New Vaccines for the World's Poorest People

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Annu. Rev. Med. 2016. 67:405–17

First published online as a Review in Advance on September 3, 2015

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-051214-024241

Keywords

product development partnerships, diseases of poverty, parasites, global access, neglected tropical diseases

Abstract

The 2000 Millennium Development Goals helped stimulate the development of life-saving childhood vaccines for pneumococcal and rotavirus infections while greatly expanding coverage of existing vaccines. However, there remains an urgent need to develop new vaccines for HIV/AIDS, malaria, and tuberculosis, as well as for respiratory syncytial virus and those chronic and debilitating (mostly parasitic) infections known as neglected tropical diseases (NTDs). The NTDs represent the most common diseases of people living in extreme poverty and are the subject of this review. The development of NTD vaccines, including those for hookworm infection, schistosomiasis, leishmaniasis, and Chagas disease, is being led by nonprofit product development partnerships (PDPs) working in consortia of academic and industrial partners, including vaccine manufacturers in developing countries. NTD vaccines face unique challenges with respect to their product development and manufacture, as well as their preclinical and clinical testing. We emphasize global efforts to accelerate the development of NTD vaccines and some of the hurdles to ensuring their availability to the world's poorest people.

INTRODUCTION

In 2000, the United Nations launched its landmark Millennium Development Goals (MDGs) for sustainable poverty reduction, which included two MDGs that focus on infectious disease control and prevention: MDG 4 ("reduce child mortality") and MDG 6 ("combat HIV/AIDS, malaria, and other diseases"). The concept that reducing mortality and morbidity from infectious diseases could be linked to poverty reduction in part arose out of evidence collected by the World Health Organization (WHO) and a Commission on Macroeconomics and Health led by the international development economist Jeffrey Sachs (1).

Since then, the global health community has mobilized resources in order to maximize the use of existing interventions, such as antiretrovirals, antimalarial drugs, and bed nets, and to develop new technologies, including vaccines. Here, we briefly review progress on the development of new vaccines needed to meet the MDG 4 and 6 targets. We then describe in more detail the progress, opportunities, and challenges of producing and testing new vaccines for an important subset of the poverty-related infectious diseases known as the neglected tropical diseases (NTDs), which are included in the "other diseases" of MDG 6.

NEW VACCINES TO COMBAT CHILDHOOD KILLER DISEASES

Progress in reducing the morbidity and mortality of the major diseases affecting particularly children under the age of five is being measured by the Global Burden of Disease Study (GBD), a comprehensive initiative led by the University of Washington's Institute for Health Metrics and Evaluation, to quantify the deaths and disability resulting from up to 300 different disease conditions that include both communicable and noncommunicable diseases as well as injuries from violence and road traffic accidents (2). In 2015, the deaths resulting from 240 different causes for the year 2013 were reported, analyzed, and then compared with the year 1990 (2). The data from the GBD 2013, as well as from a similar analysis by the United Nations Development Program (UNDP) (3), showed great progress toward MDG 4. There has been a profound reduction in deaths resulting from the major childhood vaccine-preventable illnesses since 1990, including tetanus (−91.2%), measles (−83.1%), *Haemophilus influenzae* type B pneumonia (−75.1%), rotaviral enteritis (−63.2%), pertussis–whooping cough (−57.1%), and pneumococcal pneumonia (−36.1%) (2, 4).

Moreover, MDG 4 provided a policy framework for establishing the Global Alliance for Vaccines and Immunisation (GAVI) to expand vaccine coverage and to advance the development of vaccines to prevent pneumococcal and rotaviral diseases, leading to many of the reductions in child mortality highlighted above (**http://www.gavi.org/about/**). However, the GBD 2013 also found that an estimated 708,600 children under age five still die from lower-respiratory infections and 474,900 die from diarrheal diseases (2). Such concerns prompted the global health community, including WHO, to launch a 2011–2020 Global Vaccine Action Plan (GVAP) (5).

Based partly on the successes of the newly developed pneumococcal and rotavirus vaccines, a key objective of the GVAP (objective #6) is to help stimulate the development of new vaccines for additional infectious disease etiologies of under-five childhood mortality (6). **Table 1** ranks the major childhood infectious killers for which there are no licensed vaccines, led by malaria and HIV/AIDS. Malaria and HIV/AIDS each affect both children and adults and are also targeted by MDG 6 (7). Ultimately, although the GBD 2013 has shown significant reductions in both malaria and HIV/AIDS mortality through mass drug treatments and use of insecticide-treated bed nets (7), it is still widely accepted that new vaccines will be required to effectively control or eliminate these diseases.

