1 Global Vaccine and Immunization Research Forum:

2 Opportunities and Challenges in Vaccine Discovery, Development, and Delivery

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15 Abstract

16 The World Health Organization, the National Institute of Allergy and Infectious Diseases, part of the
17 National Institutes of Health, and the Bill & Melinda Gates Foundation convened the first Global Vaccine
18 and Immunization Research Forum (GVIRF) in March 2014. This first GVIRF aimed to track recent
19 progress of the Global Vaccine Action Plan research and development agenda, identify opportunities
20 and challenges, promote partnerships in vaccine research, and facilitate the inclusion of all stakeholders
21 in vaccine research and development. Leading scientists, vaccine developers, and public health officials
22 from around the world discussed scientific and technical challenges in vaccine development, research to

improve the impact of immunization, and regulatory issues. This report summarizes the discussions and conclusions from the forum participants.

Introduction

In March, 2014 the World Health Organization (WHO), the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and the Bill & Melinda Gates Foundation (BMGF) welcomed more than 175 leading scientists, vaccine developers, regulators and public health officials from around the world as participants in the first Global Vaccine and Immunization Research Forum (GVIRF). The GVIRF was organized to further the research and development objectives of the Global Vaccine Action Plan (GVAP) ([Global Vaccine Action Plan 2011-2020](#)). The GVAP, which was endorsed by the 2012 World Health Assembly, grew out of the Decade of Vaccine Collaboration and seeks to improve health by extending the full benefits of immunization to all people. The GVIRF will be held every second year, in accordance with the monitoring and evaluation framework of the GVAP.

Keynote lectures delivered by Dr. Anthony Fauci, Director of NIAID, Dr. Margaret Chan, Director-General of WHO, and Dr. Trevor Mundel, President of the Global Health Division at BMGF, opened each day of the forum, highlighting recent advances and the broad scope of vaccine research and development, research for universal health coverage, and the importance of innovation in addressing global health gaps in the developing world, respectively. The agenda for this first GVIRF was designed to track progress of the GVAP research and development agenda, identify opportunities and challenges in vaccine and immunization research and development, promote the development and maintenance of partnerships within the research community, and facilitate inclusion of stakeholders in the development and implementation of a research and development agenda. Discussions at the forum addressed three overarching themes: scientific and technical challenges in vaccine development, research to improve the impact of immunization, and regulatory issues.

Scientific and Technical Challenges in Vaccine Development

The GVIRF provided an opportunity to discuss challenges and approaches to vaccine development in sessions focused specifically on: vaccines against HIV, tuberculosis (TB), and malaria; universal influenza vaccines; as well as sessions on cross-cutting issues of vaccine development and approaches to overcome challenges in vaccine development.

HIV Vaccines. Multiple HIV candidate vaccines have been developed and tested in more than 200 clinical trials; to date, however, only one vaccine candidate has shown modest efficacy (Esparza, J. 2013; Rerks-Ngarm, et. al., 2009). Historical discussions at the Forum suggested that innovative methods to develop a vaccine against HIV are needed to prevent and control HIV infection. The induction of immune mechanisms that occur infrequently during natural infection, such as development of broadly neutralizing antibodies and broadly reactive cell-mediated immune responses, are promising research and development directions to pursue. Scientific challenges include: the genetic and immunologic hypervariability of HIV; the host controls against the development of broadly neutralizing antibodies and the viral evasion mechanisms employed by HIV to “escape from” broadly neutralizing antibodies; HIV targeting of immune cells; latent HIV reservoirs; and integration of the HIV genome into the host genome. To address the challenges of HIV vaccine development, research is being pursued on a variety of topics, such as next-generation immunogens (e.g., native envelope trimers) and platforms (including replicating viral vectors to provide protective immunity by mimicking live attenuated vaccines), the induction of immune responses to conserved regions of HIV, and the use of mosaic antigens to provide optimal coverage of HIV epitopes.

