNγ as a marker of protective immunity. Only recently have these findings gained critical mass, with multiple voices calling on vaccine developers to look beyond cell-mediated immunity and IFNγ readouts as primary measures of immunogenicity.

New genetic analyses of MTB strains from across the world raise an even more uncomfortable notion: not only is Th1 immunity insufficient for achieving protection, but triggering it may actually play into MTB’s hand. MTB has coevolved with humans for at least 70,000 years, giving it ample time to learn the tricks of our immune system and turn them against us. The suggestion that MTB has conserved the very epitopes that our immune system recognizes means that vaccine candidates constructed to overexpress these epitopes may actually work against protection. This is exactly how most candidates in the pipeline are designed. In most pathogens, antigens recognized by the immune system show the greatest genetic variability in order to help the organism evade detection by the host. In MTB, however, genes coding for the epitopes recognized by human T cells appear the least changed over time. Detection by T cells may actually benefit MTB in several ways, including aiding transmission to future hosts given the role T cells appear to play in the formation of cavitary TB (a highly contagious condition in which MTB infection and subsequent inflammation destroy lung tissue). Future vaccination strategies may need to target more variable parts of the MTB genome, rather than the T-cell epitopes that MTB has conserved.

Even the central tenet of TB pathogenesis—that infection and disease exist as binary states—has come under scrutiny. Much TB drug, diagnostic, and vaccine research has proceeded from the long-held idea that latent TB infection and active TB disease exist as mutually exclusive worlds. Emerging consensus that infection and disease lie along a continuum requires recognizing related immunologic states with greater nuance behind them rather than a simple distinction between active and latent. Driving this conceptual shift is work suggesting that MTB may be more extracellular than assumed. Dominant thinking portrays MTB as an intracellular organism that sequesters itself in fortress-like granulomas in the lung in a dormant state of low activity until an “event” (e.g., a weakened immune system owing to diabetes, aging, or HIV infection) provides an opportunity for escape. New thinking suggests that even when checked into latency by the immune system, some bacteria persist outside of the cell. More than a point of scientific clarification, better characterizing
the intracellular/extracellular nature of MTB along the continuum of infection and disease holds important implications for the TB vaccine pipeline. Most vaccines in the pipeline are designed to trigger T-cell responses, yet extracellular bacteria live beyond the reach of T cells.\textsuperscript{32}

Our understanding of how MTB behaves—even within the cell—is being overturned. New work points to substantial variability in the activity of MTB across individual granulomas within the same host. Macaques with active and latent TB both appear to have granulomas containing live bacteria and others that are sterile (the immune system has already killed the bacteria).\textsuperscript{33,34} Understanding why the immune system produces different results in different granulomas may illuminate biomarkers correlating with progression to active or reactivated disease.\textsuperscript{35} In the meantime, acknowledging the gray scale between latent infection and active disease may guide researchers in targeting vaccines to account for MTB’s ability to be resting/active, intracellular/extracellular all within the same person.

**Preclinical screening: lost in the animal kingdom**

All of these advances in basic science point to one word: diversity. Whether discussing different strains of BCG, the mycobacterial exposures in dissimilar climates, or the genetic and biological differences within and across human populations, the component parts of TB immunology can no longer be taken as uniform. Acknowledging diversity holds major implications for the preclinical testing of TB vaccine candidates in animal models and how researchers employ these results to select candidates for future testing in humans.

First, MTB itself, like many bacterial pathogens, is not a uniform organism, but instead exists as many strains actively evolving in response to environmental pressures. The rise of drug-resistant strains of MTB—and the recent discovery that some drug-resistant strains may even be developing “compensatory mutations” enabling them to spread faster\textsuperscript{36,37}—signals the need to create a TB vaccine that can act against all forms of TB. Yet most preclinical programs continue to screen vaccine candidates against weaker laboratory strains (H37Rv, Erdman) instead of clinical isolates of MTB that are circulating in communities and making people sick.\textsuperscript{38,39,40}

