# The Tuberculosis Prevention Pipeline

By Mike Frick

After decades of receiving short shrift from most national TB programs and international organizations, tuberculosis (TB) prevention is finally coming into the mainstream. In 2015, the World Health Organization (WHO) published its first-ever *Guidelines on the Management of Latent Tuberculosis Infection*. The launch of these guidelines has awakened countries and donors to the idea that TB prevention is an area ripe for intervention—and for intensified research. In March 2016, the executive board of the global health financing mechanism UNITAID endorsed TB prevention as one of three "areas for intervention" that should be prioritized for targeted investments in its TB portfolio. This support will likely include funding for research projects seeking to shorten and simplify preventive therapy for the groups that are most at risk of developing active TB disease: children and people with HIV. On the other side of the Atlantic, the U.S. White House's *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* lists TB prevention—specifically, "increasing options for preventing active TB, latent TB infection, and TB transmission"—as the first objective toward its goal of accelerating basic and applied research to overcome the threat of drug resistance.<sup>3</sup>

As exemplified by these new guidelines and plans, a more focused TB prevention research agenda is beginning to take shape. This agenda involves tackling TB infection from two angles. First, preventive therapy is used to keep asymptomatic infection with *Mycobacterium tuberculosis* (MTB) from progressing to active, symptomatic TB disease. Second, vaccination is administered either pre-exposure to prevent infection with MTB altogether, or post-exposure to prevent infection from developing into disease. To date, research and development (R&D) on TB preventive therapies and vaccines have progressed with little interaction, despite the common goal of using new preventive therapies and vaccines to greatly hasten the decline in TB incidence by reducing the number of people with MTB infection who may one day develop transmissible disease. Indeed, mathematical modeling shows that the dramatic reductions in TB incidence required to meet the TB elimination targets of the WHO's End TB Strategy will require addressing TB infection—first through preventive therapy and then through vaccination.<sup>4</sup>

To acknowledge the momentum building behind TB prevention as a unified field of research, this year's *Pipeline Report* jointly reviews progress in the clinical development of TB preventive therapy and TB vaccines. (Advances in infection control—the administrative, environmental, and personal protective measures that reduce the risk of TB transmission in the built environment—fall outside of the biomedical focus of this chapter.) There is much to be gained from breaking the habitual thinking that has placed TB drug development in one camp and vaccines in another. For one, a joint discussion reveals that initiatives to develop new TB preventive therapies and vaccines face a shared thicket of thorny scientific issues, whose lack of resolution has snarled progress toward both ends. Approaching TB preventive therapy and vaccines as related endeavors may also jumpstart an advocacy movement for TB prevention that is more forceful than disjointed efforts to hold public and political attention on separate technological fixes (an approach that can sometimes be misinterpreted by politicians as an either/or choice between treatment and prevention). Finally, prevention research raises a number of unique ethical considerations, with corresponding implications for engaging communities in TB research that both drug and vaccine developers will need to address.

### PROGRESS IN TB PREVENTION SCIENCE

Developing new tools to prevent TB will require an intensification of basic science research that can inform product development, so it is fitting that some of the most notable achievements over the past year have

come from the laboratory. Scientists are employing a range of tools to shine new light on how MTB interacts with its human host—sometimes literally, as with the application of positron emission tomography (PET) and X-ray computed tomography (CT) to visualize and map inflammation-based immune activity to MTB as it unfolds across the geography of the lung.<sup>5</sup> An array of studies—some in animals, others in humans; some observational, others experimental—are illuminating the hidden corners of genome, blood, and lung to improve our understanding of the dynamic nature of MTB infection, how it progresses over time, and why it sometimes spills over into active TB disease.

# Predicting Disease Progression through Gene-based Signatures of Risk

The central challenge in TB prevention research is that scientists have yet to establish a firm link between the appearance of any specific biomarker in individuals with asymptomatic MTB infection and progression to active TB disease. Biomarkers are measurable characteristics, such as gene activity, biological processes, or clinical phenotypes, whose presence signifies either a particular disease state or the body's response to vaccination or drug therapy.<sup>6</sup> The quest to identify biomarkers that act as prospective signatures of risk for developing TB disease among individuals infected with MTB has animated much of TB prevention research.<sup>7,8</sup> Current methods for diagnosing MTB infection—the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—cannot predict whether individuals with MTB infection will develop TB disease. (An estimated 10% of MTB-infected people will develop active TB at some point in their lifetimes.<sup>9</sup>)

Once validated in late-stage clinical trials, a biomarker that could reliably predict disease progression or distinguish between individuals with high or low risk would be a powerful tool for guiding public health intervention efforts by identifying individuals most in need of preventive therapy, thereby creating opportunities to interrupt transmission by preempting disease progression. Biomarker-guided interventions might require fewer resources than less-targeted approaches by placing only those people most likely to progress to disease on treatment. More immediately, a biomarker of prospective risk could streamline the clinical development of new TB vaccines and preventive therapies by allowing clinical trials to enroll persons with the greatest risk of developing active TB disease. This targeted approach would reduce the costs of research by allowing investigators to conduct smaller, more quickly enrolling studies.<sup>10</sup>

Biomarker identification efforts took a significant step forward in 2016 with the publication of a prospective cohort study of over 6,000 South African adolescents with MTB infection. Investigators reported discovering a blood-based RNA signature comprised of 16 genes that predicted the risk of TB disease progression over a two-year period. These 16 genes, collectively referred to as a gene signature, appeared to be more active in 46 adolescents who developed TB than in 107 matched controls who remained healthy. Notably, the gene signature's predictive power increased when measured at time points closer to TB diagnosis (sensitivity of 71.2% at 6 months before diagnosis compared with 62.9% at 6 to 12 months and 47.7% at 12 to 18 months, reported at a specificity of 80%). In the significant step forward in 2016 with MTB infection. In the publication of a prospective cohort study of TB disease progression over a blood-based RNA signature comprised of 16 genes that predicted the risk of TB disease progression over a two-year period. These 16 genes, collectively referred to as a gene signature, appeared to be more active in 46 adolescents who developed TB than in 107 matched controls who remained healthy. Notably, the gene signature's predictive power increased when measured at time points closer to TB diagnosis (sensitivity of 71.2% at 6 months before diagnosis compared with 62.9% at 6 to 12 months and 47.7% at 12 to 18 months, reported at a specificity of 80%).

