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**Vaccines and Global Health: In Search of a Sustainable  
Model for Vaccine Development and Delivery**

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## VACCINES

# Vaccines and global health: In search of a sustainable model for vaccine development and delivery

Rino Rappuoli<sup>1,2\*</sup>, Steven Black<sup>3</sup>, David E. Bloom<sup>4</sup>

**Most vaccines for diseases in low- and middle-income countries fail to be developed because of weak or absent market incentives. Conquering diseases such as tuberculosis, HIV, malaria, and Ebola, as well as illnesses caused by multidrug-resistant pathogens, requires considerable investment and a new sustainable model of vaccine development involving close collaborations between public and private sectors.**

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## INTRODUCTION

Vaccines are among the most important public health interventions currently available. Together with antibiotics and clean water, vaccines have increased life expectancy in both high- and low-income countries by eliminating many of the diseases that historically killed millions. Vaccination was introduced in most high-income countries in the 1950s but lagged markedly in low-income countries. The Expanded Programme on Immunization (EPI) was established by the World Health Organization (WHO) in 1974. The subsequent standardization of immunization schedules by WHO in 1984 recommended vaccination worldwide against diphtheria, tetanus, and pertussis (DPT); poliomyelitis; measles; and tuberculosis (TB) (1). The EPI led to a rapid global increase in childhood vaccination rates in the late 1980s from about 20 to 70% (Fig. 1). During the 1990s, however, progress in vaccination rates stalled with developing countries struggling to maintain their vaccination campaigns.

The stagnation of vaccination rates and the challenge of introducing new vaccines combined with the need to plan the introduction of vaccines in the late stages of development led to the establishment of the Global Alliance for Vaccines and Immunization (now Gavi, The Vaccine Alliance; [www.gavi.org/about/mission/history](http://www.gavi.org/about/mission/history)), supported by donations from the Bill & Melinda Gates Foundation and various international governments (2). Beginning in 2007, Gavi established the advanced market commitments initiative, forming legal contracts that guaranteed a market for vaccines before manufacturing commenced (3). With these advanced market commitments, Gavi sought to accelerate the development of pneumococcus and rotavirus

vaccines for low-income countries (Fig. 1). Meanwhile, Gavi also procured basic EPI vaccines for most of the countries that could not afford them. Global vaccination rates for the EPI-recommended vaccines quickly reached 85%. In addition, Gavi has enabled the introduction of vaccines against hepatitis B virus (HBV), *Haemophilus influenzae* type B (Hib), pneumococcus, and rotavirus with global vaccination rates for these vaccines reaching 84, 72, 44, and 28%, respectively, in 2017 ([www.who.int/news-room/fact-sheets/detail/immunization-coverage](http://www.who.int/news-room/fact-sheets/detail/immunization-coverage)). Not surprisingly, vaccination rates have not increased much since 2017 (Fig. 1), yet many new vaccines are entering the late stages of development. Change is clearly needed in the form of a new approach that transforms global priorities by ushering in a new era of vaccination with the goal of conquering TB, malaria, human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), typhoid fever, shigella, and other diarrheal diseases, as well as emerging infectious disease threats such as Ebola, pandemic influenza, and multidrug-resistant bacterial pathogens. Here, we analyze the current challenges in the vaccine field and discuss possible steps to facilitate the next wave of vaccination in the developing world.

## The challenge of late-stage vaccine development

Development of a new vaccine usually requires 15 to 20 years and financial resources upward of a billion U.S. dollars (4). This journey can be roughly divided into three phases: discovery, early development, and late development (Fig. 2). Once vaccines receive regulatory approval, they are recommended for adoption by national immunization programs and enter the commercial phase during which they are

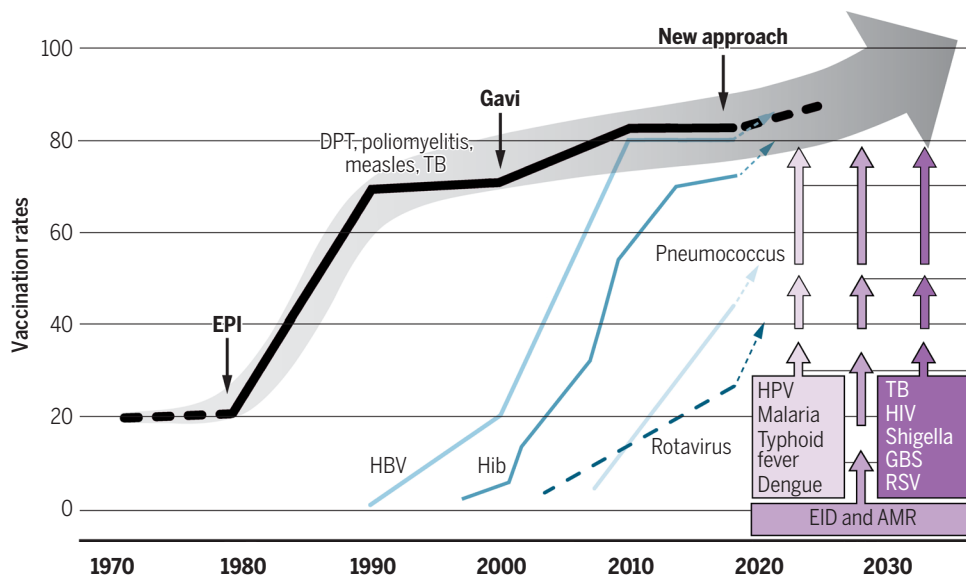
produced, procured, deployed, or stockpiled, depending on the need.

