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Perspective

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Establishing a Global Vaccine-Development Fund

Stanley A. Plotkin, M.D., Adel A.F. Mahmoud, M.D., Ph.D., and Jeremy Farrar, M.D., Ph.D.

As the Ebola epidemic in West Africa continues, albeit at a much lower level than it reached in the spring, we still lack a vaccine that has been shown to be safe and effective. There has been no shortage of basic research: by 2009, at least seven Ebola vaccines had been tested in monkeys, with encouraging results.[1] But before the West African epidemic, only one of these vaccine candidates was tested in healthy humans, in phase 1 trials to evaluate its safety, and it was subsequently abandoned.[2] No vaccine had reached the later processes that would lead to licensure, and none was available in sufficient supply to be deployed in an emergency. Unfortunately, the same applies to many other infections: vaccines against them are not available because collectively we have not been willing or able to invest in the costly and complex development process that would be required to establish safety and immunogenicity, at a minimum.

Vaccine development is facing a crisis for three reasons: the complexity of the most challenging targets, which necessitates substantial investment of capital and human expertise; the diminishing numbers of vaccine manufacturers able to devote the necessary resources to research, development, and production; and the prevailing business model, which prioritizes the development of vaccines with a large market potential. We consider an international vaccine-development fund to be urgently needed to provide the resources and the momentum to carry vaccines from their conception in academic and government laboratories and small biotechnology firms to development and licensure by industry. Such a fund would enable basic scientists to move candidate vaccines from the laboratory through the so-called valley of death — the critical steps after good preclinical data have been obtained, comprising manufacture to Food and Drug Administration standards, a phase 1 clinical trial, and proof of concept in terms of protective immune responses. This support would permit efficacy assessment to begin — and thereby avert a repetition of the Ebola crisis.

Much attention has appropriately been directed at major disease targets such as human immunodeficiency virus (HIV), tuberculosis, and malaria, for which organizations such as the National Institutes of Health, the Bill and Melinda Gates Foundation, and the Wellcome Trust are providing considerable financial sup-

Vaccine-Preventable Diseases and Infections and Targets Currently Uncontrolled by Vaccination.*

Diseases and infections with commonly used vaccines	
Diphtheria	Polio
Haemophilus influenzae type b	Pneumoccocus
Hepatitis type A	Rabies
Hepatitis type B	Rotavirus
Human papillomavirus (HPV)	Rubella
Influenza types A and B (seasonal)	Smallpox
Japanese encephalitis	Tetanus
Measles	Tickborne encephalitis
Meningococcus	Typhoid
Mumps	Varicella (chickenpox)
Pertussis (whooping cough)	Yellow fever
Diseases and infections with limited-use vaccines	
Adenovirus types 4 and 7	Anthrax
Diseases and infections with no vaccines or only partially effective vaccines	
Campylobacter	Lyme disease
Cancer	Malaria
Candida	MERS
Chikungunya	Metapneumovirus
Chlamydia	Moraxella (for otitis)
Clostridium difficile	*Neisseria gonorrhoeae*
Cryptosporidium	Norovirus
Cytomegalovirus	Nosocomial bacteria
Dengue	Parainfluenza
Ebola and viral hemorrhagic fevers	Plague
Enterovirus including EV71, EV68, CA16	Rhinovirus
Epstein–Barr virus	RSV
Escherichia coli	*Salmonella paratyphi*
Helicobacter pylori	SARS
Haemophilus influenzae, nontypable	Schistosomiasis
Helminths (numerous)	Shigella
Hepatitis type C	Staphylococcus
Hepatitis type E	Tuberculosis
Herpesvirus type 6	Strep group A
Herpes simplex	Strep group B
HIV–AIDS	Toxoplasmosis
Influenza, universal	Trypanosomiasis
Influenza, avian types H5 and H7	West Nile virus
Leishmaniasis	

* Information is from the Foundation for Vaccine Research. MERS denotes Middle East respiratory syndrome, RSV respiratory syncytial virus, and SARS severe acute respiratory syndrome. Vaccines for some of the targets indicated above are in advanced development, but most are not.

port. Similar attention has been devoted to the provision of currently licensed pediatric vaccines, which is supported by GAVI (formerly the Global Alliance for Vaccines and Immunization). However, there are many infectious disease targets for which vaccines are both badly needed and feasible but which are not being developed owing to either a lack of governmental prioritization or a lack of incentives because the market has been considered too small to justify the capital investment, to allow development costs and to reward the required investment risk. These targets, listed in the box, include Ebola, chikungunya, Middle East respiratory syndrome coronavirus (MERS-CoV), the severe acute respiratory syndrome (SARS) virus (which is not extinct in its animal reservoir), West Nile virus, and Lyme disease, to name a few. They are not attractive to major manufacturers because the anticipated revenues would be small. In the table, we compare the three major global health funds with the vaccine-development fund that we are proposing.

There are now only four major manufacturers that focus on vaccine development: GlaxoSmithKline, Merck, Pfizer, and Sanofi Pasteur. These days, the development of just one new vaccine requires a capital investment ranging from $500 million for the least complex to $1 billion or more for the most complex, including construction of facilities for manufacture.[3] Moreover, only about 7% of vaccine development projects that reach the preclinical development phase result in a licensed vaccine.[4] With few exceptions, the scores of biotechnology companies and government and university laboratories engaged in vaccine discovery and

Comparison of Existing Global Health Funds and Proposed Vaccine-Development Fund.*

