

THE TB PREVENTION PIPELINE

By Mike Frick

INTRODUCTION

One of the tuberculosis (TB) field's most often voiced truisms has been that one-third of humanity is infected with *Mycobacterium tuberculosis* (MTB), the causative agent of TB disease. This estimate is invoked so frequently that it has become conventional wisdom and outgrown the need for a citation. A new estimate of the global burden of MTB infection, published in the past year, has brought this well-worn number into the present by accounting for changes in demography, the shifting size and distribution of the TB epidemic, and scientific advances that have improved our ability to detect and study MTB.¹ The revised figure suggests that nearly a quarter of the world's people (1.7 billion individuals) are infected with MTB. Although lower than the previous appraisal, this new estimate is far from a reassurance that the response to TB is on track. Instead, it points to the sizeable group of people in need of better options to prevent MTB infection from progressing to active, transmissible TB disease. This massive number thereby motivates the need to accelerate the development of new TB vaccines and preventive therapies and increase support for the basic science and translational research that enables progress in both areas.

The vast majority of the estimated 1.7 billion MTB-infected individuals alive today will never see their infection progress to active TB disease. But for some, events over the life course (e.g., aging, pregnancy), the presence of immune-compromising conditions (e.g., diabetes, HIV), and predisposing factors yet to be discovered increase the likelihood that what is termed latent TB infection (LTBI) will turn into symptomatic illness.² Why some people are more likely to progress from infection to disease, and how to identify these individuals within the larger group of MTB-infected people at less risk, pose two of the central questions animating research and development (R&D) for new TB vaccines and other preventive strategies, including better diagnostics and shorter, safer therapies. Answering these questions would allow public health programs to steer interventions toward those most in need and would increase the speed and efficiency of clinical trials, allowing studies to enroll fewer participants by focusing on those at greatest risk. The answers can only come from advances in basic and translational science and will likely take the form of biomarkers—the measurable biological processes, clinical phenotypes, or gene activities that signify either particular infection or disease states or the body's response to vaccination or treatment.³ The lack of biomarkers that act as prospective signatures of risk of progressing from infection to disease is one of the primary barriers slowing progress for TB prevention R&D.

Recognizing the importance of basic science to the TB prevention pipeline, this chapter opens by surveying recent advances and promising directions in understandings of host-pathogen interaction and TB pathogenesis before reviewing progress in the clinical pipelines for new TB vaccines and preventive therapies. Viewed from any of these three angles—basic science, TB vaccine development, and R&D for new chemoprophylaxis—TB prevention research is gaining momentum and entering a period energized by new thinking. Promising moves on the scientific front are being matched by increasing political attention to TB prevention. The chapter closes by discussing recent steps taken by governments to break the cycle of transmission that fuels the global TB epidemic by intervening before MTB infection becomes symptomatic, infectious illness. Garnering the political will to create, through research, and expand, through public health programs, new interventions to prevent TB rests on recognizing the estimated 1.7 billion people with MTB infection as a population with unmet health needs. Future TB cases will arise from this cohort—as well as from those yet to be infected—so governments should see investments in TB prevention R&D as part of a commitment to ensuring the health of present and future constituents.

PROGRESS IN TB PREVENTION SCIENCE

In January 2017, scientists gathered in Vancouver, Canada, at a Keystone Symposium to discuss new developments in basic understandings of TB. Samuel Behar, one of the scientific chairs of the conference, opened the meeting by recounting the example of Nobel Prize–winning physicist Isidor Rabi, who worked on the Manhattan Project during World War II and later became an advocate against nuclear proliferation. Behar set the tone for the meeting by quoting Rabi’s mother, who at the end of each school day asked her son not “what did you learn today?” but instead “did you ask a good question today?” Judging by presentations at the Vancouver Keystone Symposium, that emphasis on asking good questions has permeated the TB basic science field, which feels more open to and better connected with other research areas, and more inclusive of a variety of disciplines, than it has in recent years.

The period following the disappointing results from the phase IIb trial of TB vaccine candidate MVA85A in 2013 sent many in the TB field back to the basics to rethink the hypotheses—some would say dogmas—that have guided the field for at least the last 15 years.^{4,5} Scientists rethought the role of the pro-inflammatory cytokine interferon gamma (IFN γ) in protection against TB disease; questioned the utility of the animal models used to test vaccine candidates before launching clinical trials; and applied new technologies (e.g., positron emission tomography/computed tomography [PET/CT] imaging) to shed light on the complex dynamics of MTB interacting with its human host at sites of infection in the lung.⁶ From this work, a more complicated story has emerged in which MTB infection and TB disease are now understood to lie along a continuum of host-pathogen activity rather than exist as separate, mutually exclusive conditions.⁷ This more nuanced framework has created the space to embrace the complexity behind once monolithic concepts (e.g., what is ‘latent’ about latent TB infection?) and to approach longstanding challenges—for example, the ability of MTB to evade, withstand, and sometimes turn the body’s immune response to its advantage—with the insights of allied disciplines at hand.

Cross-disciplinary insights into MTB

If discussions during the “back to basics” years sometimes felt like circling the same ground repeatedly, the revised story has come with a habit of asking good questions that are taking the field in new directions. This habit is borne by the encouragement of what Valerie Mizrahi, the co-chair of the Vancouver Keystone Symposium, called “orthogonal thinking.” Two lines are orthogonal if they intersect at right angles, and TB basic science is now rife with examples of research projects that combine the tools and approaches of different, intersecting disciplines to make headway on longstanding challenges. One promising example is the combination of structural chemistry and molecular biology to visualize and understand the unique properties of MTB’s cell wall.⁸ The mycolic acids (essentially long chains of carbon atoms) that compose the outer membrane of the MTB cell wall give it its famous “waxy” character, which protects the organism from the body’s immune response as well as from many antibiotics. Better understanding the features of this mycolic acid–rich membrane could clear a path for developing new diagnostics and therapeutic agents. Progress here has benefitted from the development of more sophisticated methods for imaging specific cell wall components.⁹

Staining techniques—such as the Ziehl–Neelsen stain, developed in the 1880s—take advantage of the unusual properties of the mycobacterial cell wall to color-label MTB cells in sputum when viewed under a microscope. This technique forms the basis of sputum smear microscopy, which remains the most widespread TB diagnostic method but comes with major limitations: it is nonspecific to MTB and cannot distinguish dead MTB cells from live ones. One study sought to tackle this problem by developing small-molecule fluorescent probes attached to a kind of sugar called trehalose that is metabolized by MTB and incorporated into the cell wall. MTB cells that take up this trehalose probe fluoresce green, but so do other non-MTB components of sputum, making it difficult to separate MTB from other organisms.¹⁰ A related study overcame this limitation by modifying the trehalose dye so that it only fluoresces after

incorporation into the MTB cell wall.¹¹ Because its uptake requires MTB to metabolize it, the resulting fluorescent dye—called DMN-tre—can distinguish live MTB cells from dead ones.

