Report from the External Scientific Advisory Committee Meeting to the Bill & Melinda Gates Foundation TB Program Strategy Team July 17-18, 2017

Introduction

On July 17-18, 2017, the TB Program Strategy Team (PST) at the Bill & Melinda Gates Foundation ("the foundation") convened a Scientific Advisory Committee (SAC) chaired by Barry Bloom (Harvard U.), which was composed of the following individuals: Clif Barry (NIH), Amy Bloom (USAID), Carrie Cox (Humacyte), Jane Coyne (UCSF), Kathy Edwards (Vanderbilt U.), Eric Goosby (UCSF, UN Special Envoy on TB), Paul Miller (Synlogic), Valerie Mizrahi (U. of Cape Town), Jeff Ravetch (Rockefeller U.), Kitty van Weezenbeek (KNCV), Tim Wells (MMV) and Douglas Young (Imperial College & Crick Institute). The foundation team aimed to bring together a diverse group of experts internal and external to the TB field who would give feedback on the strategy and portfolio of work. The key questions that the SAC members were asked to consider were:

- *Is the foundation making appropriate progress and contributions toward the accumulation of knowledge and development of new tools that will drive the acceleration of the reduction in TB incidence?*
- *Given that the foundation knows that a combination of interventions is needed to impact the TB epidemic, are there additional areas that <u>we at the foundation</u> should target for funding?*
- *Are there ways the foundation could facilitate and/or inform more efficient use of global funding for TB?*
- *Are there new innovations/technologies/methodologies/approaches that the foundation could better leverage to optimize the investments we are making to accelerate our progress?*

The SAC members received strategy documents for the program as a whole and for each initiative therein as pre-reads. Over the course of the two-day meeting (full agenda in Appendix 1 below), the foundation team presented the various portfolios of work, including progress to date, and new data to inform the path forward. At the end of each day, there was a closed session for the SAC members to discuss candidly their reactions to the presentations, vote on project priorities and indicate their feedback to the foundation team. The report below was compiled by Barry Bloom as chair of the SAC with support from Becky Bartlein, Senior Program Manager of the foundation's TB Team, and has been reviewed by all SAC members.

Scientific Advisory Committee Review of the Bill & Melinda Gates Foundation TB Strategy

General evaluation on the program and progress to date

- There is no other non-governmental entity in the world that is funding all aspects of TB research in as comprehensive a way as this program. This is a strength of this program that should be preserved.
- Since convening the External Advisory Committee in 2013-2014 and redefining the upstream research agenda, the program has made impressive progress toward filling knowledge gaps in TB pathogenesis and immune responses.

- The portfolio is well thought through and is based on analyses of multiple perspectives, including the patient pathway through the health system, the lifecycle of the disease and the basic biology of TB.
- The patient pathway and cascade-of-care analysis that was carried out by the foundation in 13 countries, with diversely sourced and detailed available data, is a valuable framework. It will be useful in assessing the effectiveness of national TB control programs and facilitating the appropriate distribution of limited resources.
- Applying the patient pathway to care framework to the analysis of the TB program highlights its breadth and interdependency of its components. The perspective of planning for the end use up front when developing new tools ensures real world impact and relevance.
- All aspects of the program contribute to the strength and comprehensiveness of the strategy, while maintaining flexibility to direct efforts to where the opportunities are greatest.
- The TB PST at the foundation is bringing the power of cutting-edge science from multiple disciplines to the challenge of TB.
- The strong role of the foundation in TB advocacy and resource mobilization helps shape the global field of TB research and the effective allocation of resources.
- The sustained, long-term funding has produced new research tools that have enabled progress in areas such as drug development and understanding transmission, and has led to major breakthroughs.
- The success of the academic and industry partnership in the TB Drug Accelerator is a model for collaboration and is attributable to the foundation's convening power and unique role.
- Years of successful work to develop relationships with the governments of China and India and more recently, South Africa, have stimulated innovative interventions focused on improving hospital, private sector and public sector services in those high-burden countries.
- The quality of the leadership of the overall TB program, and the leadership in each of the initiatives, has been outstanding, resulting in many accomplishments in this most challenging disease area.