During the discovery phase, basic scientific questions are tested in the laboratory until proof of concept is achieved, demonstrating that the vaccine is scientifically feasible. This process is a collaboration among academia, biotechnology companies, and industry and usually requires about 10% of the total vaccine development budget. The discovery phase has greatly accelerated over the past 40 years, owing to new technologies that have made it easier to develop and engineer new antigens and adjuvants and to incorporate them into new vaccine formulations. New technologies have allowed the development of complex conjugate vaccines, such as pneumococcal and meningococcal conjugate vaccines; recombinant viral vaccines, such as those against HBV and human papilloma virus (HPV); the discovery of new antigens for meningococcus B by reverse vaccinology; structure-based antigen design to engineer potent RSV antigens; and vaccines against emerging pathogens that use viral vectors or engineered nanoparticles composed of bacterial outer membrane vesicles (5).

The discovery phase is followed by the early development stage (Fig. 2). This stage consists of the translational research necessary to achieve clinical proof of concept in humans and usually requires 20% of the total vaccine development budget. During early development, scientific discovery must be transformed into a vaccine that is shown to be safe and effective in people. This requires successful testing of preclinical assays and a demonstration that the process for production at scale and release of all vaccine components can be optimized and specified. The candidate vaccine must then pass toxicology tests and, lastly, be tested in phase I (and sometimes phases 2a and 2b) clinical studies. Fifteen years ago, the expertise to carry out early development was scarce and

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**Fig. 1. Historical and projected vaccination coverage rates.** The graph shows expansion of global vaccination rates over the past 50 years for vaccines against DPT, poliomyelitis, and measles and the BCG (Bacillus Calmette-Guérin) vaccine for TB, all of which were recommended in 1984 by the WHO EPI. In 2000, the establishment of Gavi allowed the acceleration and global expansion of vaccination efforts against hepatitis B virus (HBV), *Haemophilus influenzae* type b (Hib), pneumococcus, and rotavirus. Licensed vaccines exist for protection against human papillomavirus (HPV), malaria, typhoid fever, and dengue, but large-scale vaccination against these diseases in low-income countries has not yet been implemented. Vaccines against TB, HIV, shigella, group B streptococcus (GBS), respiratory syncytial virus (RSV), antimicrobial-resistant pathogens (AMR), and emerging infectious diseases (EIDs) are likely to reach the late stages of development during the next 3 to 10 years. EIDs refer to about 30 different pathogens that have the possibility to cause outbreaks and pandemics and for which we do not yet have vaccines (37).

resided mostly in industry and biotechnology companies. This stage was probably the main challenge in vaccine development and was nicknamed “the Valley of Death.” During the past decade, research into the development of new vaccines has been encouraged by strong public-private collaborations sponsored by the Bill & Melinda Gates Foundation, the Wellcome Trust, the European Commission, and the U.S. Department of Health and Human Services, among others. In addition, new players in the field conducting this work now include the GlaxoSmithKline (GSK) Vaccines Institute for Global Health, the Hilleman Laboratories ([www.hillemanlabs.org](http://www.hillemanlabs.org)), and the global health organization PATH (Program for Appropriate Technology in Health; [www.path.org](http://www.path.org)). Furthermore, new organizations have been created such as the Bill & Melinda Gates Medical Research Institute ([www.gatesmri.org](http://www.gatesmri.org)), and there has been a refocusing of established institutes dedicated to neglected and emerging diseases, including the IVI (International Vaccine Institute; [www.ivi.int](http://www.ivi.int)), the Jenner Institute ([www.jenner.ac.uk/home](http://www.jenner.ac.uk/home)), and the Human Vaccines Project ([www.humanvaccinesproject.org](http://www.humanvaccinesproject.org)). Recently, the Coalition for Epidemic Preparedness Innovations (CEPI) was established to accelerate vaccine development

against emerging infectious diseases (EIDs) and enable access to vaccines during outbreaks ([cepi.net/about/whyweexist](http://cepi.net/about/whyweexist)). Although the early development phase of vaccines is still a challenge, multiple entities shepherding vaccines to a clinical proof of concept represent a remarkable step forward in the vaccination field (Fig. 2). However, proof-of-concept challenges remain for a number of desired high-efficacy vaccines, such as those for dengue, shigella, malaria, TB, influenza, HIV, antibiotic-resistant bacteria, emerging infections, chronic infections, and cancer.