If validated in field settings, this imaging technique could represent a major advancement over traditional staining by offering an improved method for sputum smear microscopy based on the same ubiquitous microscope platform. More immediately, it could provide a powerful tool for monitoring the progress of clinical trials by allowing researchers to measure reductions in pulmonary bacterial burden in TB treatment trial participants. For basic scientists, the DMN-tre dye might provide a way to investigate the changing dynamics of the MTB cell wall at different points in the adaptive immune response with a high degree of spatial resolution.¹² Work on DMN-tre is continuing, and the dye is currently being studied for its ability to selectively label MTB cells that are live and replicating and distinguish these from live but non-replicating organisms.¹³ This application would be a major boon to TB treatment and prevention science, as the field has lacked satisfactory ways to study the behavior of the live, non-replicating cells thought to exist during various stages of infection and disease.

Advances in translational science

The multiple potential applications of the DMN-tre dye, spanning from the lab to the clinic, offer a good example of the translational science that now occupies a more central place in TB prevention research. Translational science refers to the iterative process of turning observations in the lab, clinic, or community into interventions that improve public health.¹⁴ Observations from all three arenas—lab, clinic, and community—are driving translational TB prevention research projects through collaborations that include once odd pairings: basic scientists are teaming up with public health practitioners; vaccine developers are building basic science into clinical trials; and animal modelers are partnering with each other to improve existing model systems and share insights gleaned from experimental work across different species. In short, there is an encouraging trend toward reciprocally informed preclinical and clinical research and studies using various animal systems in synergy.

The merits of the several animal models used in TB R&D have inspired considerable debate, and conversations on the subject tend to pick up in intensity after major clinical trials return disappointing findings (as after the MVA85A phase IIb trial).^{15,16,17,18} When wading through the thick details of these discussions, it is helpful to recognize the bigger context in which animal modeling occurs. Animal models are tools that, like analogies, enable scientists to make comparisons between two things based on partial similarities.¹⁹ No single animal model system recapitulates MTB infection and TB disease in humans perfectly, but for these comparisons to be useful, animal models need to represent human TB in significant and meaningful respects. In the spirit of the Vancouver Keystone Symposium, what is at stake is less about selecting the right animal model and more about asking good questions given the models at hand, keeping limitations in mind when interpreting results, and working to improve model systems to pursue questions that cannot be answered with available frameworks.

An example of the latter approach is the use of Collaborative Cross (CC) mice to achieve greater genetic diversity in the mouse model. CC mice overcome the limited genetic repertoire and non-ideal population structure of the mouse models commonly used in medical research by offering a large panel of well-characterized, multiparental, recombinant inbred lines with greater genetic diversity.²⁰ One recent study used CC mice to investigate the relationship between bacillus Calmette-Guérin (BCG) efficacy, host genotype, and TB susceptibility.²¹ The investigators found that, on an aggregate level, mice from different lines displayed variable susceptibility to TB, different immunological responses to infection, and no durable protection from BCG vaccination—all to be expected from observations in humans. However, at the level of individual mouse genotypes, the story was more complicated: TB pathogenesis and immune responses differed across CC mouse strains; BCG efficacy varied by host genotype; and these qualities—MTB susceptibility and BCG efficacy—were separable, heritable genetic traits.²² The lack of BCG efficacy

overall was driven by a few mouse lines in which vaccination offered no protective effect as measured by reduction in bacterial load in the lungs and spleen. In the words of the investigators: “Based on these findings, it is not clear that optimizing a vaccine to protect a single standard laboratory strain of mouse will produce an intervention that is broadly efficacious in an outbred population, or even that a single vaccine is capable of protecting genetically diverse individuals.”²³

An extension of this project is using CC mice to model the complex interaction between environment, host genotype (susceptibility), bacterial genotype (virulence), and phenotype (outcome of MTB exposure or infection).²⁴ Essentially, the investigators are asking: What happens when one takes a panel of diverse mice, combines that with a panel of diverse MTB clinical isolates, and starts getting closer to the host-pathogen dynamics found in the real world? The study seeks to identify host-pathogen quantitative trait loci (QTLs), or sections of DNA (the loci) that correlate with variations in a given phenotype (the quantitative trait). Many QTL mapping studies focus on either the host or the pathogen genome, but the approach being pursued here takes into account the complex interaction between QTLs underlying host phenotypes (e.g., bacterial burden in the lungs or how well an animal controls infection) and bacterial fitness.²⁵ The incorporation of host and pathogen diversity into animal model systems may clear a path for experimentally pursuing a number of questions of importance to TB vaccine developers. For instance, what does protective immunity look like within and across genetically diverse human populations encountering genetically diverse strains of MTB? How can researchers account for the complex interplay between MTB, its human host, and the broader social and natural environment when designing vaccines? Can a single vaccine protect all people from all strains of MTB?

CC mice are one example of broader efforts to better represent the complexity of human TB within animal model systems. Other research projects are working with several different animal models to provide new insights into one of the thorniest questions in TB prevention science: What role do T cells play in protective immunity, and how do they play it? A growing body of detailed immunology work in mice and nonhuman primates suggests that some CD4+ T-cell responses can be protective while others may be pathogenic, and understanding the difference will be critically important for designing effective vaccines. Most TB vaccine candidates to date have sought to generate protection through immunity mediated by CD4+ T cells that release type 1 helper (Th1) cytokines such as IFN γ and tumor necrosis factor alpha (TNF α).²⁶ The emphasis on Th1 immunity reflects a wealth of data showing that humans and other species deficient in CD4+ T cells are extremely susceptible to MTB infection and progressive disease. And yet a study measuring BCG-specific CD4+ and CD8+ T-cell responses in nearly 6,000 infants found no correlation between the magnitude of expression of Th1 cytokines and protection against developing TB over two years of follow-up.²⁷ Genetic analyses suggest that the MTB genes coding for the epitopes most frequently recognized by human T cells appear little changed over time, raising the possibility that detection by Th1 T cells may somehow aid MTB.²⁸ That could be the case if overproduction of pro-inflammatory cytokines such as IFN γ by T cells reflects a loss of immune control or ongoing damage to lung tissue, which could create opportunities for the onward transmission of MTB.

In this vein, one recent study of MTB infection in mice suggests that overproduction of IFN γ can lead to worse outcomes, but that the role of IFN γ may change at different sites of infection (e.g., lung versus spleen).²⁹ In the lung, IFN γ accounted for only 30 percent of CD4+ T cell-dependent bacterial control (measured by reduced bacterial load six weeks post-exposure) but was responsible for over 80 percent in the spleen.³⁰ While increasing IFN γ production by CD4 T cells aided bacterial control in the spleen, it worsened pathology in the lung and led to earlier death. Importantly, the PD-1 receptor (a type of off switch that keeps T cells from attacking other immune cells) prevented excess IFN γ production.³¹ These findings hold a number of implications. First, it may be just as important for TB vaccines to promote regulation of IFN γ as it is expansion of IFN γ -producing T cells. Second, even if some amount of IFN γ production is necessary for protection, it may not be the most interesting thing T cells do when responding to MTB infection in the lungs (although it may have more importance when fighting disseminated TB).

