



Strengthening the United States Government's Role in Product Development for Global Health

Authors

Gavin Yamey, Andrea Thoumi, Jonathan Gonzalez-Smith, Cynthia Binanay, Ipchita Bharali, Zeena Johar,
David Ridley, Nick Chapman

Strengthening the United States Government's Role in Product Development for Global Health

Authors

Gavin Yamey is Director of the Center for Policy Impact in the Duke Global Health Institute (DGHI), Professor of Global Health and Public Policy, and Associate Director of Policy at DGHI, Duke University.

Andrea Thoumi is a Managing Associate at the Duke-Margolis Center for Health Policy, Duke University.

Jonathan Gonzalez-Smith is a Senior Research Assistant at the Duke-Margolis Center for Health Policy, Duke University.

Cynthia Binanay is the Director of Operations for the Duke Hubert-Yeargan Center for Global Health and Senior Project Leader at the Duke Clinical Research Institute.

Ipchita Bharali is a Policy Analyst at the Center for Policy Impact in Global Health at the Duke Global Health Institute.

Zeena Johar is a Research Fellow with the Global Health Innovation Center and Duke-Margolis Center for Health Policy.

David Ridley is an Associate Professor of the Practice and the Faculty Director of the Health Sector Management program at Duke University's Fuqua School of Business.

Nick Chapman is the Executive Director of Policy Cures Research.

Acknowledgements

We thank Jennifer Kates at the Kaiser Family Foundation, Michael Merson and Mark McClellan at Duke University, and Courtney Carson, Marissa Chmiola, and Matt Robinson at GHTC for their helpful comments on the first draft of this paper.

Strengthening the United States Government’s Role in Product Development for Global Health

Table of Contents

Executive Summary	vii
Introduction	1
Section 1. How We Conducted this Study	3
<i>Desk Review.....</i>	<i>3</i>
<i>Key Informant Interviews</i>	<i>3</i>
<i>Defining R&D for Global Health.....</i>	<i>4</i>
Section 2. Levels and Trends in USG Funding for Global Health R&D	6
<i>How much does the USG invest in global health product development?.....</i>	<i>6</i>
<i>What does the USG fund?</i>	<i>7</i>
<i>Recent trends in USG funding.....</i>	<i>10</i>
Section 3. USG Agencies: Global Health R&D Funding, Decision-making, and Coordination	11
<i>Department of Health and Human Services</i>	<i>12</i>
Biomedical Advanced Research and Development Authority.....	13
National Institutes of Health	15
Centers for Disease Control and Prevention	19
US Food and Drug Administration (FDA)	22
<i>United States Agency for International Development.....</i>	<i>24</i>
<i>Department of Defense</i>	<i>28</i>
<i>Office of Management and Budget.....</i>	<i>31</i>
Overview	31
Funding Decisions.....	32
Section 4. The Appropriations and Budget Process: Influence on Global Health R&D	33
<i>Budget Formulation</i>	<i>33</i>
<i>Appropriations Timeframe.....</i>	<i>33</i>
Section 5. Catalysts and Barriers to USG Support for Global Health R&D	36
<i>Catalysts to USG agency support for global health R&D.....</i>	<i>36</i>
Collaborative Approaches within and between Agencies and Programs.....	36
Market incentives offered by the USG	38
Supportive legislative changes	38
Regulatory incentives	39
<i>Barriers to USG support for global health R&D</i>	<i>39</i>
Institutional siloes, unwieldy systems, and the difficulty of coordination	39
Insufficient funding	40
Under-use of effective agencies.....	41
Inadequate incentive structures	42
No clear mechanism to track USG funding for global health R&D	42
Section 6. Perspectives from Industry, Product Development Partnerships, and Foundations	43
<i>Perspectives from Industry</i>	<i>43</i>
<i>Perspectives from NGOs, PDPs, and Foundations</i>	<i>46</i>
Section 7. Stakeholders’ Suggestions for Reform Recommendations	49
Conclusions and Recommendations	54
References	59

Strengthening the United States Government’s Role in Product Development for Global Health

Figures

Figure 1. US Investment in Global Health R&D With and Without Ebola Funding.....	viii
Figure 2. Guiding Framework for the Key Informant Interviews.....	4
Figure 3. Government Funding for Global Health R&D, 2015	6
Figure 4. USG Funding for Global Health R&D in 2015 by Disease.....	7
Figure 5. USG Funding for Global Health R&D in 2015 by Type of Research	9
Figure 6. USG Departments, Agencies, Offices, and Institutes with a Key Role in Supporting Global Health R&D	11
Figure 7. USG Funding for Global Health R&D by Agency, 2015	12
Figure 8. USG Funding for Ebola and Other African VHF, 2015	13
Figure 9. NIH Funding in 2015 for Global Health R&D by Disease	16
Figure 10. CDC Funding in 2015 for Global Health R&D by Disease.....	20
Figure 11. USAID Funding in 2015 for Global Health R&D by Disease	25
Figure 12. USG Funding for Reproductive Health R&D Needs in LMICs, 2015	25
Figure 13. USG Funding in 2015 for PDPs that Develop Products for Global Health, by Recipient and Agency	27
Figure 14. DoD Funding in 2015 for Global Health R&D by Disease.....	29
Figure 15. Illustrative Timeline of Appropriations Process.	35

Tables

Table 1. Overview of USG Agencies, Departments, and Offices	ix
Table 2. New Therapeutic Products Approved or Recommended by Different Regulatory Bodies, by Disease Category, 2000-2011	2
Table 3. Key Informants Interviewed for the Study, by Sector	3
Table 4. USG Funding in 2015 for Global Health Product Development, by Disease—Showing Primary Investment Areas and Key USG Agencies Involved	8
Table 5. Examples of Successful Global Health R&D Coordination Between the NIH and Other Federal and Non-federal Agencies.....	19
Table 6. Examples of Successful Global Health R&D Coordination Between the CDC and Other Federal and Non-federal Agencies.....	22
Table 7. Appropriation Committees and Subcommittees in the 114 th Congress that Oversee Agencies Involved in Global Health R&D.....	34

Boxes

Box 1. Definition of Global Health R&D Used in Our Report.....	5
--	---

Strengthening the United States Government’s Role in Product Development for Global Health

Abbreviations

AAAS	American Association for the Advancement of Science
ADEPT	Autonomous Diagnostics to Enable Prevention and Therapeutics
AMCs	Advanced market commitments
AMR	Antimicrobial resistance
AMRH	African Medicines Harmonization Program
AU	African Union
BARDA	Biomedical Advanced Research and Development Authority
BSC	Board of Scientific Counsellors
BMGF	Bill and Melinda Gates Foundation
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CBRN	Chemical, biological, radiological and nuclear defense
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CEWG	Consultative Expert Working Group on Research and Development
CGH	Center for Global Health
COR-NTD	Coalition for Operational Research on Neglected Tropical Diseases
CRADA	Cooperative Research and Development Agreement
DAH	Development assistance for health
DALYs	Disability-adjusted life years
DARPA	Defense Advanced Research Projects Agency
DCs	Developing countries
DFID	Department for International Development
DNDi	Drugs for Neglected Diseases initiative
DoD	Department of Defense
DTRA	Defensive Threat Reduction Agency
EID	Emerging infectious diseases
EMA	European Medicines Agency
EOP	Executive Office of the President
EU	European Union
FAR	Federal Acquisitions Regulations
FDA	Food and Drug Administration
FENSA	Framework of Engagement with Non-State Actors
G20	Group of Twenty
GAO	Government Accountability Office
GDP	Gross Domestic Product
G-FINDER	Global Funding of Innovation for Neglected Diseases
GHI	Global Health Initiative
GHITF	Global Health Innovative Technology Fund
GHTC	Global Health Technologies Coalition
GHSA	Global Health Security Agenda

Strengthening the United States Government’s Role in Product Development for Global Health

GNNTDs	Global Network for Neglected Tropical Diseases
GPGs	Global public goods
HHS	United States Department of Health and Human Services
IAVI	International AIDS Vaccine Initiative
IFPMA	International Federation of Pharmaceutical Manufacturers
IMDRF	International Medical Device Regulators Forum
IP	Intellectual property
IVCC	Innovative Vector Control Consortium
LICs	Low-income countries
LMICs	Low- and middle-income countries
MassBio	Massachusetts Biotechnology Council
MCM	Medical countermeasures
MDIC	Medical Device Innovation Consortium
MDR-TB	Multi-drug resistant tuberculosis
MDSAP	Medical device single audit program
MENA	Middle East and North America
MHS	Military Health System
MMV	Medicines for Malaria Venture
MPP	Medicines Patent Pool
MSF	Médecins San Frontières (Doctors without Borders)
NAFTA	North American Free Trade Agreement
NAM	National Academy of Medicine
NCATS	National Center for Advancing Translational Sciences
NCE	New chemical entity
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
ND	Neglected disease
NGO	Non-governmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMRC	Naval Medical Research Center
NSC	National Security Council
NSTC	National Science and Technology Council
NTD	Neglected tropical disease
NVPO	National Vaccine Program Office
OAR	Office of AIDS Research
ODA	Official development assistance
OECD-DAC	Organization for Economic Cooperation and Development-Development Assistance Committee
OGA	Office of Global Affairs
OGAC	Office of the U.S. Global AIDS Coordinator and Health Diplomacy
OMB	Office of Management and Budget
OPA	Orphan Drug Act

Strengthening the United States Government’s Role in Product Development for Global Health

OSTP	Office of Science and Technology Policy
OTA	Other Transaction Authority
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCAST	President’s Council of Advisors on Science and Technology
PDP	Product development partnership
PDVAC	Product Development for Vaccines Advisory Committee
PEPFAR	US President’s Emergency Plan for AIDS Relief
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PMI	President’s Malaria Initiative
PPPs	Public private partnerships
PRV	Priority review voucher
R&D	Research and development
RFA	Request for applications
RFP	Request for proposals
RMNCH	Reproductive, maternal, newborn and child health
RMO	Resource Management Office
SADC	South African Development Community
SARS	Severe acute respiratory syndrome
SBIR	Small Business Innovation Research
SDG	Sustainable Development Goals
SIB	Social investment bond
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TB	Tuberculosis
TOSSD	Total Official Support for Sustainable Development
USPTO	United States Patent and Trademark Office
USAID	United States Agency for International Development
USG	United States government
VHF	Viral hemorrhagic fever
VICP	National Vaccine Injury Compensation Program
VRC	Vaccine Research Center
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WRAIR	Walter Reed Army Institute of Research

Strengthening the United States Government's Role in Product Development for Global Health

Executive Summary

Despite recent progress in global health, poor populations in low- and middle-income countries (LMICs) continue to be disabled or die disproportionately from neglected diseases and conditions of poverty. While some of this burden of disability and death could be averted by improving the delivery of existing health tools, new technologies to address unmet need are also urgently needed.

A major barrier to investing in the research and development (R&D) of new products for diseases of poverty is the lack of sufficient incentives. The time, cost, technical challenges, and risk of failure during product development create a formidable disincentive to product developers. Furthermore, existing technologies may not account for contextual factors in LMICs that may hinder the uptake and use of these innovations. As a result, research on the regulatory approvals of new drugs and vaccines since 1975 has shown that few of these new products are for neglected diseases and conditions of poverty.

The United States government (USG) is the world's largest funder of product development for global health, but as we show in this report, its funding for such research and development (R&D) is in decline. The report aims to identify opportunities to strengthen USG's role in supporting global health product development. It does so by examining the landscape of USG funding for such global health R&D; describing catalysts and barriers to increasing USG funding and coordination of global health R&D; providing perspectives from both USG and private actors (e.g., industry and foundations); and proposing initial ideas for reform. We use the term "global health R&D" to refer to product development for new medicines, vaccines, diagnostics, and other health technologies to tackle a specific list of poverty-related and neglected diseases and conditions (adapted from the G-FINDER surveys produced by Policy Cures Research).

We based our study on a desk review and 36 key informant interviews with senior representatives from government and private sector (for-profit and non-profit) organizations.

LANDSCAPE OF USG FUNDING FOR GLOBAL HEALTH R&D

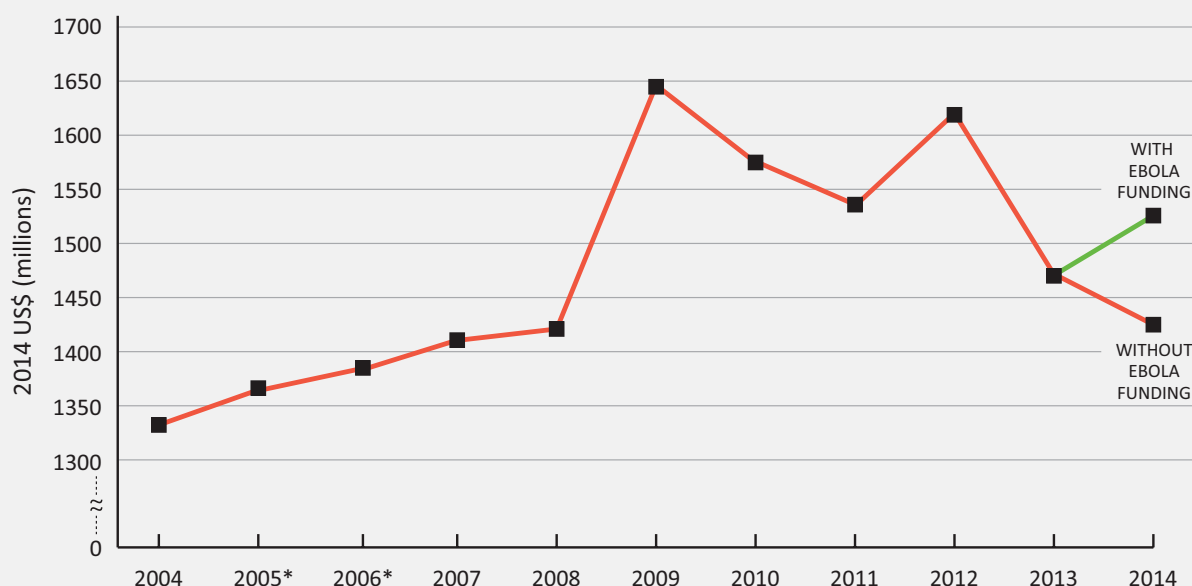
Levels and trends in USG funding

The USG is the world's most significant funder of global health R&D, investing \$1.7 billion in 2015—three quarters of all government funding worldwide. However, it directs twice as much global health R&D funding to basic and early stage research as it does to late-stage product development. This discrepancy results from the focus of the National Institutes of Health (NIH), which accounts for 80% of USG funding, on early-stage research. The only US agency to invest more in clinical development than basic and early stage research is the United States Agency for International Development (USAID), but USAID is responsible for just five percent of all USG funding for global health R&D.

The largest share of USG global health R&D funding in 2015 went to HIV/AIDS (45 percent), followed by Ebola and other African viral hemorrhagic fevers (VHFs, 16 percent), tuberculosis (TB, 13 percent), and malaria (12 percent). The focus on Ebola and Africa VHFs was prompted by authorization of emergency funding and leveraging existing R&D programs, allowing the USG to rapidly mobilize significant R&D resources in response to the 2014 Ebola outbreak. But this funding surge hid a major decline in R&D funding for other neglected diseases, which has fallen since its peak in 2009 (Figure 1). Adjusted for inflation, annual USG investment in neglected disease R&D has fallen every year but one since 2009, and is now more than a quarter of a billion dollars below its 2009 peak (down \$263 million, or a reduction of 16 percent).

Strengthening the United States Government's Role in Product Development for Global Health

Figure 1. US Investment in Global Health R&D With and Without Ebola Funding



Source: Chmiola M, Carson C, Kelley K, Morton EW, Robinson M. Achieving a bold vision for global health: Policy solutions to advance global health R&D. Global Health Technologies Coalition; 2016.

USG agencies: funding, decision-making, and coordination

The USG invests in global health R&D across multiple agencies and programs, and there is no “whole-of-government” strategy. Individual agencies or offices operate mostly autonomously, including setting their own R&D priorities, though we did find some examples of successful cross-agency collaboration. Table 1 summarizes our analysis of the five largest funders of global health R&D, along with the US Food and Drug Administration (FDA), which is not a major funder but which has influence in other ways. These agencies are the NIH, Department of Defense, Biomedical Advanced Research and Development Authority (BARDA), USAID, and Centers for Disease Control and Prevention (CDC).

Strengthening the United States Government’s Role in Product Development for Global Health

Table 1. Overview of USG Agencies, Departments, and Offices

Agency or office	Funding for global health R&D, 2015	Focus areas	Decision-making	Examples of successful coordination cited by stakeholders
NIH	\$1.3 billion (80% of total USG funding)	<ul style="list-style-type: none"> HIV/AIDS (50% of 2015 funding), TB (15%), malaria (12%) Three-quarters of allocated funding was for early and basic stage research 	<ul style="list-style-type: none"> About 90% of budget is for extramural research, awarded via a bottom-up approach through competitive peer-reviewed grant application process Some flexibility in using intramural funds in top-down way to respond to global health emergencies 	<ul style="list-style-type: none"> Partner in Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) NIH-industry collaboration: Cooperative R&D Agreements (CRADAs) between federal laboratories and non-federal parties
DoD	\$123 million (7% of total USG funding)	<ul style="list-style-type: none"> Ebola and other African VHF (41% of 2015 funding), malaria, (24%), HIV/AIDS (23%) Other priorities, e.g., leishmaniasis and dengue, reflect disease threats facing soldiers overseas 	<ul style="list-style-type: none"> Investment in intramural infectious disease research is driven by two streams: work force health protection (i.e. needs of military personnel) and biodefense needs. These overlap with needs of affected populations in LMICs (e.g., dengue vaccine development) 	<ul style="list-style-type: none"> Partner in PHEMCE and Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Key member of Global Health Security Agenda (GHSA)
BARDA	\$104 million (6% of total USG funding)	<ul style="list-style-type: none"> All funding was for Ebola and other African VHF (BARDA was not a major funder of global health R&D until the 2014 Ebola outbreak) Develops medical countermeasures (MCMs e.g., vaccines, therapeutics) against naturally occurring or intentional public health threats 	<ul style="list-style-type: none"> Only civilian entity with sole focus on late stage R&D for medical products Funding decisions and budgets are driven largely by its 5-year strategic plan BARDA model has provided an attractive ecosystem to incentivize industry into global health product development; model involves advanced (“push”) R&D funding; procurement funds (“pull” incentives) to develop stockpiles (e.g., <i>Project BioShield</i> procurement fund); and technical assistance and infrastructure support 	<ul style="list-style-type: none"> Participates in PHEMCE; key actor in CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), a new public-private push mechanism
USAID	\$87 million (5% of total USG funding)	<ul style="list-style-type: none"> HIV/AIDS (66% of 2015 funding), TB (15%), malaria (11%), and reproductive health needs in developing countries (8%) USAID provides three quarters of all USG funding for reproductive health needs in developing countries 	<ul style="list-style-type: none"> Supports global health R&D through its Center for Accelerating Innovation and Impact; Global Development Lab; Grand Challenges program; disease-specific programs R&D funding decisions are made at individual program level Multiple, separate funding streams for different diseases or conditions; no-overarching agency-wide strategy 	<ul style="list-style-type: none"> Partner in multiple PDPs, including International AIDS Vaccine Initiative (IAVI), Medicines for Malaria Venture, and Innovative Vector Control Consortium Grand Challenges program

Strengthening the United States Government’s Role in Product Development for Global Health

Agency or office	Funding for global health R&D, 2015	Focus areas	Decision-making	Examples of successful coordination cited by stakeholders
CDC	\$18 million (1% of total USG funding)	<ul style="list-style-type: none"> TB (48% of 2015 funding), Ebola and other African VHF (45%) Funding for R&D for a core list of 34 neglected diseases was halved from 2014 to 2015, falling by \$9 million 	<ul style="list-style-type: none"> Budget is heavily earmarked and so, unlike NIH, CDC does not have much flexibility on how to spend its budget 	<ul style="list-style-type: none"> Partner in PHEMCE Inter-agency collaboration: CDC works with DoD and NIH to produce multiplex assays (which detect several infectious agents in a single clinical specimen) International collaborator in Meningitis Vaccine Project and International AIDS Vaccine Initiative (IAVI) Lead agency for GHSA
FDA	No funding (but has funded global health R&D in the past)	<ul style="list-style-type: none"> Significant non-financial contributions to global health R&D, e.g., priority review voucher (PRV) scheme, granting of orphan drug status, foreign posts to inspect manufacturing globally, regulatory harmonization efforts 	<ul style="list-style-type: none"> Objective eligibility criteria limit FDA discretion on PRVs and orphan drug status, but there is some flexibility, e.g., in 2015, FDA expanded voucher eligibility to include Chagas disease and neurocysticercosis 	<ul style="list-style-type: none"> Issued Broad Agency Announcement to solicit collaboration on R&D to support regulatory science and innovation Partner in PHEMCE

Appropriations and budget process

The appropriations process is key to US support for global health R&D because it ultimately determines the R&D funding envelope within which the individual agencies must operate. Congress allocates funding for federal global health R&D activities through an annual appropriations process. Congressional committee staffers meet with executive agency officials and non-government stakeholders to consider high-level budgets, then specific appropriations for individual agencies and programs. While Congress occasionally delineates specific funding amounts for global health R&D through individual earmarks, it generally funds disease or technology-specific accounts and yields to implementing agency leaders to determine R&D prioritization within that account. While the federal budget and appropriations process we describe below is the way that the process is intended to occur, the reality is that most years have been exceptions to this rule.