To validate these results, researchers tested the gene signature in two separate cohorts of HIV-negative adult household contacts of people with pulmonary TB: one from South Africa and the other from The Gambia. Successful validation in these cohorts led the investigators to ask two additional questions. First, given that sensitivity increased closer to diagnosis, could this signature of risk discriminate between MTB infection and active TB disease? When applied to published data from other adult cohorts in the United Kingdom, South Africa, and Malawi, the gene signature distinguished active TB from both MTB infection and other pulmonary diseases, including in people coinfected with TB and HIV (a population that usually presents more diagnostic challenges). Second, could a risk signature found in adolescents perform well in younger children? Here, too, the researchers found that the signature could distinguish between MTB infection and culture-confirmed TB disease in children (but not culture-negative TB). Children with culture-positive TB have more bacteria in

their lungs than those with culture-negative disease; thus, the signature's discriminatory capability in this group suggests that activity in these 16 genes might be related to the number of replicating bacteria in the lung (i.e., bacterial load). Consistent with this idea, the gene signature gradually disappeared when researchers looked for it in patients receiving treatment for drug-sensitive TB.<sup>14</sup>

Discovery of this 16-gene risk signature was made possible by the kind of collaborative team science that requires time and sustained financial support. The cohort of South African adolescents that provided data for the primary analysis enrolled its first participant in 2005 and completed follow-up in 2009. That means that the adolescents who participated in the study are now adults. No doubt many have since fallen sick from TB, and some may even have died from it. To build on the contribution of these then-teenagers, investigators should continue to follow them into adulthood to understand how risk of disease progression changes over the life cycle. Evaluating how well this risk signature performs in a larger number of participants drawn from a more general population with less exposure to TB is also important, as biomarker identification studies may have cohort biases that limit their generalizability across different populations. This cohort drew adolescents from an area with an extraordinarily high TB incidence rate (1,400 per 100,000 people), where the lifetime risk of progressing from MTB infection to TB disease far exceeds the 10% risk observed in any given population.

### Failures of Translation between Markers in the Blood and Events in the Lung

One lingering question from this genetic risk signature study is the extent to which a signature identified from the blood reflects concurrent pathogenesis in the lung. Scientists are increasingly recognizing how the initial lung environment encountered by MTB is important for determining the outcome of infection, but these processes may not be well represented by immune cells circulating in peripheral blood. <sup>18,19</sup> Acknowledging this limitation, investigators countered that circulating white blood cells "can serve as sentinels of lung pathophysiology." <sup>20</sup> However, the fidelity with which measurements taken from peripheral blood mirror disease processes unfolding in the lung remains far from settled. <sup>21</sup> Long-held assumptions about the relationship between lung and blood in TB are being rethought on the basis of evidence from a range of studies (many in nonhuman primates) that is rewriting the script on the classic symbol of TB pathology, the granuloma, and its role in disease progression.

Granulomas (TB's signature pulmonary lesions) are organized collections of macrophages and other immune cells that flock to sites of MTB infection in the lung. Traditional thinking has likened granulomas to immune fortresses that serve an essential protective function by containing MTB in a quiescent state. In the canonical view, people who develop active TB mount a less-effective immune response than individuals who maintain MTB infection without falling ill. This implies that different granulomas in a given individual all behave similarly, and that differences in granuloma activity between individuals result in one of two divergent clinical outcomes: latent infection or active disease.<sup>22</sup>

Nothing seems so simple anymore. As one recent review put it, "the clinical hallmark of TB is the granuloma....[Yet] the field is even at a loss as to whether granuloma formation ultimately benefits host or bacterium, and which is the master of the situation." Under certain conditions, granulomas appear to offer MTB a niche in which it can replicate and persist, whereas the granuloma at other times becomes the focal point at which immune cells marshal a coordinated response to control MTB. Whether a granuloma becomes a site of vulnerability or protection appears to depend on the nature of the local CD4+ T-cell response, particularly the ratio of pro- and anti-inflammatory cytokines present in the granuloma. CD4+ T cells are critical for immunity against TB, and TB vaccine research has focused on achieving protection through cell-mediated immunity by developing vaccines that trigger CD4+ T cells to release type 1 helper (TH1) cytokines such as interferon-gamma (IFN $\gamma$ ), tumor necrosis factor-alpha (TNF $\alpha$ ), and

interleukin-2 (IL-2).<sup>26</sup> (Cytokines are small proteins that call and direct the behavior of other immune cells.) However, because immune responses to TB are usually measured in blood—which is easier to collect from humans than lung tissue—not much is known about the profile of local T-cell responses in the granuloma itself.<sup>27</sup>

A clearer picture is starting to form from a series of studies in cynomolgus macaques, which have become an important animal model for TB prevention research, as they can develop either clinically active TB disease or latent TB infection with granulomas similar to those seen in humans. In addition, the MTB epitopes recognized by human CD4 T cells overlap substantially with those in macaques. (Epitopes, or small cell-surface proteins, are the parts of antigens that are recognized by immune cells). Research summarized in last year's *Pipeline Report* shows that a spectrum of lesion activity exists in individual macaques with either active disease or latent infection. Animals with active TB disease can have sterilized lesions, but, critically, they also contain a number of granulomas in which infection is not controlled, resulting in disease progression. This spectrum of activity in an individual suggests that the outcome of MTB infection is determined locally at the level of the granuloma and not systemically, where the immune response is more conveniently sampled from circulating blood. What controls infection at the granuloma level, and to what extent is this local response represented by immune readouts taken from the blood?