Third, timing as well as location matter when measuring pathogenic versus protective qualities of CD4+ T-cell responses. Studying the lungs and spleen of mice after necropsy is relatively straightforward, and PET/CT imaging has allowed researchers to produce composite pictures of inflammation-based activity in the lungs of larger mammals like nonhuman primates. However, most immunology work in humans still depends on assaying samples of peripheral blood. The extent to which measurements taken from blood reflect disease processes in the lung is unknown, and studies in nonhuman primates have found that T cells in circulating blood (the systemic immune response) do not closely reflect T-cell responses observed in lung lesions (the local immune response).^{32,33} By relying on peripheral blood, there is a risk that researchers will miss observing the complexities of host-pathogen interaction directly and instead only view the traces of this activity that end up in blood.³⁴ A similar qualification applies to the endpoints used in animal model versus human studies. Most studies in animals gauge “control” by assessing bacterial load in the lungs—the one thing usually not measured in clinical trials. This difference in endpoints offers an important reminder that animal model systems are by definition approximations, not mirrors, of human TB.

Related work in mice has shown that the differentiation of CD4+ T cells is another important factor in their ability to effectively respond to MTB.^{35,36} (Differentiation is the process by which T cells assume specialized phenotypes—e.g., becoming either memory or effector cells—when presented with antigen by other immune cells that have encountered a pathogen.) In one study, the outcomes of differentiation shaped how well CD4+ T-cell subsets migrated into the lung from the lymph node and circulating blood. Less differentiated cells appeared better at migrating, whereas those with more terminal differentiation tended to remain in the lung vasculature.³⁷ The ability of T cells to enter the lung may prove more important for protection against MTB than their ability to produce large amounts of IFN γ . A follow-on study identified characteristics of Th1 immunity that influence the differentiation of T cells into more and less protective types.³⁸ Considered together, these findings suggest that vaccine developers will need to look beyond whether candidate vaccines can expand IFN γ -producing CD4+ T cells to consider other factors such as a vaccine’s effect on cell differentiation.

Much of this work has taken place in mice, but supporting observations have also been made in nonhuman primates. A presentation of these results at the Vancouver Keystone Symposium ended with a vibrant, fluorescent image of a granuloma from a macaque lung.³⁹ The image revealed a pileup of T cells clustered around the edge of the granuloma with just a few at the site of infection in the central core. The photograph was beautiful and offered a striking example of the power of imaging to open new windows into seeing human cells in physical relation to MTB. When one zooms out from the particular details of individual studies, many of the recent advances in TB basic and translational science coalesce into the insight that relationships matter. It matters how we relate observations of host-pathogen interactions made in animal models to the more complicated humans they stand in for before TB prevention concepts and constructs enter clinical testing.

Movements in experimental medicine

Progress in translational science for TB prevention ultimately hinges on opportunities to work in humans. To this end, vaccine developers have made concerted efforts to design vaccine trials in ways that promote collaboration between basic scientists and product developers. One strategy involves nesting small experimental medicine studies into larger clinical trials. Such studies take advantage of the opportunity to work in humans to conduct detailed immunology or to develop tools for pursuing such work.⁴⁰ For example, last year’s *Pipeline Report* reviewed a phase I study of TB vaccine candidates H4:IC31, H56:IC31, and BCG revaccination in South African adolescents. Sponsored by Aeras and the U.S. National Institutes of Health (NIH) HIV Vaccine Trials Network, the study aims to collect a wide array of immunological data to inform the development of novel immune assays that may help to identify correlates of risk or protection.⁴¹ Another experimental medicine study sponsored by Aeras will open

soon at St. Louis University. Fifteen adult volunteers will undergo leukapheresis (a process in which white blood cells are separated from other parts of the blood) at two time points: pre-BCG vaccination and post-BCG vaccination.⁴² White blood cells (leukocytes) are central actors in the immune system, and this study will collect the large quantity of these cells needed for assay development and a range of other scientific applications (e.g., exploring the function of particular immune cell subsets).

PROGRESS IN TB VACCINE DEVELOPMENT

On the clinical side, TB vaccine developers are preparing to release results from several large trials for the first time since the 2013 publication of initial findings from the phase IIb trial of MVA85A. TB vaccine candidates M72/AS01E and H4:IC31 are expected to complete phase IIb and phase IIa trials, respectively, within the next year. In some respects, these two studies represent the before and after of a major shift in strategy that took place in the TB vaccine field after 2013. Up until that point, most clinical development programs focused on testing the ability of candidate vaccines to prevent TB disease (POD). In recent years, developers have started designing studies around two alternative primary outcomes: prevention of infection (POI) and prevention of recurrence (POR). POI studies assess whether vaccines can prevent MTB infection, whereas POR trials evaluate the ability of vaccines to prevent relapse or reinfection in the estimated four to six percent of people who develop disease after successfully completing treatment.

Both POI and POR trials “are intended to show the biologic activity of vaccine candidates using more focused populations specifically selected to reduce sample size.”⁴³ In other words, POI and POR studies are tactics on the road to licensing a new vaccine that prevents TB disease. The hope is that POI and POR trials will shorten this road by quickening the pace and decreasing the cost of clinical trials while yielding glimpses of efficacy at earlier time points to inform the selection of candidates to take forward into larger efficacy trials. The success of these tactics will depend on the extent to which the underlying mechanisms of prevention of infection or recurrence correlate to prevention of disease. Because this correlation is unknown, prevention of disease will likely remain the primary outcome measure of late-stage efficacy trials, as regulatory authorities may be reluctant to approve a new TB vaccine based on surrogate markers related to POI or POR. This qualification is compounded by the fact that there is no direct test for MTB infection. Available methods for diagnosing MTB infection—the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—only measure immune reactivity to MTB. Furthermore, these tests cannot reliably predict an MTB-infected individual’s likelihood of disease progression.

While the strategy has changed, the composition of the TB vaccine pipeline bears marked similarity to previous years. The 2017 pipeline contains 14 candidates under active clinical development, representing three main constructs (**Table 1**). Four subunit vaccines pair different combinations of MTB antigens with immune-modifying adjuvants; five viral-vectored vaccines employ weakened viruses to deliver antigen; and five whole-cell vaccines are based on genetically attenuated MTB or closely related mycobacterial species. These vaccines have been studied in a range of populations—from BCG-vaccinated infants to HIV-infected adults—with current efforts now focused on POI or POR trials among HIV-negative, MTB-uninfected adolescents and adults.

Prevention of disease trials

GlaxoSmithKline’s (GSK’s) **M72/AS01E** TB vaccine candidate is nearing the conclusion of a phase IIb efficacy trial in 3,573 MTB-infected, HIV-negative adults in South Africa, Kenya, and Zambia. M72/AS01E is a subunit vaccine that pairs two MTB antigens (32A and 29A) with the AS01E adjuvant. Participants received either two intramuscular doses of M72/AS01E or placebo administered 30 days apart. The primary endpoint is incident cases of pulmonary TB disease (unassociated with HIV), and the primary outcome analysis is case driven, meaning that the trial must accrue a sufficient number of TB cases in order to trigger the analysis.⁴⁴ GSK reported that it was close to nearing the required number in

April 2017, and GSK and Aeras expect to release the first efficacy results in early 2018.⁴⁵ As this is the first efficacy study of a TB vaccine since the MVA85A phase IIb trial, these results will generate substantial interest.