The appropriations process is meant to begin when the President submits an annual budget to Congress in February for the following fiscal year. The Office of Management and Budget (OMB) prepares this budget, reflecting the President’s priorities for government spending. Stakeholders described OMB as the “center of government,” working closely with executive agency officials and others—including advocacy groups—during the budget preparation process and throughout the year while monitoring the budget implementation. Because OMB staff is divided along agency lines, the office is challenged in its ability to comprehensively coordinate the funding of global health R&D across all of USG. When considering budget requests, OMB staff favor programs or policies that demonstrate clear needs and tangible outcomes, and rely on data provided by individual agencies and advocates to help guide this decision-making. This preference can make prioritization of global health R&D spending difficult, as R&D requires long-term investments and does not always yield short-term results. Political factors—including Presidential interest, campaign pledges, and current events— can also drive OMB’s funding decisions.

Congress receives the President’s budget, and begins its own decision-making and funding prioritization process. While this process is often guided by the President’s budget, Congress ultimately sets funding levels independently, and it can accept or reject the Administration’s requests. In recent years, such

Strengthening the United States Government's Role in Product Development for Global Health

independence has been prevalent in global health funding, with Congress rejecting funding cuts for tuberculosis and nutrition proposed by the President, and Congress cutting funding to family planning and reproductive health accounts despite requests for budget increases in the President's budget.

CATALYSTS AND BARRIERS TO USG SUPPORT FOR GLOBAL HEALTH R&D

Several cross-cutting, cross-agency themes emerged from our study, related to catalysts and barriers to supporting global health R&D. within the US government and through private sector and NGO partners.

Catalysts

Our analysis found four main categories of **catalysts** to enhance product development:

- **Cross-agency initiatives and programs.** Stakeholders described several examples of USG actors collaborating effectively to achieve greater impact in global health R&D. They argued that such cross-agency collaboration can catalyze innovation by sharing of ideas and resources (e.g., laboratories or samples) and it can drive efficiency through cost savings. The Grand Challenges model, for example, was praised for allowing “organic and productive” collaboration and providing funding across the whole product development continuum. When there is an urgent public health problem and clear ask, there is a stronger motivation for breaking down institutional and inter-agency barriers; without a crisis, collaboration is much harder. Similarly, there is a tension between the short-term goal of addressing an emergency and long-term objective of creating a sustainable funding environment. Cross-agency global health efforts have succeeded when they are led by the Administration or through sustained, coordinated efforts led by agencies, as seen with the Global Health Security Agenda (GHSA) led by CDC. The imprimatur of a high-level federal advisory council was viewed as critical to bringing about productive collaboration, as seen with the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), which aims to accelerate product development by streamlining efforts at the highest level.
- **Market incentives offered by USG.** The market incentives provided by BARDA were seen as a successful model for USG engagement in product development partnerships (PDPs). These include BARDA's integrated push and pull mechanisms (funding for translational R&D and advanced market commitments [AMCs]), as well as its Other Transaction Authority (OTA), which facilitates its ability to establish long term portfolio partnerships with industry. Such portfolio partnerships have encouraged industry to stay in the antibiotic development space. The priority review voucher (PRV) scheme aimed at incentivizing the development of drugs for a selected list of infectious and parasitic diseases affecting LMICs is seen by some as a welcome addition to the range of government incentive mechanisms to support R&D. However, the impact of the PRV to date is unclear.
- **Supportive legislative changes.** There have been several examples of Congress being persuaded to alter legislation in ways that strengthen USG's role in global health, including global health R&D, suggesting that advocacy to Congress can be effective. For example, BARDA's remit was expanded to include product development for antimicrobial resistance (AMR), which allows the agency to consider work outside the biodefense space.
- **Regulatory incentives.** FDA has at its disposal a range of regulatory incentives that can help to catalyze product development for global health challenges. Examples include fast-track and orphan drug designations (these were granted, along with priority review, to the drug bedaquiline for treating multidrug-resistant TB) and emergency use authorization (granted for Ebola countermeasures).

Strengthening the United States Government's Role in Product Development for Global Health

Barriers to global health product development

Our analysis found five main categories of **barriers** to global health product development:

- **Institutional siloes and unwieldy systems make coordination difficult.** Despite examples of successful inter-agency coordination, agencies largely work in siloes, hampered by systems barriers. The failure of the Global Health Initiative exemplifies the difficulties in addressing coordination across agencies and suggests that trying to “force” a collaboration can have the opposite effect, particularly when they lack clear leadership, budgetary authority, or a unifying mandate mission. Even within agencies, there may be divisions that can impede global health R&D. R&D efforts within an agency are often divorced from its disease control programs and scale-up efforts, a missed opportunity for testing innovative products in the field. Jurisdictional divisions between Congressional appropriations sub-committees, mirrored in OMB offices, can stovepipe R&D funding decisions and impede interagency coordination and collaboration. In addition, the inability of Congress to enact a regular appropriations bill before the start of the fiscal year also hinders strategic planning.
- **A funding gap for translational and product development.** A major challenge to product innovation is the funding gap for this type of research. Low levels of funding at CDC, for example, has slowed down the development of a promising diagnostic for trachoma. Budget caps and sequestrations have shrunk already limited global health R&D funding, slowing down product development efforts at several agencies. Ebola vaccine development was stalled, for example, as a result of the sequester. Financing of later-stage clinical trials has become prohibitively expensive. Nevertheless, some stakeholders argued that just increasing funding alone will not accelerate global health R&D unless other weaknesses in the complex R&D “ecosystem” are addressed.
- **Under-use of effective agencies.** There is significant, under-used value in the Department of Defense (DoD) overseas labs for global health R&D, including for vaccine development. Stakeholders argued that DoD’s medical R&D does not get the recognition that it deserves and is dwarfed by higher profile defense projects.
- **Inadequate market incentive structures.** Previous market failures highlight the inadequacy of the current incentive structures to promote product discovery and development in the areas of antimicrobial resistance (AMR), emerging infectious diseases, and neglected tropical diseases. Recent outbreaks (e.g., Ebola) were never anticipated and the existing structures were not easily adaptable to meet these outbreaks. The USG does not have R&D surge capacity; such capacity would need a new appropriation.
- **Lack of a clear mechanism to track USG funding for global health R&D.** There is no common, standard working definition of R&D across executive agencies and no clear mechanism to track R&D funding flows. This inconsistency prevents OMB from adequately tracking global health R&D across multiple executive branches and limits conversations about coordination that might otherwise have been triggered.

PERSPECTIVES FROM INDUSTRY, PDPS, NGOS, AND FOUNDATIONS

In addition to USG stakeholders, we also interviewed private sector actors (for-profit and non-profit) to understand their experiences of partnering with USG on global health R&D.

Industry stakeholders indicated that they are incentivized to conduct global health R&D by the push and pull mechanisms offered by the USG, such as the PRV and orphan drug designation. However, these are not the key driver in their decision-making, in part because the incentives only account for a fraction of

Strengthening the United States Government's Role in Product Development for Global Health

the total cost of developing a product. They experience significant barriers to partnering with USG, including bureaucratic processes, complex reporting requirements, slow FDA approval systems, limited levels of translational funding, and overall lack of political will to partner. Several industry stakeholders engage with PDPs to leverage expertise and financing not available within the parent company. But some industry stakeholders interviewed for this report argued that there are advantages to going it alone because industry goals are not always aligned with those of PDPs; they see technology transfer as an equally viable model for product development and access.

NGO, PDP, and foundation stakeholders also face practical hurdles collaborating with USG. They highlighted two barriers: the lack of an explicit priority setting process for global health R&D and the relative lack of funding for product development compared with early stage or operational research. They had mixed views on the PRV, but felt it was too early to judge its impact, and positive views on their experiences working with industry, including in PDPs, seeing benefits from greater USG-industry collaboration. NGOs who work on advocacy for increased global health R&D find the USG's long, complex budget and appropriations process a major barrier. NGOs and PDPs interviewed received funding from the Bill and Melinda Gates Foundation (BMGF) and their R&D prioritization was influenced by the Foundation's priorities. They expressed concerns about the Foundation's recent shift in its focus away from vaccine development through PDPs towards industry players.

STAKEHOLDERS' SUGGESTIONS FOR REFORM

Key informants gave six main suggestions on ways to strengthen USG support for global health product development.

1. USG should implement strategies to support leadership and collaboration at the Agency level—for example, a new forum or blue ribbon task force could be established to help NIH with global health R&D priority setting. USG stakeholders recommended a “Manhattan Project” type program for global health R&D targeted to help overcome the challenge of maintaining individual agency mission while working collaboratively.
2. The USG should invest in R&D capacity building in LMICs. Such investment should include strengthening regulatory capacity in LMICS.
3. The USG needs to increase its efforts on collaboration and knowledge exchange with outside partners, both domestically and internationally (especially with the WHO), to help inform global health R&D prioritization and improve R&D efficiency. USG should make use of opportunities to better engage with industry and nongovernment actors, such as through the creation of platforms to share knowledge and create economies of scale. There are also valuable lessons to learn from Europe's successes in creating an infrastructure to fund global health R&D.
4. The USG should allocate funding more strategically to address gaps in product development, including translational support for global health R&D. There should be an increase in USG funding for global health R&D, especially clinical trials, whether through providing better incentive mechanisms or innovative and additional financing mechanisms. Stakeholders were divided on whether USG should participate in an international pooled fund for global health R&D. Creative and innovative approaches to R&D financing should be tried, such as developing blended financing mechanisms to bring together public, private, and philanthropic funding.
5. The USG's push and pull incentive mechanisms should be refined to improve their impact. For example, the PRV could be redesigned to include commitments to register the drug and make it available and affordable to patients and treatment providers.

Strengthening the United States Government's Role in Product Development for Global Health

6. Scaled up and more strategic advocacy efforts could help improve USG support for global health R&D. Strategic advocacy and “good story telling” could help to improve funding and prioritization of global health R&D. Creative approaches to advocacy are needed, such as showcasing the economic benefits of global health R&D, its potential to create jobs, and its role in maintaining USG’s reputation as the global leader in product development and innovation. Advocacy efforts should include pushing for regulatory review processes for global health products to be harmonized across countries. The FDA can play an important mentoring role in the harmonization of regulatory processes while also building in-country regulatory capacity.

CONCLUSIONS AND RECOMMENDATIONS

Our study found that while USG plays a vital role in supporting global health product development, there are many ways in which this support is being weakened or threatened. We draw nine major conclusions, each accompanied by our initial recommendations.

- **Conclusion 1: There is an ongoing struggle to find the correct balance between USG agency autonomy and greater inter-agency coordination.** While the challenge of coordination has been well described, the “positive consequences” of the fractured USG infrastructure for global health R&D have received less attention. A fractured architecture may well generate more innovation than trying to have all agencies in lock-step.

Recommendations: The debate on whether greater coordination will improve R&D is unlikely to be settled without a deep analysis of the current institutional arrangements and the development, piloting, and evaluation of new inter-agency coordination mechanisms. Such an analysis should also learn lessons from the success of mechanisms such as PACCARB and PHEMCE.

- **Conclusion 2: The USG is missing opportunities to strengthen its external collaborations with other actors in the global health R&D space.** In particular, there is a real hunger for the USG to become a more serious participant in and funder of PDPs.

Recommendations: USG should become a more significant participant in PDPs. The NIH should consider directing a portion of its extramural funding to the highest-impact PDPs. USAID should expand its role in support of PDPs, including developing new reproductive health technologies (e.g., tools for post-partum hemorrhage), a role that would be a natural fit for USAID’s core mission. Improving USG’s collaborative efforts with the WHO is low hanging fruit that could have a large payoff.

- **Conclusion 3: The declining USG funding for R&D, including global health product development, is an existential threat to the USG’s impact, influence, and credibility within the R&D landscape and jeopardizes the USG’s reputation as a global leader in innovation.** It is no exaggeration to say that falling funding levels have reached crisis point, hamstringing agency efforts and sending a signal to the world that the US may be relinquishing its leadership role.

Recommendations: There has never been a more important time for the advocacy community to make the public health, economic, business, and moral case for USG support for global health R&D. Given the early indications that economic and business interests will dominate the new administration’s approach to global health, there is a time-critical need to document and demonstrate the extraordinary returns to investing in global health R&D. For example, out of every dollar that USG invests in global health R&D, around 89 cents goes to supporting jobs in the US, boosting U.S. research and technological capacity, and providing a direct investment into the US economy.

Strengthening the United States Government's Role in Product Development for Global Health

- **Conclusion 4: BARDA's ecosystem of push and pull mechanisms and the Other Transaction Authority used by BARDA and the Defense Advanced Research Projects Agency to establish long term partnerships with industry have been successful incentive mechanisms.** BARDA's integrated model of push and pull mechanisms, which requires significant funding, has been effective in addressing market failures for a number of conditions. There has been enough flexibility to allow its mandate to be expanded to include AMR, which may have opened the door to finding ways to include additional global health challenges.

Recommendations: Successful incentive mechanisms should be expanded to other diseases and replicated by other agencies and offices. Not all market failures have the same causes, and a BARDA-type model used for different obstacles may need refinement to make it specific to the actual challenge.

- **Conclusion 5: Better leveraging of what is working well is a principle that can also be applied when it comes to the under-use of effective agencies.** In particular, the DoD's medical research capabilities are under-recognized and under-used.

Recommendations: The new Administration has pledged a huge increase in defense spending. While there are certainly risks in the "securitization" of global health (it can be dangerous to conflate the principles of public health with those of national security), this increase may represent an avenue to boost USG support for global health R&D if some of it can be directed to DoD's global health research.

- **Conclusion 6: Although the USG is generally seen as a giant bureaucracy, it has had the foresight to expand its global health R&D remit.** Legislation has been amended and agency mandates have been revised to include additional diseases.

Recommendations: Important lessons could be learned from an analysis of how these shifts happened—for example, who were the key actors involved and what were the levers that allowed change to happen? These lessons could be applied to find other legislative changes to strengthen USG support for global health R&D.

- **Conclusion 7: There is no standard definition of what constitutes global health R&D used uniformly across USG agencies, including the OMB.** USG needs a clear definition and typology of global health R&D, to allow better tracking of funding flows and help drive more explicit prioritization.

Recommendations: A definition and typology should be urgently developed, which would go a long way to enhancing the efforts of researchers, advocacy groups, and the government itself to track funding levels, distributions, and trends. The timing is right for agreeing on such a definition, given that the donor community is currently updating the way that it measures official development assistance to include funding for global public goods, such as global health R&D.

- **Conclusion 8: The future of USG support for global health R&D must include a transition to greater support for developing in-country R&D and regulatory capacity.** This would help with longer term sustainability plans.

Recommendations: In the 2015-2030 Sustainable Development Goals era, an increasing proportion of US development assistance for health that is directed to individual countries should be spent on developing domestic R&D capabilities. Fogarty would be ideally placed to provide leadership for such a strategy.

Strengthening the United States Government's Role in Product Development for Global Health

- **Conclusion 9: Advocacy for global health R&D has an impressive history of success—and will have a particularly important role with the new Administration.** There is an urgent need to continue developing, testing, and refining advocacy efforts to influence major decision makers such as the Congress.

Recommendations: Building an evidence base on “what works” in mobilizing USG support for global health R&D—for example, whether it is emphasizing the number of lives saved or the boost to the US economy—has gained increasing importance given how little is known about the new Administration’s global health commitment. One strategy to consider is to focus on the link between adequate investment in R&D as a critical precursor for the USG to maintain its preeminent position as a global innovator.

Strengthening the United States Government's Role in Product Development for Global Health

Introduction

Over the past two decades, global health has been transformed by increased attention and funding, a rise in the number of global health organizations, economic growth of low- and middle-income countries (LMICs), and the advent of powerful new health technologies. Aid for global health tripled during the “golden decade” of global health (2000-2010), from about \$10 billion to \$30 billion annually, much of it targeted at highly effective infectious disease control initiatives.¹ Many national governments in LMICs increased their focus on health sector improvements, often through increased domestic health financing.² And new technologies became available, including the development and large-scale deployment of highly active antiretroviral medications, long-lasting insecticide-treated bed nets, and artemisinin-based combination therapies for malaria treatment.³

While there has been a dramatic decline in avertable deaths in LMICs, poor populations in LMICs still die disproportionately from potentially preventable and treatable scourges of poverty. These scourges include measles, malaria, tuberculosis (TB), diarrhea, and post-partum bleeding. For example, in 2012, infections and reproductive, maternal, newborn and child health (RMNCH) conditions in LMICs accounted for 34 percent of disability-adjusted life years (DALYs)—the number of “healthy” years that a person lost due to illness—and for 23 percent of total deaths worldwide.⁴ Poor populations are also hit “first and worst” by outbreaks of emerging infections, as seen with the recent Ebola outbreak in West Africa.