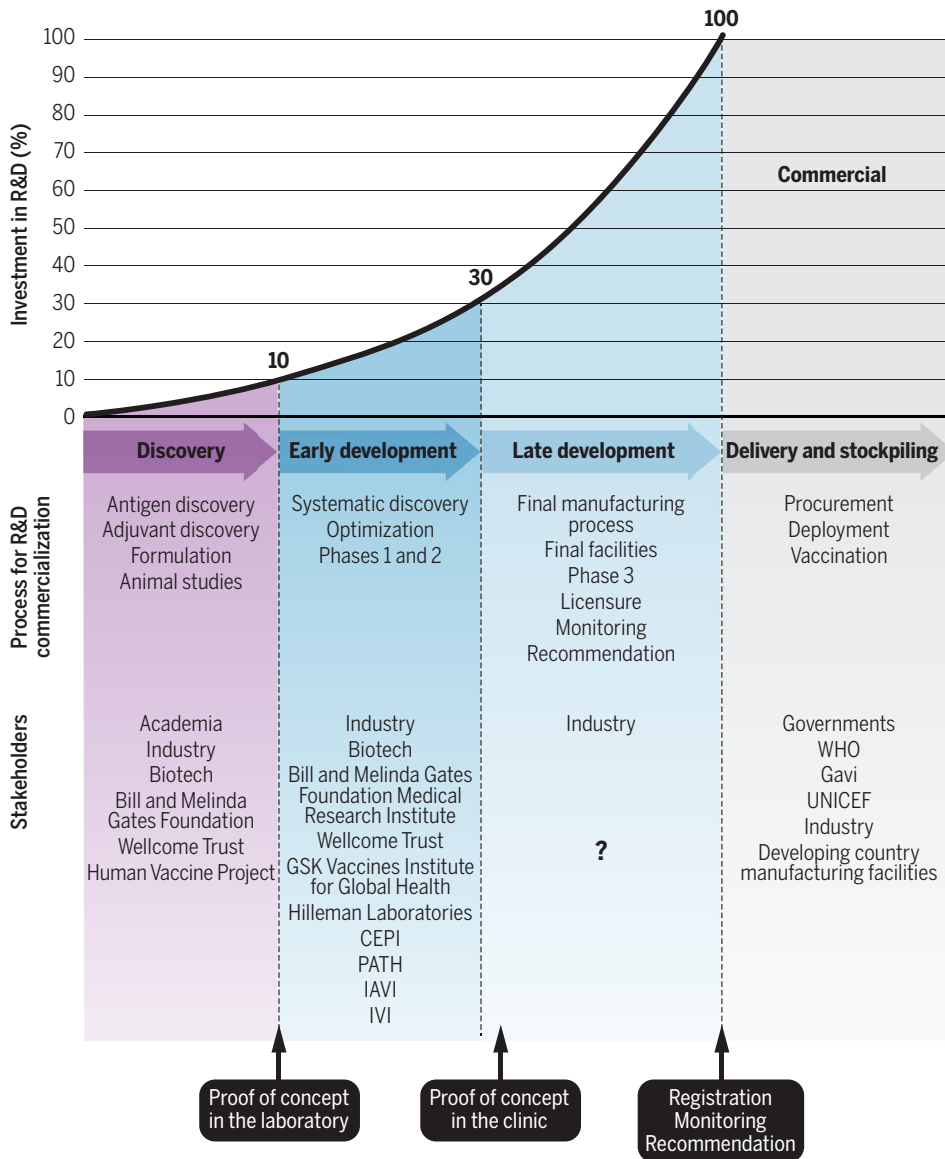
These improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase. Late development is the most labor- and budget-intensive phase of vaccine development and requires about 70% of the total development budget (4). During this stage, vaccine candidates need to be produced according to good manufacturing practice (GMP) regulations and in final production facilities, which usually need to be built specifically for this purpose. Vaccines are then tested in phase 3 clinical trials, and the data are submitted to regulatory agencies for approval. Once approval is obtained, postmarketing commitments frequently

require monitoring the safety and performance of vaccines on a large scale before their use can be formally recommended. Accomplishing each component benchmark requires both technical expertise and large financial and time commitments. In general, the expertise to go through this process and conduct GMP manufacturing rests primarily with a small number of large pharmaceutical companies.

This way of developing vaccines has been effective historically because most vaccines have been developed for a dual vaccine market, i.e., targeting both developed and developing countries. Under such circumstances, the financial incentives associated with high-income markets have been sufficient to justify the commitment to vaccine development by large pharma, which has made most of its vaccine profits in high-income countries while selling the same vaccines at lower prices in low- and middle-income countries. This model, however, has been complicated recently as pharmaceutical companies have found themselves involved in the development of several vaccines that lack a dual market, including vaccines against the Ebola

virus and Zika virus and vaccines for endemic diseases that are present predominantly in low- and middle-income countries, such as malaria and TB. The financial burden of developing such vaccines has made the historical approach to late-stage development unsustainable for large pharma. In January 2018, three of the four major vaccine manufacturers announced that the world should not count on them to develop vaccines with no return on investment (6).