Table 1. TB Vaccines in Development

Agent	Class/Type	Sponsor(s)	Status
<i>M. vaccae</i>	Whole-cell <i>M. vaccae</i>	Anhui Zhifei Longcom	Phase III
M72/AS01E	Protein/adjuvant subunit vaccine	GSK, Aeras	Phase IIb
DAR-901	Whole-cell <i>M. obuense</i>	Dartmouth University, Global Health Innovative Technology Fund	Phase IIb
VPM1002	Live rBCG	Serum Institute of India, Vakzine Projekt Management, Max Planck Institute for Infection Biology, TBVI	Phase IIb
H4:IC31	Protein/adjuvant subunit vaccine	Aeras, SSI, Sanofi Pasteur, Valneva	Phase IIa
H56:IC31	Protein/adjuvant	SSI, Aeras, Valneva	Phase IIa
MTBVAC	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI, Aeras	Phase IIa
ID93/GLA-SE	Protein/adjuvant	Infectious Disease Research Institute	Phase IIa
RUTI	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1.85A + MVA85A	Viral vector	Oxford University	Phase I
MVA85A (aerosol)	Viral vector	Oxford University, TBVI	Phase I
MVA85A-IMX313	Viral vector	Oxford University, Imaxio	Phase I
TB/FLU-04L	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase I
rCMV	Viral vector	Oregon Health and Science University, VirBio, Aeras	Finishing preclinical development
ChAd3 + MVA (aerosol)	Viral vector	GSK, Transgene, Aeras	Finishing preclinical development

ChAd: chimpanzee adenovirus vector

GSK: GlaxoSmithKline

MTB: *Mycobacterium tuberculosis*

MVA: modified vaccinia virus Ankara

rBCG: recombinant bacillus Calmette-Guérin

rCMV: recombinant cytomegalovirus

SSI: Statens Serum Institut

TB: tuberculosis

TBVI: TuBerculosis Vaccine Initiative

Prevention of infection trials

TB vaccine candidate **H4:IC31** is nearing the end of a phase IIa trial in 990 South African adolescents. H4:IC31 is a subunit vaccine that combines MTB antigens Ag85B and TB10.4 with IC31, an adjuvant owned by the French company Valneva. The vaccine was developed by the Statens Serum Institut (SSI) of Denmark and licensed by Sanofi Pasteur. The phase IIa trial contains three arms: one-third of participants received two doses of H4:IC31, one-third received placebo, and one-third were revaccinated with a

single dose of BCG. The first two arms are double-blinded; the BCG revaccination arm is open label. The trial is powered to compare H4:IC31 versus placebo and BCG revaccination versus placebo, but not to compare H4:IC31 to BCG. Primary outcome measures include safety and prevention of MTB infection as measured by rates of IGRA (in this case, Qiagen's QFT-Gold test) conversion from negative to positive. The trial needs to accrue 64 cases of MTB infection for the primary outcome analysis. Aeras reports that the trial reached this milestone in the summer of 2016, when the data safety and monitoring committee, after reviewing the available data, recommended that the study complete the protocol and continue to accrue additional cases during follow-up.⁴⁶ Aeras expects to release results in the first quarter of 2018.

As the first phase IIa study of a TB vaccine candidate under the POI paradigm, the phase IIa trial of H4:IC31 had to stake out a position on one of the thorniest issues for POI trials: selecting the right primary endpoint. It remains unclear what effect H4:IC31 or BCG would have on QFT conversion if efficacious. If a protective effect appeared soon after vaccination, would it prevent QFT conversion from happening at all? Or would vaccination primarily help the recipient clear infection by controlling bacterial replication rather than blocking infection entirely? In this event, trial participants could QFT-convert from negative to positive upon infection post-vaccination and then revert to negative at a later time point. To unpack this question, the phase IIa trial contains many secondary outcomes, including assessing prevention of MTB infection by comparing rates of *sustained* IGRA conversion (defined as conversion to positivity with no reversion during the follow-up period).⁴⁷ To inform the secondary analyses, participants who QFT convert are undergoing repeat testing according to a carefully determined schedule to assess whether conversions remain stable over time.⁴⁸ The complexity involved here is a product of the limitations of available diagnostic technologies, as the meaning of IGRA conversion is unclear. Rather than detect the presence of infection directly, IGRAs measure the release of IFN γ by circulating white blood cells in response to MTB antigens. We know that QFT converts to positive when infection occurs, but we cannot assume the opposite: that QFT will revert to negative when infection is cleared.

The H4:IC31 phase IIa study is the first prospective, randomized, placebo-controlled clinical trial to evaluate whether BCG revaccination can prevent MTB infection. If the study finds that adolescents revaccinated with BCG have lower rates of QFT conversion than those receiving placebo, it could generate substantial public health interest, as BCG is safe, inexpensive, licensed, and widely used. Under this scenario, Aeras has considered conducting a follow-on phase IV trial in the same adolescent population to see if BCG revaccination could prevent TB disease—similar, perhaps, to the BCG-REVAC cluster-randomized community study done in Brazil in the early 2000s.^{49,50} Such a study would require a very large sample size but could be simpler to conduct in comparison to a phase III trial of an investigational product. A phase IV study would provide the opportunity to collect biological samples, which could be analyzed for correlates of protection to inform future research. In contrast, a compelling result for H4:IC31 might lead to a phase IIb/III POD trial in a broader population under a global licensure strategy.⁵¹

The **MTBVAC** vaccine candidate is a live, genetically attenuated form of MTB made less virulent by the deletion of two genes (*phoP* and *fadD26*). Discovered at the University of Zaragoza, MTBVAC is being developed in collaboration with Biofabri, a Spanish biotechnology company, with support from the Tuberculosis Vaccine Initiative. MTBVAC completed a first-in-human phase I safety study in Switzerland in 2015 and is currently completing a phase Ib safety, dose-escalation, and immunogenicity study comparing three doses of MTBVAC to BCG in South African infants.^{52,53} This trial includes an initial safety arm in adults; with safety demonstrated in this group, the study proceeded to the infant cohort in February 2016. A phase IIa study in South African newborns is planned for 2018.⁵⁴ In addition, MTBVAC is preparing for a phase IIa trial in QFT-negative and QFT-positive South African adults.⁵⁵ Participants will receive either one dose of MTBVAC (at one of four dose levels) or placebo administered intradermally. Primary outcome measures will assess safety, whereas secondary outcomes will investigate POI measured

by QFT conversion in adults without MTB infection at study start.⁵⁶ MTBVAC provides an interesting example of a vaccine candidate following two lines of development: the infant studies are assessing whether MTBVAC can replace BCG, while the work in adults is designed to test whether MTBVAC can boost BCG.⁵⁷

