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# Meeting report: Global vaccine and immunization research forum

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ABSTRACT

Building on the success of the first Global Vaccine and Immunization Research Forum (GVIRF), the World Health Organization, the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health in the United States of America, and the Bill & Melinda Gates Foundation convened the second GVIRF in March 2016. Leading scientists, vaccine developers, and public health officials from around the world discussed scientific advances and innovative technologies to design and deliver vaccines as well as novel tools and approaches to increase the uptake of vaccines throughout the world. This report summarizes the discussions and conclusions from the forum participants.

## 1. Introduction

Research on the discovery, development, and delivery of vaccines is an integral part of the Global Vaccine Action Plan (GVAP) and essential to achieving the vision of the "Decade of Vaccines" [1,2]. The World Health Organization (WHO), the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH), and the Bill & Melinda Gates Foundation (BMGF) convened the second Global Vaccine and Immunization Research Forum (GVIRF) in March 2016. This GVIRF tracked recent progress of the GVAP's research and development agenda, identified opportunities and challenges, promoted partnerships in vaccine research, and aimed to facilitate the inclusion of all stakeholders in vaccine research and development. Particular consideration was given to the contribution of research to achieve some of the GVAP's goals and to shape the immunization agenda beyond the Decade of Vaccines. Leading scientists, vaccine developers, and public health officials from around the world discussed scientific and technical challenges in identifying, developing, and manufacturing candidate vaccines; dealing with regulatory issues; and improving the impact of immunization. This report summarizes the discussions and conclusions from the forum participants in order to broaden the audience for this exchange of ideas. Presentations and other information from the 2016 GVIRF can be found at http://www.who.int/immunization/research/forums_and_initiatives/gvirf/forum_2016/en/.

## 2. Progress and lessons learned

### 2.1. HIV vaccines

On the heels of the positive efficacy signal in the RV144 trial conducted in Thailand that evaluated a prime-boost approach to immunize against HIV [3], three strategies to develop a vaccine against HIV are being pursued. One strategy builds on the success of the RV144 trial to design and evaluate a clade C specific vaccine to improve regional relevance, vaccine immunogenicity and durability. Such a vaccine is currently being evaluated in South Africa. A second strategy targets multiple HIV clades using a vectored vaccine and prime/boost regimen. A vaccine based on this strategy is slated to enter clinical trials in 2017. The third strategy uses the broadly neutralizing monoclonal antibody, VRC01, which has exhibited antibody-dependent cell-mediated cytotoxicity activity in *in vitro* studies and has shown promise in non-human primates [4,5,6]; further evaluation in clinical trials in sub-Saharan Africa and the Americas is planned.

### 2.2. TB vaccines

Fifteen TB vaccine candidates using three different platforms – recombinant protein, viral vector, and whole cell or extract – are in clinical development with many more at the preclinical stage. A heat-killed whole-cell vaccine candidate is the most advanced and is currently being evaluated in a Phase III clinical trial. A live-attenuated, persistently infecting cytomegalovirus-vectored TB vaccine candidate produced encouraging results in non-human primate *Mycobacterium tuberculosis* challenge studies.

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Choosing appropriate trial endpoints (i.e., prevention of infection, prevention of disease, or prevention of recurrent disease), identifying target patient populations, and determining the effect of comorbidities (e.g. diabetes mellitus) on vaccine response are among the challenges impacting on the development of TB vaccines.

### 2.3. Malaria vaccines

Development of vaccines against malaria continues to be a priority, with numerous candidates advancing in both preclinical and clinical development. In light of recent successes in reducing the prevalence and incidence of malaria worldwide, vaccines to prevent infections and reduce the burden of disease, as well as vaccines to prevent malaria transmission are being promoted. Subunit recombinant proteins, vectored vaccines, and prime-boost combinations are being pursued. In addition, significant progress has been made with attenuated whole parasite vaccines. GVIRF participants discussed the need to ensure adequate research capacity in endemic areas, and the use of controlled human malaria infection studies to provide preliminary indications of safety and efficacy of candidate vaccines in endemic populations.

Recent results from a large, multicenter Phase III clinical trial of the most advanced candidate vaccine, RTS,S/AS01 (MosquiRix®), demonstrated modest efficacy in infants and young children (18 percent in infants, 26 percent in young children) over a three- to four-year follow-up period after receiving three doses of vaccine [7]. The trial suggested that declining efficacy could be boosted with a fourth dose of vaccine given 18 months following the initial immunization series. Although the European Medicines Agency (EMA) issued a "positive opinion" following review of the data, the Strategic Advisory Group of Experts on Immunization (SAGE) at WHO recommended further pilot studies to assess the feasibility of delivery, safety, and potential impact of this vaccine under field conditions before widespread deployment.