One recent study in MTB-infected macagues sought to answer this question by comparing the T cells and cytokines found in granulomas to those observed in circulating blood.<sup>31</sup> Investigators used PET/CT imaging to track granuloma formation in 28 cynomolgus macagues, 13 of which developed active TB disease and 15 of which remained latently infected. After macagues were necropsied (killed), granulomas identified by PET/CT underwent histological examination, quantification of bacterial burden, and immunological analysis to measure the presence of pro-inflammatory cytokines (IFNy, IL-2, TNF, and IL-17) and the anti-inflammatory cytokine IL-10.32 The results add several layers of complexity to our understanding of how cell-mediated immunity operates locally in TB. In a particular macague, different granulomas exhibited highly variable cytokine profiles. Most T cells in granulomas produced a single type of cytokine (i.e., were monofunctional), but granulomas themselves contained a mix of T cells that produced different cytokines.<sup>33</sup> (This stands in contrast with the stated intention of many TB vaccine studies, which judged the immunogenicity of vaccine candidates by looking for polyfunctional T cells in blood.<sup>34</sup>) Granulomas in which T cells produced both pro- and anti-inflammatory cytokines were more likely to be sterile or have lower bacterial burdens.<sup>35</sup> This is consistent with an emerging consensus that stimulation of pro-inflammatory cytokines such as IFNy is necessary, but not sufficient, for protection; there must be a counterpoint to inflammatory activity, as too much can damage the lung and impair protection.<sup>36</sup> Finally, in most of the macaques, T-cell responses measured in circulating blood (the systemic immune response) did not closely mirror T-cell responses observed in granulomas (the local immune response).<sup>37</sup>

A related study in macaques probed the differential fates of granulomas from the perspective of MTB itself.<sup>38</sup> Investigators added genetic barcodes to individual MTB isolates, tracked the formation of lesions using PET/CT, and, after necropsy, quantified the relative frequency of each MTB barcode in different lesions. They observed that most granulomas were founded by a single bacterium and that bacterial burden varied greatly across lesions, even in the same animal.<sup>39</sup> Differences in bacterial burden may reflect variability in the killing efficacy of the immune response at the level of the individual lesion, as animals with active disease also had sterilized granulomas. Given this heterogeneity, the investigators commented that "it is not surprising that relevant predictors of disease outcome have been hard to identify from peripheral measures of immune response."<sup>40</sup>

The combination of PET/CT, genetic barcoding, and histopathology has revealed that, so long as TB vaccine developers continue to measure success through blood-based immune assays, they risk overlooking important details of what effective immunity against MTB looks like at sites of infection in the lung.<sup>41</sup> Although it is now

possible to closely examine lung responses in nonhuman primates, investigators working in the clinic have few alternatives at hand. Some have predicted that PET/CT may one day be used in clinical trials to track biological signals of an effective vaccine. These signals might include observing fewer granulomas form early in infection, no dissemination of granulomas after infection, or lower levels of lung inflammation—as indicated by radiological markers picked up by PET/CT (e.g., 18-F fluorodeoxyglucose). However, due to concerns about exposing humans to repeated radiation without clear therapeutic necessity, PET/CT cannot be applied for routine monitoring in large clinical trials, and, even if the technique could, the composite vision of inflammation produced by PET/CT is not yet well enough defined to serve as a reliable surrogate of protection, much less a clinical trial endpoint. Other sampling methods, such as bronchoalveolar lavage (BAL)—a technique used to sample cells from the airway—yield closer approximations of the lung environment than blood, but there may be important differences between T cell responses in the airway and lung that make BAL an imperfect alternative.<sup>42</sup> In addition, given that BAL requires passing a bronchoscope through the mouth or nose into the lung, it may be too invasive to perform on the scale of a clinical trial. Although formidable, these limitations should not inspire a sense of futility among vaccine developers. Work to develop blood-based assays that provide indications of vaccine-induced immunity in the lung should be a priority for the field. Using assays that measure more than IFNy and other TH1 cytokines may also yield a more complete picture of vaccine-driven immune responses for guiding clinical development.

# Bacterial Individuality and Persistence

The ability to attach genetic barcodes to individual bacteria, as described above, has made it possible to speak of bacterial *individuality* and recognize that, just as not all granulomas behave identically, not all MTB cells are homogenous. Most MTB cells are susceptible to the bactericidal effects of the immune response or antibiotic therapy, but in any given population of MTB, a few bacteria are able to survive these assaults. Sometimes referred to as *persisters*, these bacterial survivors are slow-growing, nonreplicating, and thought to develop noninheritable resistance to antibiotics and the body's adaptive immune response. The recalcitrance of these persisters contributes to the lengthy duration of treatment for both TB disease and MTB infection, and likely gives rise to a range of observed phenomena in TB infection and disease, from latency to disease progression to posttreatment relapse.

Understanding the biological mechanisms of persistence and how to overcome them is a major priority for TB drug developers working on prevention. Several TB drug research networks have formed scientific working groups to address the problem of persisters, and the topic has featured prominently in satellite meetings organized by the WHO at the 2014 and 2015 Conference on Retroviruses and Opportunistic Infections. A7,48 Of immediate concern for the development of new TB preventive therapies, some drugs may be more effective against persisters than others. For example, drugs with sterilizing activity such as rifapentine and pyrazinamide appear to be more capable of killing persistent organisms than bactericidal agents such as isoniazid, which is thought to be more active against replicating bacteria. Research into MTB persistence has also raised more fundamental questions, leading many scientists to ask, "What is latency anyway?" The initial challenge has been to disentangle terminology that is often conflated in the drug development vernacular—for example, the terms latency, persistence, and dormancy, which likely point to related, yet distinct, concepts.

### PROGRESS IN TB VACCINE DEVELOPMENT

The past year has served as the opening chapter in the TB vaccine field's "shift to the left," a strategy in which major funders such as the Bill & Melinda Gates Foundation are moving resources to basic discovery, preclinical development, and phase I and II trials (events located on the left side of the clinical development pipeline).<sup>51</sup> No new vaccines have entered clinical testing since TAG's 2015 *Pipeline Report*, although many

of the 14 candidates in the pipeline have initiated new trials (see table 1). Thus far, the thrust of activity under this shift to the left has been directed toward two tactics: experimental medicine studies and novel clinical trial designs. Taken together, the intention behind deploying these tactics is to first generate a more diverse stable of vaccine concepts, and then to more efficiently triage these in early-stage trials so that only the most promising candidates advance to larger, costlier efficacy trials.<sup>52</sup> This strategy aims to correct a glaring weakness in the composition of the TB vaccine pipeline: the viral-vectored and adjuvanted subunit vaccines under development were all designed to play the same notes, just in slightly different combinations. For example, six of the eight subunit vaccines contain an Ag85 antigen (either Ag85A or Ag85B), and the majority of candidates were designed to provoke cell-mediated immunity driven by CD4 and CD8 T cells, resulting in vaccines with little immunologic diversity.<sup>53</sup>