Another whole-cell mycobacterial vaccine candidate—**DAR-901**—is continuing a phase IIb POI trial among BCG-vaccinated, MTB-uninfected adolescents in Tanzania.⁵⁸ DAR-901 is a form of inactivated *Mycobacterium obuense* developed at Dartmouth University and manufactured from the master cell bank of SRL 172, an earlier vaccine candidate studied in the phase III DarDar trial.⁵⁹ The primary difference between DAR-901 and SRL 172 is that DAR-901 is grown in broth rather than agar, a more scalable production method. The phase IIb POI trial is fully enrolled with 650 adolescents aged 13–15.⁶⁰ Participants received either three 1 mg doses of DAR-901 or placebo administered intradermally and will undergo repeat IGRA testing using Oxford Immunotec's T-Spot at 12 and 24 months after immunization.⁶¹ The 1 mg dose was selected based on a three-dose phase I study among BCG-vaccinated adults in the United States conducted by Dartmouth University and Aeras. Results showed that a 1 mg dose was safe and well tolerated and induced cellular and humoral immune responses to MTB antigens comparable to those observed with a five-dose series of SRL 172 in the DarDar trial.⁶² Investigators expect to complete the phase IIb adolescent study by the end of 2018 and are planning for a possible phase III prevention of disease trial to start in 2019.⁶³

H56:IC31 is a subunit vaccine developed by SSI that contains three MTB antigens (Ag85B, ESAT-6, and Rv2660c) in combination with the IC31 adjuvant. This vaccine will soon begin a phase IIa POI trial at two sites in Tanzania and South Africa. It took considerable effort to prepare H56:IC31 for POI work. First, SSI had to develop an IGRA without ESAT-6 since this antigen is present in both commercially available IGRA tests such as QFT-Gold and in the H56:IC31 vaccine itself.⁶⁴ Using QFT-Gold to measure MTB infection in H56:IC31-vaccinated participants could result in false positives if the ESAT-6 in the vaccine were to prime the same antigen-specific T cells that the test looks for as an indication of MTB infection. The ESAT-6-free IGRA contains four antigens (CFP10, Rv3865, Rv3615c, and Rv2348), and studies in Denmark, Egypt, Tanzania, and South Africa suggest it performs comparably to QFT-Gold.⁶⁵ Second, in order to design the phase IIa study with sufficient statistical power, Aeras and SSI had to conduct a pilot study to determine the background rate of QFT conversion in the target population at the site in Tanzania, which is participating in a TB vaccine trial for the first time.⁶⁶

With the ESAT-6-free IGRA in hand and the pilot project completed, Aeras and SSI expect the phase IIa study to open for enrollment in September 2017.⁶⁷ The study will enroll 1,400 adolescents in two arms: participants in the first will receive two doses of H56:IC31 and those in the second will receive two doses of placebo. The 5 µg dose of H56:IC31 was selected in part based on the immune profile associated with this dose level in a phase I study. In this study, vaccination with 5 µg of H56:IC31 stimulated robust T-cell activity while avoiding the terminal differentiation and T-cell exhaustion seen at higher doses.⁶⁸ As summarized above, related work in mice suggests that T cells with less differentiated phenotypes are better at migrating to sites of infection in the lung. The primary outcome will compare the rate of conversion between those vaccinated with H56:IC31 and placebo, and secondary endpoints will assess sustained conversion based on repeat testing.

Prevention of recurrence trials

Prevention of recurrence work remains more nascent than the POI trials, but several POR studies are underway or planned. SSI and Aeras have applied for funding for a POR trial of H56:IC31.⁶⁹ Data in mice and nonhuman primates indicate that vaccination with H56:IC31 could reduce the risk of reactivation and help control MTB infection as measured by microbiological, immunologic, and radiographic assessments.^{70,71} One key difference between the animal model work and the pending

trial is that the mice and nonhuman primates in the preclinical studies were vaccinated before infection, whereas the phase IIa study will give H56:IC31 to people who already have active TB disease. As designed, participants will enter the trial upon diagnosis of active TB, at which point MTB will be isolated from their sputum. After six months of standard TB treatment, participants will be vaccinated with either H56:IC31 or placebo and followed for two years for recurrent disease, defined as either reinfection or relapse.⁷² Secondary endpoints will try to distinguish between these two possible causes. Individuals with recurrent disease will submit a sputum sample at re-diagnosis to see if the strain of MTB is identical to the one taken from the first sample (likely relapse) or a new strain (likely reinfection).⁷³

The subunit vaccine **ID93/GLA-SE** is completing a phase IIa dose-ranging study in 60 South African adults who have completed treatment for TB disease in preparation for future POR work. Developed by the Infectious Disease Research Institute, ID93/GLA-SE combines MTB antigens Rv2608, Rv3619, and Rv3620 with the GLA-SE adjuvant. The phase IIa trial is evaluating the safety and immunogenicity of two doses of ID93/GLA-SE administered intramuscularly at three dose levels.⁷⁴ In January 2017, the trial reached the final date of data collection for its primary outcome measure; results will inform a future phase IIb POR trial.

According to news reports, **VPM1002**—a live, recombinant form of BCG—is being readied for POR work among adult TB patients in India.⁷⁵ First developed by the Max Planck Institute for Infection Biology, VPM1002 was licensed to the biotech company Vakzine Projekt Management, which subsequently out-licensed development and marketing rights to the Serum Institute of India in 2013.⁷⁶ In addition to the planned POR trial in India, VPM1002 has entered a phase IIa safety, tolerability, and immunogenicity study in BCG-naïve, HIV-exposed and HIV-unexposed South African newborns.⁷⁷ This study reflects VPM1002's original development pathway as a potential BCG-replacement vaccine.

Preclinical watch: innovative concepts approaching clinical development

Sizing up the pipeline for new TB prevention tools requires considering its roots in preclinical research. A comprehensive review of vaccines and preventive therapies in preclinical development is beyond the scope of this chapter, but a few promising activities are worth highlighting.

Scientists at Oregon Health & Science University (OHSU) are developing a viral-vectored TB vaccine based on recombinant cytomegalovirus (rCMV) with backing from Vir Biotechnology, a new company that has funding from the Bill & Melinda Gates Foundation and venture capital firms.^{78,79} This work is closely related to longstanding efforts by the same team at OHSU to develop CMV as a potential HIV vaccine. In 2013, investigators published results showing that a rhesus CMV vector led to impressive clearance of simian immunodeficiency virus (SIV) in macaques.⁸⁰ CMV is believed to be a potent inducer of the effector memory T-cell responses seen as critical in the control and clearance of infections.⁸¹ Publication of nonhuman primate data on the use of CMV as a TB vaccine vector is forthcoming.