To highlight the magnitude of this new problem, Fig. 3 shows the number of vaccine doses delivered globally from 1970 to the present, as well as the expected number of doses needed from now until 2030. The graph shows that the vaccine doses needed in high-income countries will remain almost flat, whereas a 10-fold increase in the number of doses delivered in low- and middle-income countries will be needed because of the introduction of new vaccines in these countries, population growth, and greater access to vaccination. With this exploding demand, the current model where ~65% of global sales revenue derives from the U.S. market alone and sustains development of vaccines for low- and middle-income countries is no longer feasible



**Fig. 2. Stages of vaccine development and delivery.** Before a vaccine is commercialized, vaccine development goes through three stages: discovery, early development, and late development. Discovery research requires about 10% of the research and development (R&D) budget, with the goal of discovering a vaccine that works in animal models. Early development requires about 20% of the R&D budget and involves finalizing the vaccine formulation, production of vaccine doses for toxicology, and phases 1 and 2 clinical testing with a demonstration that the vaccine is safe and effective in humans. The late development stage, which requires 70% of the R&D budget, involves all of the activities required for industrial-scale production of the vaccine and the phase 3 clinical trials necessary to support regulatory approval (32, 33). Below the graph are shown the three stages of the vaccine life cycle, the commercialization process, and the stakeholders involved at each step. CEPI, Coalition for Epidemic Preparedness Innovations; PATH, Program for Appropriate Technology in Health; IAVI, International AIDS Vaccine Initiative; IVI, International Vaccine Institute; GSK, GlaxoSmithKline; UNICEF, United Nations Children's Fund.

([www.who.int/immunization/research/forums\\_and\\_initiatives/1\\_ABatson\\_Global\\_Vaccine\\_Market\\_gvirf16.pdf](http://www.who.int/immunization/research/forums_and_initiatives/1_ABatson_Global_Vaccine_Market_gvirf16.pdf)). To develop solutions to this problem, we next review the history of several vaccines that have faced challenges in late development, summarize the lessons learned, and outline pragmatic considerations for the global health community moving forward.

**Vaccines developed despite weak market incentives**  
**Meningococcus C vaccine in the United Kingdom**

Meningococcal meningitis disease rates in the United Kingdom traditionally have been high, exceeding two cases per 100,000 people. During the 1990s, this translated to ~3000

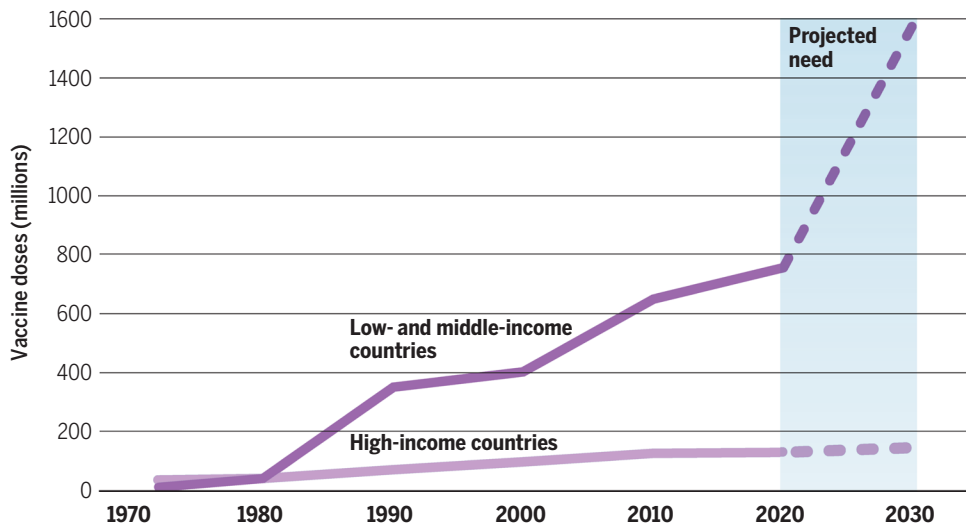
cases per year nationwide, half of which were caused by meningococcus serogroup B and the other half by meningococcus serogroup C of the bacterial pathogen *Neisseria meningitidis*. Following proof-of-concept studies in 1991 that a conjugate vaccine against meningococcus A and C serogroups was possible for adults (7) and then for infants (8), David Salisbury (then head of the U.K. National Immunisation Programme) started lobbying vaccine manufacturers to develop a conjugate meningococcus C vaccine, which led to meetings with scientists from Chiron Corporation, North American Vaccine, Wyeth, and Sanofi Pasteur. Salisbury committed to accelerate the clinical development and regulatory processes for a conjugate meningococcus C vaccine with the goal of introducing the vaccine as soon as it was licensed. As vaccine lots became available, the U.K. government partnered with the developers and started phases 1 and 2 clinical trials to establish safety, immunogenicity, and immune correlates of protection (bactericidal activity). Results from these trials were presented to regulatory agencies and the national policy advisory committee. The push from the U.K. government was the driving force for this accelerated vaccine development program, which was strongly supported by successive U.K. governments (9). The manufacturer timeline for vaccine development predicted licensure of the vaccine no earlier than 2002, but the collaboration spearheaded by Salisbury helped to produce the first vaccine license before the end of 1999. By early 2000, two additional meningococcus C vaccines were licensed, and within 1 year, all U.K. residents ranging from 2 months to 18 years of age were vaccinated. One year later, the cases of meningococcus C in the United Kingdom had decreased by more than 90% (10).