Table 1. TB Vaccines in Development

Agent	Strategy	Туре	Sponsor(s)	Status
М. vaccae	Immunotherapeutic	Whole-cell <i>M. vaccae</i>	AnHui Longcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
H4 + IC31	Prime-boost	Protein/adjuvant	Protein/adjuvant Statens Serum Institut (SSI), Sanofi Pasteur, Valneva, Aeras	
H56 + IC31	Prime-boost	Protein/adjuvant	/adjuvant SSI, Valneva, Aeras	
MTBVAC	Prime	Live genetically attenuated M. tuberculosis (MTB)	University of Zaragoza, Biofabri, TuBerculosis Vaccine Initiative (TBVI)	Phase IIa
VPM1002	Prime	Live recombinant rBCG	Serum Institute of India, Vakzine Projekt Management, TBVI, Max Planck Institute for Infection Biology	Phase IIa
Dar-901	Prime-boost	Whole-cell <i>M. obuense</i>	Dartmouth University, Aeras	Phase IIa
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
ChAd0x1.85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Viral vector Oxford University, Imaxio	
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for Biological Safety Problems	Phase I

### **Experimental Medicine Studies**

Experimental medicine refers to studies in humans—usually small and often nested into larger clinical trials—that are intended to ask and answer scientific questions that may inform vaccine discovery and product development. These studies take advantage of opportunities to work in humans to further our understanding of the biological mechanisms underlying infection and disease. For the purposes of TB vaccine R&D, one major objective of experimental medicine studies is to develop new vaccine concepts by looking beyond immunity mediated through CD4 and CD8 T cells to consider other cell types (e.g.,  $\gamma\delta$  T cells, mucosal-associated invariant T cells, CD1-restricted T cells, antibodies produced by B cells, etc.). The overarching goal is to elevate the role of biological investigation in TB vaccine R&D and, in doing so, refashion product development from a strictly linear pathway to an iterative exchange between clinical work in humans, preclinical testing in their animal model counterparts, and basic research in vitro. The vaccine is a strictly linear pathway to an iterative exchange between clinical work in humans,

Vaccine developers have already responded to the call to incorporate experimental medicine into clinical testing. For example, Aeras is working with the HIV Vaccine Trials Network of the U.S. National Institutes of Health (NIH) on an immunology study that aims to better understand the assays used to assess the immune responses generated by subunit vaccines that are currently in the pipeline.<sup>57</sup> In this study, South African adolescents will receive either the H4 + IC31 vaccine, the H56 + IC31 vaccine, or revaccination with bacillus Calmette-Guérin (BCG), the existing TB vaccine, which was first licensed in 1921 and used to prevent severe forms of TB in children. This is not a head-to-head trial between H4 + IC31, H56 + IC31, and BCG; rather, blood will be sampled at different time points and analyzed to generate a trove of immunological data on vaccine responses using validated and exploratory assays that may one day be evaluated as possible correlates of risk or protection. 58,59 There is interest in conducting similar experimental medicine studies involving whole-cell mycobacterial vaccines. 60 In such studies, the goal would be to refine assays to better distinguish the immune response provoked by whole-cell vaccines from that stimulated by BCG, or to develop assays to measure the activity of unconventional T cell subsets such as  $\gamma\delta$  T cells or CD1-restricted T cells. The field aspires to initiate one to two experimental medicine studies per year, and although each will have its own sharp focus, the overarching goal is to probe important scientific questions and increase our understanding of the biology of MTB infection in humans.<sup>61</sup>

# **Novel Clinical Trial Designs**

In parallel with experimental medicine studies, vaccine developers are employing novel clinical trial designs in early stages of testing. This has mostly entailed getting creative with clinical trial endpoints by designing phase lla trials around the primary outcome of prevention of MTB infection as opposed to prevention of TB disease. 62,63 As with any departure from convention, this strategy offers both risk and reward. Unlike TB disease, which can be microbiologically confirmed through diagnostic tests such as GeneXpert/MTB RIF or mycobacterial culture, MTB infection is difficult to reliably identify with extant tools. Prevention-of-infection trials define infection using blood-based IGRAs such as Qiagen's QuantiFERON Gold In-Tube (QFT-Gold), a test that converts from negative to positive when it detects cell-mediated immune responses (i.e., IFN $\gamma$ ) to MTB antigens. 64 However, the well-documented variability of IGRA results, and the potential of a positive IGRA to sometimes revert to negative after repeat testing, means that investigators must proceed cautiously. 65,66,67 Without a gold-standard diagnostic test for MTB infection, and without validated correlates of protective immunity, regulatory authorities are unlikely to license a new TB vaccine that is based on endpoints other than prevention of disease. 68

As a result, prevention-of-infection is not being pursued as a licensable vaccine indication, but rather as a tool for winnowing vaccine concepts before mounting efficacy studies with traditional prevention of TB disease endpoints. Given that infection with MTB is a more common occurrence than TB disease, prevention-of-

infection trials promise to save money by enrolling fewer participants in less time.<sup>69</sup> The first results from this approach may be just around the corner. Aeras is conducting a three-arm phase IIa study of H4 + IC31 and BCG revaccination in 990 BCG-vaccinated, HIV-negative adolescents in South Africa's Western Cape province.<sup>70</sup> The H4 + IC31 candidate pairs MTB antigens Ag85B and TB10.4 with IC31, an adjuvant owned by Valneva. One-third of participants will receive two doses of H4 + IC31, one-third will be revaccinated with a single dose of BCG, and the final third will receive two doses of placebo.<sup>71</sup> The primary outcome is MTB infection, as defined by sustained IGRA conversion (in this case, QFT-Gold), and the primary analysis will occur when the study accrues 64 cases of MTB infection. Aeras reports that it is close to reaching this point and expects to release the results in 2017.<sup>72</sup>

The subunit vaccine H56 + IC31, developed by the Statens Serum Institut of Denmark (SSI), will soon be used in a prevention-of-infection trial in Tanzania. H56 + IC31 consists of three MTB antigens (Ag85B, ESAT-6, and Rv2660c) paired with Valneva's IC31 adjuvant. Given that the ESAT-6 antigen is present in both the H56 vaccine and the QFT-Gold test, the SSI first had to develop an IGRA without ESAT-6 before it could study H56 in a prevention-of-infection trial. (Using QFT-Gold to measure MTB infection in participants vaccinated with H56 could result in false positives, as the ESAT-6 in H56 could prime the antigen-specific T cells that the test looks for as an indication of MTB infection). The resulting ESAT-6-free IGRA contains four antigens (CFP10, QTC6, QTC7, and QTC13) and has been evaluated in studies in Denmark, Egypt, Tanzania, and South Africa; its performance appears to be on par with that of QFT-Gold. This ESAT-6-free IGRA was developed as a companion diagnostic for the H56 vaccine and is not intended to be a commercial alternative to QFT-Gold. The trial in Tanzania will contain two arms—one with H56 and the other with placebo—and enroll 1,400 adolescents. Aside from the lack of a third arm looking at BCG revaccination, the major difference between this study and the H4 prevention-of-infection trial is that the incidence of MTB infection in this part of Tanzania is much lower than that in South Africa's Western Cape.