Cross-cutting comments on the TB Program

Following the review of each of the programs, the SAC made the following comments and suggestions to leadership (not necessarily in order of priority):

- Despite an initial sense that the TB program was too diffuse and needed greater focus, after reviewing each program individually, the SAC decided that although members had preference for different components, the interdependency of all the elements of the program made it difficult to eliminate any of the initiatives. However, it was emphasized that each of the initiatives should be integrated into the framework, with continued reprioritization over time.
- Members of the SAC felt that support for research capability development and clinical studies sites should continue in South Africa, and should be initiated in additional countries, as there is a concern that the capacity for clinical research to test new drugs and vaccines in TB-endemic countries may be insufficient and may limit progress in these areas. The group suggested the possibility of utilizing Gates-funded non-TB research sites in other countries to expand the range of sites available for TB studies.
- The committee questioned whether there may be a way to engage China and India as donors for basic TB R&D. Pursuing the possibility of engaging pharma companies in India as potential partners in TB drug development was also recommended.

- The SAC thought it would be important to have greater Low and Middle Income Country (LMIC) representation in TB Modelling Analysis Consortium (TB MAC) to diversify input to the models. It was suggested that expanded local capacity for modelling and economic evaluation in high-burden countries would improve the quality of information available for policy development, as well as evaluation of impact of interventions.
- Experimental animal models have been useful, particularly the recent studies of non-human primate (NHP) testing of vaccines. However, until successful phase II data that will back-validate the models are obtained, the value of the candidates is uncertain. Consequently, there was enthusiasm to expand the experimental medicine studies in humans to test hypotheses generated in animal models. There was agreement that greater understanding of human pathogenesis and immune responses to TB will be crucial to the development of better drugs and vaccines.
- Optimizing the introduction and uptake of new technologies that result from this research program must be considered as the technologies are being developed. Consideration should also be given to issues related to the impact of these advances on existing infrastructure and traditional approaches to TB control.
- The increased focus on implementation science was appreciated by the SAC, as was the stated need to ensure that the data derived were used to inform decision-making.
- There were concerns about how the Gates Medical Research Institute would impact the existing landscape and programs. And whether it will serve to encourage greater support in industry for TB drug and vaccine development or whether the foundation will lose its ability to leverage co-funding. There was also concern that the transition to the Gates MRI will cause disruption in that project timelines may slip while they hire staff and ramp up operations to be able to begin work on projects.
- The quest for an effective TB vaccine should continue and should focus on strategies that are safe and able to be implemented in humans.
- In the context of the presentations, it was the sense of the SAC that it would be helpful if the initiatives more clearly delineated their short, intermediate and long-term deliverables.

Review of individual initiatives

Diagnostics

The goal of this program is to develop an inexpensive, rapid, sensitive and specific Level 1 point-of-care (POC) test for TB that can be used to diagnose the disease in both symptomatic and asymptomatic individuals at risk of TB. To be more useful than current diagnostics, a new test must use a sample specimen that is easier to obtain and process than sputum, e.g. urine, saliva, blood or exhaled air. The development and introduction of GeneXpert shortened diagnostic time from 3-10 weeks to 90 minutes. However, the test is expensive and cannot be used at POC, so continued development is warranted.

Innovative technologies to improve the sensitivity and practicality of testing are currently being funded:

1. Antibody-based (Abs) testing of LAM in urine, where the antigen is concentrated by various mechanisms
2. Measurement of TB-specific volatile organic compounds (VOCs) in exhaled air and sweat
3. A Correlates of Risk (COR) test using RNA signatures in peripheral blood to provide an opportunity for early intervention during latent TB infection before active disease develops. Potential use of the COR as a blood-based diagnostic test or a test of treatment response should

also be pursued. These offer new opportunities for early intervention to detect disease sooner and prevent transmission.
4. Other host markers including blood proteins are also being considered as back-up programs.

The concept of a triage test that can be taken to scale before use of more precise expensive molecular tests was viewed as valuable. The members of the SAC were supportive of the approach that the team is taking to develop a triage test and recommended that it be continued and be prioritized.