**Meningococcus B vaccine (MenZB) in New Zealand**

An epidemic of meningococcus B disease started in New Zealand in the early 1990s with incidence rates above 14 per 100,000 in the general population and more than 120 cases per 100,000 in Maori children below 1 year of age. To address this health emergency, the New Zealand government mobilized a large team of meningococcal experts, including global experts from the WHO and the U.S. Centers for Disease Control and Prevention. Developing a vaccine against

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**Fig. 3. Delivery of vaccine doses over time worldwide.** The graph shows the historical, current, and projected delivery of vaccine doses for low- and middle-income countries and for high-income countries from 1970 to 2030. Data up to 2020 come from the multiplication of the vaccination rates shown in Fig. 1 by annual numbers of births for each world region (34). Vaccine doses needed in 2030 have been calculated assuming that the vaccines in Fig. 1 have not yet been deployed in low- and middle-income countries and that those currently under development will be deployed in these countries by 2030. Predictions account for expected population growth. Combination vaccines have been considered as one vaccine even if they protect against multiple diseases.

the disease-causing strain was not technically difficult; in similar situations, Cuba and Norway had successfully developed a vaccine composed of bacterial outer membrane vesicles from the epidemic strain. However, production of a vaccine targeting only the 4 million people in New Zealand was not commercially attractive, and development failed to progress. The situation changed when the New Zealand government announced a call for proposals, earmarking about US\$200 million for the development and implementation of a meningococcus B vaccine. Of the four groups who submitted proposals, an alliance between the biotechnology company Chiron and the Norwegian National Institute of Public Health won the bid and undertook a collaboration with the New Zealand government. A team was established under the leadership of Jane O’Hallahan to coordinate the development and implementation of the vaccine. Phases 1 and 2 clinical trials were undertaken in 2002 to 2003, demonstrating safety and immunogenicity. Accelerated regulatory pathways were developed in collaboration with WHO experts to obtain approval using a “provisional licensure” procedure. By 2004, the vaccine was licensed, manufactured, and ready to be implemented. Almost the entire population of New Zealand from 2 months to 20 years of age was vaccinated with three doses of vaccine. One year later, the meningococcus B epidemic in New Zealand had been eliminated (11, 12).

### **Meningococcus A conjugate vaccine for Africa**

More than 90% of the global meningococcal meningitis disease burden is concentrated in the so-called “African meningitis belt,” which stretches from Senegal in the west through central Africa to Ethiopia in the east. Until recently, *N. meningitidis* serogroup A accounted for 80% of these cases, with focal epidemics occurring every year and major epidemics every 7 to 14 years; a large epidemic in 1997 saw 188,000 cases. In 2000, encouraged by the progress of the United Kingdom’s meningococcal C vaccine campaign, the WHO recommended the development of a conjugate vaccine for the “meningitis belt” population. However, there were no plans by large pharma to develop a meningococcal vaccine for Africa because they could see no path to profitability. In 2001, the Bill & Melinda Gates Foundation committed US\$100 million to fund a 10-year development program for such a vaccine, with the goal of eliminating epidemic meningitis in Africa. Given the low priority of this vaccine for large pharma and the availability of long-term funding from the Bill & Melinda Gates Foundation, the Meningitis Vaccine Project was established in 2002, with Marc La Force appointed to lead the program (13). Vital to the eventual success of the program was the early engagement of African public health officials, beginning in 2001. Initial discussions revealed that the cost of the vaccine would be a key driver of

eventual widespread use and that large vaccination campaigns would be impossible if the cost of the vaccine was more than US\$0.50 per dose. The Serum Institute of India then accepted that financial condition and technology transfers began, followed by vaccine production. In the absence of large pharma experience, the vaccine had to be redeveloped from scratch. A phase 1 clinical trial in India in 2005 was followed by phase 2 clinical trials in Mali and Gambia starting in 2006. Commercial manufacture and phase 3 clinical trials started in 2007. The polysaccharide A–tetanus toxoid (PsA-TT) conjugate vaccine called MenAfriVac was licensed in India in 2009, and WHO prequalification came in 2010 (14, 15). The PsA-TT vaccine was introduced in Burkina Faso, Mali, and Niger in December 2010, just 5 years after clinical trials began, with more than 20 million doses administered at a cost of US\$0.40 per dose. By the following year, meningitis due to *N. meningitidis* serogroup A had been virtually eliminated from the countries participating in the vaccination program (15).