In addition to prevention of infection, TB vaccine developers are designing trials to evaluate prevention of recurrence, defined as either reactivation of disease from latency (i.e., relapse) or reinfection with MTB after treatment completion.<sup>77</sup> Similar to MTB infection, the incidence of recurrent TB disease is higher in any given population than new cases of TB. Anywhere from 2–8% of treated TB patients will face recurrent disease, and the vast majority of these cases occur in the first 12 months after completing therapy.<sup>78,79</sup> Consequently, prevention-of-recurrence trials offer similar advantages as prevention-of-infection trials in terms of demonstrating the mettle of vaccine candidates before selecting which ones to move forward to efficacy trials looking at prevention of disease. Successful prevention-of-recurrence trials might also create a pathway for developing therapeutic vaccines to either shorten the duration of treatment or bolster chemotherapy.<sup>80</sup>

Several prevention-of-recurrence studies are under way. A phase IIa prevention-of-recurrence trial was recently begun for the subunit vaccine ID93 + GLA-SE in 60 South African adults who successfully completed therapy for drug-sensitive TB (DS-TB). Developed by the Infectious Disease Research Institute (Seattle, Washington), ID93 + GLA-SE combines the MTB antigens Rv2608, Rv3619, and Rv3620 with the GLA-SE adjuvant. The trial contains four arms and is testing two intramuscular injections of vaccine—given at three different doses—against placebo (saline solution). This safety and dose-ranging study will inform planning for a phase IIb prevention-of-recurrence trial of ID93 + GLA-SE that will enroll up to 450 adults per arm. In addition to ID93 + GLA-SE, H56 recently completed enrollment in a phase I safety, immunogenicity, and dose-escalation study among 24 HIV-negative adults that were previously treated for DS-TB; results are forthcoming. H56 + IC31 is being studied as an adjunct to TB therapy when paired with COX-2-selective inhibitors (a type of nonsteroidal anti-inflammatory drug). The idea is that COX-2 inhibitors will strengthen the vaccine response to H56, and that the two together will shorten the duration of chemotherapy for multidrug-resistant TB. This initial study is recruiting participants in Oslo, Norway and is supported by the Norwegian Research Council. L64 Despite these interesting applications of H56 during and after TB drug therapy, the SSI has indicated that future development efforts will focus on prevention-of-infection trials rather than prevention-of-recurrence trials.

### Other Approaches and Developments

The TB vaccine field's only ongoing phase IIb efficacy trial is evaluating whether two intramuscular doses of M72 + AS01, a subunit vaccine developed by GlaxoSmithKline (GSK) that pairs MTB antigens 32A and 29A with GSK's AS01 adjuvant, protects MTB-infected, HIV-negative adults from TB disease progression compared with placebo.<sup>86</sup> The trial, which opened in 2014 and is being conducted in South Africa, Kenya, and Zambia, reached its targeted enrollment of 3,500 participants in 2015 and is now in follow-up for the primary outcome analysis, which will be case driven. The analysis will be conducted after investigators detect 21 cases of pulmonary TB; results are expected in late 2018.<sup>87</sup>

Activity also continues on the development of two vaccines designed to replace BCG and be administered to infants soon after birth: VPM1002 and MTBVAC. VPM1002, a live, recombinant form of BCG developed by Vakzine Projekt Management in Germany and licensed to the Serum Institute of India (SII), recently began a phase Ila trial in over 400 South African newborns. The study will compare the safety and immunogenicity of VPM1002 versus BCG in both HIV-exposed and unexposed infants.<sup>88</sup> The SII is currently in discussions with regulatory authorities in India to take VPM1002 into two larger studies: a phase IIb BCG-replacement trial in newborns (pending a favorable outcome from the South African study), and a phase III prevention-of-recurrence trial in adults.<sup>89</sup> Work also continues on MTBVAC, a live, genetically attenuated form of MTB that was made less virulent by the deletion of two genes (phoP and fadD26). A phase Ila safety, dose-escalation, and immunogenicity study of MTBVAC in South Africa is currently recruiting participants in two phases. The first will randomize MTB-negative, BCG-vaccinated adults to receive either MTBVAC or BCG. If safety is demonstrated in this group, the trial will progress to the second stage and randomize infants to receive either BCG or MTBVAC at one of three doses.<sup>90</sup> A phase IIa study among South African adults is also planned.<sup>91</sup>

Efforts to replace BCG will likely receive less financial and intellectual attention in the coming years. In contrast with earlier phase IIa and IIb trials, many of which were conducted in either adults with HIV or infants, 92,93 vaccine developers are now focusing on HIV-negative adolescents and adults, who account for the majority of MTB transmission globally. (This may be one reason why VPM1002 and MTBVAC—each designed as BCG-replacement vaccines—are also being tested in adult prevention-of-recurrence and prevention-of-infection trials). By conducting fewer clinical trials in children and people with HIV, TB vaccine developers are effectively making the decision to direct research away from the two groups most vulnerable to TB. If focusing testing on adults without comorbidities shortens the clinical development timeline, and if the resulting vaccine averts cases of TB in children and people with HIV through a herd immunity effect by interrupting TB transmission among the adult contacts around them (as modeling suggests could occur), 94 then this may prove to be a prescient move. But that string of assumptions contains many uncertainties, and developers should acknowledge that the current strategy risks leaving behind two key TB-affected populations with greatly enhanced risks of disease and death that rightly draw significant attention from global health actors.