While some of these deaths could be averted by improving the delivery of existing medicines, vaccines, and other health tools, new products to address unmet need are also critical. Appropriate tools and technologies may not exist, or existing tools may not account for contextual factors in LMICs that may limit the uptake or use of these innovations. A major barrier to investing in the research and development (R&D) of new products for diseases of poverty is the lack of sufficient incentives and subsequent market failure to produce new technologies for global health diseases and conditions.⁵⁻⁷ The time, cost, technical challenges, and risk of failure during product development create a formidable disincentive to product developers. As a result, research on the regulatory approvals of new drugs and vaccines since 1975 has shown that few of these new products are for neglected diseases of poverty (Table 2).⁸⁻¹¹ The independent research group Policy Cures Research notes that there are 145 “missing” drugs, vaccines, diagnostics, microbicides, vector control agents, and technologies that are needed to reach the health targets in the Sustainable Development Goals (SDGs).¹²

Although the United States government (USG) is the world’s largest funder of global health R&D, the total amount represents a tiny fraction of total USG expenditure, and its funding for global health R&D is in decline. The USG is a major funder of both global health programs and global health R&D. From 2010-2014, it allocated an annual average of just under \$10 billion to improve overall health outcomes in the world’s poorest and most vulnerable populations.¹³ In 2014, it was responsible for about 45 percent of all international funding for neglected disease R&D (\$1.5 billion out of a total of \$3.4 billion).¹⁴ However, this amount of R&D funding is equivalent to less than 0.01 percent of the U.S. national budget and, leaving aside Ebola, the levels of USG funding for global health R&D are falling. Most of the funding is directed toward basic science and early-stage development rather than getting promising products to market, and a number of critically needed products, such as new contraceptives and drugs to treat post-partum bleeding, have received little R&D funding.^{7,15}

This report, commissioned by the Global Health Technologies Coalition (GHTC), aims to identify opportunities for strengthening the USG’s role in supporting global health product development. It does so through a three-step approach:

Strengthening the United States Government's Role in Product Development for Global Health

- First, it examines the *current landscape of USG funding for such R&D*, including funding levels and trends, the comparative role of the different USG agencies in supporting R&D for global health, and the decision-making processes and timelines that influence this support.
- Second, it describes *incentive mechanisms and barriers* to increasing USG funding and coordination of global health R&D.
- Finally, based on the findings from the first two steps, it puts forward an *initial set of ideas on opportunities* for the USG to strengthen its role in the funding and coordination of global health R&D. We aim to further develop and refine these ideas in future research.

The report has seven sections, followed by our conclusions. In *Section 1*, we briefly describe the methods that we used to conduct our study, a combination of a desk review and key informant interviews. In *Section 2*, we provide new data on levels and trends in USG funding for global health R&D. *Section 3* gives a detailed agency-by-agency account of funding, decision-making, and coordination. In *Section 4*, we describe the USG's appropriation and budget process and how these influence support for global health R&D. *Section 5* presents our synthesis of key cross-cutting, cross-agency findings on catalysts and barriers to USG agency support for global health R&D. In *Section 6*, we briefly summarize perspectives of key informants from outside government—specifically, from industry, foundations, and product development partnerships (PDPs)—focusing on how their perspectives diverge from those of the USG key informants. *Section 7* gives the recommendations of key informants for reforms that could improve the way in which the USG supports global health R&D. Finally, we present our nine key conclusions—each accompanied by our recommendations on how USG could strengthen its role in global health product development.

Our chief focus in this report is how USG is supporting product development, rather than the delivery of new or existing health technologies. We recognize that research on development and delivery must go hand in hand for technologies to have an impact in improving global health, and we do touch on this topic in our report. Nevertheless, our remit was to focus to the ways in which the USG is financing and coordinating product innovation for global health.

Table 2. New Therapeutic Products Approved or Recommended by Different Regulatory Bodies, by Disease Category, 2000-2011

	NCE (n=336)	Other New Product (n=420)*	Vaccine or Biological (n=94)†	Total (n=850)
Neglected Diseases				
Malaria	3 (1%)	9 (2%)	0	12 (1%)
Tuberculosis	0	7 (2%)	0	7 (1%)
Diarrheal Diseases	1 (<0.5%)	3 (1%)	3 (3%)	7 (1%)‡
Neglected Tropical Diseases	0	5 (1%)	0	5 (1%)§
Other	0	1 (<0.5%)	5 (5%)	6 (1%)¶
Subtotal	4 (1%)	25 (6%)	8 (9%)	37 (4%)
Other Infectious Diseases	35 (10%)	48 (11%)	66 (70%)	149 (18%)
All Other Diseases	297 (88%)	347 (83%)	20 (21%)	664 (78%)

Source: Table originally published in Pedrique et al (2013)⁹

NCE: new chemical entity

* New indication, new formulation, or fixed-dose combination. † Includes immunoglobulins and other biological products.

‡ For diarrhea, cholera, cryptosporidiosis, and giardiasis. § For human African trypanosomiasis, Chagas disease, and leishmaniasis.

¶ For Japanese encephalitis, hemorrhagic fevers, and snakebite.

Strengthening the United States Government’s Role in Product Development for Global Health

Section 1. How We Conducted this Study

We conducted a desk review of peer-reviewed and grey articles and combined the findings with those from 36 key informant interviews with stakeholders from government, industry, foundations, and PDPs.

DESK REVIEW

We conducted a desk review of relevant English language literature published over the last 10 years. We developed key search terms to identify articles published in English between 2006 and 2016 in PubMed, Embase, and Ebsco Global Health databases; USG databases; and grey literature published by leading global health organizations. The project team also identified additional articles from bibliographies of selected, highly relevant articles. Search terms included: neglected diseases; neglected tropical diseases; global health; individual diseases, such as HIV/AIDS, tuberculosis, and malaria; product or drug development; research and development; financial incentives; global burden; appropriations; and funding. The initial search produced several thousands of articles. We examined article titles and abstracts and used these to select full texts of articles based on relevance to this project. Our final review included 147 full text articles.

KEY INFORMANT INTERVIEWS

We conducted 36 semi-structured interviews with stakeholders from three sectors—the USG, industry, and foundations/PDPs (Table 3)—using one of three interview guides that we developed for this study (one for each sector). We identified key informants through referrals and academic references. Most key informants worked in the United States. Interviews were mostly one-on-one, although we also conducted three group interviews. Several stakeholders provided insights from multiple perspectives, having served both in the public and private sectors in numerous capacities. Figure 2 shows the *guiding framework* for these key informant interviews.

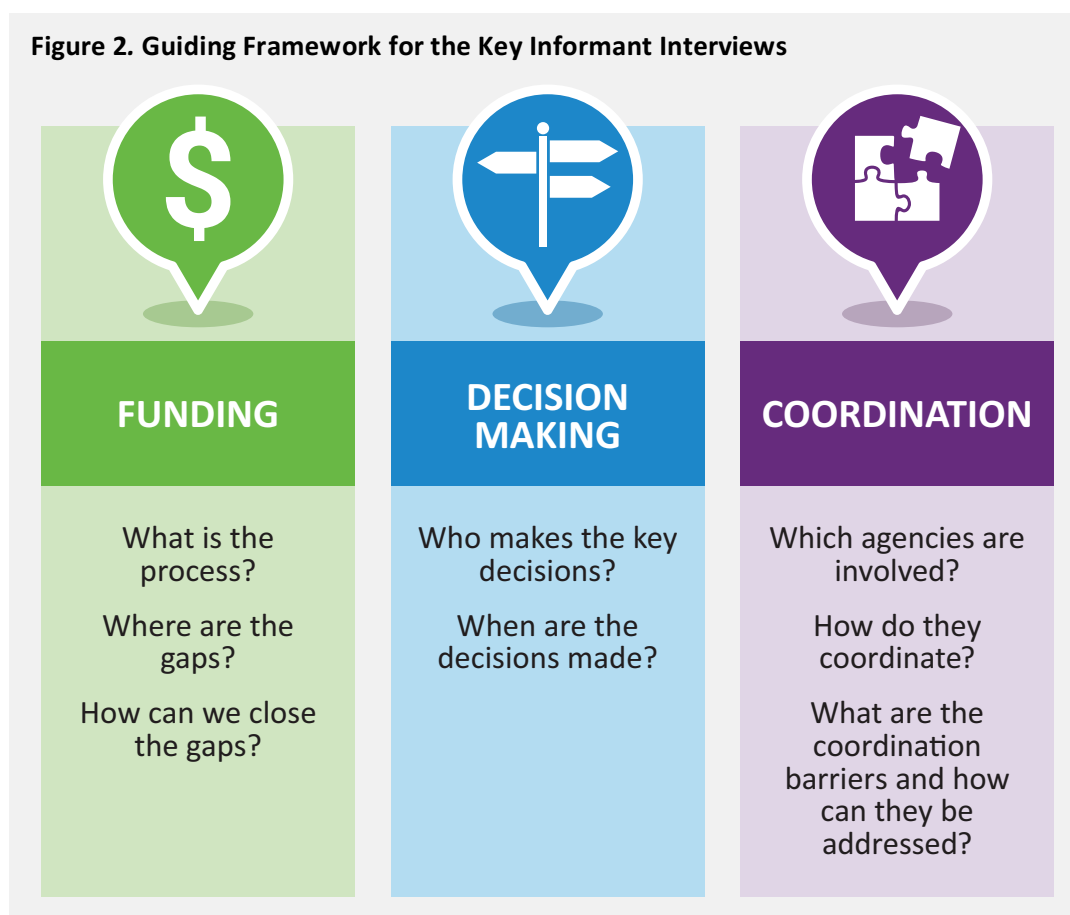
Table 3. Key Informants Interviewed for the Study, by Sector

Sector	No. of Interviews	Institutions
USG	22	HHS (including BARDA), OMB, USAID, NIH, CDC, FDA, State, former representative of DoD
Foundations and PDPs	8	GNNTDs, BMGF, MMV, AAAS, MSF, DNDi, FHI360, Task Force for Global Health
Industry	6	Anacor, Becton Dickinson, Novartis Institute of Tropical Diseases, Sanofi, Gilead, Janssen

Key to abbreviations is found on pages iv-vi of this report.

Strengthening the United States Government's Role in Product Development for Global Health

Figure 2. Guiding Framework for the Key Informant Interviews



DEFINING R&D FOR GLOBAL HEALTH

For this report, “global health R&D” refers to product development for new medicines, vaccines, diagnostics, and other health technologies to tackle a specific list of poverty-related and neglected diseases and conditions. As described below, this list includes mostly infectious diseases and selected reproductive health conditions that disproportionately affect LMICs. In determining which diseases or conditions to include, particularly in Section 2 (on funding levels and trends), we used a combination of: (a) the core list of 34 infectious diseases in the annual Global Funding of Innovation for Neglected Diseases (G-FINDER) report produced by the policy research group Policy Cures Research, (b) Ebola and other African viral hemorrhagic fevers (VHFs), and (c) the list of reproductive health conditions and unmet needs specific to developing countries that were included in G-FINDER’s 2014 *Reproductive Health Report*.¹⁶

Strengthening the United States Government's Role in Product Development for Global Health

Box 1 summarizes the rationale for the inclusion of these diseases in the definition. The term “neglected diseases” in G-FINDER is broader than the World Health Organization (WHO) definition of “neglected tropical diseases”—the WHO definition has just 17 diseases. Some diseases, particularly pandemic influenza and Zika, are *not* included in the G-FINDER definition, and so they are not included in our data on funding levels and trends (Section 2). However, because the USG has supported innovation efforts to control pandemic influenza and Zika, and both diseases were frequently mentioned in key informant interviews, they *are* discussed in other sections of the report.

Our report focuses on product development rather than the delivery or implementation of technologies in the field. The report therefore excludes financing for programmatic activities, such as the delivery of antiretroviral medications or bed nets to prevent malaria transmission.

Box 1. Definition of Global Health R&D Used in Our Report

This report uses the term “global health R&D” to refer to product development for a list of diseases and conditions included in the G-FINDER surveys produced by Policy Cures Research. As described by Policy Cures Research, the disease or condition has to meet the following criteria to be included in the list:

- “(1) Disease morbidity and mortality disproportionately affect people in developing countries; AND
- (2) There is no existing product to treat/prevent that disease, OR a product exists but is poorly suited for developing country use; AND
- (3) There is no commercial market to stimulate R&D by industry.”¹⁷

The core set comprises HIV/AIDS, tuberculosis, and malaria; diarrheal diseases; kinetoplastids (leishmaniasis, sleeping sickness, and Chagas disease); worms and flukes; dengue; bacterial pneumonia and meningitis; Salmonella infections; hepatitis C genotypes 4, 5 and 6; leprosy; trachoma; cryptococcal meningitis; Buruli ulcer; leptospirosis; and rheumatic fever.

In addition to the core set of diseases, we have included Ebola and other African viral hemorrhagic fevers (VHFs), and the reproductive health needs of developing countries, as defined by Policy Cures Research: post-partum hemorrhage, contraception, syphilis, and other sexually transmitted infections.

Section 2. Levels and Trends in USG Funding for Global Health R&D

This section summarizes the most recently available, high-quality survey data on how much the USG invests in global health product development; which diseases and which types of research receive the most funding; and how levels of funding have changed in recent years. The data on R&D funding for infectious neglected diseases, including Ebola and other African viral hemorrhagic fevers (VHFs), are taken from the G-FINDER survey, covering the period 2007-2015. Data on reproductive health funding were collected as a supplement to the G-FINDER survey, and were only available for 2013 and 2015. Any analysis comparing the USG with the rest of the world, analysis of trends over time, or analysis of investment focus by product type exclude funding for reproductive health R&D. Furthermore, as noted in prior G-FINDER surveys, funding is generally difficult to track because agencies lack specific budget line items for global health R&D.

Throughout Section 2, the funding data refer *only* to product development. The data do not include other types of R&D (such as implementation or operations research).

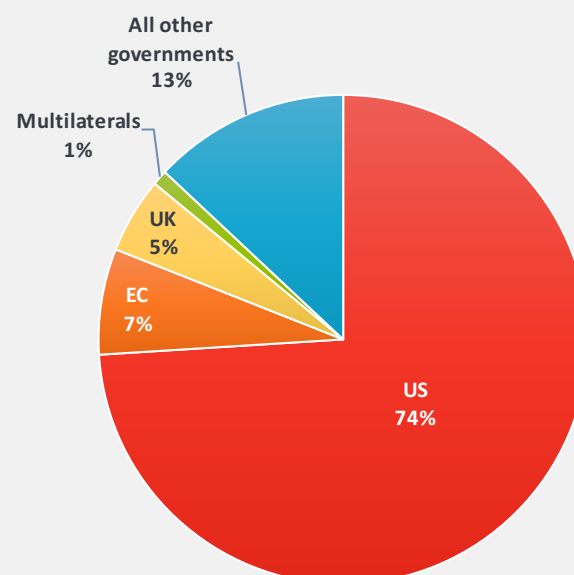
HOW MUCH DOES THE USG INVEST IN GLOBAL HEALTH PRODUCT DEVELOPMENT?

The USG is by far the most significant funder of global health product development globally. Since 2007, it has invested \$13.9 billion in R&D to deliver new global health technologies. This was nearly 13 times greater than the contribution of the second biggest government funder over the same period (the United Kingdom, with \$1.1 billion). It was also close to half (48 percent) of total global funding from all sources.

In 2015, the USG invested \$1.7 billion in global health product development (Figure 1). Of this amount, \$1.4 billion (83 percent) was for neglected diseases (as defined by the 2016 G-FINDER report), \$276 million (16 percent) was for Ebola and other African VHFs, and the remaining \$10 million (one percent) was for reproductive health technologies designed to meet the needs of LMICs.

The USG's \$1.7 billion investment represented three-quarters (74 percent) of all government funding worldwide in 2015 (Figure 3). The next largest government funder in 2015 was the European Commission, which provided \$171 million.

Figure 3. Government Funding for Global Health R&D, 2015



Abbreviations: EC: European Commission, UK: United Kingdom, US: United States.

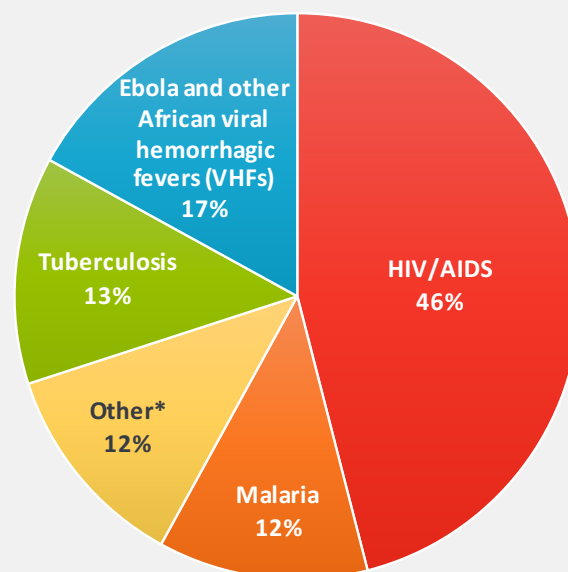
Source: authors' own analysis based on data from G-FINDER 2016

Strengthening the United States Government's Role in Product Development for Global Health

WHAT DOES THE USG FUND?

The primary focus for USG funding for global health R&D is HIV/AIDS, reflecting the unprecedented challenge that this emerging disease presented and the need for ever-improving drug treatments (antiretroviral therapies), diagnostics, and preventive technologies. USG funding for product development for HIV/AIDS is now heavily focused on vaccine development and basic research. The disease has consistently received around 55 percent of USG neglected disease R&D funding in each of the last nine years. HIV/AIDS still accounted for 45 percent of USG funding for all global health R&D in 2015 (Figure 4), despite the fact that 2015 funding levels included significant new funding for Ebola and other African VHFs. Table 4 gives a summary of USG funding for 2015 by disease, main type of research, and key agencies involved.

Figure 4. USG Funding for Global Health R&D in 2015 by Disease



Source: authors' own analysis based on data from G-FINDER 2016

*Other: other neglected diseases and reproductive health

Strengthening the United States Government's Role in Product Development for Global Health

Table 4. USG Funding in 2015 for Global Health Product Development, by Disease—Showing Primary Investment Areas and Key USG Agencies Involved

Disease Category	Total (millions) 2015 ^a	Share of Total USG R&D Spending (%) 2015 ^a	Primary Investment Area (2015)	Total (millions) 2014 ^b	USG Funding as % of Total Global R&D Spending for the Specific Disease or Condition ^b	USG Agencies Funding Product Development (2015) ^{a,c}				
						NIH	DOD	USAID	CDC	BARDA
HIV/AIDS	\$753.8	45.0%	Vaccines	\$792.8	73.4%	X	X	X	X	
Ebola and Other African Viral Hemorrhagic Fevers (VHFs)	\$275.5	16.5%	Drugs	\$100.6	60.0%	X	X		X	X
TB	\$217.7	13.0%	Basic research	\$323.2	35.5%	X		X	X	
Malaria	\$194.5	11.6%	Basic research	\$177.9	29.2%	X	X	X		
Dengue	\$46.7	2.8%	Basic research	\$40.5	45.8%	X	X		X	X
Diarrheal Diseases (Cholera, Shigella, rotavirus, etc.)	\$44.6	2.7%	Basic research	\$180.0	46.4%	X	X			
Kinetoplastids (Chagas, leishmaniasis and human Africa trypanosomiasis)	\$38.6	2.3%	Basic research	\$41.6	27.9%	X	X			
Helminth Infections (soil-transmitted helminths, lymphatic filariasis, onchocerciasis, schistosomiasis)	\$28.4	1.7%	Basic research	\$31.1	32.0%	X	X			
Salmonella Infections	\$28.2	1.7%	Basic research	\$30	44.4%	X				
Hepatitis C Genotype 4	\$4.6	0.3%	Vaccines	\$6.5	16.3%	X				
Trachoma	\$4.6	0.3%	Vaccines	\$6.4	93.4%	X				
Leprosy	\$4.2	0.3%	Basic research	\$5.6	52.7%	X				
Cryptococcal Meningitis	\$3.5	0.2%	Drugs	4.1	71.2%	X				
Bacterial Pneumonia & Meningitis	\$1.2	Less .1%	Vaccines	\$2.1	2.7%	X				
Rheumatic Fever	\$1	less 0.1%	Vaccines	\$.5	37%	X				
Leptospirosis	\$.3	less 0.1%	Diagnostics	\$.3	20.7%	X				
Buruli Ulcer	N/A	N/A	N/A	\$4.1	NA					

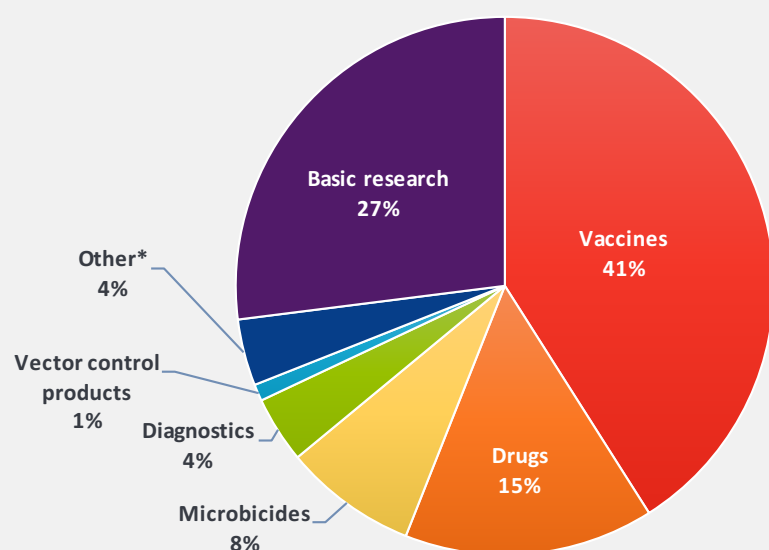
^a Data from G-FINDER 2016, ^b Data from G-FINDER 2015, X = funds R&D (as defined by G-FINDER), ^c It is important to note that agencies also invested significantly in global health research not related to the development and introduction of new health technologies (such as program effectiveness evaluation and other health systems research), which is outside the scope of the G-Finder analysis. For example, while USAID did not provide any product development funding in 2015 for Ebola/VHF R&D, the agency contributed to program delivery on the ground and related evaluation research.