### **A vaccine for Ebola**

Disease caused by the Ebola virus was first identified by the global scientific community in 1976 after outbreaks in Sudan and the Democratic Republic of Congo (DRC) near the Ebola River, from which the disease derives its name. In regions where health systems are often severely understaffed, underfunded, and underprovisioned, the case fatality rate for Ebola may be as high as 90%. In addition, as the disease spreads to health workers, attacking a critical human resource and undermining health-seeking behavior, outbreaks can produce a compound burden of morbidity and mortality from other diseases and conditions as happened during the 2014 outbreaks in Guinea, Sierra Leone, and Liberia. These 2014 outbreaks were associated with the Zaire strain of Ebola virus, which is believed to be the most lethal of the five known Ebola virus strains. With more than 28,600 cases and 11,325 deaths, these outbreaks were the worst on record, even without taking into account severe underreporting of Ebola due to fear, stigma, and poor health surveillance (16). The 2014 outbreaks spread the disease to Mali, Nigeria, Senegal, Spain, Italy, the United Kingdom, and the United States. The 2018 summer outbreak in the DRC reaffirmed the relevance, urgency, and difficulty of addressing disease caused by the

Ebola virus. As of May 2019, there were 1877 reported cases and 1248 deaths in the DRC outbreak. More than 103,800 contacts of infected individuals have been identified, and 121,147 people have received Merck's rVSV-ZEBOV (replication-competent vesicular stomatitis virus expressing the EBOV glycoprotein) Ebola vaccine. Of those, 33,046 are contacts, 87,886 are contacts of contacts, 31,016 are health care workers, and 34,522 are children 1 to 17 years of age (17). Notwithstanding these efforts, the outbreak has been difficult to control because of a combination of population mobility associated with civil unrest and a weak health system that is plagued by distrust of health care providers.

Research on Ebola vaccines started in 1980 after discovery of the viral pathogen. However, most of the research remained in the animal study phase until 2014, principally because of the absence of a market for a vaccine and the difficulty of obtaining licensing of a vaccine for a lethal disease without evidence of protection in humans, which can only be generated during an outbreak. The 2014 epidemic greatly accelerated the development of several Ebola vaccines, with 46 clinical trials launched in the past 4 years (18, 19). Despite several promising candidates, there is still no licensed vaccine available with U.S. Food and Drug Administration (FDA) approval and WHO prequalification. The rVSV-ZEBOV vaccine candidate was developed by the Public Health Agency of Canada and licensed to NewLink Genetics Corporation. Merck & Co. Inc. bought the worldwide commercial rights to this vaccine candidate in November 2014. This is the only candidate that has completed phases 1, 2, and 3 clinical testing. It was recommended for use by the WHO in the 2018 DRC outbreak. This vaccine candidate was part of the PREVAIL (Partnership for Research on Ebola Virus in Liberia) trial with phase 2 or 3 testing in 28,000 people, and the STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola) trial with phase 2 or 3 testing in 6000 people (20). It also underwent a phase 2 or 3 ring vaccination trial, with more than 4000 people vaccinated, and showed 100% efficacy (21). This vaccine candidate is the only one that has efficacy data from a phase 3 trial. This vaccine is moving sluggishly through the post-phase 3 licensing stage, with Merck's license application to the FDA targeted for later this year.

Johnson & Johnson is pursuing the Ad26-ZEBOV vaccine. Johnson & Johnson's vac-

cine vector was combined with Bavarian Nordic's MVA-BN virus vaccine and was tested in a phase 2 trial in July 2015. In October 2015, phase 2 and 3 clinical trials were started in Sierra Leone to test the safety and immunogenicity of this combined vector vaccine candidate; the data for the phase 3 trial are currently being collected (22).

The vaccine candidate being pursued by GSK is the chAd3-EBOZ. The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center collaborated with the U.S. Army Medical Research Institute of Infectious Diseases and with Okairo, a biotechnology company acquired by GSK in 2013, to develop this vaccine candidate. During phase 1 clinical trials in 2014 in the United States, the NIAID/GSK Ebola vaccine proved to be safe and induced an immune response in recipients. The vaccine candidate began phase 2 testing in February 2015 in Liberia as part of the PREVAIL I trial. This randomized, placebo-controlled clinical trial enrolled 1500 participants. It was originally designed to advance to a phase 3 trial among 28,000 volunteers but was scaled back because the decline in new Ebola cases made it impossible to conduct such a large study. Results in February 2016 from phase 2 testing showed that the vaccine was well-tolerated and induced an immune response (23).