### PROGRESS IN TB PREVENTIVE THERAPY DEVELOPMENT

Although they are no longer the focus of TB vaccine development, children and people with HIV still occupy the center of efforts to develop new or improved TB preventive therapies (see table 2). Research into preventive TB treatment is pursuing answers to two primary questions. First, what are the most effective regimens for treating MTB infection, particularly in high-risk groups, including children, people with HIV, and pregnant women? And second, how should physicians treat probable infection with drug-resistant TB (DR-TB)?

As with the overall TB drug pipeline (see "Tuberculosis Treatment Pipeline," page 163, for a detailed overview), there are few new drug candidates available for investigators to study. Consequently, much of the activity has focused on optimizing existing drugs for TB prevention (e.g., rifapentine, a rifamycin that is closely related to rifampin and is off-patent and marketed by the French pharmaceutical company Sanofi) or studying

the chemoprophylactic potential of new drugs (e.g., delamanid, a nitroimidazole developed by the Japanese company Otsuka and approved for the treatment of DR-TB). Despite the limited armamentarium, the field is poised to make major strides in coming years with planned or ongoing phase III trials that, if successful, could dramatically refashion treatment guidelines.

Table 2. Clinical Trials to Prevent Tuberculosis Disease

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + isoniazid for 1 month (vs. isoniazid daily for 9 months) NCT01404312*	Fully enrolled	People with HIV either living in high-TB prevalence regions or with a positive TST or IGRA (QFT or T-SPOT TB test)	ACTG
A5300/PH0ENIX 6 months daily delamanid (vs. isoniazid)	Beginning enrollment Q4 2016	High-risk (HIV+, TST/IGRA+, or ≤5 years old) household contacts (adults, adolescents, and children 0–5 years old) of individuals with MDR-TB	ACTG, IMPAACT
WHIPP TB 6H versus 3HP (given once) versus p3HP (given once a year for two years)	Beginning enrollment Q3 2016	People with HIV without active TB in high–TB prevalence regions	KNCV, USAID
TBTC Study 37 6 weeks of daily rifapentine (P) versus rifamycin-based standard of care regimens (3HP, 4R, 3HR)	Protocol development	Household contacts, people with HIV, individuals with recent TST or IGRA conversion	TBTC, TBESC, UK MRC, University College London
4R versus 9H 4 months daily rifampin (self-administered) NCT00931736*	Fully enrolled	Adults with positive skin test or QuantiFERON-TB blood test, including people with HIV who are not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR
V-QUIN 6 months daily levofloxacin (vs. placebo) ACTRN12616000215426**	Protocol development	Household contacts (adults, adolescents, and children ≥3 kg) of individuals with MDR-TB	NHMRC, VNTP
P2001 12 weeks of supervised 3HP NCT02651259*	Protocol development	HIV-positive and HIV-negative pregnant and postpartum women with MTB infection	IMPAACT
CORTIS 3HP versus no intervention and active surveillance for TB NCT02735590*	Beginning enrollment Q3 2016	HIV-negative adults with MTB infection in high-risk individuals identified by a gene-based signature of risk	University of Cape Town, Bill & Melinda Gates Foundation

<sup>\*</sup> Clinicaltrials.gov identifier; for more details, see http://www.clinicaltrials.gov

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases (NIAID)

ARVs: antiretrovirals

CIHR: Canadian Institutes of Health Research

IGRA: interferon gamma release assay (QuantiFERON-TB Gold In-Tube (QFT) or T-SPOT TB test)

IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group, NIAID

NHMRC: National Health and Medical Research Council (Australia)

NIAID: National Institute of Allergy and Infectious Diseases (U.S.)

TBESC: Tuberculosis Epidemiologic Studies Consortium, U.S. Centers for

Disease Control and Prevention

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and

Prevention

UK MRC: Medical Research Council, United Kingdom

VNTP: Vietnam National Treatment Program

<sup>\*\*</sup> Australian New Zealand Clinical Trials Registry identifier; for more details, see http://www.anzctr.org.au

### Treating MTB Infection in Household Contacts of People with DR-TB

The question of how to treat MTB infection among individuals exposed to DR-TB is one of the most vexing, and least studied, in TB prevention. To date, no randomized controlled trials have been conducted to guide prophylactic treatment of people exposed to DR-TB, who are often people living in the same household as someone with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). For household contacts of DR-TB patients, MTB infection is an experience fraught with uncertainty, as progression to active disease could entail an MDR-TB or XDR-TB diagnosis. The lack of research on this topic has resulted in wildly divergent guidelines. On one end of the spectrum, the U.S. Centers for Disease Control and Prevention (CDC) outlines a range of treatment options—typically 6–12 months in duration—based on the idea that physicians should treat probable DR-TB infection with two or more drugs to which the infecting organism is believed susceptible. On the other end, the WHO contends "strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment."

To help fill this evidence gap, the AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) are collaborating on the PHOENIx study, which will enroll HIV-infected and uninfected child, adolescent, and adult household contacts of adults newly diagnosed with MDR-TB, pre-XDR-TB, and XDR-TB. The since being described in last year's Pipeline Report, the study has undergone an important modification to the composition of the experimental arm and will now compare the safety and efficacy of delamanid, rather than levofloxacin, to isoniazid—each given daily for six months—for preventing active TB among individuals exposed to DR-TB. Eligible household contacts include people with HIV of any age, children ages 0–5, and anyone older than 5 years who reacts positively to TST or IGRA. Delamanid has several qualities that make it an attractive potential treatment for probable DR-TB infection. Most importantly, it is effective at treating DR-TB, at least according to the phase IIb data that underpinned its approval by the European Medicines Agency in 2015. It also appears to be generally safe and well tolerated; has few drug-drug interactions with antiretrovirals that might limit its use among people with HIV; can be given as a single daily dose (thereby promoting adherence); and can be administered safely to children (a safety study of delamanid in children at all age groups is nearing completion).

Given that PHOENIx is the first large MDR-TB household study undertaken by ACTG and IMPAACT, the two networks have been conducting an observational feasibility study to prepare for the larger trial. Clinical trial sites participating in this preparatory study hit the targeted enrollment of 300 adult MDR-TB index cases and over 800 household contacts much faster than investigators had anticipated, suggesting that TB prevention trials among DR-TB patients and their close contacts are feasible despite a lack of experience in this area. In addition to PHOENIx, two other randomized controlled trials are investigating approaches to treating probable DR-TB infection. In Vietnam, the V-QUIN study is testing six months of treatment with levofloxacin versus placebo in Vietnamese adult, adolescent, and child household contacts of MDR-TB patients. In South Africa, the TB CHAMP study will compare levofloxacin versus placebo in children ages five years and younger (see "Pediatric Tuberculosis Treatment Pipeline," page 181, for a detailed discussion of pediatric TB drug research).