Strengthening the United States Government’s Role in Product Development for Global Health

The presence of existing R&D programs in Ebola and other African VHFs—coupled with the authorization of emergency funding—allowed the USG to rapidly mobilize significant R&D resources in response to the 2014 West African Ebola outbreak. G-FINDER only started tracking investment in Ebola R&D in 2014 (and only expanded this category to include other African VHFs in 2015). The estimated annual USG investment in R&D for Ebola and other African VHFs prior to 2014 was only around \$5-10 million per year—representing less than one percent of annual USG funding for global health R&D, or about the same amount it invested in leprosy R&D. In 2015, the USG invested \$275 million in Ebola and other African VHFs, making VHFs the second highest funded disease category after HIV/AIDS, ahead of malaria and TB.

Basic research and vaccine development collectively accounted for just over two-thirds (68 percent) of all USG funding for global health R&D in 2015, with vaccine development (41 percent) receiving by far the largest share (Figure 5). The influx of VHF funding in 2015 did little to change the long-term averages in the breakdown of spending (e.g., basic research continued to receive just over a quarter of all funding). The picture for VHFs alone was different: with a focus on rapidly advancing existing candidates through the pipeline, basic research accounted for just 12 percent of all USG funding for VHF R&D, while vaccines and drugs accounted for around a quarter each.

Figure 5. USG Funding for Global Health R&D in 2015 by Type of Research



Source: authors' own analysis based on data from G-FINDER 2016

*Other: other neglected diseases and reproductive health

Given that 80 percent of USG funding for product development goes to the NIH (see Section 3), it is perhaps not surprising that the USG directs twice as much funding to basic and early stage research than it does to late-stage (clinical) product development. As described in Section 3, the only agency to invest more in clinical development than basic and early stage research is USAID. However, USAID funding has only a minimal impact on the overall picture, given that USAID is responsible for just five percent of all USG funding for global health R&D.

Strengthening the United States Government's Role in Product Development for Global Health

RECENT TRENDS IN USG FUNDING

USG funding for global health R&D in 2015 was the highest ever recorded—but a surge in funding for Ebola and other African VHFIs hid a large decline in funding for other neglected diseases (this trend analysis excludes investment in reproductive health R&D, which was only collected for 2013 and 2015). Two key events have shaped USG funding for global health R&D since 2008: the ‘great recession’ of the late 2000s and the 2014 West African Ebola outbreak. Stimulus spending by the USG in response to the financial crisis—most notably under the American Recovery and Reinvestment Act of 2009—led to a sharp increase in USG funding for global health R&D, which totaled \$1.65 billion in 2009. The 2014 Ebola outbreak elicited a similarly robust response, pushing USG 2015 funding for global health R&D to \$1.66 billion (Figure 1); this was not only its biggest annual contribution since 2009, but also the largest ever recorded.

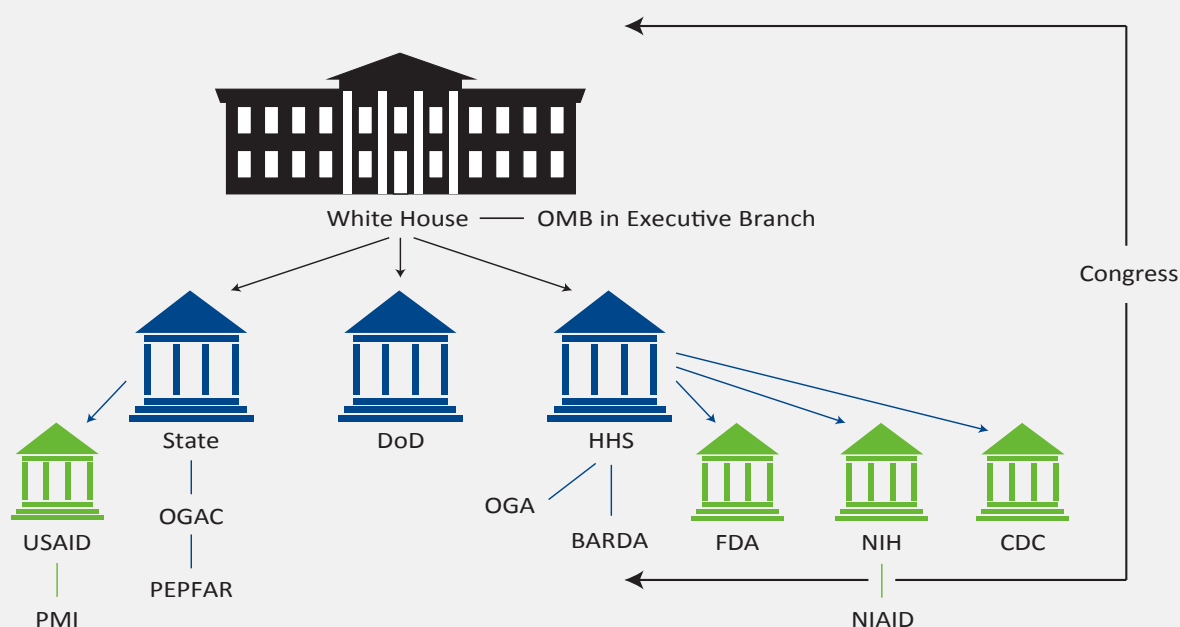
There has been a remarkable mobilization of R&D funds in response to the Ebola threat. From negligible levels prior to 2014, USG funding for R&D to tackle Ebola and other African VHFIs topped \$275 million in 2015. This amount is more than the USG invested in any other disease except HIV/AIDS. However, the surge of funding for Ebola is a one-time, emergency appropriation, not sustainable, annually appropriated funds.

In contrast, USG funding for global health product development has been falling steadily since its 2009 peak. Adjusted for inflation, annual USG investment in such product development has fallen in every year but one since 2009 (Figure 1) and is now more than a quarter of a billion dollars below its 2009 peak (down \$263 million, or a reduction of 16 percent).

Section 3. USG Agencies: Global Health R&D Funding, Decision-making, and Coordination

In this section, we focus on those US agencies that play the most important role in global health R&D as well as the White House Office of Management & Budget (OMB). We report 2015 funding levels for the largest funders of global health R&D. We describe how decisions on global health R&D funding are made within each agency and the ways in which agencies coordinate with each other, and with organizations outside the USG, in the research enterprise. Figure 6 shows the agencies that are the main focus of discussion in our report and Figure 7 shows the share of funding by agency.

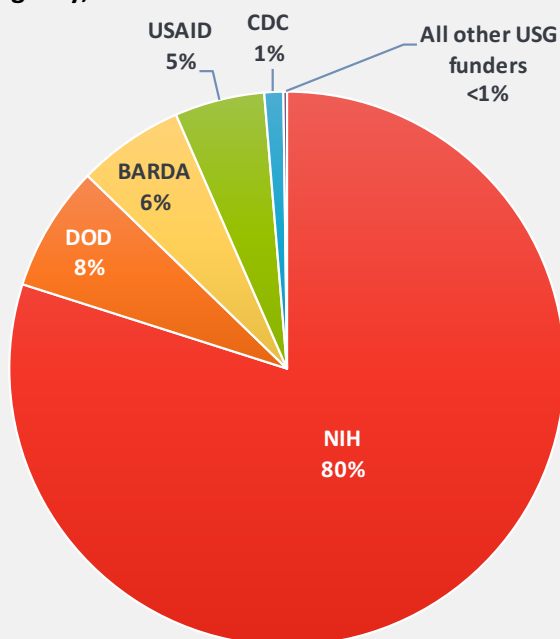
Figure 6. USG Departments, Agencies, Offices, and Institutes with a Key Role in Supporting Global Health R&D



Abbreviations: BARDA: Biomedical Advanced Research and Development Authority, CDC: Centers for Disease Control and Prevention, DoD: Department of Defense, FDA: Food and Drug Administration, HHS: US Department of Health and Human Services, NIAID: National Institute of Allergy and Infectious Diseases, NIH: National Institutes of Health, OGA: Office of Global Affairs, OGAC: Office of the U.S. Global AIDS Coordinator and Health Diplomacy, PEPFAR: The US President's Emergency Plan for AIDS Relief, PMI: President's Malaria Initiative, USAID: US Agency for International Development. Source: adapted from a figure by the Global Health Technologies Coalition¹⁸⁵

Strengthening the United States Government’s Role in Product Development for Global Health

Figure 7. USG Funding for Global Health R&D by Agency, 2015



Source: authors' own analysis based on data from G-FINDER 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The primary focus of the Department of Health and Human Services (HHS) is to enhance and protect the health and well-being of the US population but many of the Department's centers and offices play a significant role in global health R&D. The four most important for global health R&D, which we focus on below, are the *Biomedical Advanced Research and Development Authority* (BARDA), the *National Institutes of Health* (NIH), the *Centers for Disease Control and Prevention* (CDC), and the *Food and Drug Administration* (FDA). HHS also leads the *National Vaccine Program Office* (NVPO), which plays a role in global immunization efforts.¹⁸ The NVPO encourages collaboration and coordination among federal agencies to reduce the burden of vaccine-preventable disease, including through the development, production, and procurement of vaccines.¹⁹ In collaboration with the *National Academy of Medicine* (NAM), the office is currently developing a software tool to help prioritize vaccine development efforts (the *Strategic Multi-Attribute Ranking Tool for Vaccines*).²⁰

The main office overseeing global health in HHS is the *Office of Global Affairs* (OGA), a policy and coordination office that identifies overseas challenges and opportunities; while it is not specifically mandated to engage in research, it is engaged in several global health R&D activities.²¹ For example, it has facilitated product development collaborations with China, India, Mexico, and South Africa; it has worked closely with WHO's Consultative Expert Working Group on Research and Development: Financing and Coordination; and it co-chairs, along with the European Union (EU), the *Trans-Atlantic Taskforce for Antimicrobial Resistance*, whose mandate includes developing "strategies for improving the pipeline of new antimicrobial drugs."^{22,23}

Strengthening the United States Government's Role in Product Development for Global Health

Biomedical Advanced Research and Development Authority

Overview and Funding Levels

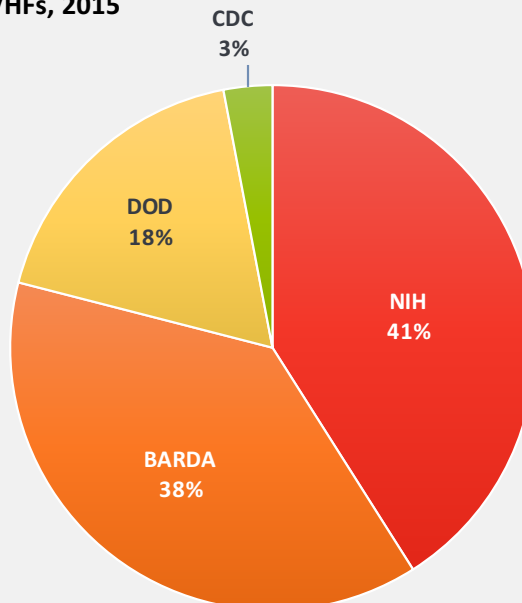
BARDA leads USG civilian R&D on medical countermeasures (MCMs), including “vaccines, therapeutics, diagnostics, and non-pharmaceutical countermeasures, against a broad array of [domestic] public health threats, whether natural or intentional in origin.”²⁴ It was established under the Pandemic All-Hazards Preparedness Act of 2006 and is housed in HHS’ Office of the Assistant Secretary for Preparedness and Response.²⁵ It is headed by the Office of the Director. In FY2016, BARDA’s budget for MCMs was \$1.3 billion, out of which \$521.7 million was earmarked for advanced R&D of 12 high-priority threats identified by the Department of Homeland Security. These threats include anthrax, Ebola and other VHF, radiation, and chemical exposure.²⁶ As described below, only a small fraction of this funding is relevant to global health R&D.

BARDA does not have a clear mandate to engage in R&D for health technologies targeting the needs of LMICs and thus was not a major player in supporting global health R&D for conditions of LMICs until the 2014 West African Ebola outbreak. In 2015, its investments in Ebola and other VHF made BARDA the third largest USG funder of global health R&D. This was due to one-time, emergency funding. Without similar funding in the future, it is unclear whether BARDA will continue to play a role in funding global health product development. In 2015, BARDA invested \$104 million in R&D for Ebola and other African VHF, providing 6 per cent of total USG funding for global health R&D. BARDA was therefore the third largest funder of global health R&D behind only NIH and DoD. All of BARDA’s global health R&D funding in 2015 was for Ebola and other African VHF. Figure 8 shows the contribution of BARDA to R&D for Ebola and other African VHF compared with that of other USG agencies.

Stakeholders described BARDA as the only civilian agency primarily focused on late stage R&D for medical products.^{27,28} These products are aimed at tackling pandemic influenza, emerging infectious diseases (EIDs), and chemical, biological, radiological, and nuclear agents.²⁸

BARDA helps to address gaps in the USG’s development and procurement process for MCMs and to bridge the “valley of death” that separates candidates identified in early research from potential FDA licensure/approval. It does so by providing “funding, technical support, and services necessary to advance candidate products through the developmental pipeline.”²⁴ This work is undertaken under seven program divisions at BARDA: Chemical, Biological, Radiological and Nuclear (CBRN)

Figure 8. USG Funding for Ebola and Other African VHF, 2015



Source: authors’ own analysis based on data from G-FINDER 2016. Note: USAID (and CDC/DoD) is funding Ebola R&D through the Ebola Grand Challenge initiative. However, this funding is for interventions such as field treatment facilities and personal protective equipment, which are outside the scope of our analysis (our analysis focuses on product development: new drugs, vaccines, and diagnostics, as well as basic research).

Strengthening the United States Government's Role in Product Development for Global Health

Countermeasures; Influenza; Strategic Science and Technology; Manufacturing, Facilities, and Engineering; Regulatory and Quality Affairs; Clinical Studies; and Modeling.²⁹

Global Health R&D Funding Decisions

BARDA's internal budgeting and budgets are driven largely by its 5-year strategic plan, first developed in 2007 and then updated in 2011. The plan is drafted in alignment with the priorities of the Administration, the Office of the Assistant Secretary for Preparedness and Response, and BARDA leadership. BARDA is charged by statute with "directing and coordinating the countermeasure and product advanced research and development activities" of HHS.²⁹

BARDA considers several guiding principles when establishing its R&D budgetary priorities. Aside from supporting the development of products to combat the 12 high-priority threats discussed above, principles driving investment include (i) engaging in public-private partnerships, (ii) supporting the development and use of adjuvant platforms to enhance currently licensed products, and (iii) prioritizing multipurpose products. As an example, BARDA will support the development of candidate antimicrobials, but only as long as private sector partners support the development of these products for biodefense threat agent indications.²⁹

Stakeholders indicated that BARDA's three-step model for product development is an attractive ecosystem to incentivize companies to develop products in the absence of significant commercial profit. The three components of the model are:

- Advanced ("push") R&D funding to help products cross "the valley of death" once they enter the clinical trials phase,
- Procurement funds or a promise to purchase products ("pull" incentives) to develop stockpiles, and
- Technical assistance and infrastructure support, which provides access to animal model/clinical study networks, manufacturing facilities, and regulatory support.

Although not specific to the global health diseases and conditions that we focus on in this report, with BARDA support, 23 products have reached FDA approval and 18 new products have entered the strategic national stockpile.^{30,31} This success is seen as being due to the combination of direct funding support for R&D, partnering with industry on product development, and providing technical assistance.³¹

An initial ten-year appropriation commitment, with the USG as a monopsony single purchaser, established BARDA's *Project BioShield*, a procurement fund (pull mechanism) for CBRN threats (e.g., smallpox vaccine development).³² This commitment was made through the Project BioShield Act, which authorized the appropriation of up to \$5.6 billion from FY2004 to FY2013 in a special reserve fund. Subsequent Congresses rescinded or transferred \$2.3 billion (over one-third) from this advance appropriation.³³ Key informants argued that the recent shift to annual appropriations has weakened the project.

In FY2016, Project BioShield was allocated \$646.4 million to support R&D and to procure seven new MCMs against CBRN agents, including Ebola vaccines. An additional \$166.0 million was allocated for U.S. and global efforts to plan for and fight pandemic influenza and emerging infectious diseases.²⁶

Strengthening the United States Government's Role in Product Development for Global Health

Global Health R&D Coordination

BARDA is charged by statute to coordinate with others; its role is to promote “collaboration and communication between the USG and parties interested in the advanced development and licensure of needed medical countermeasures.”²⁹ It works with manufacturers and the NIH, CDC, FDA, DHS, DoD, and to a lesser extent USDA and Veterans Affairs, to guide the transition between early preclinical development through later stage development. For example:

- BARDA has developed a collaborative relationship with FDA to enhance flexibility and ensure regulatory processes run smoothly by working with groups on the unique challenges of MCMs.
- It also works with the CDC to develop concepts of operations and clinical use guidelines and to ensure that the CDC’s stockpile is ready to receive products.
- One of BARDA’s guiding principles specifically lays out the importance of ensuring that it integrates its portfolio with the DoD to optimize the use of resources.

BARDA has adopted an intensive approach to project, program and portfolio management called a “case management” matrix organizational structure. The structure ensures that intra- and inter-agency stakeholders are kept informed about progress and challenges throughout the course of product development (e.g., establishing cost and schedule metrics for each phase of development, allowing USG stakeholders to be aware of long-term budgetary implications). It also provides an opportunity for collaborators to identify and share best practices and hopefully intervene when things are not going well.

