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Vaccine 37 (2019) 7519–7526

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Meeting report: Global vaccine and immunization research forum, 2018

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ARTICLE INFO

Article history:
Received 19 April 2019
Received in revised form 27 September 2019
Accepted 1 October 2019
Available online 14 October 2019

Keywords:
GVIRF
GVAP

ABSTRACT

Every two years, the Global Vaccine and Immunization Research Forum takes stock of global research in vaccines and immunization. As in prior years, the 2018 meeting addressed vaccine discovery, development, decision-making, and deployment. This time, however, it also featured two overarching themes: "Innovating for Equity" and "End-to-End Integration." Significant advances have been made in the last two years, but participants noted that some important goals of the Global Vaccine Action Plan are not being met and called urgently for innovation in improving access to vaccines. Two factors were highlighted as crucial to improving coverage: a focus on equity and sustainability throughout the immunization ecosystem, and an enabling political environment that prioritizes health and immunization.

1. Introduction

The Global Vaccine Action Plan 2011–2020 (GVAP) is a framework endorsed by the World Health Assembly to improve health by, "Extending the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live." [1] In March 2018, 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 leading scientists, vaccine developers, and public health officials from around the world for the third Global Vaccine and Immunization Research Forum (GVIRF), held in Bangkok, Thailand. As with previous meetings, this GVIRF tracked progress in the GVAP's research and development agenda, identified opportunities and challenges in meeting GVAP goals, and promoted partnerships in vaccine research [2,3].

While progress in the GVAP research and development agenda has been strong, many other important GVAP targets have not been met. In particular, global coverage with basic vaccines has improved very little since 2010, leaving an estimated 19.9 million children unreached or incompletely vaccinated in 2017 [4–6]. In response to these gaps, this GVIRF featured two overarching themes, "Innovating for Equity" and "End-to-End Integration." This report summarizes the forum discussions; presentations and other materials from the 2018 GVIRF can be found at http://www.who.int/immunization/research/forums_and_initiatives/gvirf/forum_2018/en/.

2. Innovating for equity

As presented at GVIRF, innovation is widespread along the immunization value chain. Progress is being made in advancing priority vaccines and enabling technologies, developing approaches to improve immunization coverage and impact, and building capacity for innovation, particularly in middle- and low-income countries.

2.1. Priority vaccines

2.1.1. Human immunodeficiency virus

Two pivotal HIV vaccine efficacy trials are underway and expected to provide efficacy signals around 2020. First, in a

Abbreviations: AMR, antimicrobial resistance; BCG, bacille Calmette-Guerin; cVDPV, circulating vaccine-derived poliovirus; CMV, cytomegalovirus; CHIM, controlled human infection model; DCVM, developing-country vaccine manufacturer; ETEC, enterotoxogenic *E. coli*; FPHVP, full public health value proposition; GBS, Group B Streptococcus; GVAP, Global Vaccine Action Plan; GVIRF, Global Vaccine and Immunization Research Forum; HCV, hepatitis C virus; HPV, human papillomavirus; IPV, Inactivated poliovirus vaccine; NRA, national regulatory authority; OPV, oral poliovirus vaccine; PCV, pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; WPV, wild poliovirus.

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https://doi.org/10.1016/j.vaccine.2019.10.011
Published by Elsevier Ltd.

follow-on from the RV144 clinical trial in Thailand that demonstrated safety and modest efficacy for an HIV preventive vaccine [7], the HVTN702 trial is testing an ALVAC-C prime with an ALVAC-C+ bivalent envelope (gp120 env) protein/MF59 boost (clinicaltrials.gov, NCT02968849). About half of the target population of 5400 adults have been enrolled in South Africa as of February 2018. Second, the HVTN705 trial, which is using an Ad26 vector prime with an Ad26+ gp140 env protein boost, is aiming for global cross-clade protection (NCT03060629). This study will enroll 2600 women in six African countries. Based on recent recommendations in high-risk populations, all participants are offered the state-of-the-art HIV risk reduction method, pre-exposure prophylaxis [8,9]. Additional studies evaluating different adjuvants and priming regimens are running in parallel to inform clinical development. HIV immunization strategies will pose delivery challenges because they will target high-risk adult populations that are not routinely vaccinated and require complex vaccination regimens: GVIRF participants noted that implementation research will be crucial to efficiently protecting these populations.

2.1.2. Tuberculosis

The pipeline of TB vaccines includes subunit protein-, viral vector-, whole-cell inactivated- and live-attenuated candidates [10,11]. A recent study in adolescents tested two approaches: H4:IC31 vaccine (a recombinant fusion protein with IC31 adjuvant) and bacille Calmette-Guerin (BCG) re-vaccination (NCT02075203). Early analysis showed that both were well-tolerated. While neither vaccine showed statistical significance in preventing initial infection, BCG re-vaccination demonstrated a statistically significant 45.4% reduction of sustained infection and H4:IC31 gave a statistically significant 30.5% reduction of sustained infection [12]. These results are informing further TB vaccine product development and may support identification of correlates of protection. Studies of additional vaccine candidates are expected to generate efficacy data in 2018. (Since this meeting, results have been published showing that the recombinant M72/AS01 vaccine was significantly protective against tuberculosis disease [13]). Priorities for TB vaccine research include developing a controlled human infection model and understanding how alternative clinical endpoints such as prevention of infection, disease, recurrence, or reinfection can be used to inform disease control strategies.