Table 1 Five leading childhood (children age 1–59 months) killer infectious diseases for which there is no licensed vaccine (2)

Disease	Number of deaths in 2013
Malaria	570,000
HIV/AIDS	63,800
Syphilis	56,900
Cholera	45,200
Respiratory syncytial virus pneumonia	41,100

Because most of the new vaccines required for the diseases listed in **Table 1** are intended primarily for populations living in low- and middle-income countries, new partners and mechanisms that do not rely exclusively on the major pharmaceutical companies are needed. Instead, these new vaccines are being advanced through innovative global partnerships that include large pharmaceutical companies, but also smaller biotechnology companies and developing-country vaccine manufacturers, working together with unique types of nonprofit organizations and consortia known as vaccine product development partnerships (PDPs) (8–11).

Vaccine PDPs apply industry practices and partner with the biotechnology industry, academia, or developing-country vaccine manufacturers to develop and test vaccines intended primarily for populations living in low- and middle-income countries. Shown in **Table 2** are the major international vaccine PDPs, many of which are partially supported by the Bill & Melinda Gates Foundation and also receive funding from governments in North America, Europe, Asia, and others.

Table 2 The vaccine product development partnerships (PDPs)

PDP	Major area(s) of interest	Location and Web site
PATH Vaccine Development	Diarrheal diseases including enterotoxigenic *Escherichia coli*, *Shigella*, meningitis, respiratory syncytial virus, polio, influenza	Washington, DC, USA **http://sites.path.org/vaccinedevelopment/**
PATH Malaria Vaccine Initiative	Malaria	Washington, DC, USA **http://www.malariavaccine.org/**
International AIDS Vaccine Initiative (IAVI)	HIV/AIDS	New York, NY, USA **https://www.iavi.org/**
Aeras	Tuberculosis	Rockville, MD, USA **http://www.aeras.org/**
Sabin Vaccine Institute PDP	Hookworm infection, soil-transmitted helminths (*Ascaris*, *Trichuris*), schistosomiasis, leishmaniasis, Chagas disease, onchocerciasis, West Nile virus, SARS	Houston, TX, and Washington, DC, USA **http://www.sabin.org/programs/vaccine-development**
Infectious Diseases Research Institute (IDRI)	New adjuvant technologies, tuberculosis, leishmaniasis, leprosy, hookworm disease	Seattle, WA, USA **http://www.idri.org/**
International Vaccine Institute (IVI)	Cholera, typhoid, and other diarrheal diseases	Seoul, Korea **http://www.ivi.int/web/www/home**
Dengue Vaccine Initiative (DVI)	Dengue	Seoul, Korea **http://www.denguevaccines.org/**

Abbreviations: SARS, severe acute respiratory syndrome; NTD, neglected tropical diseases.

An example of a vaccine that emerged from the PDP business model of development is the new malaria vaccine known as RTS,S/AS01, which has advanced through phase III clinical trials thanks to a partnership between the PDP called PATH-Malaria Vaccine Initiative and GlaxoSmithKline (12). Initial results of the phase III study showed that overall vaccine efficacy was 36.6% (13), and 18 months after the third dose, vaccine efficacy was 46% against clinical malaria and 34% against severe malaria (14). Because RTS,S/AS01 is a partially protective vaccine, important decisions will need to be made on how to integrate this new technology into malaria control efforts that continue to require the use of insecticide-treated bed nets and antimalarial drugs. Thus, the introduction of the RTS,S/AS01 malaria vaccine may require a significant departure from typical approaches taken with childhood vaccines, such as for measles or polio, which represent stand-alone technologies. A new global health policy is needed in order to ensure this malaria vaccine is widely used.