BARDA is one component of a broader public health collaborative effort led by the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE).³⁴ PHEMCE brings together leaders from NIH, DoD, CDC, FDA, the US Department of Veterans Affairs, and the US Department of Agriculture to overcome barriers encountered across the product development cycle for VHFs, pandemic influenza, and other threats. It is run by the Assistant Secretary for Preparedness and Response within HHS.

BARDA provides support to the WHO to improve global vaccine production capacity in developing countries, including through supporting training courses.³⁵ Its initial vaccine production training course included 16 participants from seven countries (Egypt, Romania, Russia, Serbia, South Korea, Thailand, and Vietnam).

BARDA is a key actor in a new public-private push mechanism, called Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). BARDA’s partners are the NIAID, the Wellcome Trust, the Massachusetts Biotechnology Council (MassBio), and the California Life Sciences Institute. CARB-X is a product accelerator aimed at tackling antibiotic resistance, focusing on preclinical discovery and development of new antimicrobial products.^{36,37} It is currently working to establish a diverse portfolio with more than 20 high-quality antibacterial products.

National Institutes of Health

Overview and Funding Levels

The mission of the NIH is to conduct scientific research to improve population health. The agency’s mandate is to conduct basic research; it is neither a directive agency nor a product development agency. The NIH relies on the best ideas of its scientists—a “bottom up” approach in which scientists determine the research rather than being told in a “top down” way what to study. As a result, NIH scientific priorities may not translate to developing products for LMICs. The Office of the Director is responsible

Strengthening the United States Government's Role in Product Development for Global Health

for policy setting for NIH and also coordinates and manages the various programs of the NIH's 27 institutes and centers.³⁸ Together these institutes and centers support the full continuum of biomedical research from basic research, pre-clinical trials, clinical research, post-clinical translational research to research on clinical and community practice.³⁹ During the financial year 2016 (FY2016), the NIH had a total budget of \$32.3 billion, up from \$30.4 billion in FY2015.⁴⁰

The NIH is by far the largest contributor to global health R&D out of all the USG agencies. Its 2015 investment of \$1.3 billion represented 80 percent of USG funding for that year. It spent about 4.3 percent of its overall budget on global health R&D in 2015. The NIH has provided 86 percent of all recorded USG funding for global health R&D since 2007.

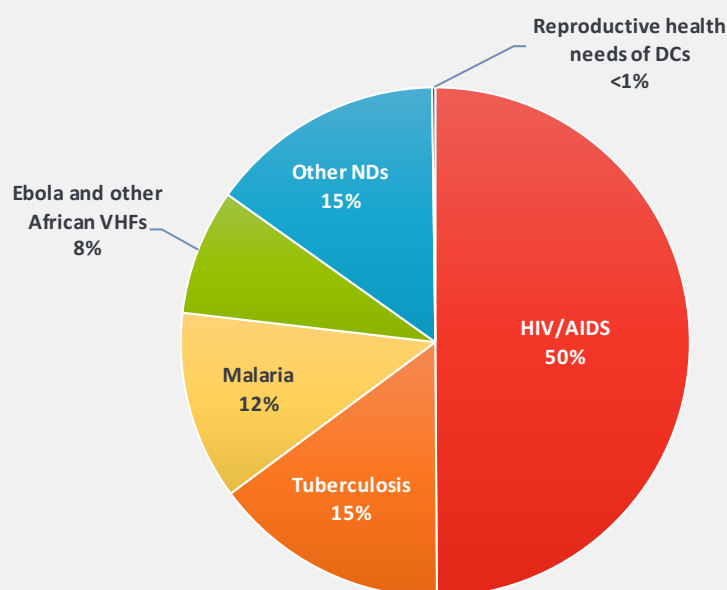
Given its dominance as a funder, the disease focus of the NIH looks very similar to that of the USG overall (Figure 9). Half of all NIH global health R&D funding in 2015 was for HIV/AIDS (\$664 million, 50 percent). The “big three” diseases (HIV/AIDS, TB, and malaria) together accounted for three-quarters of such funding (\$1.0 billion, 76 percent). About three quarters (74 percent) of the funding that could be allocated (i.e., allocable funding, which excludes unspecified funding) was for basic and early stage research. The largest share (41 percent of funding) was for vaccine development, with just 11 percent for drugs, seven percent for microbicides, and four percent for diagnostics.

Funding for Ebola and other African VHFs (\$113 million) accounted for eight percent of total NIH investment in global health R&D in 2015. While this is a relatively small fraction of NIH support, the absolute amount was large enough to make NIH the major funder of R&D for Ebola and other VHFs among all the USG agencies, contributing 41 percent of the USG total.

NIH funding for R&D on other neglected diseases follows a similar pattern: although these diseases receive only a minor share of total NIH funding, the NIH is generally among the top global funders for most of these diseases. Indeed, NIH is the most significant USG funding agency for every area of global health R&D except reproductive health needs in developing countries.

Key NIH institutes or centers that deal with global health R&D are the Office of AIDS Research (OAR), the National Institute of Allergy and Infectious Diseases (NIAID), the Fogarty International Center, and the National Center for Advancing Translational Sciences (NCATS).

Figure 9. NIH Funding in 2015 for Global Health R&D by Disease



Source: authors' own analysis based on data from G-FINDER 2016. NDs: neglected diseases, DCs: developing countries

Strengthening the United States Government's Role in Product Development for Global Health

- The *OAR*, which has requested a budget of \$62.25 million for FY2017, coordinates all aspects of the NIH's domestic and global HIV research and produces the annual trans-NIH AIDS research budget together with the NIH Director.
- The *NIAID* provides scientific leadership, policy guidance, and overall operational and administrative coordination to the various extramural and intermural divisions focusing on basic research for HIV/AIDS, infectious diseases and allergy, immunology, and transplantation.⁴¹ NIAID's other mandate is to provide a research response in an emergency, so it must have flexible dollars readily available in order to respond. Stakeholders indicated there is no precise means to determine exactly how much funding is allocated for flexible purposes as there are diverse ways to fund urgent needs. NIH's intramural program is one mechanism that allows for greater agility in changing research directions. In FY2016, NIAID received \$4.615 billion, or the second largest budget of NIH centers and institutes.⁴²
- The *Fogarty International Center* builds international partnerships to facilitate basic, clinical, and applied research and training in global health by both US and international investigators.⁴³ It is one of the most poorly funded of the NIH institutes or centers, receiving a budget of just \$70.11 million in FY2016.⁴⁴
- The mission of the *NCATS* is to enhance translational research by catalyzing innovations in technology that will improve the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions, including neglected diseases in LICs and MICs. The center's approach is known as "the 3Ds" – *developing* new approaches, technologies, resources, and models; *demonstrating* their usefulness; and *disseminating* the data, analysis, and methodologies to the community. A recent example of an NCATS global health R&D project was the screening of a huge collection of approved and investigational malaria drugs to identify promising antimalarial drug combinations. The center had a budget of \$ 685.41 million for FY2016.⁴⁵ Although NCATS has a program on therapeutics for rare and neglected diseases, to date this has focused much more on rare diseases in the US rather than neglected diseases of LMICs. Overall, the role of NCATS in global health R&D has been modest.

Nearly 90 percent of NIH funding is dedicated to extramural research that funds other academic and research institutions. This prioritization limits the NIH's role in product development for global health, as such product development is more likely to happen in PDPs and industry than in academic settings.

NIH's diverse peer-reviewed grant and contract funding mechanisms are viewed as an organizational strength by USG stakeholders. NIH typically funds only about 17 percent of the proposals it receives. The current Director has stated that the fraction of proposals worthy of funding is closer to 50 percent, meaning that a lot of potentially innovative and groundbreaking ideas that could lead to product development are left unfunded.⁴⁶

NIH does leverage several programs, including the Small Business Innovation Research (SBIR) program and Cooperative Research and Development Agreements (CRADAs), to support commercialization of NIH-funded products and translate research into new products.⁷ NIH also receives funding as an implementing partner of PEPFAR.¹³

Global Health R&D Funding Decisions

NIH's funding allocations rely on a "bottom-up" approach, whereby the centers and institutes rely on the submission of competitive peer-reviewed grant applications to generate the best ideas, although when necessary, there is also flexibility to respond in a "top-down" way for urgent needs. Stakeholders

Strengthening the United States Government's Role in Product Development for Global Health

noted that historically, the NIH has been able to pivot to areas where there is an urgent need, as was the case for bioterrorism preparedness after 9/11 and Ebola, or where there is an opportunity for transformative research. However, it is getting increasingly difficult to do so with current funding trends. When addressing urgent needs, stakeholders described funding allocations as “top-down”—calls for applications are issued after consultation with scientists and with the Council of Advisors, which gives overall input to the NIH Director.⁴⁷ The NIH Advisory Councils have a prominent role in the budgetary process. Institutes may also individually adjust their funding allocations in response to what other private or government counterparts (e.g., the Bill & Melinda Gates Foundation, the UK’s Medical Research Council) are doing to proactively develop underfunded research areas, as was the case for drug-resistant TB.⁴⁸ Additionally, Institutes try to stay attuned to policy issues and have been known to shift funding priorities, as was the case for HIV/AIDS research in the wake of pressure from vocal advocacy groups.

While NIH funding decisions are typically research driven, at times Congress does earmark funding for specific priorities. This has included targeted funding for early stage, innovative product development and partnerships with industry. Stakeholders noted that the research areas of these earmarks have generally been broad and that NIH earmarks have historically been limited in number. Largely scientists have been “left alone when it comes to congressional earmarks,” and can determine through scientific merit how the funds should be spent. Challenges arise when congressional report language does not increase funding but is directive about priorities because that results in reducing funding elsewhere.

The underlying mission and mandate of the NIH, and its focus on extramural funding, are factors in why funding is directed mostly at basic and vaccine research. Key informants within the USG gave a number of explanations for why only a small proportion of NIH funding is directed towards translational research, including:

- There is a conscious effort on behalf of the NIH to distance itself—to maintain an arm’s length—between the use of public funds and any perception of supporting one specific aspect of the private sector. Congress might not appropriate the funds if these were viewed as being for product development.
- Funding basic research within academic institutions, seen as the nexus of scientific discovery, is a major thrust of NIH funding. The academic institutions also exert strong influence over their congressional representatives.

Global Health R&D Coordination

The NIH has a variety of formal and informal collaborations within and across agencies and with external partners; key informants argued that strengthening these existing arrangements is preferable to trying to “force” new collaborations. Stakeholders argued that trying to push or force agencies to collaborate does not always work and often depends on the personality of the individuals in leadership positions. They argued that there were already several successful collaborations that could be built upon (Table 5).

Strengthening the United States Government's Role in Product Development for Global Health

Table 5. Examples of Successful Global Health R&D Coordination Between the NIH and Other Federal and Non-federal Agencies

Type of Collaboration	Examples
Federal Interagency Collaboration	<ul style="list-style-type: none"> NIAID has a governance role in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), which coordinates federal efforts to prepare for chemical, biological, radiological and nuclear threats and emerging infectious diseases. PHEMCE's efforts include supporting R&D for pandemic influenza and VHF (e.g., Ebola, Marburg). NIAID and the National Cancer Institute both participate in the National Interagency Confederation for Biomedical Research, a biotechnology and biodefense partnership across US federal agencies. The Deputy Director for Clinical Research and Special Projects at NIAID liaises with the Department of Defense and Homeland Security. This work comes at the directive of the NIAID Director, often as a result of interagency and interdepartmental forums. Funds for special projects, such as Ebola, come from either reserved funds or supplemental appropriations.
Collaboration with Foundations	<ul style="list-style-type: none"> Multiple institutes meet with the Bill and Melinda Gates Foundation (BMGF) in formal, high level meetings at least twice a year, with numerous phone interactions throughout the year down to the scientist manager level. NIAID has many seats at the table because infectious diseases are a high priority for BMGF. These meetings provide a forum to discuss funding priorities and to avoid duplication of effort. NIAID coordinates informally with the Wellcome Trust and, to a lesser extent, with other foundations.
Collaboration with Industry and Academia	<ul style="list-style-type: none"> NIH investigators can collaborate with industry and academic partners through CRADAs, agreements between a federal laboratory and a non-federal party for conducting specified R&D.^{49,50} The purpose of CRADAs is "to make Government facilities, intellectual property, and expertise available for collaborative interactions to further the development of scientific and technological knowledge into useful, marketable products."⁵⁰

Centers for Disease Control and Prevention

Overview and Funding Levels

The CDC's mission is to protect the US from health, safety, and security threats, both foreign and within the US. As the USG's federal public health agency, CDC conducts research to detect and respond to emerging health threats and develops technologies to detect, prevent, and respond to diseases. It also promotes healthy and safe behaviors and provides training to the public health workforce.⁵¹ In this role, it must be able to generate data to inform and provide technical expertise. The CDC's expertise, especially in implementation science, helps to influence decisions both within and outside the USG. CDC provides guidance from data obtained through its surveillance arm and works with partners to identify what products are needed and to develop interventions, emphasizing point of care diagnostics. For example, it is attempting to create effective multi-target diagnostic assays, which simultaneously detect several infectious agents in a single clinical specimen, to increase efficiency.⁵² CDC is led by the Office of the Director.

Strengthening the United States Government's Role in Product Development for Global Health

CDC provided \$18 million in funding for global health R&D in 2015 (1% of USG funding), almost entirely comprised of funding for TB (\$9 million, 48 percent) and Ebola and other African VHFs (\$8 million, 45 percent) (Figure 10). Although total CDC funding for global health R&D in 2015 was essentially unchanged from the previous year, this hid a halving of its funding for neglected disease R&D (which fell by \$9 million), with new investment in VHFs (up by \$9 million) taking its place.

Key CDC institutes or centers that impact global health R&D are the Center for Global Health (CGH) and the Office of Infectious Diseases. The office houses the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) and the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP).

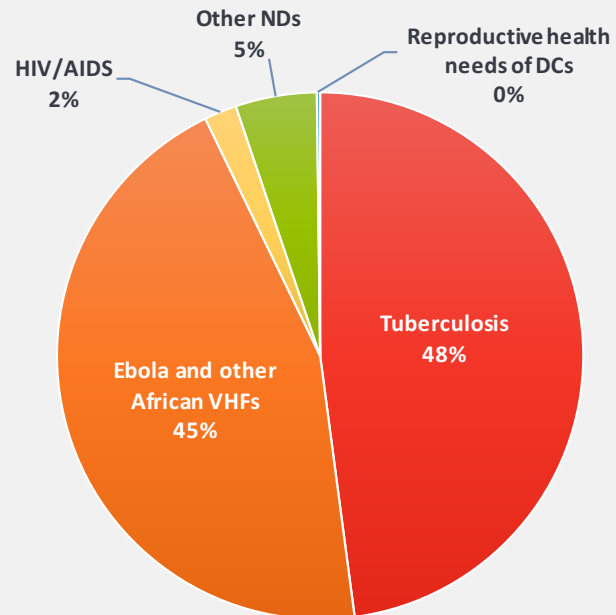
- The CGH's mission is to protect and improve health globally through science, policy, partnership, and evidence-based public health action. The CGH sits within the Office of the CDC Director and is responsible for coordinating and providing strategic direction across CDC global health work while harmonizing CDC global health priorities with host country priorities.
- NCEZID, headed by its director, uses its epidemiologic and laboratory expertise to tackle bacterial, viral, and fungal pathogens as well as infectious diseases of unknown origin.⁵³ The center focuses on improving infectious disease surveillance, outbreak response, and epidemiology; improving core laboratory capacity; and accelerating development and application of novel diagnostic methods.
- NCHHSTP, headed by its director, supports research, surveillance, and control programs for its focus diseases.

While CDC's 2015 global health R&D budget was dominated by TB and VHFs, it was also focused internationally on control of neglected tropical diseases (NTDs) and malaria. Stakeholders described the CDC as focused on achieving the NTD goals detailed in the London Declaration and WHO's 2020 Roadmap on NTDs, and on the malaria goals delineated in the PMI strategic plan 2015-2020 and WHO's Global Technical Strategy for Malaria 2016-2030.⁵⁴⁻⁵⁶ CDC sits on the panels that develop these documents, which in turn guide long range CDC priorities.

Global Health R&D Funding Decisions

CDC designates only a limited amount of funding for R&D because its primary mission is health protection and not product development. It prioritizes its budget for R&D based on disease burden, severity of disease, opportunities for impact, perceived gaps, and the need for enhanced disease prevention and control.

Figure 10. CDC Funding in 2015 for Global Health R&D by Disease



Source: authors' own analysis based on data from G-FINDER 2016.
NDs: neglected diseases, DCs: developing countries

Strengthening the United States Government's Role in Product Development for Global Health

Unlike the NIH, the CDC does not have much flexibility on how to spend its budget. Instead a very directed budget limits CDC's ability to make independent funding decisions.

Stakeholders described the CDC budget process as both a formal and informal process—a balance between top down and bottom up. In this process, individual program experts formulate opinions about where the gaps are and target areas they think merit additional funding.

Developing evidenced-based targets has not been implemented when making budgetary requests, although public health emergencies (e.g., outbreaks) have been used as triggers to request increased funding. Even then, “the pie never grows,” so while the CDC may want to take on new efforts, it means balancing these while downsizing other priorities.

Global Health R&D Coordination

Opportunities and mutual interests drive the multiple formal and informal channels for collaboration at the CDC. One coordination mechanism is the CDC Board of Scientific Counselors (BSC), Office of Infectious Diseases (OID), which holds meetings at least twice a year supplemented by conference calls.⁵⁷ The BSC, OID includes ex-officio members from the DoD, the FDA, the NIH, the HHS National Vaccine Program Office, and the US Department of Agriculture. Key informants indicated that these agencies talk regularly and interface at a strategic agency level. There are also collaborations with staff from various disease-specific programs. For instance, CDC sits on several FDA, NIAID, and USAID Advisory Committees and review panels, which discuss broad concepts and funding decisions about borderline grant applications.

CDC also helped implement the Global Health Security Agenda in coordination with other U.S. agencies and global partners.⁵⁸ This agenda is a multinational, multi-sectoral initiative launched in February, 2014 to “strengthen both the global capacity and nations’ capacity to prevent, detect, and respond to infectious diseases threats whether naturally occurring, deliberate, or accidental.”⁵⁹

CDC participates in NIH's strategic planning process, which consists of formally planned, quarterly meetings independent of the budgetary cycle. CDC priorities are not necessarily determined based on what the NIH is doing, but they are coordinated to create a cohesive work flow. For example, the NIH does not have field sites but funds staff to work at CDC field sites, and the CDC also has expertise at field sites that can be used by NIH. In general, CDC's goal is to allow different US agencies to maximize and leverage their strengths and to minimize duplication. It identifies collaboration opportunities on a case-by-case basis and will leverage projects occurring in other agencies. It also collaborates with other agencies through the development of country work plans for cross-cutting programs, such as PEPFAR, to help target and implement program goals based on burden of disease.

The CDC offers technical scientific expertise through cooperative agreements, setting aside 3% of its extramural budget for NIH's SBIR program that provides grants to small biotechnology companies for product development.⁶⁰ Companies can propose topics to access these funds. The CDC has a Technology Transfer Office that partners with industry, academia, nonprofits and other USG agencies to transfer its research portfolio into product innovation. It specifically sets aside a portion of its budget for collaborations with academia.⁶¹

Strengthening the United States Government’s Role in Product Development for Global Health

CDC’s collaboration on global NTD research is coordinated through a variety of coordination venues and mechanisms. These include:

- WHO technical expert meetings, which facilitate overall global coordination of the NTD research agenda.
- Meetings of the Task Force for Global Health (which receives funding from BMGF).⁶²
- The annual American Society of Tropical Medicine and Hygiene meeting, which is another opportunity for collaborative priority setting on NTD research
- The Coalition for Operational Research on Neglected Tropical Diseases (COR-NTD), supported by USAID and BMGF.⁶³

Stakeholders indicated that research prioritization for malaria occurs in a different venue with PMI, USAID, and CDC.