2.1.3. Malaria

Having received a positive scientific opinion from the European Medicines Agency (EMA), the first malaria vaccine, RTS,S, (GSK, MosquiRix®) will be deployed in pilot studies in Ghana, Kenya, and Malawi beginning in 2019. These studies are assessing the operational feasibility, safety, and impact of RTS,S and will yield results in 2022, informing WHO recommendations for use and funding decisions [14]. While RTS,S is predicted to have substantial health impact [15], GVIRF participants observed that there remains a need for malaria vaccines with high and durable efficacy that are effective against both *Plasmodium falciparum* and *Plasmodium vivax*, that can interrupt transmission, and that are suitable for use in older children and adults (including pregnant women). Many of these gaps are being addressed through a diverse pipeline that includes monoclonal antibodies as well as vaccines that target parasites in pre-erythrocytic stages, asexual blood stage, and sexual stages [16].

2.1.4. Influenza

Cross-protective, "universal" influenza vaccines would transform both seasonal influenza prevention and pandemic response, as annual revaccination would no longer be necessary and doses could be stockpiled for rapid deployment in the event of a pandemic. Multiple candidates targeting conserved regions of the hemagglutinin protein are in clinical development [17]. To facilitate development of a universal influenza vaccine, NIAID has established a definition for universal influenza vaccines, described a strategic plan and a research agenda for vaccine development, and is providing technical assistance for influenza vaccine research [18]. Under this definition, a universal influenza vaccine would be at least 75% efficacious against symptomatic influenza infection, protect against both group I and II influenza A viruses for at least one year, and be suitable for all age groups.

2.2. Enabling approaches

2.2.1. Immunology

New *in vitro* technologies for human immunology research and vaccine evaluation described at GVIRF include mass cytometry (CyTOF), which allows simultaneous analysis of 30–50 markers at single-cell resolution; single-cell T-cell receptor (TCR) sequencing combined with Grouping of Lymphocyte Interactions by Paratope Hotspots (GLIPH), to identify convergence groups of TCRs and discover ligands or antigens for future vaccine design [19,20]; and the MIMIC® system, which uses human peripheral blood mononuclear cells to simulate innate and adaptive immune responses in an *in vitro* model of the human immune system intended to provide clinically relevant information much earlier in the development process. MIMIC is now being used to identify malaria peptides with strong CD4+ T-cell response profiles for consideration in a novel malaria vaccine [21,22]. It is expected that these and other immunological tools will contribute to a better understanding of protective immunity and to accelerated development and approval of new vaccines.

2.2.2. Vaccine vectors

Among the many available vaccine vectors in development, two were highlighted at the conference: cytomegalovirus (CMV)-based vectors and Plasmid Launched Live-Attenuated Vaccines (PLLAV). CMV-based vector vaccines elicit and maintain high frequency "effector memory" T-cell responses in mucosal sites, lymphoid tissues, and parenchymal organs of nonhuman primates. Because they efficiently re-infect and persist despite robust anti-CMV immunity, CMV-based vectors can be used repeatedly to induce responses against successive antigens [23]. A highly attenuated human CMV-vectored HIV vaccine is now in cGMP manufacturing and slated for clinical testing in 2019. PLLAV are *E. coli*-produced DNA vaccines that upon administration replicate in mammalian cells, assemble into virus particles, and infect and are amplified by surrounding cells. They can function as a live-attenuated yellow fever vaccine, as demonstrated by proof-of-concept studies in small animals and non-human primates. This approach has the potential to serve as a platform technology for other targets, including pathogens of epidemic potential such as Lassa fever virus.

2.2.3. Human challenge models

Controlled human infection models (CHIMs) can accelerate vaccine development for diseases in which the infectious agent and its clinical course are appropriately understood, and where the CHIMs are safe and give consistent rates of infection. As described at GVIRF, CHIMs have been used to study pathogenesis, assess correlates of protection, and provide efficacy data for cholera and typhoid vaccine licensure, and down-select among enterotoxogenic *E. coli* (ETEC) vaccine candidates. Development of CHIMs for some diseases has been challenging due to complexity in infectious agents and host-pathogen interactions, variable infection rates, and complex disease profiles. Participants called for: greater standardization of CHIMs; guidelines for CHIM studies used to support licensure; focus on end-user populations, for example through

CHIM sites in endemic areas; and application of advanced immunology in CHIMs to identify correlates of protection.

2.2.4. Monoclonal antibodies

Equine and human antibodies have been used for over a century to provide passive immunity; now monoclonal antibodies (mAbs) offer the potential for safer and more effective passive immunization. GVIRF presenters described progress in developing mAbs for prophylaxis and treatment of multiple diseases. For rabies, the first prophylactic mAb (Serum Institute of India, Rabishield), has been approved in India. To facilitate broader licensure and use of rabies mAbs, the U.S. Food & Drug Administration (FDA) is clarifying regulatory considerations, and WHO is evaluating policy recommendations. For HIV, the Antibody Mediated Prevention studies are testing a broadly neutralizing HIV-1 mAb, VRC01 (e.g. NCT02411539). These studies are expected to provide results in the 2020 timeframe. For respiratory syncytial virus (RSV), a prophylactic mAb that requires monthly administration (AstraZeneca, palivizumab) has been on the market for over a decade. A Phase 2B study of an extended half-life RSV prefusion F-protein mAb in healthy preterm infants is nearing completion with results expected in 2018 (NCT02878330). If successful, this product would be more affordable than the existing mAb and require only a single administration. For influenza, broadly protective mAbs have applications in the treatment of severe influenza, prevention of infection when vaccination is not feasible (such as early during a pandemic), and for vaccine antigen discovery. The influenza mAb pipeline includes candidates with confirmed effects on virus shedding when administered post-challenge in CHIMs [24].

For impact in low-income countries, mAbs must be affordable and available in sufficient supply. Antibody engineering is being used to improve potency, pharmacokinetics, and productivity to meet challenging target product profiles. Computational analysis is identifying mAbs predicted to have improved thermostability and other characteristics that support development. Alternative hosts and novel expression systems are reducing production costs. GVIRF participants commented that robust regulatory guidance and a WHO prequalification pathway will be essential to facilitate licensure, use, and impact of mAbs.