With respect to progress for new vaccines targeting the other major childhood killers listed above, the PDP called the International AIDS Vaccine Initiative is promoting new and promising HIV/AIDS vaccine candidates, with several in early- and mid-stage development (15). More than 50 vaccine candidates are also in different stages of development in order to prevent cholera and other viral and bacterial causes of acute gastroenteritis (16). Among the important recent developments against cholera is evidence of the effectiveness of oral cholera vaccination (using inactivated bivalent whole-cell vaccine) in a reactive setting following an outbreak of cholera in rural Haiti (17), and the clinical testing of a newer single-dose live cholera vaccine (18). Several vaccines to prevent respiratory syncytial virus (RSV) pneumonia are currently in early development and gaining momentum after rebounding from the decades of caution that followed studies conducted in the early 1960s, when a formalin-inactivated vaccine resulted in immune enhancement that exacerbated the disease (19).

In addition to malaria and HIV/AIDS, a third major adult killer being targeted by MDG 6 is tuberculosis, which, according to the GBD 2013, is the cause of 1.29 million deaths annually and the second leading infectious disease killer of adults behind HIV/AIDS (2). Both Aeras and the Infectious Disease Research Institute are PDPs advancing several tuberculosis vaccines through product and clinical development. In a recent phase IIb trial, a modified vaccinia Ankara–based vaccine expressing antigen 85A failed to further protect those infants vaccinated with the *Mycobacterium bovis*–derived BCG (*bacille Calmette-Guerin*) vaccine against tuberculosis (20). However, Aeras is evaluating a pipeline of additional tuberculosis vaccine candidates, including adenovirus-based vaccines designed to stimulate protective T cell immunity (21).

DISABILITY- AND POVERTY-RELATED DISEASES

Beyond HIV/AIDS, malaria, and tuberculosis, another very important group of infectious diseases that mostly affect people living in poverty and represent key targets for MDG 6 are the neglected tropical diseases (NTDs) (22, 23). The NTDs are predominantly chronic and debilitating infections, many of which are parasitic in origin, such as hookworm disease and related intestinal helminth infections, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma, as well as kinetoplastid infections like African trypanosomiasis, Chagas disease, and leishmaniasis. The original list of 13 NTDs for Africa (22) has subsequently been expanded to 17 NTDs by WHO (24).

The visceral form of leishmaniasis (also known as kala-azar), African trypanosomiasis, and rabies are examples of highly lethal NTDs. Some experts also include Ebola virus infection as an important and highly lethal NTD. However, most of the NTDs are nonlethal conditions, so expressing their disease burden purely in terms of annual deaths would underestimate their global health impact. Instead, the GBD study recently ranked these major NTDs by the number

Table 3 Ranking of major neglected tropical diseases by disability-adjusted life years (DALYs) and cases (25)

Disease	DALYs	Number of estimated cases
Cutaneous and visceral leishmaniasis	3.32 million	10.1 million
Schistosomiasis	3.31 million	252 million
Hookworm disease	3.23 million	439 million
Lymphatic filariasis	2.78 million	36 million with lymphedema and/or hydrocele
Food-borne trematodiases	1.88 million	16 million
Rabies	1.46 million	1,100
Ascariasis	1.32 million	819 million
Dengue	0.83 million	179,000 symptomatic
Trichuriasis	0.64 million	465 million
African trypanosomiasis	0.56 million	37,000
Chagas disease	0.55 million	7.5 million
Cysticercosis	0.50 million	1.4 million epilepsy cases
Onchocerciasis	0.49 million	30.4 million
Trachoma	0.33 million	4.4 million with low vision or blindness
Echinococcosis	0.14 million	1.1 million symptomatic
Leprosy	<0.01 million	<0.2 million according to WHO
Yaws, Buruli ulcer	Not determined	Not determined

of people they affect and a measure of disability known as disability-adjusted life years (DALYs), a combination of years of life lost from premature death and years lived with disability (**Table 3**) (25).

Still another measure of the impact of the NTDs is their economic effects based on studies showing that NTDs promote poverty by thwarting child growth and cognitive development, by interfering with adult worker productivity, and through their maternal effects during pregnancy (26–28). For that reason, vaccines that target NTDs are sometimes referred to as "antipoverty vaccines" (26, 28).