Key informants described many examples of successful coordination (Table 6) and noted that the success of these programs depended on commitment, understanding, and trust.

Table 6. Examples of Successful Global Health R&D Coordination Between the CDC and Other Federal and Non-federal Agencies

Type of Collaboration	Examples
Federal Inter-agency Collaboration	<ul style="list-style-type: none">• CDC is working with DoD and NIH to produce multiplex assays, which can simultaneously detect several infectious agents in a single clinical specimen, and is evaluating how to get them to the next development phase on a case-by case-basis• FDA and CDC are collaborating on a project to control cyclosporiasis, a food-borne parasite, through genome sequencing and identification of new species⁶⁴• CDC, NIH, and BARDA are working together on Ebola vaccine development• CDC, NIH and PMI collaborate on malaria vaccine development
Collaboration with Product Development Partnerships	<ul style="list-style-type: none">• CDC was a collaborator on the Meningitis Vaccine Project, to support meningitis A vaccine development⁶⁵• CDC is a collaborator on the International AIDS Vaccine Initiative

US Food and Drug Administration (FDA)

Overview and Funding Levels

The FDA is the US regulatory authority that ensures safety of human and veterinary drugs, biological products, and medical devices. It also promotes innovations to develop more effective, safer, and affordable medical products and products that would help tackle emerging public health threats.⁶⁶ The FDA is headed by the Office of the Commissioner. Four directorates within FDA oversee the core functions of the agency: Medical Products and Tobacco, Foods, Global Regulatory Operations and Policy, and Operations.⁶⁷ The FDA budget for FY2016 is \$4.9 billion, and the FY2017 request is for \$ 5.1 billion.⁶⁸ The key directorates and centers that play a role in global health R&D are the Office of Global Regulatory Operations and Policy and three centers within the Medical Products and Tobacco directorate. The Office of Global Regulatory Operations and Policy regulates product quality and safety efforts, including global collaboration, global data sharing, development and harmonization of standards, field operations, compliance, and enforcement activities.⁶⁹ Within the Office of Medical Products and Tobacco, three centers—the Center for Biologic Evaluation and Review, the Center for Drug Evaluation and Research, and the Center for Devices, and Radiological Health—are responsible for drug, device, and biologic research and regulation for product safety.

Strengthening the United States Government's Role in Product Development for Global Health

The FDA did not provide any funding for global health R&D in 2015, although it has awarded grants for global health R&D in the past. An example of its past funding is its Critical Path Initiative, which in 2010 issued a competitive call to fund the development of new TB drugs, vaccines, and diagnostics.^{70,71} However, the size of the FDA's financial contribution (less than \$5 million between 2010 and 2013 for the initiative) is not in the same league as that of the other USG agencies. The FDA does provide ongoing core funding to the non-profit, public-private partnership C-Path Institute—created by FDA under the auspices of the Critical PATH Initiative—a founding partner of the Critical Path to TB Drug Regimens (CPTR) initiative.

The FDA provides significant non-financial contributions to global health R&D—such as through the priority review voucher (PRV) scheme, which has been established through legislation, and providing technical support and capacity building for regulatory authorities in LMICs. Key informants described multiple ways in which the FDA supports global health, including R&D for neglected diseases:

- It can award a PRV for development of drugs for a selected list of infectious and parasitic diseases affecting LMICs. The voucher, which can be sold, grants the bearer faster FDA review of a different drug (a highly profitable “blockbuster” drug); priority review can be worth more than a hundred million dollars.^{72,73} To date, however, PRVs have been awarded to drugs already available in other countries (such as artemether/lumefantrine) and to drugs already at a late stage of development (such as bedaquiline).
- By designating drugs as eligible for orphan designation, FDA makes the drug developer eligible for many benefits, including tax credits for half of all clinical trial costs. Drugs, vaccines, and diagnostics qualify for orphan status if they are intended to treat a disease affecting fewer than 200,000 American citizens (even if the disease has a high burden outside the US) or if there is no expectation of profit after R&D costs have been incurred. For example, malaria drug treatments would qualify for orphan drug tax credits, though a vaccine may not (as more than 200,000 American citizens could potentially benefit). The Orphan Drug Act reduces development costs, but does not eliminate those costs, and does not make the product profitable. Hence, this incentive alone is insufficient for motivating drug development by commercial manufacturers. Non-pecuniary motivation or additional push and/or pull mechanisms are needed.
- FDA approval of a product provides a signal to regulators in other countries of the quality of that product, which can have knock-on effects for its approval outside the US. For example, Mexico might go ahead and approve an FDA-approved product and then other Latin American countries might approve products that Mexico has approved. In this way, FDA approval can directly and indirectly influence regulatory approval in other countries.
- It inspects manufacturing facilities around the world. In 2008, Congress allocated funds to establish foreign posts in strategic locations around the world, following incidents of tainted heparin and baby formula. By 2016, FDA had posts in Belgium, Chile, China, Costa Rica, India, and Mexico.
- FDA has worked for regulatory harmonization through bodies such as the International Medical Device Regulators Forum (IMDRF) that was led by FDA's Center for Devices and Radiological Health (CDRH).⁷⁴ The IMDRF has implemented a medical device single audit program (MDSAP) with FDA, the European Medicines Agency (EMA), Brazil, and Canada working together toward a single audit in order to avoid redundancy.
- It facilitates knowledge transfer to product development firms in LMICs and technical support and capacity building for regulatory authorities in these countries.

Strengthening the United States Government's Role in Product Development for Global Health

- It reviews antiretroviral drugs that are intended for purchase by USAID under PEPFAR. FDA can certify the quality of an antiretroviral drug, even if it cannot be sold in the US due to patent (or other exclusivity) protection. If the drug has patent protection in the US, FDA can issue a “tentative” approval rather than a “full” approval. The tentative approval signifies that the product meets all safety, efficacy, and manufacturing quality standards for marketing in the US. Under PEPFAR, any implementing agency can purchase a product that has either a tentative or full FDA approval.⁷⁵

Global Health R&D Funding Decisions

FDA's authority to grant orphan drug status and award PRVs aims to incentivize global health R&D funding; while objective eligibility criteria limit FDA discretion, there is some flexibility. USG stakeholders noted that one area of discretion is that the FDA has the authority to expand the list of tropical diseases eligible for a PRV. In 2015, for example, the FDA expanded voucher eligibility to include Chagas disease and neurocysticercosis.⁷⁶

Global Health R&D Coordination

The FDA has a number of mechanisms that it can potentially use to collaborate with international and private sector entities to improve global health R&D. FDA's Centers of Excellence in Regulatory Science and Innovation facilitates collaborations between FDA and academic institutions for innovative research for improved regulation.⁷⁷ The FDA has issued Broad Agency Announcements as a contract mechanism open to private sector participants to collaborate on regulatory science R&D.⁷⁸ The Medical Device Innovation Consortium (MDIC) at FDA is a public-private partnership that allows industry, government, and patient organizations to collaborate on medical device and technology research.⁷⁹

UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT

Overview and Funding Levels

USAID is the USG's civilian foreign aid agency whose mission is to partner to end extreme poverty and promote resilient, democratic societies while advancing US security and prosperity. USAID was created in 1961 through the passage by Congress of the Foreign Assistance Act of 1961. USAID is headed by the Office of the Administrator. The Assistant Administrator for global health leads the Global Health Bureau at USAID.⁸⁰ USAID had a budget of \$22.3 billion in FY2016, of which \$2.8 billion was allocated to its global health programs.⁸¹ The 2017 USAID budget request sets aside \$2.9 billion for its global health programs. It is unclear how much of the global health budget will be directed to global health R&D.⁸²

USAID is the fourth-largest USG funder of global health R&D (after NIH, DoD, and BARDA). In 2015 it invested \$87 million, or five percent of all USG funding. However, while it may be a smaller funder relative to other agencies, USAID is the only USG agency with a clear global health and development mandate and a mandate to conduct R&D for technologies targeting the specific health needs of people in LMICs.

USAID's product development for global health is directed almost exclusively to the 'big three' neglected diseases (HIV/AIDS, TB and malaria) and the reproductive health needs of developing countries (Figure 11). All of its investment in 2015 was in these four areas, and historically these areas account for more than 99 percent of all the agency's global health R&D investments since 2007. Two-thirds of USAID's 2015 funding (\$58 million, 66 percent) was for HIV/AIDS, with the remaining third divided between TB (\$13 million, 15 percent), malaria (\$9 million, 11 percent), and reproductive health technologies (\$7

Strengthening the United States Government's Role in Product Development for Global Health

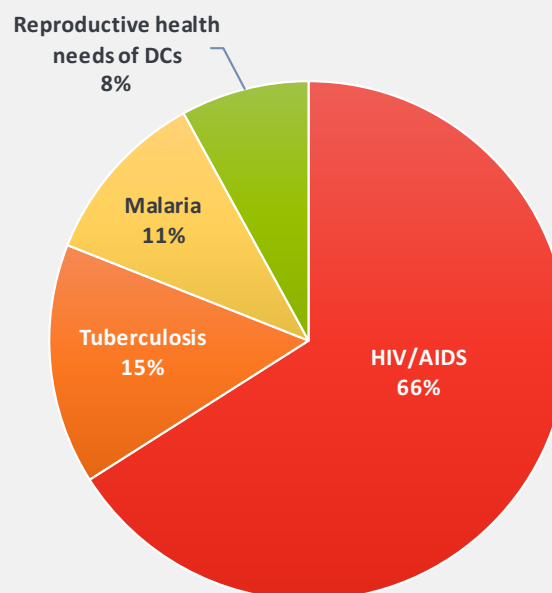
million, eight percent). In 2015, USAID was by far the largest USG funder of reproductive health technologies for developing countries (Figure 12).

It is important to note that USAID also invests significantly in global health research that is not related to the development and introduction of new health technologies, such as program effectiveness evaluation and other health systems research. Such research is outside the scope of our analysis. Similarly, whilst it did not provide any product development funding in 2015 for product development for Ebola and other VHF in 2015, the agency was a significant contributor to program delivery on the ground and related evaluation research during the recent West African Ebola outbreak.

Within USAID, two centers have a key role encouraging innovation to advance global health R&D—the Center for Accelerating Innovation and Impact and The Global Development Lab.

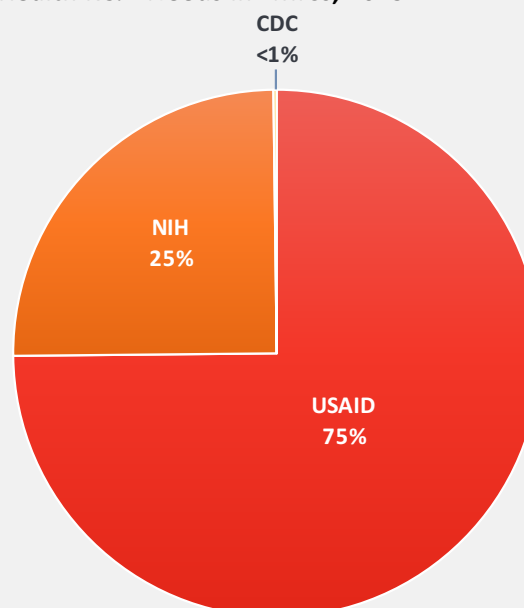
- *The Center for Accelerating Innovation and Impact* focuses on developing and scaling up health interventions through a business minded approach.⁸³ It provides seed finance for promoting innovative technologies and interventions. It focuses on identifying state of the art practices, catalyzing innovation and partnerships, and scaling for impact.
- *The Global Development Lab* was launched in April, 2014 with a view to “increase the application of science, technology, innovation, and partnerships to accelerate the Agency’s development impact in helping to end extreme poverty.”⁸⁴ The lab acts as a central hub for information on innovation, and its work is organized across five main centers: Development Research, Digital Development, Development Innovation, Transformational Partnerships, and Agency Integration. It is led by an Executive Director, who oversees programs and management activities.⁸⁴ For FY2017, the Global Development Lab has a \$170 million budget request for work that includes global health R&D.⁸²

Figure 11. USAID Funding in 2015 for Global Health R&D by Disease



Source: authors' own analysis based on data from G-FINDER 2016

Figure 12. USG Funding for Reproductive Health R&D Needs in LMICs, 2015



Source: authors' own analysis based on data from G-FINDER 2016G-FINDER 2016

Strengthening the United States Government's Role in Product Development for Global Health

USAID's Grand Challenges for Development initiative was launched in 2011 to tackle some of the greatest international development problems and to foster innovative solutions through science and technology partnerships. It engages both traditional and non-traditional actors. USAID has launched eight grand challenges to date, of which three are directly related to global health: Fighting Ebola; Combating Zika and Future Threats; and Saving Lives at Birth.⁸⁵ R&D through the Center for Accelerating Innovation and Impact, The Global Development Lab, and the Grand Challenges program, most USAID support for global health R&D occurs within its disease-specific programs. These include programs on malaria, HIV/AIDS, maternal and child health, and neglected tropical diseases.

The President's Malaria Initiative, led by USAID, is mandated to scale up *proven interventions* and so does not directly support product development, but it does fund operational research, product development partnerships, and both DoD partners and private contractors (e.g., for malaria vaccine development). Stakeholders described the initiative as a program mandated by the White House and Congress to reduce malaria-associated morbidity and mortality by supporting the scale-up of proven interventions in specific countries based on evidence from the past 10 years. Its mandate *requires* that it work with other USG agencies. While PMI dollars are not directly invested in vaccine, drug, or other technology development, they are invested in operational research to understand how to improve programming and to build an evidence base on scale-up of operations.

Stakeholders indicated that while USAID has a strategy for global health, the agency does not have one unified strategy for promoting global health product development. However, they argued that there is a great deal of synergy and coordination across different parts of USAID and, as described below (under coordination), with other USG agencies, even non-traditional partners such as the Department of Homeland Security.

USAID prepares an annual Health-Related Research and Development Progress Report to Congress.⁸⁶ This provides detailed information on its R&D portfolio and highlights successes from year to year. A broader, more comprehensive view of its R&D is in the Five-Year Research and Development Strategy Report.⁸⁷

Stakeholders thought that it is important for USAID to maintain flexibility in identifying the right framework (e.g., Grand Challenges or PDPs) to accelerate specific product development. USAID is the third largest international investor in global health PDPs.⁸⁸ Key informants argued that other USAID-supported models, such as the Grand Challenges related to Ebola, Zika, and newborn survival and working directly with innovators in preparing product dossiers, have also been effective in promoting product development. For the Ebola Grand Challenge, USAID support was directed at interventions such as personal protective equipment (rather than medicines, vaccines, and diagnostics).

Global Health R&D Funding Decisions

Congress generally does not earmark funding for R&D at USAID. Rather, it funds programs for specific diseases and health conditions. Decisions on how to allocate this funding for R&D purposes are then made at the individual program level. Stakeholders indicated that teams decide how much funding is allocated to R&D versus implementation and there is no one from above challenging the decisions. The exception is legacy earmarks for certain types of R&D for HIV/AIDS (e.g., development of microbicides

Strengthening the United States Government’s Role in Product Development for Global Health

and HIV vaccine development). This highlights the importance of having champions for R&D within disease-specific programs at USAID, as exemplified by USAID’s NTDs Program.

USG stakeholders believed that the perception that USAID only invests in implementation and not translational research was inaccurate; its portfolio is diverse across the development chain. For example, it has made investments in maternal and child health at the prototype stage and worked to take these through the entire product development cycle. Rather than just being a gap filler, USAID looks to see at which points in the R&D cycle it can have the greatest added value. It has also supported a diverse array of PDPs (Figure 13).

Global Health R&D Coordination

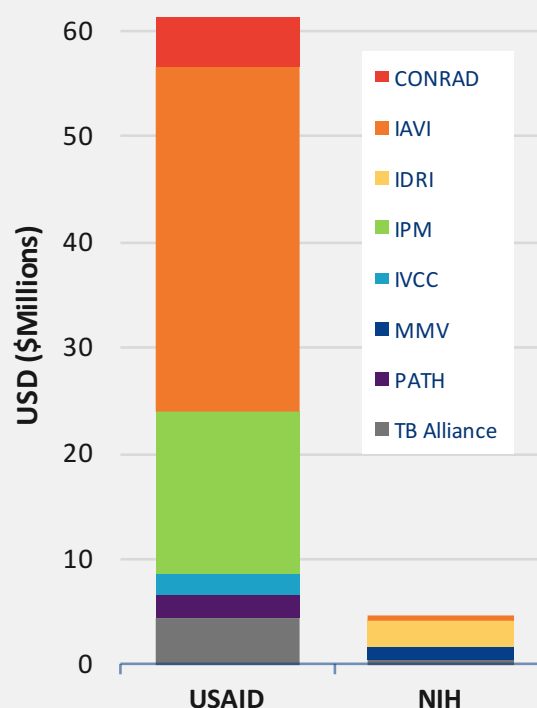
Stakeholders described the Grand Challenges as “cross agency collaboration at its best.” They described four key strengths of this program:

- Project teams at staff level from different USG agencies have been able to build effective relationships.
- It uses a staged funding approach across the development continuum: seed grants for developing prototypes, transitioning to scale, to fully deploying products in the field.
- It pools different expertise from different agencies—for example, the Ebola Grand Challenge was led by USAID, but DoD provided technical expertise on personal protective equipment and the CDC’s National Institute of Occupational Safety and Health tested the new suits in its labs.
- Grand Challenges have had a catalytic effect in raising funds from other sources. For example, the Saving Lives at Birth Grand Challenge has been “a great leverage story”—an initial \$20 million investment subsequently attracted additional \$110 million in funding from numerous investors.

The Center for Accelerating Innovation and Impact has strong cross-agency support.⁸⁹ It has successfully built bridges for inter-agency collaboration, sought out expertise across the USG, and worked to ensure alignment in order to avoid duplication.

USAID is a partner in multiple PDPs, including IAVI, the Medicines for Malaria Venture (MMV), and the Innovative Vector Control Consortium (IVCC).

Figure 13. USG Funding in 2015 for PDPs that Develop Products for Global Health, by Recipient and Agency



Abbreviations: USAID: United States Agency for International Development, NIH: National Institutes of Health, CONRAD: Contraception Research and Development, IAVI: International Aids Vaccine Initiative: Infectious Disease Research Institute, IPM: International Partnership for Microbicides, IVCC: Innovative Vector Control Consortium, MMV: Medicines for Malaria Venture, TB Alliance: Tuberculosis Alliance.

Source: authors’ own analysis based on data from G-FINDER 2016. Note: G-FINDER data for PATH includes funding for the Malaria Vaccine Initiative (MVI), Technology Solutions, Vaccine Development, Vaccine Access and Delivery and WomanCare Global

Strengthening the United States Government's Role in Product Development for Global Health

- USAID has supported IAVI since 2001; its support is aimed at accelerating the development and clinical testing of new vaccine candidates, strengthening research capacity in LMICs, and strengthening “the global environment for AIDS vaccine development and future access.”⁹⁰
- PMI supports MMV and the IVCC, helping to create new malaria vaccine and insecticide candidates and allowing PMI to be a long-term beneficiary of the innovations produced, giving it access to lower-price points for these products. The technical staff at PMI work directly with both of these PDPs, and PMI participates at the board level of both. PMI collaborates with MMV in developing malaria eradication strategies and product access initiatives, and in reviewing drugs in the pipeline and challenges and solutions for addressing regulatory hurdles. It also has an agreement with MMV to purchase promising products for country operations. PMI's role in the IVCC is to help test new insecticides and identify which new tools would be beneficial for malaria control. The PDPs facilitate regulatory approvals for PMI programs at an international and country-specific level.