#### Treating MTB Infection in People with HIV

Work to develop better TB prevention options for people with HIV is also progressing, and most of this work is revolving around rifapentine. The notion of using rifapentine to prevent TB has amassed considerable interest in the wake of the landmark phase III trial by the Tuberculosis Trials Consortium (TBTC), which demonstrated the safety and efficacy of 12 once-weekly doses of rifapentine and isoniazid (the 3HP regimen). 104 However, most participants in this trial were HIV-negative, raising questions about the effectiveness of the 3HP regimen

in people with HIV. The TBTC recently published the results of a 403-person substudy conducted with the ACTG and IMPAACT under the larger trial that showed 3HP is as safe and effective at preventing TB among people with HIV as nine months of daily isoniazid (9H) and is better tolerated. These findings complement a study among nearly 1,150 adults with HIV and MTB infection in Soweto, South Africa, in which 3HP treatment had similar (although not superior) efficacy in preventing TB disease, fewer side effects, and better treatment completion rates than six months of isoniazid treatment. The superior of the superior o

New research is investigating whether administering multiple courses of 3HP over several years offers people with HIV more durable and long-lasting protection against TB compared with a single round of 3HP in high-TB-burden countries. (Previous Pipeline Reports have summarized related work investigating the durability of daily isoniazid preventive therapy, or IPT). The proposed Weekly High-dose Isoniazid and Rifapentine [P] to Protect against TB (WHIPP TB) study will investigate this question using a two-part approach. 107 Part A is an observational, randomized comparison of 3HP versus six months of daily isoniazid (6H) treatment among people with HIV. The primary objective is to compare treatment completion between the two regimens; secondary objectives will compare 3HP to 6H with respect to TB incidence, all-cause mortality, and discontinuation of therapy as a result of adverse events. 108 If 3HP performs favorably in part A, the results could lead the WHO to recommend the provision of 3HP to prevent TB among people with HIV in TB and HIV high-burden countries, offering an alternative to IPT. Part B is a randomized, controlled trial with three arms and will enroll concurrently to part A. Participants in the first arm will receive one course of 6H; those in the second will receive one round of 3HP; and those in the third will receive two rounds of 3HP, one given each year for two years (referred to as pulsing 3HP, or p3HP). The trial will enroll 4,000 participants at 12–14 sites in Ethiopia, Malawi, South Africa, and Mozambique. After two years of follow-up, the primary outcome analysis will compare the effectiveness of a single round of 3HP versus p3HP in preventing TB disease among people with HIV.<sup>109</sup> The study is sponsored by the KNCV Tuberculosis Foundation and funded by the U.S. Agency for International Development (USAID); Sanofi is donating drugs for the study. Investigators have received ethics approval and are awaiting final regulatory go-ahead from the South African Medicines Control Council. They expect to begin enrollment in June 2016. 110

The ACTG is also investigating the potential of daily rifapentine and isoniazid (HP) to prevent TB in people with HIV in study A5279. This phase III clinical trial is comparing the effectiveness of daily HP given for 4 weeks to daily isoniazid given for 36 weeks (9H) among 3,000 people with HIV 13 years of age and older who either have MTB infection or live in high-transmission areas. The study reached its targeted enrollment at the end of 2014 and will complete follow-up in November 2017.<sup>111</sup> Building on this effort, the TBTC, together with the U.S. CDC's Tuberculosis Epidemiological Studies Consortium (TBESC), the U.K. Medical Research Council (MRC), and University College London (UCL), is developing a study of daily rifapentine in settings of low-to-medium TB incidence. The study is still in the early stages of protocol development, but the current plan is to study the safety, tolerability, and efficacy of six weeks of daily rifapentine (P), primarily among HIV-negative individuals.<sup>112</sup> As written, the control arm in the study will be a composite of the three rifamycin-based standard-of-care regimens included in the WHO Guidelines on the Management of Latent Tuberculosis Infection: 3HP, three months of daily rifampin plus isoniazid (3HR), or four months of daily rifampin (4R).

The considerable potential of rifapentine to improve TB preventive therapy can only be unlocked if the drug becomes more widely available. Currently, rifapentine is approved for the treatment of MTB infection in just a single country, the United States, despite being studied through a series of public-private partnerships in at least a dozen more. Sanofi has made some progress over the past year in broadening access to rifapentine, most notably through its decision to list rifapentine in the catalogue of the Global Drug Facility (GDF). This means that, for the first time, TB programs outside of the U.S. will have a direct route for purchasing rifapentine and may even be able to start using the drug while registration is pending by exercising import waivers and other pre-approval access mechanisms. Sanofi has also taken steps to register rifapentine in a wide swath of countries, with the most progress seen in East Asia (Taiwan and Hong Kong).

rifapentine remains far too constrained given its central role in the TB prevention research agenda. For their part, investigators should be asking more of Sanofi in terms of securing commitments to making rifapentine available swiftly and without undue delay after the conclusion of efficacy trials. This is all the more justifiable considering that the lion's share of investment in rifapentine has come from the public sector. In the United States alone, three public agencies (CDC, NIH, and USAID) are footing the bill for trials that may expand the use of rifapentine to a broader array of countries and patient populations.

### PROGRESS IN PUBLIC ENGAGEMENT IN TB PREVENTION RESEARCH

The strategies being pursued by developers of TB vaccines and preventive therapies carry a mixture of risk and reward. For clinical trial participants, the decision about whether to enroll in a study involves a more personal risk/benefit calculus. Progress in the clinical research efforts described above will depend on the willingness of people at risk of TB to participate in experiments with uncertain outcomes. A similar bargain is struck by preventive interventions given that, as the writer Eula Biss reminds us, "it is through us, literally through our bodies, that certain public health measures are enacted." For prevention, especially, it is important that these measures be safe, effective, and acceptable for the healthy individuals who will be asked to take therapy or undergo vaccination to ward off an event whose occurrence is probabilistic and may never come to pass. Cutting-edge science alone is not enough to guarantee that new TB prevention methods will be acceptable to their intended users—a group that at its largest could include all 2 billion people estimated to be infected with MTB globally. TB prevention science must progress in lockstep with the meaningful engagement of the communities that will be asked to embrace any resulting new technologies and that will be called, time and again, to participate in the research to develop them.