Tuberculosis vaccines. Approximately one third of the world’s population is thought to be infected with *Mycobacterium tuberculosis*, the pathogen that causes TB, but most infected individuals do not develop active disease, suggesting that the immune system can mount a protective response. The currently available Bacillus Calmette-Guérin (BCG) vaccine protects children against death from non-pulmonary TB

and positively impacts protection from other childhood infections. It also appears to provide some cross protection against leprosy. However, as this live vaccine is given early in life and re-administration later in life as a booster does not improve efficacy, it does not provide reliable protection against pulmonary TB in adults and adolescents. Research to develop better protective vaccines for TB are following several different strategic pathways: (1) a vaccine administered prior to infection to prevent, either initial infection or establishment of the granuloma (aggregates of immune cells that function to localize and contain M.tuberculosis while concentrating the immune response to a limited area); (2) a vaccine administered post-infection to prevent disease and activation of TB from latent infection; and (3) a therapeutic vaccine that could minimize/reduce the course of chemotherapy and decrease relapse or reinfection rates. Researchers are exploring a variety of protein and non-protein antigens as vaccine candidates and the role of immune responses, both cellular and humoral immunity, in protection against infection or disease. However, since an efficacious vaccine is not available, and immune responses in individuals who do not develop TB (i.e., are naturally protected) may be different from those needed in persons who are susceptible to disease, correlates of protection have yet to be identified to guide antigen and vaccine selection. Also impeding the development of vaccines against TB are limitations in the tools that are available to measure exposure to M. tuberculosis, or latent infection, to identify persons with the highest risk of progressing to active TB, and reliable measurement of cure. Animal models of TB are limited and do not reflect the full spectrum or dynamics of pathology or immune responses; therefore, researchers are developing approaches and strains to establish a human challenge model of TB to help in identifying critical tools and correlates of protection (see below).

Malaria Vaccines. The session on vaccines against malaria began with an overview of the first generation malaria vaccine, RTS,S/AS01. In a Phase III multicenter clinical trial involving 11 different sites, the first-generation malaria vaccine candidate demonstrated modest protection against clinical malaria with a reduction in incidence of severe malaria, malaria hospitalizations, and all-cause

hospitalizations observed at all trial sites (Agnandji, et. al., 2011; RTS,S Clinical Trials Partnership et. al., 2012). Superior efficacy was seen in individuals between 5-17 months of age compared to those between 6-12 weeks of age (Agnandji, et. al., 2011; RTS,S Clinical Trials Partnership et. al., 2012). However, waning efficacy observed in the 18 months following vaccination highlights the need for a booster dose. The ensuing discussion focused not only on development and evaluation of second-generation malaria vaccines, but also critical issues relevant to future delivery of such vaccines. Specific topics of discussion included the need to strengthen pharmacovigilance systems in developing countries given their predominant use in those countries; regulatory approval strategies for vaccines that provide protection only at the community level (e.g. vaccines to interrupt malaria transmission); human vaccinology research to identify and evaluate preferred platforms to effectively target antigens to the immune system, to identify biomarkers of protection, and to validate targets for subunit vaccine development; and the limitations of current preclinical models through back-validation from clinical to preclinical data.

Universal Influenza Vaccines. Discussion on vaccines against influenza touched on the limitations of the current vaccines and the expectations of and approaches towards development of a universal influenza vaccine. Current influenza vaccines are limited by the antigenic drift of seasonal influenza strains, the mismatch between approved vaccines and circulating virus strains, and the limited efficacy of the inactivated vaccine in the elderly. Additionally, months of preparation are needed to produce vaccines against pandemic influenza strains. A universal influenza vaccine would address some of these limitations by eliciting cross-strain protection that is long-lasting. The development of a universal influenza vaccine, however, is a long-term objective, and in the interim, vaccines that protect against antigenic drift variants may serve as important milestones towards that goal. Approaches to developing a universal vaccine include: vaccines that target the hemagglutinin (HA) stem region or common determinants of the HA head; vaccines containing conserved internal proteins such as the nucleoprotein

and the extra-cellular domain of influenza M2 protein; multimeric vaccines containing conserved regions from the HA and internal proteins; and DNA-based vaccines. Research to understand the basic biology of the immune response to influenza antigens is essential, and must focus on factors that elicit neutralization and protection. Furthermore, current correlates of protection based on simple binding studies and assays correlating vaccine efficacy with hemagglutination are unlikely to be sufficient, necessitating the development of novel assays to analyze the safety and efficacy of a potential universal influenza vaccine. Furthermore, guidance on clinical evaluation of universal influenza vaccines and consensus on performance characteristics, including clinical trial endpoints, are needed to provide orientation to the field. Implementing efforts to improve current influenza vaccines and increasing the pipeline of candidate universal influenza vaccines will contribute to the achievement of a universal influenza vaccine.