Concerns

- The roadmap to achieving these goals in a 5-year timeframe is, as yet, uncertain. Many of the projects presented are still high risk in terms of probability of technical and regulatory success. More detailed development plans and timelines would be helpful.
- A simple triage test that rules out non-TB cases and prevents excessive use of more expensive tests would be very valuable. It was not clear whether the diagnostic team is planning for a single test that meets the ideal criteria fulfilling both point-of-care case detection and triage. The SAC recommended that the team consider that multiple tests may be needed to fulfill these two separate functions.
- The SAC recommended that the foundation contribute to a global effort to develop a diagnostic implementation framework to address market shaping, new product introduction and measurement of the impact of new tests early in the product development program. The committee suggested that lessons learned from the launch of GeneXpert regarding introduction and adoption challenges be incorporated into the implementation framework in coordination with other implementing agencies.
- The committee pointed out that an Mtb strain sequencing platform that could be used to detect and monitor drug resistance is dependent on the accuracy of phenotyping and that, in the absence of high-quality phenotypic data, the platform may not serve the intended purpose. It was recommended that the team be clear as to the added value of (targeted) sequencing of all available strains of Mtb.
- The committee urged that cost alone not rule out potentially transformative diagnostic technologies.
- The presentation to the SAC only focused on the development of new technologies. The foundation should also consider its role in the downstream space of promoting launch and uptake of technologies that are closer to market (i.e. GeneXpert Omni or computer-assisted X-ray screening as a triage test).

Drugs

The goal of the TB Drug Initiative is to develop universal regimens that are safe and effective in treating drug-resistant (DR) and drug-susceptible (DS) TB, and ideally shorter than 6 months. After a period of almost 50 years without new TB drugs, in a remarkably short period, the program has been catalytic in replenishing the pipeline: in addition to the two new drugs developed by pharmaceutical companies that are now approved for treatment, the foundation has catalyzed the development of six new drugs now in clinical trials and a pipeline of 14 lead compounds. The TB Drug Accelerator (TBDA) is an extraordinary achievement in that it uniquely promotes cooperation between industry and academia to access diverse chemical libraries, identify new hits and leads as well as new targets and advance promising candidates through preclinical development. This has enabled a high-quality, standardized

drug discovery and early development cascade. In addition, the foundation has facilitated collaboration among partners to share information, reduce redundancy and shorten development timelines. It has also capitalized on internal and external expertise in small molecule drug discovery to guide decision-making. The foundation is supporting the development of regimens that appear to be effective in treating both DR as well as DS TB, while also easier to apply and less toxic than existing MDR/XDR TB regimens. In addition, the program has funded the adoption of novel advanced methods to improve drug development, including the use of PET/CT to study pathogenesis and progression of lesions in patients and NHPs. The application of MALDI imaging technology with the capacity to ascertain where and whether multiple drugs are able to penetrate lesions is also a major advance. These represent breakthroughs as important new research tools to understand the impact of treatment.

Concerns

- A universal regimen is an ideal goal, but resistance to components of any TB regimen will inevitably develop, necessitating that surveillance for resistance to the new and current drugs continue. Managing the pipeline of new drugs appropriately to anticipate that possibility will be important. Given the current pipeline, there is the potential to develop more than one effective regimen, thereby providing alternative options for treatment.
- Due to the challenges of treatment completion, drugs have to be effective but also acceptable. Efforts to develop long-term depot-delivery of a single administration of drugs, which would last for 3-6 months, could be transformational. The committee recommended considering this approach in the future.
- In the downstream space, the SAC recommended that the team consider how the model of collaboration and engagement of pharma companies in the TBDA be used to inform cooperation in late phase clinical trials and commercialization. Additionally, the committee encourages the foundation to think ahead about how funding mechanisms can be used to guarantee purchasing of new regimens (e.g., as PEPFAR did for HIV drugs) to promote uptake.