Regarding other vaccine efforts, Russia and China both have vaccines for Ebola, but these vaccines have not yet undergone phase 3 clinical trials and do not have efficacy data available. They are neither FDA-approved nor WHO-prequalified. The Chinese vaccine has been licensed in China, and a stockpile has been produced for use among Chinese workers in Africa should the need arise. This vaccine was licensed on the basis of immunogenicity data only and not on the basis of clinical trial data. Regulatory approval is still pending for both vaccines subject to the availability of phase 3 efficacy data.

All of the aforementioned vaccine candidates have made it past the first Valley of Death, which is the clinical proof-of-concept phase 2a step. They have all stalled around phase 2b or 3 clinical testing, which is the second Valley of Death during late-stage vaccine development. The World Bank estimated that the 2014–2016 Ebola outbreak cost Guinea, Liberia, and Sierra Leone US\$2.8 billion. Preventing a future outbreak of a similar magnitude would therefore offer a substantial social benefit. However, a commensurate level of benefit to the private

sector is not expected because of the small anticipated market for a vaccine, despite a promise from Gavi to stockpile 300,000 units. The expected low (and potentially negative) return on investment for an Ebola vaccine is currently deterring companies from attempting to traverse the second Valley of Death.

### Addressing the last mile of vaccine development

As outlined so far, among the three stages of the vaccine life cycle (Fig. 2), there has been good progress in the discovery and early development stages. Although investment in these two stages must continue apace, it is expected that several new vaccines against malaria, TB, shigella, and nontyphoid salmonella will arrive at the clinical proof-of-concept stage soon. Governments, Gavi, and UNICEF continue to procure existing vaccines (Fig. 1), and it is reasonable to expect that these stakeholders will also procure future vaccines. Importantly, the only phase of vaccine development that is not addressed by the public sector is late-stage development. There is an urgent need to bridge the late-stage development gap as underscored by the successful early development of a new TB vaccine, followed by encouraging results from phase 2b trials (24); this vaccine is awaiting late-stage development. There are several options for progress.

One possibility is for donors such as the Bill & Melinda Gates Foundation and Wellcome Trust to begin directly funding late-stage development in a large-scale comprehensive way. A second possibility is for established entities such as the International AIDS Vaccine Initiative (IAVI; [www.iavi.org](http://www.iavi.org)), PATH, IVI, and CEPI to start a major fund-raising initiative. A third possibility is for Gavi and governments to fund the late-stage development of vaccines that they intend to procure in the future. A fourth possibility is the formation of a new entity—an organization that would raise money from governments and funders alike and would be fully dedicated to funding late-stage development and producing sustainable vaccines that are not supported by the commercial market. A mix of these four proposals may be the most pragmatic way forward. Whatever the ultimate solution, there are a number of points that need to be considered.

We argue that the vaccine projects that have succeeded have several common elements. The first element is a long-term partnership between funders and vaccine developers, because research grants that undertake

projects without a complete vision from beginning to end rarely bring projects to fruition. For example, the successful effort to create a meningococcus C vaccine in the United Kingdom was made possible because of a full commitment from the U.K. government to be a partner in clinical trials and to purchase the vaccine for the country as soon as it was licensed. In the case of the New Zealand meningococcal B vaccine, an orphan vaccine was developed because the government committed about US\$200 million for the development and implementation of a vaccine and established a team to work in concert with the manufacturer for the entire span of the project. The MenAfriVac vaccine was supported with US\$100 million upfront, a 10-year commitment, and an agreement from African countries to procure a successful vaccine at US\$0.50 per dose.

Studying successful vaccines also reveals the importance of a champion advocating for the vaccine from the public sector. David Salisbury and Jane O'Hallahan were instrumental in accelerating vaccine development in the United Kingdom and New Zealand, respectively, and Mark La Force was key in the development of the MenAfriVac vaccine.

The third observation is that vaccine development and supply must be sustainable for all parties involved. Sustainability means that all parties need to expect a reasonable return, which encourages sustained and repeated investments. We favor a partnership where large pharma is involved in early development, providing available technologies, intellectual property (IP), know-how, and early GMP manufacturing, as well as ushering the vaccine to clinical proof of concept alongside clinical partners. Once clinical proof of concept is achieved, large pharma can decide to carry on late-stage development on its own if a dual market is present. If not, then it could transfer the technology—relieving itself of late-stage development and marketing costs—to a new entity, possibly a developing country manufacturer, which would carry out the late stage of development and commercialize the vaccine, thus making a reasonable profit. This model would be sustainable for all parties. Large pharma would obtain financial support to test and de-risk new technologies, to generate new IP, and to test innovative regulatory pathways, and pharma employees would likely be motivated by the opportunity to contribute to the global good. At the same time, funders and governments would benefit from the increased success rates of projects dedicated to vac-

cine development and from the increased availability of tools to protect the health, social, and economic well-being of the populations they serve. Last, manufacturers in developing countries would increase their profitability, gain access to new technologies, and increase their vaccine development expertise.