Cross-cutting Issues of Vaccine Development. Almost all discussions on vaccine development touched on the need to develop better animal models and human challenge models. Other recurrent themes included: determining mechanisms exploited by pathogens to evade the immune system; identifying correlates of protection; inducing mucosal immunity; and identifying better immunogens. Moreover, participants discussed scientific challenges associated with vaccine immune responses and infrastructure limitations in the developing world including: ways to overcome weakened immune systems; novel ways to boost vaccine responses; and the development of heat-resistant vaccines to address limited cold chain storage capacity. Additionally, some of the scientific challenges may be addressed through the application of advanced vaccinology tools, such as structure-based vaccine design, development of new vaccine platforms, and production, implementation, and application of more effective adjuvants.

Approaches to Overcome Challenges in Vaccine Development. Two approaches to overcoming challenges in vaccine development were discussed in depth: systems vaccinology and WHO's Preferred

Product Characteristics (PPCs). Systems vaccinology applies the tools of systems biology to identify predictors of vaccine efficacy or safety, and provides new insights into the mechanisms of protective immunity through the identification of molecular signatures. While the systems vaccinology approach is data intensive, the potential for new insights into improved understanding of vaccine-elicited physiological responses is enormous. Nevertheless, this approach presents additional challenges to the development of vaccines, including the need to develop quality standards and validation of tests, in particular if such data should ultimately be used for regulatory purposes. The establishment of partnerships between vaccine developers and systems biologists in the early stages of development to facilitate design and interpretation of the studies is essential.

The concept of WHO PPCs was presented as a mechanism to build consensus on essential performance characteristics of priority vaccines and avenues to measure these characteristics. PPCs provide guidance for early stage research and development to translate the vision, strategic goals, and milestones from a roadmap into relevant details to guide development of public health relevant vaccines. Furthermore, PPCs can help define areas and indications for product development and stimulate interest among developers. The utility of PPCs was discussed using the examples of vaccines against respiratory syncytial virus (RSV) and Group A streptococcal disease.

Outcomes. The challenges to vaccine development discussed at the GVIRF highlight the need to move beyond the conceptual basis of traditional vaccine development and the recapitulation of natural immunity to more innovative methods, including those that explore the induction of immune responses different from those elicited upon natural infection. While the scientific and technical challenges in vaccine development seem daunting, the approaches discussed offer pathways to ensure the development and production of safe and efficacious vaccines.

Research to Improve the Impact of Immunizations

The GVIRF, particularly the second day of the Forum, focused on strategies to improve the public health impact of immunization. Vaccines have greatly reduced the infectious disease burden in many parts of the world, virtually eliminating diseases in some regions, and in that way have greatly contributed to Millennium Development Goals (MDG) 4 and 5. For many diseases for which highly efficacious vaccines are not yet available, however, other approaches are needed. Throughout the day, amid discussions on maternal immunization, vaccines of modest efficacy, integrating vaccines with other disease control interventions, and optimizing vaccine coverage and delivery, a recurrent theme emerged: quality data on disease burden and program performance are needed.

Maternal Immunization. While global mortality of children younger than five years of age has declined substantially in the last two decades, mortality during the neonatal period is decreasing at a slower rate (United Nations Children's Fund, 2013). Maternal immunization has the potential to prevent disease and death in newborn children as well as their mothers. Experts discussed the biological basis of maternal immunization, the promise for integrating the strategy into existing health systems, and opportunities for using antenatal care platforms for future vaccines.

For example, the Mother's Gift Trial, a randomized clinical trial of influenza vaccination of pregnant women in Bangladesh, found that the vaccine prevented influenza disease in newborn children of vaccine recipients (Zaman, et. al., 2008). This important proof-of-concept study brought attention to the potential use of influenza vaccine in low-resource settings, and triggered further research to corroborate these findings. Data on vaccine performance and safety, as well as the burden of influenza disease during pregnancy and the newborn period, contributed to subsequent WHO recommendations that countries expanding or initiating influenza vaccine programs should prioritize pregnant women for vaccine receipt (Weekly Epidemiological Record, 23 November 2012). The long success of maternal immunization against tetanus and the new WHO recommendation for influenza vaccination in

pregnancy, and the prospect of new vaccines, highlight the potential of a maternal immunization platform for prevention of other high-burden diseases in pregnancy or the newborn period.

Discussants emphasized the need for more data to support maternal immunization policies. Burden of disease studies are needed to quantify the contribution of vaccine preventable diseases to maternal and child mortality and morbidity (including prematurity and low birth weight), and to facilitate comparison to other public health priorities. Well-designed clinical research in different geographic and socioeconomic regions could reassure decision makers about vaccine performance and safety in high-risk communities. Further work on factors associated with vaccine receipt and confidence will help to target public health messaging.