2.2.5. Research and development for emerging infectious diseases

In response to the 2014 West African Ebola outbreak, the WHO *R&D Blueprint for Action to Prevent Epidemics* was launched in May 2016 to accelerate research and development for vaccines, treatments, and diagnostics for epidemic prevention and response. As of 2018, the diseases prioritized under the *Blueprint* are Crimean-Congo haemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome, Nipah and henipaviral diseases, Rift Valley fever, Zika, and "Disease X", which refers to an emerging pathogen yet to be identified that may cause epidemic human disease in the future. Under the *Blueprint*, roadmaps and target product profiles are being developed; current versions of these documents are available on the WHO website [25–27]. Norms and standards tailored to the epidemic context are being formulated, including approaches to regulatory pathways and ethical issues, clinical trial design, data and sample sharing, and capacity building. These roadmaps and guidelines should reduce the time between the start of an outbreak and the testing of candidate interventions.

2.3. Delivery

2.3.1. Implementation research

As highlighted by keynote speaker Dr. Alejandro Cravioto, implementation research, delivery innovations, national immunization program strengthening, and strong overall health systems are essential to ensure all children receive the vaccines they need. Addressing inequities in access to vaccines requires innovation to find the children who are missed, to understand and address the reasons they are un- or under-vaccinated, and to make products more robust and easier to deliver.

Adding to the promise and the challenge of immunization are new target populations such as adolescents and new vaccines with complex regimens that will be difficult to deliver, especially in low-resource settings. Implementation research will be required to inform policy decisions and to guide delivery, as demonstrated by the malaria vaccine pilot studies [14]. Because such studies are large and expensive to conduct, a new paradigm is needed in which implementation research is an integral part of vaccine development. This new paradigm is crucial to realizing the full benefits of immunization.

2.3.2. Mission Indradhanush

India's Mission Indradhanush (MI) was launched in 2014 to improve immunization coverage in children and pregnant women. It ultimately reached 528 districts across 35 states and union territories, strengthening immunization through a multi-dimensional approach that combined capacity building, detailed planning, measurement and accountability, and use of information technology to find and reach the unreached. With political support at the highest levels, MI helped increase the proportion of fully immunized infants in India from 65% in 2014 to 78% in 2017. Its successor, Intensified Mission Indradhanush, is aiming to fully immunize 90% of Indian infants in 2018 [28].

2.3.3. Social media outreach

Innovative programs are using social media to target underserved populations and address vaccine hesitancy. In Suzhou, China, a New Citizen Transaction Center is registering migratory children, and a public service account on the WeChat social media app is being used to schedule vaccination appointments, send reminders, and disseminate information. In the Ukraine, group chats with health professionals are being organized in parent communities to address concerns about vaccination. GVIRF participants observed that technology and social media have enormous potential to improve social mobilization and vaccine acceptance [29,30].

2.3.4. Human papillomavirus vaccine

The human papillomavirus (HPV) vaccine experience has shown that country-driven operational research and implementation science are needed to achieve high coverage in non-infant populations. Most countries conducting HPV demonstration projects have implemented school-based programs targeting adolescent girls, and many have also provided the vaccine through health facilities to reach girls who are not in the formal school system. GVIRF participants noted that school-based programs could provide a platform for delivery of additional services to adolescents but must be complemented by programs targeting the 263 million children who are out of school. To facilitate high coverage, social mobilization is needed to increase awareness and reduce vaccine hesitancy [24,25].

2.3.5. Maternal immunization

Immunization in pregnancy is a well-established approach to preventing disease in mothers and infants. WHO recommends influenza and tetanus vaccines in pregnancy; additional vaccines are recommended in specific situations, such as disease outbreaks. Vaccines are also in development for maternal immunization to protect infants from RSV and Group B Streptococcus (GBS). Programs immunizing pregnant women against tetanus have shown that multiple delivery approaches may be needed to reach the

most vulnerable populations, and that issues of service quality and vaccine hesitancy must be addressed. GVIRF participants commented that operational research will be needed to efficiently deliver new maternal immunization vaccines and that introducing new vaccines for pregnant women will create opportunities to strengthen antenatal care. Any introduction must be supported by robust monitoring for poor pregnancy outcomes and adverse events following immunization, whether related or unrelated to the vaccine. The risk of a false attribution of poor outcomes to new products must be addressed, including by proactively educating communities about the frequency of poor pregnancy outcomes in the absence of vaccination.

2.4. System capacity

2.4.1. Regulatory authorities

Capacity for vaccine evaluation is crucial, particularly in public health emergencies. Regulatory decision-making in low- and middle-income countries is being strengthened through regulatory training exercises, joint evaluations, and initiatives such as the Developing Countries Vaccine Regulators Network and the African Vaccine Regulatory Forum. Challenges remain, especially when human efficacy studies are not ethical or feasible. The EMA and U.S. FDA have implemented alternative regulatory pathways to facilitate the evaluation, licensure, and use of new vaccines, including those for emerging infectious diseases. Other national regulatory authorities (NRAs) have similar, but not necessarily equivalent, programs. To streamline regulatory processes, the International Council for Harmonisation and WHO are engaged in regulatory harmonization and convergence to align requirements, technical guidance, and procedures. GVIRF participants emphasized the importance of reliance mechanisms, whereby high-capacity NRAs provide assistance to NRAs in other countries. WHO is developing guidance for countries on implementing these mechanisms.