Delivery

The goal of the TB Delivery Initiative is to develop innovative approaches to closing gaps in the care cascade and to prepare for new TB interventions. The strategy derives from an analysis of the gaps in the patient pathway to care in 13 countries and their specific major research efforts in China, India and South Africa. The focus has been to innovate in the areas of improving quality of care, engaging the private sector and facilitating linkages to care using information communications technology (ICT), thereby addressing major bottlenecks in health systems. In addition, the program has funded development and validation studies of adherence tools, including a small box that records drug adherence and blister packs to facilitate cell phone reporting of drug uptake. A great strength of the program is that the innovations are owned and implemented by the countries themselves with catalytic involvement of the foundation, which improves the likelihood of long-term sustainability. For example:

- In China, the program has helped facilitate improved coordination of hospitals with the CDC and primary care clinics to improve the quality of care that patients receive. Use of molecular diagnostics in the program has reduced the time required to identify rifampicin resistance from two months to one week. The government of China is now scaling up the program in three additional provinces as well as one city in each of the remaining provinces.
- In India, an ICT system has been created to integrate TB notifications from the private sector and public sector in statewide and nationwide databases for the first time. The system is now being rolled out in two states, which could be transformational, since ~80% of patients access care in the private sector.

Concerns

- There are exciting innovations in this portfolio of work, but the extent to which they can be scaled up is still unknown. It will be important to document the impact of these innovations on surveillance, case finding and treatment completion, as well as lessons learned in catalyzing changes to entrenched systems. In addition, experience with pathway analyses over the last decades have shown that findings show significant in-country variations, which require different solutions. Hence, countries should be encouraged to further differentiate and analyze sub-national data.
- Many ICT solutions are country-specific. The SAC raised the question as to what extent these innovations are generalizable and can be applied to other, particularly smaller and lower-income, countries. Assessing the applicability and impact of lessons learned in one country to the issues in another will be important to measure.
- The foundation's TB delivery program should give consideration to successful interventions in other disease programs (e.g., HIV) that could be relevant or adaptable to TB.

Vaccines

The goal is to develop vaccines that are safe and effective in preventing infection with Mtb or progression from latent to active disease. Modelling has shown that compared to other interventions, even partially effective vaccines would have the largest impact on the epidemic and the greatest cost-savings. However, TB vaccines represent a long-term challenge, with a relatively low probability of success in the short term. Numerous innovative advances have been leveraged by the program. The team has made advances in studying the central role of the granuloma in influencing immunity and protection. It has supported the development of a safe live human Mtb challenge system similar to those that have been used in other diseases, such as malaria. The potential role of antibodies in protection, long neglected, is being more comprehensively evaluated, comparing subjects who have been exposed and not infected with those who have been exposed and infected. The program has brought together cutting-edge new technologies including CyTOF and single cell RNA sequencing to reveal potential mechanisms of protection that are contributed by multiple cell types of the immune system. The recent studies in NHPs have provided new insights into pathogenesis, development of lesions and mechanisms of protection against TB challenge and, while expensive, should continue to be pursued.

Apparent breakthroughs have emerged that appear to provide protection in NHP models including the Cytomegalovirus (CMV)-based vaccine candidate (CMV-TB).

- The striking protection observed in NHPs provides a unique opportunity to understand the immunological mechanisms necessary and sufficient for protection. Following proof of safety of candidate vaccines, the new approaches may form the basis for subsequent experimental medicine studies to measure the relevant parameters in humans.
- It is clear from previous results that it will be advantageous, if not essential, to understand immunological mechanisms of protection from both infection and disease in humans, which may well be distinct. The identification of biomarkers of protection would accelerate a rational evaluation of individual candidate vaccines in humans.

Finally, the foundation has been instrumental in increasing the capacity for TB vaccine research. The support of the South African TB Vaccine Initiative has created an extraordinary infrastructure and model

for testing and evaluating vaccines in a highly endemic country. In creating the Collaboration for TB Vaccine Discovery (CTVD), the foundation has engaged a community of scientists to work collaboratively to move the field forward more rapidly.