Vaccines of Modest Efficacy. Vaccines that demonstrate only modest efficacy in clinical trials may still have enormous public health impact in populations with high disease incidence and burden. Both regulatory as well as public considerations of such vaccines were discussed. An example of a licensed vaccine with high public health impact, despite modest efficacy (42-49 percent), is the rotavirus vaccine, which has demonstrated public health impact in high burden countries such as Malawi and Bangladesh (Madhi, et. al., 2010; Zaman, et. al., 2010). Another prominent example is the RTS,S malaria vaccine, which is currently in late stage development and only showed modest efficacy against malaria episodes (Agnandji, et. al., 2011; RTS,S Clinical Trials Partnership et. al., 2012). Participants also discussed the prospect of licensing a safe HIV vaccine with at least 50 percent efficacy, which could be effective in preventing HIV infection and deployable to areas of the world with the greatest burden of HIV/AIDS.

As vaccines are developed against complex diseases, an increase in the number of vaccines of modest efficacy is anticipated, raising the need to determine the utility and optimal use of such vaccines. Besides the gathering of data on vaccine effectiveness and impact beyond the efficacy demonstration in clinical trials, carefully adapted communication strategies will become important.

212 More guidance is also needed both for regulation and public health recommendations of vaccines of
213 modest efficacy, and the need for post-registration studies for proper benefit/risk assessment.

214 Integrating Vaccines with Other Disease Control Interventions. Vaccines have the potential to contribute
215 to the control of diseases for which other approaches exist. For example, available therapeutics and
216 vector control tools to combat malaria have been associated with decreased mortality, but an urgent
217 need for an effective vaccine remains. Discussants used leishmaniasis as a case study to examine this
218 topic further.

219 Each year, Leishmaniasis causes approximately 1.3 million new incident cases and 20,000 to
220 40,000 deaths (Alvar, et. al., 2012). Current approaches for control and prevention of leishmaniasis
221 include sand fly or reservoir control, drug treatment, and active case detection and management.
222 Despite significant incidence reduction of visceral leishmaniasis in India and other high endemic foci in
223 Africa and Brazil, the disease seems to rebound every few years. A vaccine could be considered as one
224 of the integrated tools for achieving the global control and elimination of the disease.

225 Optimizing Vaccine Coverage and Delivery. Discussions on optimizing vaccine coverage and delivery
226 transpired in multiple sessions and covered a diverse group of topics including research capacity
227 strengthening to foster implementation research, optimizing the use of existing vaccines, new and
228 innovative technologies applicable to vaccine delivery, a model to secure efficient supply chains, and
229 immunization program monitoring.

230 Significant gaps in immunization coverage remain in several low- and middle-income countries,
231 and research is needed to identify the underlying reasons as well as strategies to achieve higher
232 coverage levels in the affected areas. Case studies of implementation research illustrated: the use of
233 volunteer health workers and issues related to measuring their effectiveness in Burkina Faso; cost of
234 immunization programs in Honduras using PAHO's ProVac tool for evidence-based vaccine decisions;

and understanding and addressing reasons for low polio vaccination coverage in Nigeria. Each case study pointed to the need to use data and information from local sources, and to factor in the local social and cultural norms and constraints.

The contribution of vaccines to decreased disease burden or disease eradication is clear and highlights the need to fully optimize the use of existing vaccines. Discussion of rabies and measles vaccines provided case studies of the myriad factors influencing vaccine coverage and the importance of obtaining and maintaining high vaccination coverage. Rabies contributes to an estimated 2.0 million DALYs and 59,000 deaths, or one death every 9 minutes, each year despite the availability of a safe and efficacious vaccine (Fooks, et. al., 2014). Additionally, the available vaccine can be administered pre- or post-exposure and induces long lasting immunity. While post-exposure prophylaxis is established policy, campaigns to provide pre-exposure prophylaxis are being implemented in some high risk areas; however, criteria to define populations at high risk are needed.

Measles, targeted for elimination in all WHO regions, requires high levels of vaccine coverage to interrupt transmission. Outbreaks can signal that routine immunization coverage is not optimal. Currently, the world is not on track to reach the 2015 global target of reducing measles deaths by 95% compared to 2000. Contributing to the potential of not meeting this global target include low vaccination coverages in many countries resulting from disruption of immunization services, lack of implementation of quality catch-up campaigns, the need to adjust recommendations to specific cohorts and provinces to achieve higher uniform coverage, the personal choice of parents to forgo vaccination for their children, and health care worker resistance to vaccination. Cambodia's implementation strategy, involving defining unreached/high risk communities, mapping and assessing true coverage and risk, and targeting high risk communities for routine Expanded Programme on Immunization (EPI) improvements, was presented as an example of a successful approach.