2.4.2. Developing-country vaccine manufacturers

Developing-country vaccine manufacturers (DCVMs) are now supplying vaccines for ~84% of the world's birth cohort annually, and 64 of the 147 WHO-prequalified vaccines are manufactured by DCVMs. Yet the low- and lower-middle-income countries they serve together account for only 12% of global vaccine revenues [31]. Meanwhile, DCVMs are under intense pressure to supply quality product at the lowest possible price. For example, UNICEF is now procuring DTP-HepB-Hib vaccine at less than $0.80 per dose, a price that may be unsustainable for some manufacturers [32]. GVIRF participants emphasized that access to affordable vaccines requires prices that are sustainable for manufacturers in the long term.

Mature DCVMs have gone beyond relying on partners for technology transfer to supporting in-house development of new products. To ensure sustained commercial viability, they require a robust business case for each product. Business risks include: long development timelines and regulatory complexities that extend time to market; lack of demand predictability, which leads to poor capacity utilization and high fixed costs; diverse procurement mechanisms; pressure for unsustainably low prices; and regional markets where it can be difficult to achieve economies of scale. Patent restrictions can also create barriers for DCVMs [33]. Participants observed that national governments and regional bodies can contribute by: strengthening national regulatory authorities; providing incentives and direct investments; fostering a supportive business environment; improving the intellectual property landscape; and building a highly skilled workforce.

2.4.3. Research capacity in India

Keynote speaker Dr. Maharaj Kishan Bhan described how a developing country can achieve not only independence in biomanufacturing, but also significant export streams. India's vaccinology effort has helped to transform its biotechnology research landscape: ten years ago, Indian vaccine companies were struggling with the basics. Today, vaccine manufacturers have developed and launched new combination vaccines and new vaccines against diseases such as Japanese encephalitis, meningitis A, rotavirus, influenza, typhoid, and cholera, and are managing robust product development pipelines. India's vaccine sector now aspires to contribute significantly to scientific knowledge, to drive innovation, and to increase impact through science and biotechnology.

In parallel, an institutional framework designed to foster innovation and support translation is taking shape, with an emphasis on evidence-based decision making and empowering industry to contribute to the economy and the public good. Through this evolution, the key lesson has been that innovation and high quality require global cooperation as well as funding. The Indo-U.S. Vaccine Action Program, a collaboration that supports a spectrum of activities relating to vaccines and immunization, shows the power of cooperation. The program helped to develop India's first indigenous rotavirus vaccine and is supporting new vaccines against dengue, malaria, TB and other diseases [34]. With such collaborations have emerged opportunities to learn from global leaders in vaccinology, a global mindset, and global ambitions for India's vaccine industry.

3. End-to-end integration

The second overarching theme of GVIRF reflected the ongoing shift from siloed approaches to an integrated end-to-end perspective that considers how a new vaccine will be deployed as part of a comprehensive disease control strategy.

3.1. Evolving disease control strategies

3.1.1. Polio

Three decades after the 1988 World Health Assembly resolution to eradicate polio, the disease remains endemic in just three countries: Pakistan, Afghanistan and Nigeria [35]. Vaccines have been the mainstay of polio eradication, but the current vaccines have limitations as well as benefits. Oral poliovirus vaccines (OPV) contain live-attenuated viruses derived from the three types of wild poliovirus (WPV). These vaccines give individual protection against paralytic polio and block transmission of the virus. Rarely, the attenuated vaccine strains can give rise to circulating vaccine-derived polioviruses (cVDPV), which resemble WPV in transmissibility and virulence. Of the three vaccine strains, the type 2 vaccine strain is the leading cause of cVDPV. In contrast, inactivated poliovirus vaccines (IPV) confer individual protection against all three types of poliovirus but do not block poliovirus transmission. As a result, in countries with a high risk of polio importation or transmission, OPV remains the primary tool for polio eradication [36].

These properties of OPV and IPV add complexity to polio eradication, as illustrated by the "OPV switch." In 2015, type 2 WPV was declared eradicated, creating an opportunity to halt use of the type 2 OPV strain. Accordingly, from April 17 to May 1, 2016, 155 countries representing approximately 130 million annual births switched from using trivalent OPV (tOPV) to a bivalent OPV without the type 2 vaccine. To reduce the risk of type 2 cVDPV emerging just as population immunity began to decline, the switch was made in synchrony in minimal time and included the destruction of tOPV stocks. In addition, inactivated polio vaccine (IPV) was introduced into the routine immunization schedules to limit the

risks of an immunity gap to type 2 poliovirus [35,37,38]. Since the switch, the number of countries detecting type 2 cVDPV has decreased by 83% [39]; it is, however, still causing outbreaks, particularly in areas with low vaccine coverage. Many of these strains arose before the switch, but some are likely to have originated from monovalent type 2 OPV used to contain outbreaks and others may have arisen from inadvertent use of tOPV.

To facilitate polio eradication, efforts are underway to develop improved IPVs that confer mucosal immunity and safer oral vaccines using genetically stable approaches or non-infectious virus-like particles. If successful, these new products will address the persistent risk of vaccine-derived poliovirus.

3.1.2. Pneumococcus

Pneumococcal conjugate vaccines (PCVs) have been introduced in 134 countries, averting an estimated 250,000 pneumococcal deaths globally from 2000 to 2015 [40]. Limited serotype replacement has been observed: non-vaccine-type invasive pneumococcal disease (IPD) has increased after PCV introduction, but increases are small compared to the impact against vaccine-type disease. Overall, PCV gives a sustained net decline in IPD [41]. GVIRF participants described two future directions in pneumococcal vaccination. The first optimizes the number of doses and their schedule to improve sustainability without sacrificing impact. Current data suggest that a two-dose primary series followed by a booster dose may provide better herd protection than the WHO-recommended three-dose primary series, and that a single primary immunization followed by a booster dose may be sufficient to maintain herd immunity. Additional studies are underway to evaluate alternative dosing regimens [42–44]. The second targets new vaccines that expand protection and prevent serotype replacement. Candidates in development include higher valency PCVs that address additional serotypes and protein or whole-cell vaccines that could have broad efficacy against all serotypes [45].