Variable	Global Fund to Fight AIDS, Tuberculosis and Malaria	GAVI	UNITAID Airline Tax	Proposed Vaccine Development Fund
Focus	HIV, tuberculosis, and malaria prevention, treatment, care, and support	Purchase and delivery of childhood vaccines	Purchase of HIV, tuberculosis, and malaria drugs	Accelerating discovery and development of new vaccines
Source of funds	Donor governments (95%); private foundations, corporate donors, and individuals (5%)	Donor governments (80%); private foundations (17%); International Finance Facility for Immunization (2%)	Airline solidarity levy	Donor governments (50%); private foundations and industry (50%) Options: financial transactions tax, tax breaks for industry donors
Eligibility	Middle- and low-income countries	Low-income countries	85% of funds must go to low-income countries	Scientists, institutions, and biotechnology companies engaged in vaccine discovery and development
Application process	Competitive country proposal	Facilitative country proposal	Funds distributed to implementing agencies and NGOs on a discretionary basis	Competitive proposal
Proposal review	Country proposals reviewed by independent technical review panel; board usually follows panel's recommendations	Country proposals facilitated by GAVI, reviewed by independent reviewers appointed by GAVI; decisions made by board	No proposals required	Proposals subject to rigorous scientific review by independent panel; board makes funding decision on the basis of scientific merit and available funds
Features	Performance-based model emphasizing results, transparency, accountability; hands-on monitoring by local fund agents and independent auditors; does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; hands-off monitoring; does not implement or fund research	Does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; independent auditors will monitor and assess performance; will not finance phase 3 clinical trials or conduct research
Governance	27-member international board representing donor and recipient countries, foundations, NGOs, industry, other stakeholders; 5 members are nonvoting representatives of WHO, U.N. agencies, and World Bank	28-member international board representing donor and recipient countries, private individuals, U.N. agencies, vaccine industry, foundations, other stakeholders	12-member executive board; 1 member is nonvoting WHO representative	Streamlined structure; medium-sized board whose majority of voting members represent donors; rest of composition to be determined
Funds disbursed through December 31, 2014	$25.8 billion	$7.8 billion	Approximately $2 billion	Goal: raise $2 billion initially

* Information is from the Foundation for Vaccine Research. GAVI denotes Global Alliance for Vaccines and Immunization, NGO nongovernmental organization, WHO World Health Organization, U.N. United Nations, and UNITAID Unity and AID.

development lack the necessary resources to carry candidate vaccines through early-stage clinical trials — let alone the costly phase 3 trials required for licensure. They and other groups must convince an increasingly skeptical investor or a major vaccine manufacturer to take up development after the initial stages.

Thus, the pharmaceutical industry's enthusiasm for vaccine development has dropped well below the levels seen in the 1980s and 1990s. The ClinicalTrials.gov website shows that only a minority of trials of vaccines against new infectious disease targets are sponsored by major vaccine companies and that the total number of trials is not increasing. Although we may hope that manufacturers in developing countries will soon be able to develop needed new vaccines from research to licensure, that is only beginning to be the case.

In addition to producing new vaccines, there is a growing need to improve old vaccines. Pertussis

and influenza vaccines, for example, are currently recommended for everyone, but their effectiveness leaves much to be desired. Efforts to improve them are stymied by the need for costly, new — and in many cases impractically large — studies of vaccine safety and efficacy to validate reformulated products. Also weighing against efforts to develop improved vaccines are the low prices of existing vaccines and the lack of economic incentives to improve them. External funding could permit the exploration of ideas for improving partially effective vaccines.

Seed money for the proposed fund could come from governments, foundations, the pharmaceutical industry, and nontraditional sources, perhaps including the insurance and travel industries. At least $2 billion would be needed at the outset. This level of funding should be achievable, even at a time when resources are scarce. Witness the cost of addressing the Ebola emergency, estimated at $8 billion to date, with the final figure likely to be far higher.

The proposed fund would invite competitive proposals from scientists, their institutions, and eligible biotech companies. Requests for support to help carry promising vaccine projects through tests in large animals, manufacturing for human use, phase 1 and 2 clinical trials, including the initial demonstration of efficacy and the production of a small stockpile, would be reviewed by an independent panel of scientists and funders. Grants would be awarded and renewed on the basis of milestones achieved and overall grant performance, which would be closely monitored by independent auditors. Institutional overhead costs would be capped. Costly phase 3 trials would have to be funded and conducted by an interested pharmaceutical partner, most likely with substantial government support or special incentives, as circumstances dictated. With initial support, however, at least a vaccine would be available for emergency use. In some cases, if phase 3 trials were impractical, results from animal or human challenge models might suffice for licensure.

An audio interview with Dr. Plotkin is available at NEJM.org

The extraordinary challenges facing vaccine developers are not dissimilar to those of developing new classes of antibiotics. Indeed, the rationale for the proposed $2 billion antibiotic-resistance fund is remarkably similar to our arguments for a vaccine-development fund; the two funds would be complementary. The economic reality today is that strategic support from government and other investors is needed to address the most difficult infectious disease problems.

The fundamental challenges facing the discovery and development of new vaccines are growing in significance and can no longer be ignored. The lack of resources at critical stages of the early development process is the key rate-limiting factor that discourages vaccine discovery and development by impeding scientific advances that could lead to new and improved vaccines. If a global vaccine-development fund had enabled just one candidate Ebola vaccine to be tested for safety and immunogenicity in humans before the 2014 outbreak in West Africa, public health workers could have begun vaccinating people at the start of the epidemic, potentially saving thousands of lives. The lesson we take from the Ebola crisis is that disease prevention should not be held back by lack of money at a critical juncture when a relatively modest, strategic investment could save thousands of lives and billions of dollars further down the line.

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From the Department of Pediatrics, University of Pennsylvania, Philadelphia (S.A.P.); the Foundation for Vaccine Research, Washington, DC (S.A.P., A.A.F.M.); the Department of Molecular Biology and the Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, NJ (A.A.F.M.); and the Wellcome Trust, London (J.F.).

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