Another example of USAID's inter-agency coordination is the Interagency Advisory Group, with representatives from USAID, CDC, DoD, Department of State, the National Security Council, and OMB, that oversees PMI. The group meets at multiple levels, including a technical working group to formulate strategy and budgetary review meetings, and it approves PMI's country Malaria Operational Plans. PMI can only add countries if funding increases. While investments in delivering on this mandate have increased, USG investments in malaria research have remained stable. Within this fixed resource envelope for developing vaccines, drugs, and insecticides, PMI works in partnership with other USG agencies to advise them on investments (e.g., giving a go/no-go signal).

Stakeholders argued that there was a great deal of synergy and coordination between different parts of USAID and between USAID and other USG agencies. USAID sees one of its important roles as building bridges with interagency colleagues, seeking out expertise from across USG, ensuring alignment, and avoiding duplication of efforts.

DEPARTMENT OF DEFENSE

Overview and Funding Levels

The mission of the Department of Defense (DoD), established in 1789, is to provide the military forces needed to deter war and to protect the security of the US.⁹¹ Headquartered at the Pentagon, it is led by the Office of the Secretary of Defense, who also serves as the principal defense policy advisor to the President.⁹² The Military Health System (MHS), headed by the Assistant Secretary for Defense for Health Affairs is responsible for serving US Army, Navy and Air force personnel worldwide.⁹³ The MHS is engaged in health care delivery, medical education, public health, private sector partnerships and health R&D. It also houses the Defense Health Agency, which executes the Defense Health Program—this program supports the delivery of health services to US defense personnel, health information technology, and R&D.⁹⁴ The purpose of the DoD's engagement in global health R&D is to protect the health of armed forces and prevent biological threats to the US population. While it does not have a specific mandate for global health, DoD research may include neglected diseases, such as malaria.

The DoD invested \$123 million in global health R&D in 2015 (seven percent of USG funding). This made it the second largest USG agency funder after the NIH.

Strengthening the United States Government's Role in Product Development for Global Health

Ebola and other African VHFs accounted for the largest share of DoD funding in 2015 (\$51 million, 41 percent; Figure 14). This amount means that DoD was the third-largest funder of VHF R&D of all the USG agencies, behind NIH and BARDA. Malaria (\$29 million, 24 percent) and HIV/AIDS (\$28 million, 23 percent) accounted for most of the remainder.

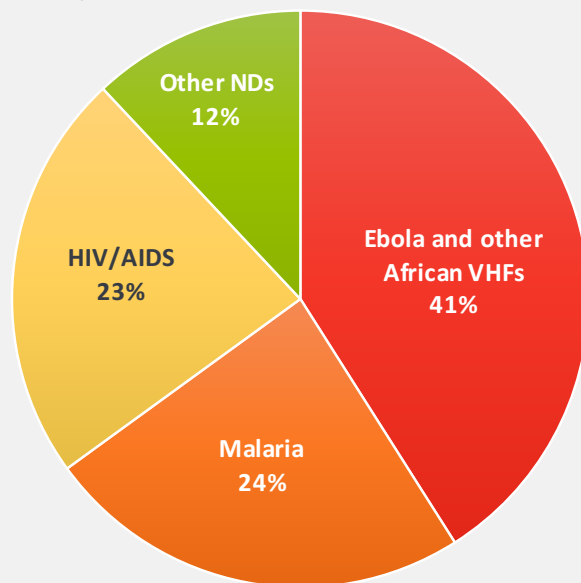
After NIH, DoD has the second most diverse portfolio of global health R&D investments. In addition to its three focus diseases, other DoD priorities included diarrheal diseases, leishmaniasis, and dengue, reflecting the key infectious diseases threats facing its soldiers overseas.

Although DoD activities are aimed at protecting military personnel and biological threat reduction the ancillary outcome of the DoD's investment in global health is technology that can treat and prevent a wide range of diseases.⁹⁵ Over 60 percent of the DoD's global health funding is used to fund discovery and preclinical stage R&D.⁷

The DoD has no department-wide policy or strategy guiding its global health R&D efforts; these efforts are largely carried out by the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), the Defense Advanced Research Projects Agency (DARPA) and DoD's overseas labs.⁹⁶

- The WRAIR was founded in 1893 as the Army Medical School and is the DoD's largest biomedical laboratory.⁹⁷ Its work mainly supports research and technology to develop and deliver lifesaving products to ensure the combat effectiveness of the US warfighter. The institute houses two Centers of Excellence: Military Psychiatry and Neuroscience Research, and Infectious Disease Research. The Infectious Disease Research Center, which works on the development of vaccines and drugs for the prevention and treatment of infectious diseases, has research programs in bacterial diseases, entomology, HIV, malaria, preventive medicine, translational medicine (this branch houses the Clinical Trial Center which conducts Phase I, II, and III human clinical trials), veterinary services, and viral diseases.⁹⁷⁻⁹⁹
- The NMRC focuses its research on traditional battlefield medical problems and natural occurring infectious diseases, as well as on non-conventional health problems related to thermobaric blast, biological agents, and radiation.¹⁰⁰ Its Infectious Diseases Directorate conducts research on significant threats to deployed sailors, marines, soldiers, and airmen and has four research divisions—malaria, enteric diseases, viral and rickettsial diseases, and wound infections. The directorate operates with an annual research budget of \$10 million.¹⁰¹
- DARPA was founded in 1957 and makes investments in breakthrough technologies for national security. It works as an innovation ecosystem with a variety of academics and corporate and government partners. It has six technical offices to work on breakthrough technologies—offices for

Figure 14. DoD Funding in 2015 for Global Health R&D by Disease



Source: authors' own analysis based on data from G-FINDER 2016

Strengthening the United States Government's Role in Product Development for Global Health

biological technologies, defense sciences, information innovation, microsystems technology, strategic technology, and tactical technology. The Biological Technologies Office works on neurotechnology, the human-machine interface, human performance, infectious diseases, and synthetic biology programs and serves as a platform for technologists, researchers, start-ups and industry. Under its Prophecy project, DARPA is developing a simple, hand-held, battery-operated point-of-care diagnostic device to rapidly identify a range of infectious diseases. DARPA's ADEPT program (Autonomous Diagnostics to Enable Prevention and Therapeutics) develops diagnostics, vaccines, new drug delivery methods, and antibodies. DARPA has a budget of \$2.87 billion in FY2016 and has requested a budget of \$2.97 billion for FY2017.^{102,103}

Global Health R&D Funding Decisions

The DoD has a large amount of discretion over the use of most of its funding. However, Congress does provide specific appropriations for its HIV/AIDS prevention program (e.g., \$8 million in 2012).^{104,105}

Stakeholders described the DoD funding process for R&D as requirements-driven. Requirements are highly bureaucratic, defined processes established internally, sometimes at the service level (e.g., navy, army, air force) or at a higher level, with input from various stakeholders (e.g., Africa command, medical command). Requirements must specify: where the technology gap is; what is needed and why; how it fits into DoD's strategy; and an estimate of the price tag. This process is the same for all requests across the entire DoD spectrum, whether for the latest military air fighter or for the development of a new vaccine.

The requirements document ultimately forms the basis for funding requests that go into the National Defense Authorization Act passed each year that specifies the DoD's budget and expenditures.¹⁰⁶ If a program is not included in the requirements document, it will be difficult, though not impossible, for the DoD to start funding something new. For instance, after early work on the Zika vaccine looked positive, public press and pressure from experts helped to break through the normal gridlock to move things forward.

DoD's intramural investment in its infectious diseases research and biological threat reduction programs is driven by the needs of military personnel, but these needs (e.g., vaccines for malaria and dengue) are often the same as those affecting populations in LMICs. This overlap provides a compelling reason for senior leaders from other USG agencies and from outside USG (across various sectors and organizations) to collaborate with DoD in global health R&D. The USG and broader global health community could do more to leverage DoD's modest investment in global health R&D.¹⁰⁷

Global Health R&D Coordination

DoD participates in a broad array of inter-agency collaborative partnerships. For example, it is a member of the Office of AIDS Research Advisory Council, which provides advice to the Director of the NIH's Office of AIDS Research; a member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), and PHEMCE, and it collaborated with USAID and CDC on the Ebola Grand Challenge.

It also participates in the Global Health Security Agenda as part of the US engagement.

Strengthening the United States Government's Role in Product Development for Global Health

OFFICE OF MANAGEMENT AND BUDGET

Overview

The mission of the OMB is to assist the White House in enacting the President's vision across the Executive Branch. OMB achieves this through two core functions: (1) preparing the federal budget to reflect the President's priorities, and (2) managing executive agencies in implementing federal programs. OMB also coordinates federal regulations and oversees the Administration's procurement, financial management, information, and regulatory policies.¹⁰⁸

Due to its extensive scope, stakeholders described OMB as the "center of government." All regulations and budgets of executive branch agencies are subject to OMB's lens, giving OMB a vantage point of the federal government that few organizations, if any, have. OMB also reports directly to the President as part of the Executive Office of the President (EOP).^{109,110} As such, although Congress has the ultimate power, OMB has significant influence over agencies while enacting the President's policy and budgetary priorities.

OMB works closely with executive agency officials and others (including advocacy groups), during the budget preparation process and throughout the year while monitoring the budget implementation. OMB meets with agency officials and stringently reviews their budget funding requests from September to February and with advocacy groups between July and August.¹¹¹ While OMB uses this process to communicate the President's preferences, it also sees this process as an open conversation with executive agencies, enabling policy priorities to percolate both down from the Administration and up from the agencies. Stakeholders have characterized this interaction between OMB and agency officials as both contentious and collaborative, depending on the level of policy disagreement between the two organizations.

OMB's expansive scope limits its ability to comprehensively coordinate across agencies. This limitation is reflected in its organizational structure, where supportive offices—known as Resource Management Offices (RMOs)—are divided into five groups by subject matter. For example, the National Security Programs RMO oversees USAID, State Department, and the DoD and the Health Programs RMO oversees NIH, FDA, CDC, and HHS. Stakeholders also noted that OMB focuses less on minute details and nuanced issues. Global health R&D programs are reviewed by different offices, and tend to receive less attention than other priorities.¹¹⁰

Across OMB's vertical hierarchy, staff can "shift the needle" in influencing budget requests. OMB has a clearly defined, but relatively flat, vertical hierarchy, giving junior staff access to senior leadership.¹¹² OMB staff, known as Program Examiners, are the focal point in OMB, serving as liaisons to agencies. They play a critical role in OMB, reviewing, monitoring, and evaluating programs and recommending programmatic funding. Deputy Associate Directors and Program Associate Directors are the senior tiers of leadership within each RMO and have significant leeway in influencing budgetary requests.

Strengthening the United States Government's Role in Product Development for Global Health

The Office of Science and Technology Policy (OSTP) and the National Security Council (NSC) are two entities within the EOP that were considered to be extremely influential on global health policy in the Obama Administration; however, given recent departures and vacancies at the leadership level of these offices, their importance may diminish and OMB may become increasingly powerful.

- The OSTP advises the EOP on the effects of science and technology on national and international affairs. Key informants cited the 2015 White House plan, guided by OSTP, the National Plan for Combating Antibiotic Resistant Bacteria, as a model for how the Administration could drive global health R&D collaboration across agencies.¹¹³
- The NSC supports the President on national security and foreign policy issues, including on the GHSA.^{114,115}

Funding Decisions

When considering budget requests, OMB staff favor programs or policies that demonstrate clear needs and tangible outcomes. For global health programs, assessment may include factors such as disease burden and impact analysis. This prioritization approach has a potential bias towards R&D products with an immediate high-impact, undercutting R&D products with longer development periods. As a result, certain global health areas are neglected partly because it is harder to measure their effectiveness. Stakeholders cited this as a potential cause for HIV budget flat-lining and the success of malaria funding.

In addition to program performance data, factors such as political concerns drive OMB's funding decisions. OMB does not directly engage in monitoring and evaluation of individual programs, but will rather rely on data provided to them by USG agencies and advocates. And while stakeholders indicated that OMB strives to stay above the political fray, staff consider the political realities of a program or budget request. With a Congress wary of increased spending, agency proposal amounts tend to be in line with previous years. OMB will consider appropriations and report language to craft policies and gauge Congressional appetite. OMB makes an exception if the Administration feels strongly about an issue.

Although OMB designed the review process to be impartial and systematic, key informants stated that funding decisions are susceptible to the personal discretion of individuals, particularly as those decisions move up the chain of command.¹¹² Stakeholders particularly noted that outcomes are more likely to be successful when individual agency directors coordinate their budget requests and overall lobbying efforts instead of adopting a piecemeal approach. OMB employees must use their judgment to interpret how to implement the President's policies.¹¹² Additionally, they may have a personal preference for specific programs. The extent and frequency of such preferential behavior is not clearly or widely understood.

Section 4. The Appropriations and Budget Process: Influence on Global Health R&D

In this section, we step back from examining individual USG agencies and focus on processes “higher up” — specifically, the overarching appropriations and budget process that ultimately determines the global health R&D funding envelope within which agencies must operate.

Note that the process below applies solely to discretionary spending, which must be reviewed annually by Congress. Discretionary spending is approximately 35 percent to 39 percent of total federal spending and encompasses the majority of global health R&D programs.¹¹⁶ Mandatory spending, which includes the DoD, is not subject to annual review and is left “ongoing.”

BUDGET FORMULATION

The federal funding process begins when the President submits an annual budget request to Congress in February for the following fiscal year (Figure 15), in accordance with the Congressional Budget Act of 1974.¹¹⁷ The proposal reflects the administration's federal priorities and provides detailed budget recommendations per federal program. The president's budget is not legally binding on Congress, but simply reflects the President's recommended spending levels for programs. Notably, Congress and the Executive Branch do not always adhere to the traditional budget and appropriations schedule. In these instances, Congress has extended the deadline statutorily or informally.¹¹⁸

Federal agencies and OMB work together to develop the budget request. Beginning in early fall, agencies submit their budget requests to OMB. Over the next several months, OMB reviews the proposals while agencies justify their requests. Agencies can accept or appeal OMB's decision.¹¹¹ OMB then develops the final budget proposal and submits it to Congress.^{119,120}

APPROPRIATIONS TIMEFRAME

In response to the President's budget, Congress adopts an annual budget resolution, drafted and finalized by the Senate Budget and House Ways and Means Committees that sets spending ceilings for the following fiscal year (known as a “302a allocation”). Under regular order, a budget should be adopted by April 15th, although Congress may enact separate motions to waive this requirement and has not met the date in recent sessions.^{116,118} The budget resolution does not appropriate funding, but rather sets top level funding ceilings for specific accounts and activities to guide the work of Congressional appropriators. Importantly, the Congressional budget does not need to mirror the President's request—and often it reflects different priorities and political ideology.

After the budget resolution is passed, the Appropriations Committees in each chamber divides the budget target among the 12 Appropriation Subcommittees, forming one top line sub-budget per subcommittee (known as “302b allocation”). Both Chambers consider appropriation bills separately and, as of more recently, concurrently.¹¹⁶ A funding bill is passed for each subcommittee, which means that under regular order, Congress passes 12 appropriations bills, which must be reconciled before the entire appropriations process is complete. Table 7 gives an overview of committees and subcommittees in the 114th Congress that oversee agencies involved in global health R&D.¹²⁰

During this time, subcommittees take testimony from agency officials to hear spending justifications.¹¹⁶ Congressional committee staffers meet with executive agency officials and non-government stakeholders to consider annual appropriations for agencies and programs. Although Congress occasionally delineates funding

Strengthening the United States Government’s Role in Product Development for Global Health

amounts for R&D, key informants stated that Congress generally funds programs at a higher level and yields to agency leaders to determine R&D priorities within those spending lines. For example, the 2011 Department of Defense and Full-Year Continuing Appropriations Act provided \$2.5 billion to USAID for global health programs without specifying how much USAID should spend on each activity.^{121,122} In response, agencies often develop their own health strategies, such as USAID’s *Global Health Strategic Framework*.

In May and June, appropriation bills are usually submitted to the House and Senate floor for consideration by the entire chamber. Since the fiscal year begins in October, little time remains for the House and Senate to resolve any differences. Congress has not enacted a regular appropriations bill before the start of the fiscal year since 2009.¹²³ When appropriations legislation is not passed by the start of the fiscal year, Congress typically enacts “continuing appropriations” to maintain temporary funding at previous year’s levels until regular bills are enacted. As continuing appropriations are frequently passed in a joint resolution they are more commonly referred to as “continuing resolutions.”¹¹⁶ If Congress has not passed an appropriations measure or a continuing resolution by the deadline, affected agencies lack budgetary authority and must cease nonessential activities.¹¹⁹

Appropriation measures are one component of Congressional funding measures. The other component, known as “authorization measures”, “establish(es), continue(s), or modif(ies) agencies or programs.”¹¹⁶ While Congress usually passes appropriations bills for each fiscal year, authorization bills are passed less frequently, since Congress can authorize an agency or program for multiple years (e.g., the PEPFAR Stewardship and Oversight Act of 2013 authorized PEPFAR through 2018).¹²⁴ While authorization legislation presents an opportunity to influence global health R&D, many programs lack active authorization, including NIH (amounting to \$31 billion in 2016). In 2016, lawmakers appropriated approximately \$310 billion for “unauthorized” programs.¹²⁵

In addition to directly funding or amending programs, Congress can prioritize global health issues, and establish targets for global health R&D, through a variety of other vehicles. These include holding hearings, reviewing legislatively-mandated reports to Congress, issuing Congressional reports, approving treaties, or confirming presidential appointees to federal agencies.¹²²

Members can also form caucuses—also known as coalitions or study groups—to focus on a specific legislative topic. Caucuses have no jurisdiction over authorizations or appropriations, but serve to bring attention to an issue. Current caucuses related to neglected diseases include: the Congressional Global Health Caucus, the Congressional HIV/AIDS Caucus, the Tuberculosis Elimination Caucus, the Congressional Caucus on Malaria and Neglected Tropical Diseases, and the Senate Caucus on Malaria and Neglected Tropical Diseases.¹²⁶