In addition to rCMV, other promising viral-vectored candidates are preparing to enter the clinical pipeline. For example, GSK and the French biotechnology company Transgene are wrapping up preclinical activities on an aerosolized TB vaccine construct that combines a chimpanzee adenovirus vector (ChAd3) with modified vaccinia virus Ankara (MVA), the same vector used for vaccine candidate MVA85A.⁸²

One of the most exciting nascent developments in TB preventive therapy is the TB LEAP project, which is exploring the potential for long-acting treatments for MTB infection.⁸³ The project is growing up in the shadow of the more firmly rooted Long-Acting/Extended Release Antiretroviral Resource Program (LEAP). Not all drugs are suitable for long-acting formulations, but those that are carry several potential advantages, including less frequent dosing, improved bioavailability, and easier patient adherence. As a starting point, TB LEAP has developed target product profiles for ideal long-acting formulations of TB preventive therapy to guide developers working in this area.⁸⁴

PROGRESS IN TB PREVENTIVE THERAPY DEVELOPMENT

The bulk of work to develop new TB preventive therapies continues to focus on the drug rifapentine; six planned or ongoing trials include rifapentine either alone or in combination with isoniazid (**Table 2**). Much of the current interest in rifapentine builds on the successful phase III trial conducted by the Tuberculosis Trials Consortium (TBTC) at the U.S. Centers for Disease Control and Prevention (CDC) and the NIH's AIDS Clinical Trials Group (ACTG) that established the safety and non-inferiority of once-weekly rifapentine given with isoniazid for 12 weeks (the 3HP regimen) compared with nine months of daily isoniazid (9H).⁸⁵ Several research groups are building on this success by studying the combination of rifapentine and isoniazid under different durations and dosing schedules. The year 2017 also saw forward movement in clinical trials investigating preventive therapy for individuals exposed to drug-resistant TB (DR-TB). Until now, no randomized controlled chemoprophylaxis trials have examined how to treat probable infection with DR-TB. As a result, clinical practice has varied widely, and the WHO *Guidelines on the Management of Latent Tuberculosis Infection* identify “adequately powered randomized controlled trials . . . to define the benefits and harms of treatment of MDR-TB contacts” as an urgent research priority.⁸⁶

Table 2. Clinical Trials of Tuberculosis Preventive Therapy

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine and isoniazid for 1 month (HP) (vs. daily isoniazid for 9 months [9H]) NCT01404312*	Fully enrolled	People with HIV either living in high-TB incidence settings or with a positive TST or IGRA	ACTG
4R versus 9H 4 months of self-administered daily rifampin (4R) (vs. 9H) NCT00931736*	Fully enrolled	TST/IGRA+ adults, including people with HIV who are not on ARVs whose efficacy is reduced by rifampin	McGill University, Canadian Institutes of Health Research
WHIP3TB 6 months of daily isoniazid (6H) versus 3HP (given once) versus p3HP (given once a year for two years) NCT02980016*	Enrolling	People with HIV (>2 years of age) without active TB in high-TB-incidence settings	KNCV, USAID

Study/Regimen	Status	Population	Sponsor(s)
V-QUIN 6 months daily levofloxacin (vs. placebo) ACTRN12616000215426**	Enrolling	Household contacts (adults, adolescents, and children) of individuals with MDR-TB	NHMRC, VNTP
P2001 12 weeks of supervised 3HP NCT02651259*	Enrolling	HIV-positive and HIV-negative pregnant and postpartum women with MTB infection	IMPAACT
CORTIS 3HP versus no intervention and active surveillance for TB NCT02735590*	Enrolling	HIV-negative adults with MTB infection deemed high risk for disease progression as identified by a gene-based signature of risk	University of Cape Town
A5300B/12003/PHOENIX 26 weeks daily delamanid (vs. isoniazid)	Beginning enrollment Q2 2018	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
TBTC Study 37/ASTERoid 6 weeks of daily rifapentine (6P) (vs. rifamycin-based standard-of-care regimens [3HP, 4R, 3HR])	Beginning enrollment Q1 2018	Household contacts, people with HIV, individuals with recent TST or IGRA conversion, and other persons at high risk of disease progression	TBTC, TBESC, UK MRC, University College London
A5365 1 month self-administered daily rifapentine given once per year for three years (vs. one round of 3HP)	Protocol development	HIV-positive adolescents and adults in settings with low to medium TB incidence	ACTG

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

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

ACTG: AIDS Clinical Trials Group, NIAID

ARVs: antiretrovirals

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

MDR-TB: multidrug-resistant tuberculosis

NHMRC: National Health and Medical Research Council (Australia)

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

TB: tuberculosis

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

TST: tuberculosis skin test

UK MRC: Medical Research Council, United Kingdom

USAID: U.S. Agency for International Development

VNTP: Vietnam National Treatment Program

For a list of TB preventive therapy trials focused on children, please see “The Pediatric Tuberculosis Diagnostics and Treatment Pipeline for Children” chapter of this year’s Pipeline Report.

Clinical trials of rifapentine-based preventive therapy

WHIP3TB is a phase III study sponsored by the KNCV Tuberculosis Foundation with financial support from the U.S. Agency for International Development (USAID) studying the safety and effectiveness of 3HP among 4,000 individuals with HIV two years of age and older in Ethiopia, South Africa, and Mozambique, settings of high TB transmission and TB/HIV coinfection.⁸⁷ The study is proceeding in two stages. The first stage is comparing 3HP to six months of daily isoniazid (6H). 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 due to adverse events. Stage 2 of WHIP3TB is enrolling concurrently with stage 1 and contains three arms. Participants

will receive either one course of 6H, one round of 3HP, or two rounds of 3HP with one given each year for two years (referred to as pulsed 3HP, or p3HP). 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 in people with HIV.

Each stage of WHIP3TB seeks to answer a question of high public health relevance. If 3HP performs favorably in stage 1, the results would support the regimen's use as an alternative to isoniazid preventive therapy (IPT), the uptake of which has remained poor in most TB/HIV high-burden countries. The p3HP strategy being tested in the second stage is intended to assess the durability of protection offered by 3HP in areas where recurrent disease is common. Understanding durability is important given evidence that the protective effect of IPT wanes soon after a person stops taking it—at least in settings with a high force of infection, such as the gold mines of South Africa.⁸⁸

The combination of rifapentine and isoniazid (HP) for TB prevention in people with HIV in high-transmission settings is being studied in the NIH's ACTG study A5279. This trial is comparing the effectiveness of self-administered daily HP taken for one month versus 9H. The primary outcome will assess the time from randomization to first diagnosis of active TB disease.⁸⁹ The trial hit its targeted enrollment of 3,000 participants at the end of 2014 and will complete participant follow-up in November 2017; results could be released as early as the first quarter of 2018. A pharmacokinetics (PK) study nested into the trial has already reported results showing that four weeks of daily HP can be safely administered to people with HIV on efavirenz-based therapy without clinically meaningful reductions in efavirenz concentrations that might jeopardize viral suppression.⁹⁰

In addition, the ACTG is developing a protocol for a study (A5365) to compare the efficacy of three annual cycles of daily HP given for one month to a single course of 3HP in people with HIV age 13 and older. The trial is intended to complement the aforementioned A5279 and WHIP3TB studies by applying the pulsed approach of WHIP3TB to the daily HP regimen studied in A5279. If approved by the ACTG, A5365 will take place in medium-to-high TB-endemic settings (places with an annual TB incidence between 40 and 300 per 100,000 population) and exclude countries with the highest TB incidence rates, such as South Africa. The study remains in protocol development.