Concerns

- In the presentations of the work, there appeared to be a disconnect between discovery activities and the strategy component of the TB PST; better integration should be sought. It was unclear how some of the cutting-edge new technologies and sophisticated science would contribute to moving TB vaccines forward. The SAC recommended stronger alignment, coordination and collaboration among the various contributors to the program to optimally achieve the shared goals.
- The SAC perceived that the members of foundation's TB Vaccine Initiative may feel inappropriate pressure to move candidates into clinical trials without sufficient understanding of what would optimize chances for success. Vaccine development is a long-term, high-risk process and the foundation is one of few organizations that can commit to such a long-term goal. It is important that the program stay the course and continue to elucidate mechanisms of action and safety, as in smaller experimental medicine studies, before moving into large clinical trials.
- More can be learned from experimental medicine studies in humans, by measuring multiple components of immune responses generated by different candidates. The presentations did not clearly delineate the information these experimental studies need to generate in the next 5 years to enable them to serve as a platform for product development and successful clinical trials. Several committee members also expressed concern that the estimated $50 million cost to move the CMV vaccine candidate through Chemistry, Manufacturing, and Controls (**CMC**) and preclinical testing was too large a commitment for such an early stage program.
- The overarching concern for any vaccine is safety, and the committee had serious concerns about the safety of new concept testing in humans. While there was great enthusiasm about what can be learned from prototypes such as CMV-TB in revealing the mechanisms underlying the protection in NHPs, the committee thought that the optimism for these as candidates for human testing was premature. The SAC encourages the team to examine lessons learned from safety issues in the malaria vaccine program to inform their path forward.
- Members of the SAC suggested considering recent publications showing T-cell fatigue is a key player in chronic infection as well as in oncology. Since there are several clinical checkpoint reagents developed for modulating T-cell suppression, particularly of CTL, from the cancer field, these could be investigated in TB and may provide some relatively quick ways forward.
- The team should consider whether funding CTVD members may catalyze more rapid innovation.

Transmission Science

The progress in transmission science and aerobiology since the last evaluation by the External Advisory Committee in 2013-2014 is impressive. In funding the development of new tools required to measure the actual transmission of tubercle bacilli, the foundation is contributing greatly to basic science and our understanding of TB. While this portfolio may not lead to direct impact on disease incidence in the short and mid-term, it is an important approach and no other organization would have funded this program.

- It is now possible to detect viable bacilli in aerosols from patients, perform whole genome sequencing of transmitted strains and map currently circulating strains within communities, which represent an enormous advance.
- Preliminary findings that strains in aerosols may be different from those in sputum raises important questions about unique characteristics of transmitted strains.

- Studies are underway to ascertain whether aerosol sampling could measure transmissible Mtb from latent individuals prior to the development of symptomatic, clinically detectable disease.
- An intriguing finding that may have implications for low-cost screening for infectivity was the correlation between coughing and the number of CFU in aerosols.

Concerns

- There is a critical need to learn more about the biology of transmission; the committee expressed some concern that this area should not be overshadowed by a focus on TB control measures in the field. The committee supported continued development of the tools needed to better understand the physiology of transmitted organisms as research tools, rather than emphasizing devices for TB control in the field.
- The SAC urged the program to consider whether these transmission measurement methods can be used to monitor the impact of new drugs and vaccines and prioritize those that rapidly impact transmission. Ultimately the team should consider whether aerosol measurements could be used in the future as a metric for success of interventions and control programs.

Short-Term 'Hits'

Each member of the SAC was asked to suggest one short-term 'hit', an opportunity to provide real impact that could be expected to be accomplished within the next five-year period. The list is obviously not meant to be comprehensive or prescriptive, but to indicate of important areas of focus that the SAC thought would have impact. When subsequently compared to the TB team's 3-5 year goals (listed below), all recommendations mapped to a subset of selected priorities. The SAC identified (in bold text below) the most valuable short-term hits for the team to work toward.

Initiative	Sub-Initiative	3-5 Year Goal
Cross-Cutting	**Transmission Science**	**Understand Mtb viability and infectivity in aerosols to inform challenge models for vaccines, impact of drugs and TB control.**
Delivery	**China**	**Support the scale-up of a new TB control model in three Chinese provinces utilizing new tools and innovative delivery approaches.**
	India	**Continue to develop innovative private provider engagement models, ICT systems and adherence tools for improved TB control in India, with the aim of catalyzing expansion to multiple states and facilitating national scale-up.**
	South Africa	**Optimize current interventions and pilot innovative models in preparation for scale-up to reduce patient loss across the TB care cascade.**
	Global Partnerships	Support countries and the Global Fund to use data and modeling to allocate resources efficiently and maximize epidemiological impact.
	Product Delivery	Facilitate the uptake and optimal use of innovative TB products and technologies in key countries.
Diagnostics	Case Detection Test	New Level 1 non-sputum-based case diagnostic test in validation phase of development.
	Triage Test	**New Level 1 triage screening test for TB that does not rely on a sputum sample, in validation phase of development at some scale.**
	Product Delivery	Facilitate the development and implementation of country strategies to close the diagnostic gap at Level 1.
	Prognostic Test	Interim validation of Correlates of Risk host response prognostic signature; go/no go decision for full In Vitro Development.
	Tools and Infrastructure	Sustainable functional consortium in place to encourage sharing of specimens and data for biomarker validation, early product development and drug resistance analyses.