### 2.4. Universal Influenza vaccines

Challenges associated with seasonal influenza vaccines, such as their variable and often moderate effectiveness and need to be matched to circulating strains, have led to research into development of broad-spectrum protective or even universal influenza vaccines. There is, however, no consensus definition of universality in the context of influenza vaccines. Does universality mean protection within an influenza subtype, protection within a hemagglutinin (HA) group, or protection against all known HAs? Pathways toward development of universal influenza vaccines discussed at the GVIRF include improving current vaccines (e.g. through novel adjuvants) and increasing the number of strains against which a vaccine protects (e.g. through induction of broadly neutralizing HA stem-specific antibodies). The complexity of advanced product development and the ability to demonstrate efficacy against severe disease continue to challenge the field.

### 2.5. Group A Streptococcus vaccines

Group A Streptococcus (GAS) causes a broad spectrum of acute and chronic conditions (e.g., pharyngitis and rheumatic heart disease). The incidence of invasive disease in high-income countries is 3–5 per 100,000 with a case fatality rate of approximately 10–15% [8]; comparable information from low- and middle-income countries is lacking, although the burden is considered to be high. The protective immune response to GAS infection, which includes the absence of disease in the middle years of life (between 10 and 60 years of age) and long-term (30- to 40-year) antibody protection, as well as results from preclinical, challenge model, and passive antibody transfer studies, suggest that long term protection via vaccination is feasible. Vaccine candidates in various stages of development, including those in clinical trials, are classified based on whether or not they target the virulence factor M protein. M-protein-based vaccine designs target either the variable region, thus requiring multi-valent vaccine candidates, or the conserved region. Non-M-protein-based vaccines target common antigens such as carbohydrates. Despite the high burden of disease, investment into GAS vaccines remains low with limited commercial interest and public engagement.

### 2.6. Schistosomiasis vaccines

Multiple pathologic consequences are associated with infection with *Schistosoma* parasites, including acute manifestations such as allergic dermatitis and chronic sequelae such as hepatosplenomegaly. Nearly 700 million people are at risk, while 252 million people need treatment, and tens of million suffer with debilitating chronic morbidity [9,10]. While mass drug administration programs achieved disease elimination in some focal areas, elimination in other areas may benefit from approaches that include vaccine strategies. Multiple vaccine candidates targeting different antigens (e.g., glutathione S-transferase, fatty acid binding protein-Sm14) and stages of the *Schistosoma* life cycle are under development; several have progressed to clinical stages. These candidates aim to prevent infection, prevent morbidity, or block transmission. Even though new vaccine candidates are on the horizon, the vaccine research and development pipeline remains weak, and collaborations and partnerships are needed.

### 2.7. Gavi's vaccine investment strategy

Gavi, The Vaccine Alliance, which finances vaccination and health systems strengthening, is a major driver in shaping current and future vaccine markets. To identify priorities and inform decisions on future financing of new vaccines, Gavi employs a Vaccine Investment Strategy (VIS) that involves review of relevant vaccine, disease and impact information; stakeholder consultations; and independent expert advice. This evidence-based process occurs every five years and assesses the value of different vaccines in absolute terms and in comparison to alternative vaccine investments. For Gavi's next VIS (in 2017–18) the candidates for consideration may include vaccines against diseases with lower mortality than those they currently support and opportunities through maternal vaccination platforms. In addition to informing Gavi investments, VIS reviews have highlighted evidence gaps for neglected vaccines, such as rabies; the challenge in comparing vaccines based on data of variable availability and quality; and the uncertainties in vaccine pipeline projections. By emphasizing the needs of low-income countries, the VIS process supports the early development of partnerships and improved communication among stakeholders to ensure successful delivery of effective vaccines.

### 2.8. Vaccines in integrated disease control

The role of new vaccines with modest efficacy in integrated disease control generated thought-provoking discussion. Studies of pneumococcal and rotavirus vaccines highlight the influence of geography, pathogen heterogeneity, and clinical syndrome-based endpoints on assessments of vaccine efficacy. Vaccines with modest efficacy can have a significant impact on reducing disease, especially in high-burden settings. In situations with a potential for herd immunity, modest-efficacy vaccines can produce substantial

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