3.1.3. Rotavirus

Rotavirus vaccines are in use in about half of all countries. There are now seven licensed rotavirus vaccines, of which four have received WHO pre-qualification. Their efficacy among children under five years of age is inversely related to the under-five mortality rate: these vaccines reduced rotavirus acute gastroenteritis hospitalizations and emergency department visits by 71% in countries with low child mortality and by 46% in countries with high child mortality. Significant reductions in hospitalizations have also been observed for non-vaccinated children in some settings, providing evidence for herd protection [46]. GVIRF participants emphasized the importance of understanding how the gut environment influences responses to rotavirus vaccines, to improve vaccine performance. Non-replicating injectable vaccines, which may have better performance in all settings, are in development as an alternative approach to improving efficacy in countries with high child mortality [45].

3.1.4. Pandemic influenza

Because existing systems and tools are inadequate to address the threat of an influenza pandemic, coordinated global efforts are underway to improve pandemic preparedness. The WHO *Pandemic Influenza Risk Management* guideline recommends that countries implement a risk-based and integrated approach to pandemic influenza preparedness [47]. More than half of countries, however, do not have publicly available national preparedness plans, and many existing plans are outdated or incomplete.

In the event of a pandemic there are multiple challenges to an effective response, including the significant delay between the start of the pandemic and the first availability of vaccine, and limited global vaccine manufacturing capacity. To address delays in vaccine availability, universal influenza vaccines are in development as described above. To address the capacity shortage and ensure national and regional supplies, several developing countries have been partnering with WHO to build domestic influenza vaccine manufacturing capacity; six have achieved approval or conducted clinical trials of pandemic influenza vaccines. Notably, Thailand is now developing and manufacturing influenza vaccines and is building an influenza vaccine-manufacturing facility that will have a capacity to produce 60 million doses of an adjuvanted monovalent pandemic vaccine each year [48].

3.2. New vaccines

3.2.1. Pipeline overviews

The Global Observatory on Health Research and Development and the WHO Vaccine Pipeline Tracker show a substantial vaccine development pipeline. Vaccines account for about half of the candidates tracked in the Global Observatory, and WHO estimates that 11 novel vaccines could be licensed by 2023. Pipeline reports summarizing vaccine research and development are available on the WHO website [45,49,50].

3.2.2. Full public health value propositions

GVIRF participants observed that, given limited resources, competing priorities, and alternative interventions for treatment or prevention, value propositions for new vaccines are an increasingly important decision tool. Full Public Health Value Propositions (FPHVPs) are intended to facilitate evidence-based decisions on vaccine investments. They help funders, manufacturers, and countries set priorities by describing the role of a new vaccine in the context of an overall disease-control strategy, providing an end-to-end review of evidence, and presenting a comprehensive analysis of the value of a vaccine. FPHVPs go beyond the customary perspective of direct individual health benefits and attempt to capture the full economic and societal benefits of vaccination. To prevent a lag between licensure and uptake, they identify evidence gaps that must be addressed, such as operational research needs for products with complex delivery requirements [51]. FPHVPs are being developed for vaccine targets such as GBS, ETEC, and herpes simplex virus, and additional FPHVPs are being considered.

3.2.3. Respiratory syncytial virus

As presented at GVIRF, the RSV research and development pipeline is robust. Three approaches are being pursued for protection of neonates and infants: maternal immunization during pregnancy; infant immunization shortly after birth; and passive immunization with mAbs. Interim efficacy results for the most advanced maternal vaccine candidate were reported after the GVIRF conference (39% against medically significant RSV lower respiratory tract infection (97.5% confidence interval: −1% to 64%)) [62]. Infant immunization strategies are in earlier phase studies. Improved mAbs for passive immunization are under development as described above. As these products approach licensure, policy considerations such as the minimum acceptable efficacy, the effects of seasonality, the impact of concurrent conditions such as HIV infection on effectiveness of maternal immunization, and the delivery capacity of health systems must be addressed.

3.2.4. Human hookworm

More than 470 million people globally are currently infected with hookworm, which causes anemia, malnutrition, physical and developmental delays, and substantial productivity losses [52,53]. In a Phase 1 trial, a human hookworm vaccine has been found to be safe, well tolerated, and immunogenic [54]. A Phase 2 trial is underway using a controlled human hookworm infection model (NCT03172975). In parallel, market research and financial

modeling of costs and benefits are being conducted to develop an integrated business case for hookworm vaccines.

3.2.5. Hepatitis C virus

Hepatitis C virus (HCV) prevalence is 71 million infections globally, causing significant mortality from liver disease and cancer. Current hepatitis C control strategies focus on improving injection safety, diagnosis, and access to treatment. The leading HCV vaccine approach uses a heterologous prime-boost strategy to elicit cell-mediated effector immune responses. This candidate is being evaluated for safety and immunogenicity in a Phase 1/2 clinical trial, with data expected in 2018 (NCT01436357). While vaccines have the potential to transform hepatitis control, given the availability of effective treatments a strong value proposition for an HCV vaccine must still be established [55].

3.2.6. Antimicrobial resistance

Vaccines for frequently drug-resistant pathogens can prevent infections, reduce antimicrobial use, promote antibiotic stewardship, and limit the emergence and spread of antimicrobial resistance (AMR) [56–58]. Ongoing activities aligned with the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria are expanding funding opportunities for vaccines targeting antimicrobial-resistant pathogens and highlighting the value of vaccines in addressing AMR. As presented at GVIRF, new vaccines targeting *Pseudomonas, Staphylococcus aureus,* and uropathogenic *E. coli* are in development to prevent human diseases that drive antibiotic use [59–61]. Participants observed that identifying and reaching the appropriate target populations for such vaccines may be challenging, especially given the low coverage achieved for well-established vaccines such as influenza.