A major policy consideration is that a key segment of the global health vaccine community, including the GAVI Alliance and GVAP, has prioritized under-five child mortality targets, with a bias toward advocating or supporting vaccines for some of the diseases listed in **Table 1**, especially malaria, RSV, and next-generation rotavirus and pneumococcal vaccines, rather than NTD vaccines to combat poverty and disability. However, in 2014, WHO established the Product Development for Vaccines Advisory Committee (PD-VAC) to provide "strategic advice and recommendations to WHO related to vaccines at the phase 2 stage of clinical evaluation or earlier," with prioritization based on (*a*) global public health needs, (*b*) product development targeted before 2020, and (*c*) the value added by WHO's engagement in addressing specific disease areas that would provide scientific advancement in that given field (29). WHO convened the first PD-VAC meeting in September 2014 and evaluated the status of 19 new vaccines in early development, which included the following:

- Vaccines for HIV/AIDS, tuberculosis, and malaria
- Vaccines for NTDs: hookworm disease, schistosomiasis, Chagas disease, and leishmaniasis
- Vaccines for diarrheal diseases: *Campylobacter*, enterotoxigenic *Escherichia coli*, norovirus, non-typhoidal *Salmonella*, paratyphoid, and *Shigella*
- Next-generation vaccines: pneumococcus, rotavirus, universal influenza
- Other vaccines: herpes simplex virus, RSV, and *Streptococcus pyogenes*

Table 4 Major vaccines for neglected tropical diseases currently in clinical trials

Disease and target organism	Lead partners	Status	References
Hookworm disease, *Necator americanus*	Sabin Vaccine Institute PDP, HOOKVAC	Phase I clinical testing in United States, Brazil, and Gabon	48, 64–68
Schistosomiasis, *Schistosoma haematobium*	Institut Pasteur	Phase III clinical testing in Senegal and Niger	69
Schistosomiasis, *Schistosoma mansoni*	NIAID, Sabin Vaccine Institute PDP	Phase I clinical testing in United States	70
Schistosomiasis, *Schistosoma mansoni*	FIOCRUZ	Phase I clinical testing in Brazil	71
Visceral leishmaniasis, *Leishmania* spp	IDRI	Phase I clinical testing in United States	72
Dengue fever	Sanofi, Butanan Institute, NIAID, US Army, Takeda	Phase I, II, III clinical testing in United States and endemic areas worldwide	73–81

Abbreviations: FIOCRUZ, Fundação Oswaldo Cruz; HOOKVAC, Hookworm Vaccine Consortium; NIAID, National Institute of Allergy and Infectious Diseases; IDRI, Infectious Diseases Research Institute; PDP, product development partnerships.

In the coming months and years, it is anticipated that this WHO committee will continue to refine and update this list for donors, partners, policy makers, and the global health community at large.

ONGOING CHALLENGES AND NEW OPPORTUNITIES IN VACCINE DEVELOPMENT

Currently, NTD vaccine development efforts are primarily being led by three PDPs—Sabin Vaccine Institute PDP (Houston, Texas, USA), Infectious Disease Research Institute (Seattle, Washington, USA), and the International Vaccine Institute (Seoul, Korea)—together with a consortium of international partners, academic research institutes, and developing-country vaccine manufacturers (30). Shown in **Table 4** are the major NTD vaccines currently in clinical trials.

The progress toward new vaccines for NTDs, specifically for dengue, hookworm, leishmaniasis, and schistosomiasis (now in clinical trials), and for Chagas disease and onchocerciasis (still in preclinical development), has recently been reviewed by our group (8, 31), as have the major scientific, technical, and operational challenges faced during the NTD vaccine development process (31–33). Here we focus on a brief review of the major challenges currently being faced by PDPs throughout the development of NTD vaccines and present examples of new opportunities and lessons learned from other vaccine programs that could provide the means to accelerate their development and increase the prospects for success.

Challenges begin during the antigen discovery stage with the assessment, ranking, and selection of a robust and optimal candidate pipeline. Challenges continue throughout product development and the preclinical and clinical testing stages. An initial hurdle in antigen discovery is successfully selecting promising antigen targets from a multitude of parasite genome projects completed over the past decade. Reverse vaccinology approaches for small bacterial genomes and moderate- to high-throughput *Escherichia coli* expression and testing have yielded promising new bacterial vaccines for *Meningococcus* serogroup B (34) and some *Streptococcus* species (35); however, such approaches have not yet been successful for eukaryotic parasites. Among the reasons are the greater complexity of the parasite genome and the requirement to employ eukaryotic expression systems in order to reliably produce soluble and properly folded antigens.