The TBTC is taking another approach by asking whether rifapentine can prevent TB when given alone, without isoniazid, in low-incidence settings. The phase III ASTERoiD trial (TBTC Study 37) will assess the safety, tolerability, and effectiveness of rifapentine given daily for six weeks (6P) in preventing TB among persons with high risk of disease progression in settings of low to medium TB incidence.⁹¹ The study is a joint effort between TBTC, the CDC's Tuberculosis Epidemiological Studies Consortium, and the U.K. Medical Research Council. Patient groups eligible for the trial include people with HIV, close contacts of people with TB, persons with a documented negative-to-positive TST or IGRA conversion within two years, or those who have recently emigrated to the U.S. or U.K. from a high-TB-burden country, among others. Data from the first 1,120 participants will inform an early safety analysis; in total, the trial will enroll 3,400 people. The investigators hope to open enrollment by January 2018.⁹²

The ASTERoiD trial will compare 6P to a composite control arm composed of three rifamycin-based standard-of-care regimens (3HP, four months of daily rifampicin [4R], or three months of daily rifampicin plus isoniazid [3HR]). 6P offers a number of theoretical advantages over 3HP. Rifapentine is thought to have less liver toxicity than isoniazid, so removing isoniazid from the regimen could improve safety. With fewer safety concerns and daily administration, 6P could be self-administered, eliminating the expense associated with direct observation of therapy. The shorter six-week duration and daily dosing schedule might also improve adherence over the longer 12-week, once-weekly dosing of 3HP. In addition, daily dosing may lessen the risk of rifapentine-associated flu-like hypersensitivity reactions seen in a minority of patients receiving HP once weekly; this syndrome appears more frequently when rifapentine is dosed

intermittently (for more on this point, see below). The trial will study rifapentine at a lower dose (600 mg) than that associated with hypersensitivity reactions in previous studies (900 mg).

Continuing the TBTC's history of including vulnerable populations in research—a commitment to equity that ensures that persons most at risk of TB can enjoy the benefits of scientific progress—ASTERoid investigators have voiced their willingness to open the trial to pregnant women in the second or third trimester pending favorable results from the early safety analysis.⁹³ Pregnant women with MTB infection face an increased risk of developing active TB yet have been systematically excluded from TB prevention trials.⁹⁴ Existing TB prevention regimens have undergone evaluation in more than 40 clinical trials, including eight phase III trials and 13 that focused on HIV-positive adults, all of which excluded pregnant women.⁹⁵ Recently, three community advisory boards issued a joint call for researchers to find ways to safely include pregnant women in TB trials in order to rectify this historic exclusion and provide evidence-based guidance to clinicians.⁹⁶ The willingness of ASTERoid investigators to consider opening the trial to pregnant women pending an interim review of safety data marks a positive step forward and follows on the heels of two studies run by the NIH International Maternal Pediatric and Adolescent Clinical Trials Network (IMPAACT) that are studying IPT and 3HP in pregnant women. P1078 is evaluating IPT given antepartum versus postpartum in pregnant women with HIV, and P2001 is studying the PK and safety of 3HP given to pregnant women with or without HIV (for more information on these trials, see “The Tuberculosis Diagnostics and Treatment Pipeline for Children” on p. 143).^{97,98}

Perhaps the biggest news in the pursuit of optimized rifapentine-based TB preventive therapy in the past year came from one of the smallest studies. At the 2017 Conference on Retroviruses and Opportunistic Infections (CROI), investigators from the NIH Clinical Center presented results from a phase I drug-drug interaction study in healthy volunteers that sought to characterize the effects of 3HP on the steady-state PK of dolutegravir, an antiretroviral drug.⁹⁹ The study stopped early when two out of four enrolled participants developed hypersensitivity reactions marked by nausea, vomiting, and fever. The biological explanation for these adverse events is unclear. Plasma samples from each participant showed higher than expected levels of isoniazid, and cytokine assays revealed increased levels of inflammatory markers such as IFN γ and TNF α following the second rifapentine dose. The investigators are planning to analyze blood samples for evidence of anti-isoniazid and anti-rifapentine antibodies that might help to explain the hypersensitivity response.¹⁰⁰

In the poster presented at CROI, the investigators conclude that “these data suggest that co-administration of dolutegravir and 3HP should be avoided.”¹⁰¹ It is too soon to foreclose on the co-administration of 3HP and dolutegravir based on a single phase I study in four healthy volunteers, but this concerning finding deserves further investigation—and sooner rather than later. Dolutegravir is already part of preferred first-line regimens for treating HIV in many high-income countries, and its use is expected to increase quickly in low- and middle-income countries thanks to sublicenses brokered by the Medicines Patent Pool between ViiV Healthcare, the originator company, and several generic manufacturers.¹⁰² The expanding reach of dolutegravir dovetails with the expected scale-up of 3HP under a project led by the Aurum Institute with support from Unitaid that will catalyze the market for 3HP by supporting its use in 12 high-TB burden countries. Very soon, clinicians will confront the question of whether people with HIV receiving dolutegravir can safely take 3HP to prevent TB. Providing fact-informed guidance on this point will require answering a number of questions, including:

- Can dolutegravir safely be given with 3HP to people with HIV? The phase I study presented at CROI was conducted in HIV-negative, MTB-uninfected volunteers. For HIV-positive people, it will be important to investigate whether the risk of hypersensitivity is associated with CD4+ T-cell levels. Rifapentine hypersensitivity reactions have been observed more frequently in persons otherwise healthy.¹⁰³ If this is the case, individuals with more CD4+ T cells might face a greater risk than those with more serious immunosuppression.

- Relatedly, can rifapentine be co-administered with dolutegravir in people with HIV without prior IGRA or TST testing for MTB infection?
- Is there a lower risk of hypersensitivity when HP is given daily rather than weekly? Some evidence suggests that intermittent administration of rifapentine increases the risk of hypersensitivity.¹⁰⁴
- Are reduced dolutegravir exposures in the presence of HP clinically meaningful? If dolutegravir needs to be dose-adjusted with HP, is it sufficient to dose-adjust just once a week (i.e., on the day 3HP is given)?

To begin answering these questions, investigators from Johns Hopkins University and the Aurum Institute are planning to conduct a safety and PK study of dolutegravir and weekly HP. Unitaid will support this study as part of the 3HP market-shaping project led by the Aurum Institute, and the investigators hope to report results by spring 2018.

Clinical trials of preventive therapy for contacts of people with drug-resistant TB

The ACTG and IMPAACT networks are partnering on the PHOENIX study (A5300B, I2003B), a cluster-randomized phase III trial that will compare the safety and efficacy of 26 weeks of delamanid versus isoniazid for preventing TB over two years of follow-up among household contacts of patients with multidrug-resistant TB (MDR-TB). The study will enroll over 3,450 household contacts from an estimated 1,725 households. Eligible household contacts include adults and children over five years of age who are HIV positive, at high risk of disease progression (e.g., on TNF treatment), or have a positive TST or IGRA; children ages 0–5 are eligible regardless of TST or IGRA status. Since this is one of the first large-scale MDR-TB household studies in history, the ACTG and IMPAACT first conducted an observational feasibility study to prepare sites for the larger trial. With the feasibility study completed, the two networks plan to open PHOENIX for enrollment in the first half of 2018 after delamanid dosing results are available for infants zero to two years old.¹⁰⁵

The V-QUIN study, sponsored by the University of Sydney with funding from the Australian National Health and Medical Research Council, is a cluster-randomized trial evaluating the safety and efficacy of six months of daily levofloxacin versus placebo for preventing TB among household contacts of MDR-TB patients in Vietnam.¹⁰⁶ The study will enroll adults and children living in the same household as MDR-TB patients within the past three months. Children under age 15 will only be randomized to receive the intervention following a favorable review of safety data in the older adolescent and adult cohort. In total, the trial aims to enroll over 2,700 household contacts from nearly 1,350 households. The TB CHAMP study in South Africa is similar to V-QUIN in comparing levofloxacin to placebo but will focus on child contacts age 5 and under (see “The Pediatric Tuberculosis Treatment Pipeline” beginning on page 143 for a detailed discussion of pediatric TB drug research).