While progress is being made in vaccines to combat AMR, GVIRF participants cautioned that awareness and acceptance of this approach remains a challenge and called on one another to: define and communicate the value of vaccines to combat AMR; identify populations who would benefit most; and consider affordability and accessibility in low- and middle-income countries.

4. Conclusions

Every two years, GVIRF takes stock of global research in vaccines and immunization. The 2018 GVIRF highlighted the power of vaccines to improve health and enable progress, and showcased the energy and creativity of immunization stakeholders worldwide. Polio is nearing eradication, demonstrating the power of a well-coordinated global effort. Pneumococcal and rotavirus vaccines have proven their value in preventing pneumonia and diarrhea, the two leading causes of child mortality, and the focus is now on improving efficacy and cost-effectiveness. Countries such as India and Thailand are making strides in their capacity to develop, manufacture and regulate vaccines; this progress was reflected by the strong participation by regional stakeholders. For the first time at GVIRF, the discussion of advances in vaccine delivery focused on health systems innovations rather than delivery devices, reflecting the end-to-end perspective needed to achieve the full potential of immunization.

Significant challenges persist, however. High efficacy HIV, TB, and malaria vaccines remain difficult targets: participants called for a greater diversity of ideas and more innovative pipelines. Prices for certain vaccines have become unsustainably low, diminishing the incentives for developers and manufacturers to enter and remain in the market. Even as new vaccines are developed and launched, nearly 20 million children still lack access to vaccines that have been available for many years. Innovation is urgently needed to improve access to vaccines and primary health care even as packages of interventions continue to expand. GVIRF participants highlighted two factors as crucial to meeting this need: a focus on equity and sustainability throughout the immunization ecosystem, and an enabling political environment that prioritizes health and immunization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the members of the scientific organizing committee for their dedication and contributions to the meeting: Dr. Jean-Pierre Amorij, Dr. Narendra Arora, Dr. Norman Baylor, Professor David Durrheim, Professor Gagandeep Kang, Dr. Odile Leroy, Dr. Kathleen Neuzil, Dr. Bernhards Ragama Ogutu, Dr. Alexander Precioso, Professor Helen Rees, Dr. Lucky Slamet, and Dr. Gerd Zettlmeissl. Additionally, we thank the session chairs, panelists, and discussants for their valuable presentations and comments; and the meeting participants for their thorough and insightful discussions. In addition, we thank Marc Perut and Jacqueline Lee Endt of WHO, Marlo Hartung of BMGF, and Dr. Andrew Ford, Dr. Shahida Baqar, Dr. Annie Mo, Dr. Nancy Touchette, Christina McCormick, Dr. Patricia Strickler-Dinglasan, Claire Schuster, and Dr. Carolyn Deal of NIAID, for their energy and dedication in organizing this meeting.

Funding

This forum was supported in part by a NIAID cooperative agreement [grant number U01AI108543] and a grant from the Bill & Melinda Gates Foundation [grant number OPP1128274].

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References

[1] World Health Organization. Global Vaccine Action Plan 2011-2020. WHO Press; 2013. <http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/> [accessed February 14, 2019].
[2] Ford AQ, Touchette N, Hall BF, Hwang A, Hombach J. Global vaccine and immunization research forum: Opportunities and challenges in vaccine discovery, development, and delivery. Vaccine 2016;34:1489–95. https://doi.org/10.1016/j.vaccine.2015.11.038.
[3] Ford AQ, Touchette N, Fenton Hall B, Hwang A, Hombach J. Meeting report: global vaccine and immunization research forum. Vaccine 2018;36:915–20. https://doi.org/10.1016/j.vaccine.2017.12.013.
[4] World Health Organization Strategic Advisory Group of Experts on Immunization. Midterm Review of the Global Vaccine Action Plan. WHO Press; 2016. <http://www.who.int/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2016_EN.pdf> [accessed February 14, 2019].
[5] World Health Organization Strategic Advisory Group of Experts on Immunization. 2017 Assessment Report of the Global Vaccine Action Plan. WHO Press; 2017. <http://www.who.int/immunization/web_2017_sage_gvap_assessment_report_en.pdf> [accessed February 14, 2019].
[6] World Health Organization. Immunization coverage: key facts. <http://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage> [accessed February 14, 2019].
[7] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009;361:2209–20. https://doi.org/10.1056/NEJMoa0908492.

[8] Hsu DC, O'Connell RJ. Progress in HIV vaccine development. Hum Vaccines Immunotherapeut 2017;13:1018–30. https://doi.org/10.1080/21645515.2016.1276138.

[9] Jefferys R, Horn T, Johnson J. HIV Research in the Era of PrEP: The implications of TDF/FTC for Biomedical Prevention Trials. Treatment Action Group; 2017. <http://www.treatmentactiongroup.org/sites/default/files/PrEP%20Prevention%20Trials%20FINAL.pdf> [accessed September 27, 2019].

[10] Voss G, Casimiro D, Neyrolles O, Williams A, Kaufmann SHE, McShane H, et al. Progress and challenges in TB vaccine development. F1000Research 2018;7:199. https://doi.org/10.12688/f1000research.13588.1.

[11] Schrager L, Olesen O, Vekemans J, Lewinsohn D, Shea J, Hanekom W, et al. Global report on tuberculosis vaccines. Global TB Vaccine Partnership; 2018. <http://www.tbvi.eu/wp-content/uploads/2018/02/Summary-SWRTV_Finalproof.pdf> [accessed February 14, 2019].

[12] Aeras. Results from innovative phase 2 tuberculosis vaccine trial offer potential for new BCG revaccination strategies, hope for subunit vaccines. <http://www.aeras.org/pressreleases/results-from-innovative-phase-2-tuberculosis-vaccine-trial-offer-potential#.W1J609JKh9B> [accessed February 14, 2019].