258 New technologies, including needle-free delivery systems that increase access and coverage
259 while decreasing fear and tension, drop-outs, the risk of cross-contamination, and accumulation of
260 sharps waste, can improve delivery. Advances such as improved space-saving packaging and
261 preservative-free presentation, new reconstitution, and filling technologies can reduce costs and
262 improve thermostability. Mucosal immunization (e.g. intranasal-spray, atomisers, and dry inhalers);
263 intradermal delivery; solid dose implants; solid, hollow, or dissolvable microneedles; disposable syringe
264 jet injectors; and electroporation may both reduce costs to the health care system and improve
265 effectiveness. Some of these technologies are available and have demonstrated their potential, while
266 others are still in development. Detailed assessment of costs and benefits at programme level are
267 needed prior to wide-scale introduction of such technologies (see below).

268 Innovation in vaccine technology, delivery, and presentation represents an exciting opportunity
269 to enhance the impact and cost-effectiveness of almost every vaccination program. One major
270 challenge centers on developing metrics that better quantify the potential gains from simplified delivery
271 technologies, such as total cost analysis, and in bringing together and cross-training experts from the
272 numerous disciplines and institutions represented by critical stakeholders.

273 In addition to overcoming the technical challenges associated with vaccine delivery mentioned
274 above, Forum participants discussed a model to address the securing of efficient supply chains.
275 VillageReach's Final 20 Project offers a sustainable approach to innovative supply chain design,
276 enhanced data collection and reporting, and public-private partnerships (Wilcox, A. 2013). In
277 Mozambique this approach resulted in a reduction in the incidence of vaccine stockouts, an increase in
278 the functional duration of the cold chain, and an increase in the percentage of children receiving
279 vaccines.

Forum participants acknowledged an urgent need to improve indicators for immunization program monitoring and address gaps in data quality. One promising avenue is the use of electronic immunization registries and related technologies, as already piloted in some countries. Improving data quality means facilitating the collection, analysis and use of data to measure and improve operational, managerial, and strategic aspects of programme performance. National electronic registries are a promising technology to measure the performance of vaccination programs, and warrant further evaluation at the country level. Countries need to establish sustainable systems at an appropriate level and use them to assess performance of vaccination programs.

Outcomes. Despite tremendous strides in vaccine development, some diseases still defy attempts to develop highly efficacious vaccines. As talks focused on the public health impact of vaccines, innovative approaches may be needed to ensure protection from infection and disease. Moving forward, maternal immunization strategies to protect newborns deserve further investigation. Vaccines with modest efficacy may still offer significant public health benefit, and combined with other strategies may result in comprehensive approaches to disease prevention. Innovative vaccine delivery methods should be studied to improve vaccine effectiveness and ease of delivery, and implementation research will be critical in determining how to best immunize more people to improve public health outcomes, even with vaccines of diminished efficacy. Most importantly, better data are needed to assess how well vaccines are working across populations, how vaccination programmes perform, and how technologies can improve efficacy, delivery and acceptance.

Regulatory Issues

Universal access to the benefits of immunization for all people is a key component of the vision of the GVAP. Realization of this vision requires innovation across the entire vaccines and immunization value chain. Participants at the GVIRF discussed the impact increased public sector funding has had on

304 patenting activity and aggregate costs as well as the role of regulatory science in vaccine development
305 and implementation.

306 Public Sector Funding Impact on Patenting Activity. Public sector funding of vaccine research has shifted
307 innovative capacity to public sector institutions and resulted in a dominant and dense patent portfolio
308 owned by these institutions. Licensing requirements stemming from the increased patenting activity as
309 well as the technical uncertainty associated with novel technologies has raised transaction costs,
310 thereby resulting in inefficiencies in vaccine development. A new business model was discussed that
311 could reduce costs and risks to industry as well as upfront costs to manufacturers through the creation
312 of an open access patent pool for vaccines expected to have a low return on investment. Furthermore,
313 development of partnerships and collaborations across academia, industry, and manufacturers in
314 industrialized and developing countries early in the vaccine development process should enable
315 sufficient supply of vaccines.