Another hurdle is the fact that most NTDs, though debilitating, are usually not fatal, so measuring the prevention of death, as is common in traditional vaccinology, is not a feasible option. But even when broader benchmarks of potency, such as reduction of the number of parasites in the host, are applied, a clear path to the full characterization of the potency of an NTD vaccine candidate is not always available (36).

During preclinical testing for our portfolio of NTD vaccines, we typically look for substantial reductions in the number of parasites or parasite load following laboratory animal challenge infections and seek out links to levels of antigen-specific antibody levels or specific T cell populations. We then use these findings to identify potential immunological parameters for measuring protection downstream during clinical testing. Alternatively, Giersing et al. (37) have proposed innovative approaches for obtaining regulatory approval when it is not possible to correlate a specific immune response with clinical protection.

Following a program of preclinical testing and final target antigen selection, we then conduct a program of scale-up process development and complete good manufacturing practices (cGMP) in order to produce sufficient clinical material for phase I clinical testing. Details have been described for both our recombinant protein hookworm and schistosomiasis vaccines (38–40).

Further adding to this complexity is our experience that for most NTDs (unlike many bacterial or viral infections), there are few entirely permissive animal models that replicate the complete parasite life cycle found in humans or that mimic the same type or severity of disease. The majority of the causative agents of these diseases are either single-celled eukaryotic or multicellular organisms, often with a multistage ontogenesis.

An attractive new opportunity is modeling NTD infections in humanized mouse models (41). Such an approach has been successfully taken with malaria, in which the mouse tissue relevant to the human stages of malaria parasites was genetically engineered to become humanized. Human liver chimeric mice, human erythroid chimeric mice, and dually engrafted mice now allow for a more faithful replication of the entire *Plasmodium falciparum* life cycle (42, 43). Several investigators are now exploring whether parasitic helminths and other NTD pathogens might also be modeled using this approach.

Our overall approach to clinical development includes phase I testing in normal human volunteers living in nonendemic areas, then proceeding to repeat testing in NTD-endemic areas. The necessity of dual clinical testing was illustrated with an early hookworm vaccine recombinant candidate, which was found to be safe and immunogenic in naive individuals but elicited urticarial responses among some individuals living in highly endemic areas who acquired antigen-specific IgE against selected larval antigens (44). As a consequence, the human hookworm vaccine program shifted away from larval antigens to adult hookworm antigens, which to date are both safe and immunogenic. Currently, a program of clinical testing is under way for both the hookworm and schistosomiasis vaccines (45). For each vaccine, the emphasis is on eliciting high levels of antiparasite antibodies directed against the selected antigens, and, in the case of the two adult hookworm antigens having enzymatic function, to elicit antienzyme antibodies. Safety and immunogenicity in these studies provide key gating criteria to proceed to phase II studies focused on parasitological and epidemiological endpoints such as mean parasite intensity and reductions in the force of infection in the community (46), as well as clinical endpoints including reductions in anemia.

However, the long time required to complete such phase II trials has prompted interest in developing human challenge models in order to obtain a faster answer on the protective efficacy of our candidate vaccines. Since the late 1980s, the malaria vaccine development field has relied on using a controlled human malaria infection in malaria-naive adults in order to define the protective efficacy of a malaria vaccine. Adapting this model for other NTD fields could accelerate the evaluation of novel vaccine candidates (47). The Sabin PDP is developing a controlled human

hookworm challenge model, and a safety trial is currently being conducted in hookworm-naive adults by administering different doses of the *Necator americanus* larval inoculum to determine the optimal dose (i.e., number of infectious larvae) that is safe and well tolerated but results in consistent infection (48). Once developed, this model could provide early proof-of-concept that a hookworm vaccine targeting the blood-feeding pathway of adult hookworms is feasible and efficacious.

DEMAND FORECASTING, FINANCING, AND GLOBAL ACCESS

Many of the NTDs require investing in innovative health interventions while simultaneously improving health delivery mechanisms and strengthening the public health systems in endemic countries. We regard vaccines as the best public health intervention to prevent a variety of infectious and communicable diseases. Vaccines against NTDs, in particular, can now become global health accelerators. Like malaria vaccines, the NTD vaccines may not necessarily be sterilizing but would still be cost effective when integrated with other measures, such as chemotherapeutics or public health infrastructure initiatives (49).