[13] Van Der Meeren O, Hatherill M, Nduba V, Wilkinson RJ, Muyoyeta M, Van Brakel E, et al. Phase 2b controlled trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med 2018;379:1621–34. https://doi.org/10.1056/NEJMoa1803484.

[14] World Health Organization. Q&A on the malaria vaccine implementation programme. <http://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/> [accessed February 14, 2019].

[15] World Health Organization. Malaria vaccine: WHO position paper - January 2016. Weekly Epidemiological Record. 2016; 4:33–52. <https://www.who.int/wer/2016/WER9104.pdf?ua=1> [accessed February 14, 2019].

[16] World Health Organization. Tables of malaria vaccine projects globally, "The Rainbow Tables". <http://www.who.int/immunization/research/development/Rainbow_tables/en/> [accessed February 14, 2019].

[17] Coughlan L, Palese P. Overcoming barriers in the path to a universal influenza virus vaccine. Cell Host Microbe 2018;24:18–24. https://doi.org/10.1016/j.chom.2018.06.016.

[18] Erbelding EJ, Post DJ, Stemmy EJ, Roberts PC, Augustine AD, Ferguson S, et al. A universal influenza vaccine: the strategic plan for the National Institute of Allergy and Infectious Diseases. J Infect Dis 2018;218:347–54. https://doi.org/10.1093/infdis/jiy103.

[19] Simoni Y, Chng MHY, Li S, Fehlings M, Newell EW. Mass cytometry: a powerful tool for dissecting the immune landscape. Curr Opin Immunol 2018;51:187–96. https://doi.org/10.1016/j.coi.2018.03.023.

[20] Glanville J, Huang H, Nau A, Hatton O, Wagar LE, Rubelt F, et al. Identifying specificity groups in the T cell receptor repertoire. Nature 2017;547:94–8. https://doi.org/10.1038/nature22976.

[21] Dauner A, Agrawal P, Salvatico J, Tapia T, Dhir V, Shaik SF, et al. The in vitro MIMIC(R) platform reflects age-associated changes in immunological responses after influenza vaccination. Vaccine 2017;35:5487–94. https://doi.org/10.1016/j.vaccine.2017.03.099.

[22] Drake D. MIMIC: an in vitro model of human immunity. Global Vaccine and Immunization Research Forum (GVIRF), Bangkok, Thailand. March 20, 2018.

[23] Fruh K, Picker L. CD8+ T cell programming by cytomegalovirus vectors: applications in prophylactic and therapeutic vaccination. Curr Opin Immunol 2017;47:52–6. https://doi.org/10.1016/j.coi.2017.06.010.

[24] Sparrow E, Friede M, Sheikh M, Torvaldsen S, Newall AT. Passive immunization for influenza through antibody therapies, a review of the pipeline, challenges and potential applications. Vaccine 2016;34:5442–8. https://doi.org/10.1016/j.vaccine.2016.08.057.

[25] World Health Organization. An R&D Blueprint for Action to Prevent Epidemics. WHO Press; 2016. <https://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf> [accessed February 15, 2019].

[26] World Health Organization. 2018 Annual review of diseases prioritized under the Research and Development Blueprint <https://www.who.int/emergencies/diseases/2018prioritization-report.pdf?ua=1> [accessed February 15, 2019].

[27] World Health Organization. R&D Blueprint Key Actions. <http://www.who.int/blueprint/priority-diseases/key-action/en/> [accessed February 15, 2019].

[28] India National Health Portal. Mission Indradhanush. <https://www.nhp.gov.in/mission-indradhanush1_pg> [accessed February 15, 2019].

[29] Lin L. Use of Multiple Measures for immunization Management in Migratory Population. Global Vaccine and Immunization Research Forum (GVIRF), Bangkok, Thailand. March 20; 2018. <https://www.who.int/immunization/research/forums_and_initiatives/gvirf/Lin_Luan_2018.pdf?ua=1> [accessed February 15, 2019].

[30] Postovoitova A. Social Media Initiative in Ukraine: Analysis of Conversations on Polio, Vaccination and Routine Immunization. Global Vaccine and Immunization Research Forum (GVIRF), Bangkok, Thailand. March 20; 2018. <https://www.who.int/immunization/research/forums_and_initiatives/gvirf/Anna_Postovoitova_2018.pdf?ua=1> [accessed February 15, 2019].

[31] Batson A. Global Vaccine Market. Global Vaccine and Immunization Research Forum (GVIRF), Johannesburg, South Africa. March 15; 2016. <https://www.who.int/immunization/research/forums_and_initiatives/1_ABatson_Global_Vaccine_Market_gvirf16.pdf> [accessed February 15, 2019].

[32] UNICEF Supply Division. DTP-HepB-Hib Price Data. <https://www.unicef.org/supply/files/DTP-HepB-Hib.pdf> [accessed February 15, 2019].

[33] M. S. F. Access Campaign. A Fair Shot for Vaccine Affordability: Understanding and addressing the effects of patents on access to newer vaccines. Médecins Sans Frontières; 2017. <https://msfaccess.org/sites/default/files/2018-06/VAC_report_A%20Fair%20Shot%20for%20Vaccine%20Affordability_ENG_2017.pdf> [accessed February 15, 2019].

[34] Department of Biotechnology. Indo-US vaccine action programme. <http://www.dbtindia.nic.in/indo-us-vaccine-action-programme-vap/> [accessed February 19, 2019].

[35] World Health Organization. Polio eradication & endgame strategic plan 2013-2018. WHO Press; 2013. <http://polioeradication.org/wp-content/uploads/2016/07/PEESP_EN_A4.pdf> [accessed February 19, 2019].