316 Role of Regulatory Science. Regulatory science is “The science of developing new tools, standards, and
317 approaches to assess the safety, efficacy, quality, and performance of human medical products to
318 ensure that innovative products are available to address public health needs” (Baylor, N. 2014). At the
319 GVIRF, discussion of regulatory science included its role in increasing access to new vaccines and vaccine
320 technologies and its potential impact with regard to maternal immunization and vaccines of modest
321 efficacy.

322 Investment of sufficient resources for regulatory science research is important for scientific
323 innovation and for promoting science-based decision making throughout the product life cycle.
324 Collaboration and partnerships between academia, industry, regulators, WHO, and NGOs are essential
325 to optimize use of resources and avoid duplication of effort. Sharing information within the global
326 framework is important to facilitate rapid exchange of knowledge. Regulators emphasized the

327 importance of having scientific expertise to review the data and understand its regulatory implications.
328 Collaboration, information sharing, and discussion in open public meetings were highlighted as key goals
329 to ensure that the best approaches are used for both product development and regulatory decision
330 making.

331 For example, participants discussed the challenges of developing a live-attenuated influenza
332 vaccine in a middle income country. Collaborating with regulators and experts from other countries
333 helped scientists test virus seeds for attenuation in ferrets, design toxicity studies, measure immune
334 responses in clinical trials, and develop potency assays in order to standardize methodologies. Such
335 collaboration provided the necessary experience and capacity for future vaccine development efforts in
336 countries with emerging regulatory authorities.

337 Despite the promise in protecting infants early in life, there is no clear regulatory pathway for
338 candidate vaccines designed for use in pregnancy. A resounding theme from GVIRF participants was
339 that the vaccine industry needs further guidance on how large safety databases should be used for pre-
340 and post-licensure evaluations; at present there is no consensus classification of adverse events in
341 pregnancy. Currently, regulatory agencies are taking a cautious approach to maternal immunization.
342 Product labelling remains conservatively worded, though agencies such as the European Medicines
343 Agency are taking initiatives to use post marketing safety surveillance to inform statements of vaccine
344 risk.

345 Currently there is limited guidance or structure from regulatory authorities in terms of how to
346 evaluate vaccines of modest efficacy, but an open dialogue with the regulators is encouraged early on in
347 clinical development. Other important factors for public health interventions, such as potential indirect
348 (herd) effects, are not considered at the time of licensure. Communication strategies are important to
349 the interpretation and understanding of the public health benefits of modestly efficacious vaccines,

particularly in the absence of clear regulatory guidelines and frameworks, and more guidance is needed both for regulation and public health recommendations of vaccines of modest efficacy. In addition, post-registration studies for proper benefit/risk assessment are also needed.

Outcomes. GVIRF participants offered several recommendations to improve the regulatory process for introducing new vaccines and ensuring their safety, for example, establishing “Centers of Excellence” to develop state-of-the-art technologies to produce and maintain standards for regulatory decision making. In addition, vaccine researchers, manufacturers and regulators could benefit from a global framework to facilitate the rapid exchange of knowledge and information and avoid duplication of efforts. Adequate financial investment by regulatory agencies and manufacturers is important for scientific innovation. Additionally, manufacturers and regulators should engage in discussions early on in the manufacturing process, especially when considering new approaches and alternative technologies for product development. Regulatory decision making could benefit from “generic” modeling for different scenarios to assist risk-benefit assessments for accelerated approvals. And, most importantly, a global commitment from vaccine developers, manufacturers, and regulators is essential to strengthen national regulatory authorities in developing countries.

Satellite Session

In addition to the topics/issues discussed above, a satellite session was convened at the GVIRF that engaged investigators in both the public and private sector on the need to continue research and development of sexually transmitted infections (STIs). This session took as a starting point the results of a recent NIAID-WHO collaboration, which was published in a special issue of the journal *Vaccine*, on identifying the challenges and gaps in the development of vaccines against STIs (Alonso, et. al., 2013). Presentations reviewed the progress and developments of new and effective vaccines against the five “neglected” parasitic, bacterial and viral STI vaccine focus areas: Herpes Simplex Virus, Chlamydia

trachomatis, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Treponema palladium*. Discussion focused on current barriers and hurdles to the development of effective vaccines against these infections, potential solutions and a possible roadmap toward development of these vaccines.