In bringing vaccines to the clinic, including shepherding them through costly clinical trials, a partnership between national governments and private and nongovernmental organizations may help to ensure success (49). An example of such a joint venture is the European and Developing Countries Clinical Trials Partnership (EDCTP) (50, 51). Under the leadership of participating African and European countries, EDCTP has brought together researchers from the developed and the developing world, as well as members of the pharmaceutical industry, to advance the clinical development of new or improved interventions, including vaccines to combat HIV/AIDS, tuberculosis, malaria, and NTDs in sub-Saharan Africa. Between 2003 and 2013, EDCTP funded 254 projects, including 100 clinical trials. With the implementation of EDCTP2 in 2014, an additional €1.4 billion will be made available to sustain the progress made in previous years and to allow further expansion of the collaboration (52).

It is also paramount to note that, according to a recent Dalberg analysis commissioned by the Bill & Melinda Gates Foundation, nine of the top 14 high-burden NTD countries are classified as middle-income by the World Bank. A new "blue marble health" framework has illustrated how most of the world's NTDs are actually found among the poor living in wealthier middle-income (and even some high-income) countries (53). These countries are reaching a position where their growing economic strength should enable them to budget for sustaining the successes reached in recent years and tackle these debilitating diseases with their own resources (54).

In developed countries, advanced market commitments (AMCs) and priority review vouchers (PRVs) represent additional "pull" mechanisms to attract manufacturers to commit to NTD vaccine development. An AMC commits donors to purchase the vaccine in advance of its availability, guaranteeing the manufacturers a certain return on their investment and thus removing unpredictability. Since 2009, for example, this scheme has been successful in the production and distribution of pneumococcal vaccines through the GAVI alliance (55). PRVs have been issued in the United States since 2009, when Novartis was awarded the first voucher for Coartem, an antimalaria medication. PRVs reward pharmaceutical companies for developing revenue-poor drugs targeting neglected diseases with a transferable voucher for priority regulatory review of another medicine, valued at hundreds of millions of dollars (56–58). In all practicality, though, as of March 2015, only two additional PRVs for tropical diseases have been awarded (for tuberculosis and leishmaniasis drugs) (59, 60). In a reaction to the Ebola outbreak in 2014, the FDA has now added certain filovirus infections to the list of PRV-eligible tropical diseases.

One of the challenges of pull funding instruments such as AMCs is that they assume a pharmaceutical entity has the up-front funds available to invest in the initial vaccine manufacture and

clinical development. However, such is not the case with most of the PDPs or developing-country vaccine manufacturers. Instead, for these entities, new "push" mechanisms are required that can provide urgently needed funds. Two good examples are the new Global Health Innovation Technology Fund from the Japanese government, which brings PDPs and other entities together with Japanese industry and academic partners (61), and a recent fund from the Dutch government (62). The Global Health Investment Fund constitutes another possible model for certain NTDs, where there is the prospect of developing countries becoming a market for the vaccine. Investors are rewarded with milestone payments and royalties, while supporting the development of late-stage vaccines for the developing world. So far, the fund has attracted more than $100 million in investments and has taken interest in, for example, a new oral cholera vaccine (63).

CONCLUDING REMARKS: THE COMING DECADE

The coming decade offers tremendous potential for the development of new NTD vaccines, as well as vaccines for some of the great childhood killers, including malaria and RSV. Although there are great scientific challenges ahead for the product and clinical development of these vaccines, the greater challenges may be the socioeconomic ones. Specifically, there is no obvious roadmap for shaping the socioeconomic and political institutions and the financial instruments for ensuring that these vaccines are made accessible to those most in need—the world's poorest people. We saw the consequences of not addressing such socioeconomic hurdles during the 2014–2015 Ebola virus outbreak in West Africa. Although the technology for the adenovirus-based platform for Ebola vaccines had been published a decade or more before, only a dramatic and frightening outbreak prompted two major pharmaceutical companies to collaborate with WHO and regulatory authorities in order to rapidly accelerate a vaccine for phase I testing. By the time the vaccine was available, the Ebola outbreak was largely over, and it is not clear whether it will be possible to test the efficacy of these vaccines. This situation illustrates the fact that market failure for neglected disease vaccines (and neglected populations) is one of our most daunting challenges.

DISCLOSURE STATEMENT

The authors are investigators and patent holders on several vaccines in development that will provide protection against diseases discussed in the article and are funded in part by grants to develop these vaccines.

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