Drugs	**Discovery - Antimicrobial**[1]	**Identify at least three new mechanistically distinct antibiotic drug candidates, including some that target organisms adapted for survival in the host, which, when combined, have the potential to both shorten treatment and be effective as a universal regimen for DS and DR TB.**
	Product Development - Antimicrobial	Proof of concept toward the development of a universal regimen for DS and DR TB that consists of new drugs, which ideally will improve and shorten therapy.
	Host Directed Therapies	Determine whether host-directed therapy can contribute to shortening treatment duration and/or reduce lung damage; select a candidate for clinical testing.
	Tools & Infrastructure	Strengthen decision-making through the development and implementation of new tools.
Global Policy & Advocacy	Policy	Support the adoption and implementation of policies that catalyze uptake of innovative tools and service delivery models.
	Resource Mobilization	**Maintain and increase funding in the foundation and globally for TB delivery and for TB R&D.**
Vaccines	**Delineating Protective Immunity**	Identify necessary and sufficient components of immune responses associated with protection against infection and against disease, from NHP studies and experimental medicine studies in humans. Particularly learn whether antibodies can protect against infection, and define specific protective epitopes and characteristics/mechanisms of action.
	New Concept Discovery & Testing	Develop new vaccine concepts that exploit immunological diversity.
	Tools & Infrastructure	Develop tools and infrastructure to support an efficient, iterative process to develop and test vaccine concepts, forming a basis for future clinical trials.
	Coordination & Collaboration	Foster greater innovation, collaboration and coordination within the TB vaccine landscape.
	Product Development	Support product development of select vaccine candidates.

The SAC expresses its appreciation for all the very the thoughtful presentations and informative background materials and wishes to acknowledge the helpful assistance of staff making the work of the committee so rewarding and, we hope, useful. Thank you to Becky Bartlein, for organizing a successful two-day meeting, assisting Barry Bloom in compiling the feedback in this report and facilitating review by the rest of the committee.

[1] Members of the committee recommended having a target of one new molecule entering phase I every year for the next five years (two enter preclinical development each year). There was some disagreement that all compounds have to be mechanistically distinct as long as their chemotypes are different, or they are solving issues identified by other (failing) compounds.

Appendix 1: Bill & Melinda Gates Foundation TB Scientific Advisory Committee Detailed Agenda

Day 1 – Monday, July 17th

Time	Session
9:00-9:30	Welcome, introductions, objectives
9:30-10:00	Overview of TB strategy
10:00-10:15	Current state of TB & why we are here
10:15-10:30	Coffee break
10:30-11:15	Patient Pathway Analysis
11:15-12:00	Vaccines
12:00-12:30	Lunch
12:30-1:30	Vaccines (continued)
1:30-2:15	Transmission
2:15-2:30	Coffee break
2:30-3:30	Diagnostics
3:30-4:15	Informational Session: Advocacy & Resource Mobilization Strategy
4:15-5:00	TB PST dismissed: SAC group discussion, recap of key points from the day

Day 2 – Tuesday, July 18th

Time	Session
8:00-8:30	Breakfast with presentation on the Gates Medical Research Institute
8:30-8:40	Welcome back: any clarifications from Day 1, moving into Day 2
8:40-10:30	Drugs
10:30-10:45	Coffee break
10:45-12:00	Delivery
12:00-12:30	Lunch
12:30-1:15	Informational Session: Impact and cost effectiveness modeling
1:15-1:30	Any questions, clarifications before the TB PST leaves?
1:30-3:00	PST dismissed: Closed session for SAC members to discuss conclusions and recommendations