Conclusion

This first GVIRF aimed to track progress of the GVAP research and development agenda, identify opportunities and challenges, promote partnerships in vaccine research, and facilitate the inclusion of all stakeholders in vaccine research and development and implementation sciences. The meeting achieved its first aim: detailed progress updates prepared for the first GVIRF were incorporated in the annual GVAP Secretariat Report (Global Vaccine Action Plan Monitoring Evaluation & Accountability) as a summary of vaccine R&D, and contributed to assessment of progress against the GVAP goals by the Strategic Advisory Group of Experts (SAGE) (2014 Assessment Report of the Global Vaccine Action Plan). These reports provide a comprehensive picture of the field in 2014 to a broad audience of stakeholders. For a summary of the progress in developing vaccines against HIV, TB, and malaria as well as progress toward development of a universal influenza vaccine(s) please see Box 1. For examples of research challenges and opportunities please see Box 2.

The GVIRF was also successful in its second aim, identifying opportunities and challenges in vaccine research, development, and implementation. Opportunities include the application of systems vaccinology to vaccine design, development of new vaccine platforms, application of PPCs to guide development, harnessing the benefits of vaccines that have modest efficacy, and the utilization of innovative technologies that facilitate vaccine delivery. Key challenges include the limited predictive value of preclinical models for innovative vaccines, the lack of correlates of protection for many vaccines and vaccine candidates, gaps in data quality, patent protections that can inhibit innovation, and the need for greater regulatory guidance, particularly for vaccines for use in pregnancy.

The remaining goals of GVIRF target partnerships and stakeholder engagement, which are needed to address these challenges and take advantage of these opportunities. The robust dialog among the scientists, regulators, developers, and public health experts is a sign that the meeting will achieve these aims as well. However, the true impact of this GVIRF will depend on how the participants act on what they learned. Planning has begun for the second GVIRF, scheduled for March 2016; that meeting will inform the success of the first GVIRF in contributing to the progress of the GVAP R&D agenda and its overall vision to extend the benefits of immunization to all people.

For Further Reading and Background:

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Box 1. Detailed progress updates prepared for the first GVIRF were incorporated into the 2014 GVAP Secretariat Report. Depicted below is a brief summary of the progress in developing vaccines against HIV, TB, and malaria as well as progress toward development of a universal influenza vaccine(s). For additional information regarding development of vaccines against these pathogens; vaccine technologies; and progress in developing vaccines against dengue, hepatitis C, cytomegalovirus, respiratory syncytial virus, group A streptococcus, leishmaniasis, and helminth diseases please see the 2014 GVAP Secretariat Report "[Global Vaccine Action Plan Monitoring, Evaluation & Accountability](#)."

GVAP Indicator	Target	Research & Development Efforts	Preclinical/Clinical Status of Vaccine Candidates
SO6.1	HIV	<ul style="list-style-type: none"> To determine immune correlates from the RV-144 trial HIV epitope-based vaccines 	<ul style="list-style-type: none"> Prime-boost strategies: <ul style="list-style-type: none"> 33 in Phase I 7 in Phase II
	TB	<ul style="list-style-type: none"> Evaluation of vectors, adjuvants and antigens that induce a cellular immune response Strategies include inactivated whole cell or whole cell extracts, viral-vectored candidates, fusion protein subunits, live recombinant BCG vaccines, and DNA vaccines 	<ul style="list-style-type: none"> 3 in Phase I 7 in Phase IIa 2 in Phase IIb 1 in a Phase III
	Malaria	<ul style="list-style-type: none"> Build upon success of RTS,S: induction of humoral and cellular immune responses to circumsporozoite proteins Approaches include pre-erythrocytic, whole parasite, subunit, and asexual blood-stage vaccines as well as vaccines to interrupt human to vector transmission 	<ul style="list-style-type: none"> P. falciparum: <ul style="list-style-type: none"> Pre-erythrocytic – 11 in Phase I, 1 in Phase II, 1 in Phase III Blood stage – 12 in Phase I, 2 in Phase II Sexual Stage – 2 in Phase I P. vivax: 1 in Phase I