In addition to screening vaccine candidates against clinical MTB isolates—including drug-resistant strains—vaccine developers should take advantage of
other opportunities to optimize animal modeling. Since TB manifests differently in animals than in humans, animal models will always contain an element of art. Yet even recognizing these biological differences, the field could do more to align animal and human testing. First, animals are typically challenged with a single, high-dose MTB lab strain while people in TB endemic countries face repeated, low-dose exposures to more virulent strains. The immune system may respond quite differently to these dissimilar levels of exposure. Second, the endpoints of animal and human trials are misaligned. Animal studies look at whether a candidate vaccine reduces the burden of TB disease as measured by bacterial load. By contrast, clinical trials measure whether candidate vaccines can prevent either MTB infection or TB disease. How results tied to these different endpoints translate across the already sizable species gap remains unclear.

The preclinical development of MVA85A, which reported good results in at least four animal models, demonstrates that achieving “modest” protection in animals does not predict the level of efficacy required in human studies. Aeras has indicated that future work will emphasize having “robust” preclinical data from nonhuman primate models before moving a vaccine into clinical testing. While encouraging, this raises questions about the harmonization of animal models; for example, nonhuman primate models alone employ three species of macaques. Harmonization may simplify the selection of candidate vaccines for human trials by increasing the comparability of results, but reliance on a few models may elide key insights about MTB diversity. Animal modeling is the crucible where basic research and product development reveal themselves as allied yet distinct enterprises. Negotiating this tension will require, if not harmonization per se, at least greater collaboration between preclinical and clinical developers, and a willingness to learn from the work of both.

NEW APPROACHES IN CLINICAL TRIALS

With so many unanswered questions in basic science, clinical trials of TB vaccines must be designed to help scientists learn about the biology of host–pathogen interaction at each step of human testing. One approach entails building hypothesis testing into larger clinical trials so that biological questions can be answered alongside traditional tests for safety and vaccine response (a strategy some have called “experimental medicine studies”). This might help alleviate the pressure to predict everything preclinically by
mainstreaming opportunities to learn about human disease dynamics into the traditional clinical development pathway. An upcoming phase II trial of TB vaccine candidate M72 + AS01, an adjuvanted subunit vaccine developed by GlaxoSmithKline, will adopt this approach. Alongside the larger trial evaluating the safety and efficacy of M72 + AS01 in adults, Aeras will run a parallel study collecting biological samples to inform biomarker research.

New trial designs may offer other ways forward. In 2013, Aeras supported the first trial combining two vaccine candidates, and began the first trial looking at prevention of MTB infection rather than TB disease as the primary endpoint.

**New endpoints: faster, cheaper, smaller trials?**

To date, most trials (including the phase IIb study of MVA85A) have used prevention of TB disease as the primary endpoint. Recognition that MTB infection is much more common than TB disease, however, has encouraged a shift to using prevention of infection as the primary endpoint in clinical evaluation. Since rates of MTB infection are typically three times higher than those of TB disease in any given population, prevention-of-infection trials will be smaller and less costly, enroll more quickly, and require shorter lengths of follow-up. Hybrid 4 + IC31 is the first TB vaccine candidate to be studied using the new prevention-of-infection paradigm.

Developed jointly by Aeras, Sanofi Pasteur, and the Statens Serum Institut (SSI) of Denmark, Hybrid 4 + IC31 contains a fusion of the antigens Ag85B and TB10.4 in the adjuvant IC31. The vaccine has completed four phase I studies establishing its safety among healthy adult volunteers. The new prevention-of-infection trial will take place at the South African Tuberculosis Vaccine Initiative (SATVI) in the Western Cape region of South Africa and enroll 990 adolescents; results are expected by the end of 2015. The trial contains three arms: one-third of participants will be revaccinated with BCG; one-third will be vaccinated with Hybrid 4 + IC31; and the final third will receive a placebo. The inclusion of a BCG-only arm will offer the first randomized controlled trial data on whether or not BCG acts against infection in this age cohort.