Thoughtful community engagement is an important element of any TB R&D endeavor, but its presence or absence invokes unique considerations for prevention research. The science underlying prevention carries profound implications, not only for its potential to avert suffering resulting from disease, but also for its ability to reshape how individuals imagine themselves as either sick or healthy in relation to new conceptions of risk and susceptibility. It validated in clinical trials, correlates of risk, such as the gene signature identified from the South African adolescent cohort study, could create whole new clinical categories of people—the presymptomatically ill—that are subject to interventions ranging from treatment to vaccination to repeat testing. It is unclear whether signatures of risk will end up expanding the proportion of people with MTB infection in need of intervention, or whether they will narrow the eligibility for TB preventive services by assigning MTB-infected individuals to a spectrum of risk with interventions reserved for those at the high end. In either case, TB prevention science promises to open many people who consider themselves healthy to new forms of medical action. Engaging communities in TB prevention research, from the laboratory to the clinic, will help to ensure that the development of new TB vaccines and preventive therapies moves forward in parallel with the knowledge, values, concerns, and needs of the communities around the world at risk for TB.

Given these potentially transformative considerations, moves by Aeras in the last year to form a community engagement program come not a moment too soon. As designed, the program contains many of the best practices developed by earlier community engagement initiatives supported by TB drug developers such as the TB Alliance and the TBTC. Community engagement in TB vaccine trials sponsored by Aeras will occur on multiple levels: individual trial sites (e.g., through local initiatives led by community advisory boards), sponsors (e.g., through community reviews of clinical trials protocols), and regional (e.g., through the formation of an Africa TB vaccine advocates network). Among the proposed activities, the most important is Aeras's plan to involve community representatives in reviewing clinical trials protocols—a key step for building scientific literacy and for incorporating community feedback into the research agenda. Funders of TB vaccine R&D should commit to funding the Aeras community engagement program and acknowledge this work as the ethical complement to other standards of clinical research, such as Good Clinical Practice.

### **RECOMMENDATIONS**

For funders: Ensure financing mechanisms are sufficiently flexible and durable to support the multi-year, collaborative research endeavors that will be required to make progress against a challenge as complex and intractable as MTB infection.

For example, nearly ten years passed between when the South African adolescent cohort enrolled its first participant in 2005 and when it published results announcing the discovery of a risk signature of disease progression in the *Lancet* in 2016. This was not time wasted, and the cohort will likely yield publications and results for years to come. Further advancing our knowledge of MTB infection and TB disease may require larger cohorts with even longer periods of follow-up. In addition, funding agencies should support translational work to bridge advancements in basic science with clinical development and maintain openness to a wide range of approaches that probe the nature of MTB infection from the perspective of both host and pathogen, and through the application of new assays and imaging technologies in both humans and animal models.

For vaccine researchers and developers: Continue to explore a greater diversity of approaches to TB vaccine development through the use of experimental medicine studies and trials designed around novel endpoints.

Ultimately, this will likely require developers to introduce wholly new vaccine candidates whose designs look beyond the narrow focus on cell-mediated immunity that has dominated past efforts. The development and introduction of new assays that are able to translate signals of immunogenicity between lung and blood (or capable of safely measuring vaccine responses directly in the lung itself) should also be a priority. Developers and their sponsors should not foreclose on clinical trials among infants and people with HIV, two of the groups most in need of a new TB vaccine. Although previous trials in these two populations have fallen short of expectations, there is much that can be learned from past failures. Rather than wholly abandon vaccine concepts and constructs that did not work, vaccine researchers and developers should more forthrightly interrogate the reasons behind disappointing results.

**For drug researchers and developers:** Accelerate research to understand MTB persistence and the nature of latency to develop new drugs targeting latent infection.

Efforts to understand MTB persistence would benefit from initiating a dialogue with researchers involved in vaccine development about differences in how the TB drug and vaccine fields approach preclinical testing. Each field is confronting challenges related to MTB persistence and the nature of latency, but vaccine and drug developers do not always measure the same pathology or immunological events using relatable endpoints or definitions of scale in the animal models in which much of this work will be conducted. Closer collaboration with their vaccine counterparts might also open the door for drug developers to use vaccines as adjuncts to shorten therapy or reduce the risk of relapse. In the meantime, ongoing efforts to shorten and simplify TB preventive therapy for children, people with HIV, pregnant women, and household contacts of people with DR-TB should continue. The advanced stage of many of TB prevention trials obligates pharmaceutical companies involved in this research—namely, Sanofi and Otsuka—to take steps to register their products more widely and facilitate equitable access through measures such as affordable pricing.

**For all researchers and developers:** Recognize community engagement in research as the ethical complement to good clinical practice and take steps to involve representatives from TB-affected communities in all stages of R&D.

The potential of ongoing or planned TB preventive therapy and vaccine studies to refashion clinical practice in ways that could render many more people with asymptomatic MTB infection eligible for medical intervention makes it imperative that developers create meaningful spaces for community voices, concerns, and priorities to enter the research process. Communities must become true partners in TB prevention research, and not merely its silent beneficiaries.

For activists: Take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes.

With the exception of TB PROOF—a South African advocacy group founded by doctors who contracted TB that is dedicated to preventing MTB infection among healthcare workers—activist voices in TB prevention have been few in number and modest in volume. This absence does not reflect a lack of need. A global shortage of BCG continues into its third year, needlessly endangering the lives of millions of infants. PR Rifapentine, the cornerstone of TB preventive therapy research, is registered for the treatment of MTB infection in just one country, despite being studied in at least a dozen more. Individuals exposed to MDR-TB have few evidence-based options to treat probable drug-resistant infection. And countries remain slow to rollout proven interventions such as IPT to people with HIV, 400,000 of whom died from TB in 2014. PR are one year closer to 2025, the year WHO says new prevention tools must be introduced to reach the End TB Strategy's goal of eliminating TB by 2035, and there is no new vaccine or transformative preventive drug regimen on the immediate horizon. The clock is ticking.

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