SO6.2	Universal Influenza	<ul style="list-style-type: none"> • Approaches include targeting the conserved HA stem region, combining conserved regions of HA and internal proteins in a single vaccine, targeting common determinants of the HA head 	<ul style="list-style-type: none"> • 7 in preclinical development • 2 in Phase I • 3 in Phase II
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Box 2. Examples of research challenges and opportunities for the main topics discussed at the 2014 GVIRF are depicted below. For additional information on challenges and opportunities in vaccine research and development please see the 2013 GVAP Secretariat Report " Decade of Vaccines Global Vaccine Action Plan Monitoring, Evaluation and Accountability " and 2014 GVAP Secretariat Report " Global Vaccine Action Plan Monitoring, Evaluation & Accountability ."		
Topic	Challenges	Opportunities
Scientific and Technical Challenges in Vaccine Development		
Cross Cutting Topics	<ul style="list-style-type: none"> • Development of human challenge models and better animal models to evaluate vaccine candidates • Need to identify correlates of protection and better immunogens 	<ul style="list-style-type: none"> • Systems vaccinology can be exploited to identify predictors of safety or efficacy
HIV Vaccines	<ul style="list-style-type: none"> • Genetic and immunological hypervariability • Difficulty in inducing broadly neutralizing antibodies • Integration of HIV genome into the host genome • Establishment of latent HIV reservoirs • Blocking infection at mucosal surfaces 	<ul style="list-style-type: none"> • The proof-of-concept with RV144 trial may enable identification of correlates of protection • Broadly neutralizing antibodies in some HIV+ people suggest the possibility of eliciting such antibodies by immunization • CMV-based SIV vaccines that control and clear SIV hold promise for a comparable HIV vaccine
TB Vaccines	<ul style="list-style-type: none"> • Limitations in available tools to measure exposure to M. tuberculosis and the burden of TB during latency 	<ul style="list-style-type: none"> • Pursuing systems immunology approaches for correlation of signatures to measures of immunogenicity or protection in efficacy studies
Malaria Vaccines	<ul style="list-style-type: none"> • Waning efficacy of RTS,S post-vaccination • Limited availability of delivery systems to induce strong humoral and cellular immune responses • Absence of reliable preclinical models 	<ul style="list-style-type: none"> • Human vaccinology research to identify/evaluate: • Platforms to target antigens to the immune system • Biomarkers of protection • Targets for subunit vaccine

	and assays with relevance to protection in humans	development <ul style="list-style-type: none"> • Systematic evaluation of sporozoite-, liver-, blood-, sexual-, sporogonic- and mosquito-stage antigens for suitability as vaccine antigens
Universal Influenza Vaccines	<ul style="list-style-type: none"> • Uncertainty regarding how conserved regions of HA stem will respond to increased immune pressure • How immunity to one viral antigen can protect or exacerbate infection with another influenza virus • Development and approval of novel assays and correlates of protection 	<ul style="list-style-type: none"> • Protection elicited by broadly cross-reactive antibodies demonstrates the potential efficacy of a universal influenza vaccine • Research defining the structure of conserved HA stem epitopes and receptor binding domain of the globular head domain provide target information
Research to Improve the Impact of Immunizations		
Maternal Immunization	<ul style="list-style-type: none"> • Lack of burden of disease studies to quantify the contribution of vaccine preventable diseases to maternal and child mortality and morbidity • Absence of well-designed clinical research from different geographic and socioeconomic regions to reassure decision makers 	<ul style="list-style-type: none"> • Further research triggered by proof-of-concept study in low-resource setting • Success of maternal immunization against tetanus highlights the potential of maternal immunization in disease prevention
Vaccines of Modest Efficacy	<ul style="list-style-type: none"> • Regulators not accustomed to evaluating vaccines with modest efficacy • Other Important factors associated with public health interventions not being considered at time of licensure • Erosion of confidence in vaccination programs by a public expecting vaccines to prevent disease 	<ul style="list-style-type: none"> • Modestly efficacious rotavirus vaccines had a high public health impact in Malawi and Bangladesh • Engaging advisory bodies in discussions about efficacy data before trial initiation may contribute positively to the licensure process
Optimizing Vaccine Coverage	<ul style="list-style-type: none"> • Securing vaccine supply sufficient to meet coverage goals • Disruption of immunization services • Need to improve immunization program monitoring indicators and gaps in data quality 	<ul style="list-style-type: none"> • Models addressing the securing of efficient supply chains have proven successful and should be studied • Technological advancements (e.g. needle-free delivery) increase access and coverage
Regulatory Issues		
Public Sector Funding Impact on Patenting Activity	<ul style="list-style-type: none"> • Dense patent portfolio owned by public sector institutions resulting in increased transaction costs 	<ul style="list-style-type: none"> • Open access patent pool for vaccines expected to have a low return on investment could reduce costs and risks to industry
Regulatory Science	<ul style="list-style-type: none"> • Advancing regulatory science research that is important for scientific innovation • Ensuring regulators have the 	<ul style="list-style-type: none"> • Early collaboration with regulators ensures that the necessary expertise is represented

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	appropriate scientific expertise	
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