Other candidates will soon begin prevention-of-infection trials, including Hybrid 56 + IC31, an adjuvanted subunit vaccine developed by SSI. Future work on Hybrid 56 + IC31 reflects SSI’s decision to discontinue development of a related candidate, Hybrid 1 + IC31. Hybrid 56 + IC31 appears more
immunogenic than Hybrid 1 + IC31 as measured by polyfunctional T-cell response, including IL-2 and TNFα dominance over IFNγ. The vaccine combines three antigens—Ag85B, ESAT-6, and Rv2660c—of which the last is considered a “latency antigen” (believed to be upregulated during periods of nutrient deprivation standing in for latent infection). SSI recently concluded a dose-finding study of Hybrid 1 + IC31 in 240 MTB-positive and -negative adolescents in South Africa; results are expected by late 2014.

Although heralded as a “new paradigm,” candidates studied under a prevention-of-infection approach with favorable results will likely enter later-phase trials assessing their ability to prevent TB disease. The idea is to take advantage of the speed of prevention-of-infection studies to obtain better information on potential efficacy before initiating larger, more expensive confirmatory trials. Of course, protective mechanisms associated with prevention of infection may appear quite distinct from those associated with prevention of disease. The bridge between prevention-of-infection and disease work may not present a straightforward crossing.

Prevention-of-infection trials must traverse several other uncertain terrains. Prevention of infection represents a “fragile” endpoint—difficult to assess and sensitive to “force of infection” in a given area (an indication of how many susceptible individuals become infected with MTB in a given period). Moreover, MTB infection is measured using interferon gamma release assay (IGRA) diagnostic tests, themselves imperfect technologies with sometimes “fragile” results. The use of QuantiFERON Gold In-Tube (QFT), a type of IGRA test, to assess infection makes use of the best available tool, but QFT is hardly ideal. The repeatability of QFT results have come under increasing scrutiny, and at least one study suggests that QFT variability may be inherent to the test itself and not due to biological factors related to host or pathogen. In the context of TB vaccine trials, using QFT conversion to determine incidence of infection may overestimate true incidence when based only on the least stringent definition of QFT conversion: negative to positive.

To allay these concerns, investigators at SATVI have conducted a small study of QFT assay reproducibility to develop stricter laboratory protocols within the manufacturer’s specifications. The trial will also collect data on stable conversion as a secondary endpoint. The prevention-of-infection trial with Hybrid 56 + IC31 will also evaluate sustained QFT conversion over many months rather than relying on a single conversion result. While these
strategies work around concerns about QFT, they illustrate how diagnostic R&D limitations hold back TB vaccine research.

The phase I prom: TB vaccines meet their matchmakers

In addition to its prevention-of-infection trials, the TB vaccine field initiated the first study combining two new vaccine candidates. Sponsored by Aeras, a phase I study begun in 2013 pairs Crucell Ad35 with MVA85A in 50 healthy adult volunteers at Oxford University. Each candidate is undergoing separate phase II trials—Crucell Ad35 in nearly 600 infants and MVA85A in 650 adults with HIV. The rationale for combining these candidates derives from the distinct immune response each induces. MVA85A appears to act primarily through CD4 T cells, while Crucell Ad35 demonstrates a more robust CD8 T-cell response. In the combination trial, Crucell Ad35 will be administered first and then boosted with MVA85A. The decision to use this order was based on malaria vaccine work suggesting that vaccines built using modified vaccinia virus Ankara (like MVA85A) seem capable of boosting prime vaccines that employ adenovirus platforms (Crucell Ad35). MVA85A is also serving as the boosting vaccine in a phase I study with a new TB vaccine candidate that uses a simian adenovirus vector: ChAdOx1 85A. The combination trial of ChAdOx1 85A + MVA85A is sponsored by Oxford University and is currently recruiting participants.

A motley crew: other candidates make noise in phase I

Other candidates continue to advance through the pipeline, with some of the most interesting work happening in phase I. MTBVAC, the first live vaccine constructed from attenuated MTB, entered a phase I study in 2013 and showed good safety results at the interim analysis point. Weakened by deleting two virulence genes from MTB, MTBVAC could replace BCG if successful in future trials.