An additional feature of successful vaccines is an upfront agreement on what success looks like and a commitment from the public sector for recommendation and procurement. In the cases of MenAfriVac and the New Zealand meningococcus B vaccine, experiences with similar vaccines in the United Kingdom and Norway had demonstrated that a meningococcal vaccine had the potential to eliminate the disease. These previous successes prompted the WHO and the New Zealand government to commit to the procurement of the new vaccine. In the case of a pneumococcus vaccine, Gavi's advanced market commitments encouraged high-income-country vaccine manufacturers to invest in manufacturing capacity for low- and middle-income countries. Undoubtedly, an upfront commitment from Gavi, governments, or UNICEF to procure a vaccine would be an important, perhaps decisive, incentive to encourage manufacturers to invest in the late phase of vaccine development. In the case of Ebola, a commitment by Gavi to stockpile 300,000 units of the vaccine is a start, but larger commitments for stockpiles from governments of affected countries and international organizations, or other guaranteed rewards, may be needed to incentivize late-stage development of an Ebola vaccine. Equally important for vaccine success is clear regulatory guidance. Requirements for regulatory approval are needed upfront and should be harmonized across regions to avoid duplication. The FDA and European Medicines Agency set global standards that should be synchronized internationally, but risk-benefit assessments should be made locally. Therefore, regional approaches to regulatory harmonization such as the Developing Country Vaccine Regulators' Network or the African Vaccine Regulatory Forum should be encouraged and supported. Expertise and capacity to monitor the introduction of new vaccines are other important elements that are currently lacking and where investment is needed. Attention should also be paid to the use of the most advanced science to define markers of immunity or immune correlates of protection. This would help to reduce the size of clinical trials, the

time to licensure, and the cost of obtaining regulatory approval.

For vaccination programs to succeed, confidence in vaccines needs to be nurtured and the benefits of vaccination need to be effectively communicated. Successful examples, such as the New Zealand meningococcus B vaccine and U.K. meningococcus C vaccine, were supported by separate budgets for vaccine campaigns to communicate the importance of vaccination for public health. Dedicated investment for such vaccine campaigns is rare, but maintaining the confidence of the populace during vaccination efforts is key. Communication must be the exclusive domain of the public sector because the industry's conflict of interest would render it untrustworthy for this purpose.

Ultimately, investment in new technologies can help to alleviate many challenges by lowering late-stage development costs and manufacturing costs. Some mature technologies, such as viral vectors (25), may reduce the need for investments in manufacturing facilities. For example, a single viral vector could be used to deliver synthetic genes against several pathogens. This would enable a single manufacturing plant and process to be used to develop vaccines against different pathogens. In addition to considerably reducing the cost of manufacturing, such an investment could also pay dividends by reducing the regulatory burden, as safety of the vaccine platform (i.e., the viral vector) must only be demonstrated once. For example, if a viral vector for an Ebola vaccine that has an approved manufacturing site and safety data is subsequently used for a different disease such as the Middle East respiratory syndrome, then it can benefit from the safety of the viral vector in the Ebola vaccine and can use the manufacturing site already approved for the Ebola vaccine. Gram-negative generalized modules for membrane antigens (GMMAs) represent a similar solution for bacterial vaccines (26). Gram-negative bacteria naturally shed particles consisting of outer membrane lipids, proteins, and periplasmic components, but the yield of these naturally shed particles is too low for use in vaccines. GMMAs are produced by Gram-negative bacteria that have been engineered to produce detoxified components of these naturally shed particles in much larger volumes (27). Potentially transformational technologies, such as synthetic vaccines (28) and RNA vaccines (29, 30), may completely change the speed of vaccine development by enabling the manufacture of millions of vaccine doses

in less-expensive and multipurpose facilities. Last, technological innovation should be applied to make it easier to fill, finish, and locally deploy vaccines once the vaccine bulk materials are produced. Indeed, fully robotic fill-and-finish units may empower low- and middle-income countries to become entirely self-sustainable in vaccine production. In addition to manufacturing the primary product, vaccine vials must be filled under sterile conditions before use. This process requires large, expensive facilities that often are used only during pandemics (e.g., the 2009 influenza pandemic). Innovation that introduces small, agile, robotic fill-and-finish facilities that can be deployed readily in low- and middle-income countries is within technical reach.

The success of early-stage development efforts for new vaccines has resulted in an unexpected potential crisis on the back end of the process, resulting in a lack of capacity and resources to push vaccine candidates through late-stage development to market introduction. If we can tackle this crisis, then we can harness the promise of prospective vaccines to improve global health for all.

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