PROGRESS IN POLITICAL WILL FOR TB PREVENTION

The spate of activity in TB prevention research is a signal of scientific opportunity, but is this signal reaching governments? In many respects, the politics of TB prevention are where the science was a few years ago—shaking off old paradigms to take the first cautious steps that mark any new direction. As the historian Christian McMillen documents in *Discovering Tuberculosis*, a global history of TB in the twentieth century, prevention took a back seat to treatment under the DOTS strategy that defined TB control in the 1990s and early 2000s.¹⁰⁷ Now, with the advent of the WHO End TB Strategy, TB prevention is finally coming to the fore. The End TB Strategy envisions a world without TB and aims to reduce TB mortality by 95 percent and TB incidence by 90 percent by 2035 compared with 2015.¹⁰⁸ Multiple mathematical models indicate that reducing TB incidence by this magnitude will require reducing the reservoir of

people infected with MTB, which will itself require research to develop better diagnostics, vaccines, and preventive therapies.^{109,110}

Governments have a pivotal role to play in supporting the development of the required new tools. Several events on the global and national levels in recent years suggest that more political attention is turning toward TB prevention, but there have also been some missed opportunities and unnecessary oversights along the way. Some of the more encouraging actions include:

- *Global guidance:* Three years after issuing its first-ever *Guidelines on the Management of Latent Tuberculosis Infection*, the WHO is updating the guidance to offer a more consolidated approach to treating MTB infection across high- and low-income countries. The original guidelines contained two sets of recommendations: one for high- and upper-middle-income countries with TB incidence less than 100 per 100,000 in the population and a second for “resource-limited countries and other middle-income countries.”¹¹¹ The new guidance will issue recommendations on several closely watched topics, namely a possible endorsement of 3HP as an alternative to IPT in high-incidence settings and a potential recommendation to give preventive therapy to all household contacts at risk of TB rather than just children under five years of age.
- *Market shaping:* The inclusion of TB prevention as an “area of intervention” in Unitaids’ TB portfolio gives governments an unprecedented opportunity to strengthen the implementation of TB preventive services.¹¹² As a first foray into this area, Unitaids’ support of the Aurum Institute–led consortium to scale up 3HP among people with HIV and children in a dozen countries will help to consolidate the market for rifapentine by driving up purchase volumes, lowering the price of the drug, and facilitating its registration in low- and middle-income countries. Key to success will be Sanofi’s willingness to expeditiously register rifapentine in TB-endemic countries and set a fair, affordable price for the drug on the international market.
- *National initiatives:* For decades, most national TB programs have thought of TB prevention as limited to IPT for narrowly defined high-risk groups or BCG vaccination for infants (although BCG is typically administered as part of the expanded program on childhood immunization outside of TB centers). Most efforts to broaden the field of action on TB prevention have proceeded slowly, but a few countries are introducing bold initiatives. For example, South Korea has announced that all Koreans will be tested for MTB infection at two points in their lives—once at age 15 and again at age 40—as part of a national push to reduce TB incidence from 86 per 100,000 to 12 per 100,000.¹¹³ In addition, the U.S. CDC has drawn up plans for a major initiative targeting the reservoir of MTB infection, which it calls “the final frontier of TB elimination in the USA.”¹¹⁴

These developments justify a cautious optimism. The decades-long saga to study and implement IPT reminds us that the history of TB prevention is a history of contestation. In *Discovering Tuberculosis*, McMillen details how IPT rose and fell in favor over the years—and not always in sync with the TB epidemic or the potential of the science. As late as 1982, on the edge of a world about to confront AIDS and the epidemics of TB/HIV and MDR-TB that would follow, a joint report by the WHO and the International Union Against TB and Lung Disease argued that “in practice, [IPT] has virtually no place in developing countries.” Interest in IPT picked up again a decade later as a way to respond to TB/HIV. In 1989, Jonathan Mann, then-director of the WHO Global Programme on AIDS, wrote that “delaying or preventing TB may be the single most important thing that can be done in developing countries for prolonging the survival of HIV-infected persons.” Following this, WHO called for and helped launch several trials of IPT in Africa, yet this renewed scientific interest was not enough to keep prevention anywhere near the center of the TB response. As McMillen notes, “during the height of research [in the early 1990s], political and administrative support for IPT was, publicly, lukewarm at best.”

To ensure the next chapter of TB prevention enjoys more consistent support, the following recommendations must be fulfilled:

- **Governments, pharmaceutical companies, and foundations must increase funding for TB prevention research.** To capitalize on the recent turn toward translational science, funding mechanisms must be flexible and durable enough to support the cross-disciplinary, multi-year, iterative work between lab, clinic, and community required to move the field forward.
- **Vaccine and drug developers should continue to design clinical trials that maximize opportunities for scientific learning.** For vaccine developers, this could entail conducting more experimental medicine studies. Similarly, drug developers should identify opportunities to support investigator-initiated science by nesting small, focused studies (e.g., of the kind funded by the NIH RO1 mechanism) in larger clinical trials. By making the most of opportunities to conduct research in humans, these studies provide a way to advance translational science alongside product development. Such studies often investigate critical questions to inform the use of novel interventions in populations most at risk of TB (e.g., children, pregnant women, people with HIV).
- **All governments must mainstream prevention into national TB strategies and begin planning for the eventual introduction of new tools—even if they remain years away.** To ensure timely access to new TB prevention products, implementation must anticipate scientific progress—as the tragically slow scale-up of new drugs and diagnostics to respond to DR-TB has demonstrated.¹¹⁵ This is especially true for TB prevention, given the longstanding neglect of the topic under previous global strategies. Many countries still consider themselves to be high incidence and therefore exempted from efforts to scale up preventive therapy. Under the End TB Strategy, this mindset must change—all countries at all epidemic levels can take steps to prevent TB by interrupting the cycle of transmission.
- **Activists and civil society must mobilize to support TB prevention research and hold governments accountable for translating scientific advances into practice.** Last year, Treatment Action Group urged activists to “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.” That advice is more important than ever. Over 60 percent of public funding for TB research comes from the United States government, and with an anti-science administration in power, defending biomedical research will require a united effort.^{116,117} Scientists, too, must become advocates and defend the instrumental and intrinsic value of their work.

Thanks to concerted research efforts, the TB field is preparing to enter an era in which prevention will mean more than BCG or IPT. But we cannot assume that the science underway will capture sufficient political will to see this research through to its end. To garner political commitment, TB prevention science will need to be translational in several respects. The same iterative approach to working between lab, clinic, and community that underlies many of the most promising scientific developments of recent years should be applied to the interface between TB prevention research and the global political agenda taking shape around TB. Politics and science may seem perpendicular to each other, but—to borrow Valerie Mizrahi’s expression—it will take orthogonal thinking to make sustained progress on a challenge as complex as preventing TB disease among the estimated 1.7 billion people with MTB infection alive today.

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