Ad5Ag85A also completed a phase I trial in 12 BCG-vaccinated and 12 BCG-naive adults in Canada. The study showed the vaccine to be safe, well tolerated, and capable of invoking CD4 and CD8 T-cell responses in both groups, although the magnitude of this response appeared greater in BCG-vaccinated participants. Safety concerns surrounding HIV vaccines constructed using adenovirus serotype 5 vectors (Ad5) have cast a cloud over Ad5Ag85A’s
prospects, as this candidate also uses an Ad5 platform. Three studies using Ad5 HIV vaccines were stopped early, with two showing an increased risk of HIV infection among vaccine recipients.\textsuperscript{73} The U.S. National Institutes of Health convened a meeting to discuss adenovirus HIV vaccines in September 2013. A subsequent meeting summary stated that “future HIV vaccine studies testing Ad5 vectors are not appropriate,” although the authors dodged the question of what this means for adenovirus vaccines for related diseases such as TB.\textsuperscript{74} In any case, Aeras has indicated that it does not plan to develop Ad5Ag85A for the market. Future work will use Ad5Ag85A to explore new routes of aerosol vaccine delivery, where it has the potential to make a valuable contribution.\textsuperscript{75} A phase I study of Ad5Ag85A administered by inhalation has been submitted to Health Canada for approval and will likely begin before the end of 2014.\textsuperscript{76}

Developed by the Infectious Disease Research Institute, the adjuvanted subunit vaccine \textit{ID93 + GLA-SE} is currently undergoing a phase I trial assessing its safety and tolerability among BCG-vaccinated adult volunteers in South Africa. A phase IIa study in South Africa planned for 2015 will evaluate whether ID93 + GLA-SE can prevent recurrence of TB disease when given to BCG-vaccinated adults previously treated and cured of TB.\textsuperscript{77} This reflects a prevention-of-recurrence strategy that would benefit a very different population than the prevention-of-infection approach being pursued by other adjuvanted subunit vaccines.

Finally, as reported last year, the whole-cell mycobacteria vaccine first studied in the phase III DarDar trial as SRL-172 re-entered the pipeline as \textbf{DAR-901}. New, more accurate phenotypic methods have identified the organism used in DAR-901 as \textit{Mycobacterium obuense}, not \textit{Mycobacterium vaccae} as previously believed.\textsuperscript{78} DAR-901 differs from the SRL-172 vaccine used in the DarDar trial only in terms of a new, more scalable production method developed by Aeras that uses broth rather than agar. A phase I trial of DAR-901 in 76 foreign-born adults with prior BCG vaccination, begun in April 2014 and cosponsored by Aeras and the Geisel School of Medicine at Dartmouth University, is under way in the United States.\textsuperscript{79}
RECOMMENDATIONS

In 2012, funding bodies spent just US$86.6 million on TB vaccine research, well short of the US$380 million called for by the Stop TB Partnership’s Global Plan to Stop TB 2011–2015. This inadequacy of resources reinforces the imperative to take advantage of each trial to learn about the biology of TB and to build stronger linkages between lab and clinic. The following recommendations outline strategies for making the most of limited resources:

1. **Increase funding for TB basic science research.** Basic science research remains the most urgent priority for the TB vaccine field. Yet funding for basic science is inadequate, totaling just US$129.6 million in 2012, nearly US$300 million short of the Stop TB Partnership’s funding target in this area. Fully funding basic science research at the level recommended by the Stop TB Partnership will speed progress in the clinical pipeline by deepening our understanding of host–pathogen interaction, the genetic adaptations of MTB, BCG immune kinetics and the related systems biology work that may shed light on correlates of immunity at different points along the continuum from MTB infection to TB disease. Building closer, mutually reinforcing relationships between lab bench and clinic will only become more important as old ideas about the interplay between MTB and the human immune system come under revisionary scrutiny.

2. **Create deeper channels of communication between research programs conducting animal modeling and human testing.** Screening vaccine candidates against clinical isolates of MTB, including drug-resistant strains, should become more common. Better aligning endpoints between animal and human studies would also strengthen preclinical development programs, in part by encouraging preclinical researchers to design animal studies with enough power to detect the same magnitude of vaccine efficacy as clinical trials. The phase IIb trial of MVA85A was designed to detect a 60 percent improvement over BCG alone, but most animal evaluations of TB vaccine candidates have demonstrated lower levels of improvement. Some decisions will require trade-offs: agreement among labs to use only certain species of animals may benefit product development, but risks limiting research to insights gleaned from just a few
models of a complex disease. Striking the right balance between extensive modeling in animals and learning from how vaccines perform in the clinic will require more direct ties between preclinical and clinical development. Experimental medicine studies that nest biological hypotheses in clinical trials, with subsequent back-translation of findings to animal models, offer one framework for achieving this.