[36] World Health Organization. Polio vaccines: WHO position paper - March 2016. Weekly Epidemiol Rec 2016;91:145–68. <https://www.who.int/wer/2016/wer9112.pdf?ua=1> [accessed February 19, 2019].

[37] Farrell M, Hampton LM, Shendale S, Menning L, Gonzalez AR, Garon J, et al. Monitoring and validation of the global replacement of tOPV with bOPV, April-May 2016. J Infect Dis 2017;216:S193–201. https://doi.org/10.1093/infdis/jiw558.

[38] Zipursky S, Patel M, Farrell M, Gonzalez AR, Kachra T, Folly Y, et al. Lessons learned from managing the planning and implementation of inactivated polio vaccine introduction in support of the polio endgame. J Infect Dis 2017;216:S15–23. https://doi.org/10.1093/infdis/jix185.

[39] Jorba J, Diop OM, Iber J, Henderson E, Sutter RW, Wassilak SGF, et al. Update on vaccine-derived polioviruses—Worldwide, January 2016-June 2017. MMWR Morb Mortal Wkly Rep 2017;66:1185–91. https://doi.org/10.15585/mmwr.mm6643a6.

[40] Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Health 2018;6:e744–57. https://doi.org/10.1016/S2214-109X(18)30247-X.

[41] Feikin DR, Kagucia EW, Loo JD, Link-Gelles R, Puhan MA, Cherian T, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med 2013;10:e1001517. https://doi.org/10.1371/journal.pmed.1001517.

[42] World Health Organization. Pneumococcal vaccines WHO position paper - 2012. Weekly Epidemiol Rec 2012;21:421-8. <http://www.who.int/wer/2012/wer8714.pdf?ua=1> [accessed February 19, 2019].

[43] Goldblatt D, Southern J, Andrews NJ, Burbidge P, Partington J, Roalfe L, et al. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. Lancet Infect Dis 2018;18:171–9. https://doi.org/10.1016/S1473-3099(17)30654-0.

[44] O'Brien KL. When less is more: how many doses of PCV are enough?. Lancet Infect Dis 2018;18:127–8. https://doi.org/10.1016/S1473-3099(17)30684-9.

[45] World Health Organization. WHO vaccine pipeline tracker. <http://who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/> [accessed February 19, 2019].

[46] Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. J Infect Dis 2017;215:1666–72. https://doi.org/10.1093/infdis/jix186.

[47] World Health Organization. Pandemic influenza risk management. WHO Press; 2017. <http://apps.who.int/iris/bitstream/handle/10665/259893/WHO-WHE-IHM-GIP-2017.1-eng.pdf> [accessed February 19, 2019].

[48] Grohmann G, Francis DP, Sokhey J, Robertson J. Challenges and successes for the grantees and the Technical Advisory Group of WHO's influenza vaccine technology transfer initiative. Vaccine 2016;34:5420–4. https://doi.org/10.1016/j.vaccine.2016.07.047.

[49] World Health Organization. Global Observatory on Health R&D: health products in the pipeline for infectious diseases; 2018. <http://www.who.int/research-observatory/monitoring/processes/health_products/en/>.

[50] World Health Organization. Immunization, Vaccines and Biologicals: vaccines and diseases. <http://www.who.int/immunization/diseases/en/> [accessed February 19, 2019].

[51] Gessner BD, Kaslow D, Louis J, Neuzil K, O'Brien KL, Picot V, et al. Estimating the full public health value of vaccination. Vaccine 2017;35:6255–63. https://doi.org/10.1016/j.vaccine.2017.09.048.

[52] Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800. https://doi.org/10.1016/S0140-6736(15)60692-4.

[53] Bartsch SM, Hotez PJ, Asti L, Zapf KM, Bottazzi ME, Diemert DJ, et al. The global economic and health burden of human hookworm infection. PLoS NeglTrop Dis 2016;10:e0004922-e. https://doi.org/10.1371/journal.pntd.0004922.

[54] Diemert DJ, Freire J, Valente V, Fraga CG, Talles F, Grahek S, et al. Safety and immunogenicity of the Na-GST-1 hookworm vaccine in Brazilian and American adults. PLoS NeglTrop Dis 2017;11:e0005574-e. https://doi.org/10.1371/journal.pntd.0005574.

[55] World Health Organization. Global hepatitis report, 2017. WHO Press; 2017. <http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf> [accessed February 19, 2019].

[56] Lipsitch M, Siber GR. How can vaccines contribute to solving the antimicrobial resistance problem? mBio. 2016; 7:e00428–16. DOI: 10.1128/mBio.00428-16.

[57] World Health Organization. Global action plan on antimicrobial resistance. WHO Press; 2015. <http://www.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1> [accessed February 19, 2019].

[58] The Review on Antimicrobial Resistance. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste; 2015. <https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf> [accessed February 19, 2019].
[59] Rello J, Krenn C-G, Locker G, Pilger E, Madl C, Balica L, et al. A randomized placebo-controlled phase II study of a Pseudomonas vaccine in ventilated ICU patients. Crit Care 2017:21–2. https://doi.org/10.1186/s13054-017-1601-9.
[60] Food and Drug Administration. Clinical development plan for Pfizer's investigational Staphylococcus aureus vaccine (SA4Ag) intended for pre-surgical prophylaxis in elective orthopedic surgical populations; 2017. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM583779.pdf>.
[61] O'Brien VP, Hannan TJ. Drug and vaccine development for the treatment and prevention of urinary tract infections. Microbiol Spectr. 2016;4. https://doi.org/10.1128/microbiolspec.UTI-0013-2012.
[62] Press Release: Novavax Announces Topline Results from Phase 3 PrepareTM Trial of ResVax™ for Prevention of RSV Disease in Infants via Maternal Immunization; 2019. [accessed 10 October 2019].