3. **Promote innovation within clinical trials and harness the potential of new study designs.** In addition to saving time and money, prevention-of-infection trials may offer clues about biological mechanisms of protection useful for future phase III studies. Still, the question must be asked: what is driving the shift to prevention of infection—science or cost savings? Although an intriguing avenue of research, prevention-of-infection trials come with several limitations, most importantly how to measure infection and then apply results from these trials back to prevention-of-TB disease work. Trials that combine different vaccines introduce a twist on the dominant prime-boost strategy to take advantage of the respective merits of candidates that previously traversed the pipeline singly and separately. The option to become even more adaptive in trial design—for example, moving from phase I to II to III as part of the same protocol—may offer another way forward. Developers should also consider head-to-head trials comparing vaccine candidates in early-phase studies.

4. **Empower and support TB-affected communities to engage in TB vaccine research.** Growing consensus supports community engagement as a pillar of ethical medical research. Efforts to incorporate greater community participation in TB vaccine R&D are long overdue, and the field can no longer rely on the exemplary efforts of a few individual trial sites to engage communities. While sites such as SATVI have formed thoughtful community partnerships, TB vaccine R&D lacks the global community advisory structures seen in TB drug development. Vaccine researchers have an abundance of examples from which to draw, including, on the global level, the Community Research Advisors Group, an advisory body to the Tuberculosis Trials Consortium, and the robust site-level community engagement supported by the TB Alliance. Frameworks such as the Good Participatory Practice Guidelines for TB Drug Trials could easily be adapted to inform TB vaccine R&D.
The recent agreement in principle between the mining company Anglo American and Aeras to conduct future phase III TB vaccine trials in South African mines illustrates the imperative for stronger community engagement in TB vaccine R&D. Miners are a particularly vulnerable study population owing not only to their hugely disproportionate risk of MTB infection, but also to their exposure to the exploitative labor practices, social deprivation, and history of living under extractive-industry and settler colonialism that aggravate this risk. It was striking to read press statements from the agreement in which Brian Brink, chief medical officer of Anglo American, said: “You [Aeras] have got vaccine candidates. We have to go to the next leg now, the big phase III clinical trials, where you need big populations. We are in the mining industry, and we have big populations.” Unfortunately, no community representative or miner shared the stage with Brink and his Aeras counterparts—a lost opportunity to hear how these “populations” might envision their participation in future TB vaccine research.

Successful TB vaccine R&D will require investments of money and talent well into the next decade. Even if the current candidates in the pipeline never reach the market, their setbacks and successes in trials will lay critical groundwork for new TB vaccine development. While the immunologic particularities of future TB vaccines remain hard to predict, the general features needed in such vaccines are already clear. A safe vaccine that provides a high degree of lasting protection against developing active TB, blocks MTB infection, or achieves complete elimination of MTB after exposure would dramatically speed progress toward achieving the goals of zero TB deaths, new infections, and suffering. New TB vaccines must meet the needs of the communities and health systems that use them. They must be small, easy to transport, heat-stabilized, needle-free, and designed to address developing-country epidemiology. Even as researchers sort out the intricate details of immunity, the field must keep this bigger picture in mind. There is no shortage of complex, careful scientific work to be done, but the ultimate goal remains a safe, effective vaccine that can end the TB epidemic in the world’s most vulnerable and hard-hit communities.

I would like to thank Christine Sizemore, Ian Orme, Richard Jefferys, and Andrea Benzacar for thoughtful reviews of early drafts.


12. Ibid.


28. Ibid.

29. Kaplan G. Changing the perspective of research to end TB.


31. Orme I. Development of new vaccines for TB.

32. Orme I. A new unifying theory.


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