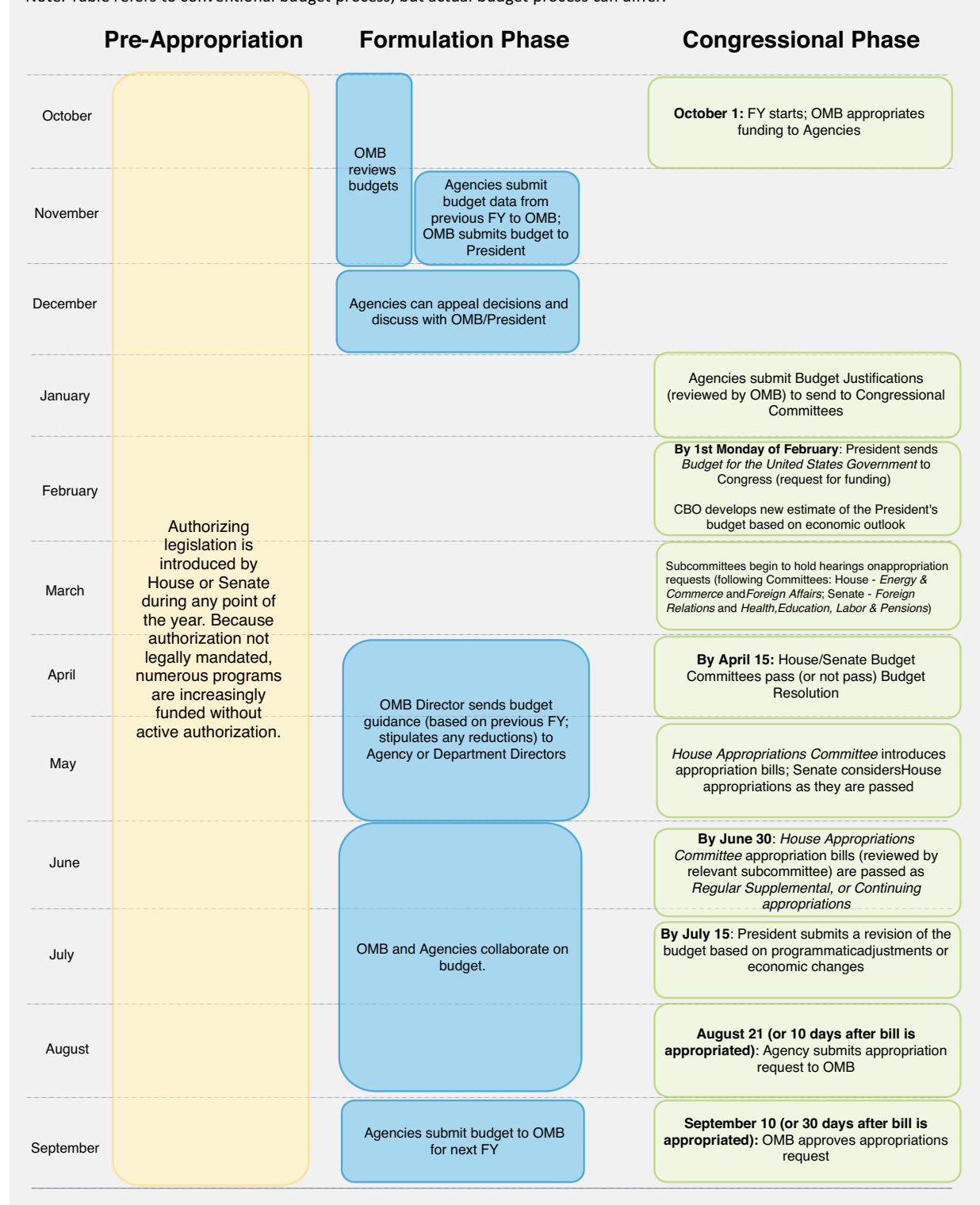
Table 7. Appropriation Committees and Subcommittees in the 114th Congress that Oversee Agencies Involved in Global Health R&D

Appropriation Committees	Function	Subcommittees	Function of Subcommittees
Senate Committee on Appropriations / House Committee on Appropriations	Appropriate funds for all agencies	Senate Labor, Health and Human Services (LHHS) / House Labor, Health and Human Services (LHHS)	Appropriates funds for HHS and related agencies with the exception of FDA
		Senate State and Foreign Operations (SFOPS) / House State and Foreign Operations (SFOPS)	Appropriates funds for the State Department and USAID
		Senate Defense / House Defense	Appropriates funds for the Department of Defense
		Senate Agriculture Rural Development, Food and Drug Administration (Ag-FDA) / House Agriculture Rural Development, Food and Drug Administration (Ag-FDA)	Appropriates funds for FDA

Strengthening the United States Government's Role in Product Development for Global Health

Figure 15. Illustrative Timeline of Appropriations Process.

Note: Table refers to conventional budget process, but actual budget process can differ.



Section 5. Catalysts and Barriers to USG Support for Global Health R&D

Up to this point in the report, we have chiefly focused on individual agencies. This is appropriate as it reflects the fact that there is no “whole-of-government” strategy for global health R&D, and there is a great deal of agency autonomy for such research activities.

Nevertheless, we believe it is valuable to try and draw “cross-cutting” lessons for USG support for global health R&D from across all agencies. In this section, we describe the *cross-cutting, cross-agency themes* that emerged when we analyzed the collective results of the literature and all key informant interviews. We have divided these themes into (a) catalysts (enabling factors) and (b) barriers to supporting global health R&D.

CATALYSTS TO USG AGENCY SUPPORT FOR GLOBAL HEALTH R&D

Our analysis found four main categories of catalysts: collaborative approaches within and between agencies and programs; market incentives offered by USG agencies; supportive legislative changes; and regulatory incentives.

Collaborative Approaches within and between Agencies and Programs

Disease-specific efforts such as PEPFAR and Office of the US Global AIDS Coordinator (OGAC) leverage multiple actors to achieve greater impact. The combined forces of the US Department of the Treasury, the US Department of Labor, the Peace Corps, HHS, DoD, USAID, CDC, and the ministries of health and defense in implementing countries resulted in moving the number of treated individuals from zero to 10 million in a record period of time. Stakeholders argued that the level of synergy and networking shown by PEPFAR and OGAC have, unfortunately, not been replicated by other parts of the USG for other diseases or for broader research efforts. But the success shows that cross-agency USG collaboration *can* be done effectively.

Several NIH vaccine research funding initiatives, such as the Vaccine Research Center (VRC), have used successful collaborative approaches to address critical health care needs.¹²⁷ Key informants argued that the VRC is a great example of evaluating needs and trying all possible avenues to develop a model with the best chance of success. The VRC was launched during the Clinton Administration, when President Clinton asked the NIH and NIAID directors about the barriers to HIV vaccine development (they explained the high risk of failure and the limited market incentives as an impediment for industry engagement). Through the VRC, the USG takes on the risk of basic discovery, candidate vaccine development, test lots production, and early stage trials. USG then licenses these products to industry. Stakeholders contend that since inception, over 50 products have gone from discovery into human clinical trials, including the SARS, pandemic flu, and Ebola vaccines. Other transformative, collaborative NIH funding initiatives include the Center for HIV/AIDS Vaccine Immunology, the HIV/AIDS Clinical Trials Network, and the AIDS Clinical Trials Group.¹²⁸⁻¹³⁰

Strengthening the United States Government's Role in Product Development for Global Health

The Grand Challenges model allows for “organic and productive” collaboration. The Grand Challenge’s staged funding approach was widely praised by stakeholders as a model for facilitating collaboration. As previously noted, Grand Challenges provides funding across the development continuum, from seed grants to product deployment. Collaborations are important in this approach because not all agencies have the necessary expertise required to bring a product to market. However, the Grand Challenges model cannot be used to advance drugs and vaccines through late stage development. The only technologies that it can feasibly take through to market are diagnostics and devices that require only small amounts of funding.

Urgent public health problems and a clear ask are strong motivation for breaking down institutional and inter-agency barriers; without a crisis, collaboration is much harder. Stakeholders pointed to the Fighting Ebola Grand Challenge, a response to the West African Ebola outbreak, as a program that enabled project teams at the staff level to build relationships and gain trust. A repeated theme emerging from our study is that this kind of “natural” trust-building can be more effective than forced collaboration, which can backfire by becoming political. Interviewees believed that the responses to the request for proposals for this Grand Challenge came in rapidly because the proposal was for a specific request (“opportunities to co-create, co-design, co-invest, and collaborate in the development, testing, and scaling of practical and cost-effective innovations that can help healthcare workers on the front lines provide better care and stop the spread of Ebola”).¹³¹ While crises have been catalysts to USG support for global health product development, they also demonstrate the clear tension between the short-term goal of addressing an emergency and the longer-term objective of creating a sustainable funding environment. Crises allow the USG to be directive, to quickly build consensus on what the issues are and who is going to tackle them, and to issue very clear calls for proposals. In contrast, under non-crisis “business as usual” conditions, when the calls for proposals are vague (e.g., “these are the diseases we are interested in broadly”), not only is it more difficult to get agency buy-in, but private industry stays on the sidelines because there is no clarity about product lines and profit margins.

Cross-agency global health efforts have succeeded when they are led either by the White House or through sustained, coordinated efforts led by executive agencies, as seen with the GHSA led by CDC.¹³² Stakeholders described this agenda as one of the most exciting areas CDC has been involved with for accelerating product development for global health challenges. The agenda aims to build capacity in countries to respond to threats; while stakeholders described capacity building as being “less dramatic than treating newborns for malaria,” they thought that it had much more long-term potential to do good.

The imprimatur of a high level federal advisory council is critical to bring about productive collaboration, as seen with PACCARB, which aims to accelerate product development by streamlining efforts at the highest level. Announced in 2015, PACCARB is a high level federal advisory committee that includes liaisons from key government agencies (including DoD, FDA, CDC and NIH), academia, and industry, with a mandate to develop recommendations to HHS on how to “de-stovepipe” concurrent efforts and reduce duplication.¹³² PACCARB was charged by HHS leadership to specifically consider what incentives might be required to spur development, deployment, utilization, and uptake of drugs, vaccines, and diagnostics. One result of the initiative was that CDC and DoD learned that they were working on a similar project and that the DoD had 36 thousand well-characterized samples that the CDC could also use. The National Vaccine Advisory Committee was highlighted as another example of a high level advisory council.¹³³

Strengthening the United States Government's Role in Product Development for Global Health

Additional high-level entities that can support collaboration include the Office of Science and Technology Policy (OSTP) and the National Science and Technology Council (NSTC). Although USAID has recently undergone a reorganization, the OSTP and the NSTC were both described as effective entities for bringing collaborative groups together for discrete purposes.^{115,134} Established by congress in 1976, OSTP is authorized to lead interagency efforts on developing and implementing science and technology policy and to work with all sectors (particularly the private sector, state and local governments, and the science and higher education communities) and other countries toward this end. Because the OSTP has convening power and is able to set up working groups and charters for operation, it was very effective during the Ebola Grand Challenge, setting a clear research agenda for the response. Stakeholders believed that using the OSTP would be unwieldy for an overall global health strategy, but that it could be very effective for discrete purposes.

Market incentives offered by the USG

BARDA's integrated push and pull mechanisms, as well as its Other Transaction Authority (OTA) that allows it to establish long term portfolio partnerships with industry, is seen as a model for USG engagement with PDPs. Through OTA (first granted to DARPA in 1989), BARDA can establish commercial relationships with private sector partners, exempt from federal acquisitions regulations (FAR).^{135,136} One such relationship is the product portfolio partnership, which pools funds for clinical development and creates a joint oversight committee comprised of BARDA and pharmaceutical representatives to share decision making for an entire portfolio of products over the long term. Before these portfolio partnerships were established, it could take up to 18 months to set up a contract for a single product. If that product failed, the contracting work was wasted. The portfolio partnership removed barriers that would have discouraged pharmaceutical developers from manufacturing certain products. For example, shortly after AstraZeneca disbanded its anti-infectives division, a five-year portfolio partnership with BARDA involving federal commitments of up to \$220 million persuaded the company back into the antibiotic R&D space.¹³⁷

Another USG market incentive, the PRV provided by the FDA, is seen by some as a welcome addition to the range of incentive mechanisms, even though its impact to date is not clear. Under the 2007 law that established the PRV, a developer of a treatment for a neglected or rare pediatric disease receives a voucher for priority review from the FDA to be used with a product of its choice or sold to another developer. Key informants argued that the PRV, which was conceptualized at Duke University, has had some success in creating an incentive mechanism for neglected disease R&D. Since its introduction, vouchers have been awarded for several neglected infectious diseases, including malaria, TB, leishmaniasis, and cholera.¹³⁸ But the overall impact remains unclear, as some products may have been developed even in the absence of the voucher scheme.

The Grand Challenges model also acts as a market incentive. The contests encourage innovators from outside government to invest in developing new technologies for specific challenges.

Supportive legislative changes

An important finding in our study is that there are examples of Congress enacting legislation in ways that strengthen USG's role in global health, including global health R&D. Congress plays an important role in strengthening the USG's role in global health, including global health R&D. Examples of legislative changes to enhance US efforts in global health R&D demonstrate the important role of advocacy to Congress.

Strengthening the United States Government's Role in Product Development for Global Health

Examples of such amendments include:

- Congress broadening CDC's mandate after CDC staff articulated a need to protect Americans globally.
- After the launch of PEPFAR, the White House established a special process for FDA to approve generic HIV drugs exclusively for use overseas. This was the first time an FDA process was created to meet this objective. FDA's work with PEPFAR has been even more effective than expected, having approved more than 180 therapies, including pediatric formulations.⁷⁵
- Legislation establishing the National Vaccine Injury Compensation Program (VICP), which provided vaccine companies protection against injury, and a similar program, the Countermeasures Injury Compensation Program related to pandemic flu vaccines and other MCMs.^{139,140}

There has been precedent for valuable expansion of a USG agency's mission in support of global health R&D. For instance, Congress and the executive branch extended BARDA's remit to include AMR.

Regulatory incentives

FDA has at its disposal a range of regulatory incentives that can help to catalyze product development for global health challenges. Two examples that were given by key informants are:

- FDA approved bedaquiline for treatment of multi-drug-resistant TB at the end of 2012, even though in the phase II trial more patients in the treatment group died than in the placebo group.¹⁴¹ FDA determined that the benefits of the drug outweighed the risks (the 10-year mortality from the disease is 70 percent). FDA approved the drug under its accelerated approval program, which "allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients."¹⁴² It also granted the drug fast track designation, priority review and orphan-product designation.
- The Emergency Use Authorization authority, which was an effective platform within FDA for fast tracking diagnostic testing for Zika and Ebola.¹⁴³

BARRIERS TO USG SUPPORT FOR GLOBAL HEALTH R&D

Our analysis found five main categories of barriers: the institutional siloes and unwieldy systems that make coordination difficult; insufficient funding and lack of a global health champion; under-use of effective agencies; inadequate incentive structures; and a lack of a clear mechanism across and within USG agencies to track USG funding for global health R&D.

Institutional siloes, unwieldy systems, and the difficulty of coordination

Though there have been some examples of successful inter-agency coordination in global health R&D, agencies largely work in siloes, hampered by systemic barriers. Two examples cited by stakeholders are:

- The NIH process is disconnected from the FDA approval process, in part due to concerns about conflict of interest.
- USG stakeholders reported that the unwieldy contracting process keeps agencies apart. If the DoD were to go to NIH to invite key researchers over to WRAIR to work on promising data coming out of its biomedical research labs, there is no easy contracting mechanism to move that forward. It would be a lengthy process to get a contract or interagency agreement in place—with the result that agencies just stick to themselves.

Strengthening the United States Government's Role in Product Development for Global Health

The failure of the Global Health Initiative (GHI) exemplifies the difficulties in addressing coordination across agencies and suggests that trying to “force” a collaboration can have unintended consequences. GHI began in 2009 as an attempt to integrate programs and consolidate separate funding streams. An Operations Committee made up of officials from USAID, CDC, and the State Department oversaw GHI, with guidance from OMB and the NSC.¹⁴⁴ By 2012, the leadership of GHI was expected to transition to USAID from the State Department's OGAC, contingent on USAID completing management benchmarks.¹⁴⁵ Ultimately GHI never lived up to its grand vision.¹⁴⁶ Stakeholders attribute this to a variety of reasons:

- GHI had no clear statutory decision-making authority or leadership structure.
- There were no separate appropriations to achieve its objectives.
- Although GHI was tasked with coordinating across participating agencies, PEPFAR—about 70 percent of GHI's budget—continued to be housed with the State Department's OGAC, separate from GHI.
- There were reports of interagency discord, with agencies unwilling to accept USAID leadership of GHI.¹⁴⁷ Stakeholders stressed the difficulty in finding an appropriate unifying global health champion but suggested the Administration should place leadership of global health with one person or entity. This person should keep everyone's eye on the target. This happened to some extent with Ebola, but that energy has faded away.
- GHI's scope was too broad, it tried to do too much (including R&D, program implementation, policy and diplomacy), and the concept itself was too vast, leading to no clear understanding of its purpose. Instead of taking on something so huge, it would have been better to agree on areas that people were investing in and seeing if these could be better coordinated.
- Funding intended for GHI ended up being siphoned off to other more high profile programs.¹⁴⁸
- Many USG stakeholders cited the failure of GHI to gain traction as a case study in how “forced” attempts to improve coordination can backfire.¹⁴⁸ Some were vocal opponents to of the concept of a “whole of government” approach and forced collaboration from above, emphasizing that global health is not monolithic, is hard to characterize, and respective agencies within the USG have their own specific goals, objectives, and mandates.

Within and between agencies, USG stakeholders indicated there may be structural divisions that can impede global health R&D. For example:

- R&D efforts within an agency are often divorced from its disease control programs and scale-up efforts—a missed opportunity for testing innovative products in the field.
- Jurisdictional divisions in Congressional appropriations and between OMB offices can stovepipe R&D funding decisions and impede coordination. While there are instances of communication across offices, given resource constraints, it is primarily limited to avoiding redundant work rather than fostering agency-wide initiatives.

Insufficient funding

A major challenge to global health product innovation is the funding gap for this type of research. Low levels of funding at CDC, for example, have slowed down the development of a promising diagnostic for trachoma that tests bacterial levels instead of requiring an eye examination. Budget cuts and sequestrations have shrunk already limited global health R&D funding, slowing down product development efforts at several agencies.¹⁴⁹ For example, Ebola vaccine development was stalled as a

Strengthening the United States Government's Role in Product Development for Global Health

result of the sequester.¹⁵⁰ One analysis of funding levels for Ebola research concluded: “clearly, budget cuts are leading to reduced dollars for finding an Ebola vaccine.”¹⁵⁰

The various institutes at NIH have reached the limit of what they can allocate and have been forced to take funds from other areas to deal with emergencies. The unpredictability of competitive grant funding has also made it difficult for the NIH to focus on long term goals. Stakeholders fears that tight budgets will allow other countries’ scientific innovation to outpace US innovation.

Funding for global health R&D is likely to be further jeopardized by the lack of an identifiable champion to drive the USG’s global health agenda; the difficulty gaining support for something not directly impacting the US population; and partisan divisions in Congress. Partisanship in Congress has resulted in a political climate where even essential legislation has trouble passing. This is particularly evident in government funding. Over the last decade, it has resorted to last-minute measures such as continuing resolutions instead of following the conventional appropriations process. Political gridlock hinders an agency’s ability to achieve a long-term budgetary outlook. Stakeholders cited the absence of a long-term appropriations framework as creating chaos.

Financing of later-stage clinical trials, critical to translating research into products, has become prohibitively expensive. New thinking is needed on how global health research can be done in more frugal and efficient ways. One of the biggest missed opportunities are lessons that could be learned from failed, unpublished clinical trials.

Another result of inadequate funding, argued several key informants, is that USG does not have sufficient R&D surge capacity. Such capacity would need a new appropriation. Some stakeholders argued that just increasing funding will not accelerate global health R&D unless other weaknesses in the complex R&D “ecosystem” are addressed. These key informants argued that (a) there is a tendency to oversimplify the problem by assuming that more money is the solution, and (b) there will need to be better incentive mechanisms and more diverse and robust funding vehicles to strengthen US support for global health R&D. Some USG stakeholders view the current conversation over global health funding levels as less important than *how to better direct existing funds* to drive the market for product development.

Under-use of effective agencies

The DoD’s global health R&D capacity is being under-used—a major missed opportunity. Key informants argued that there is significant, under-used value in DoD overseas labs for global health R&D, including for vaccine development. There is a perception within the USG that when you need vaccine development, you must go to the NIH because that is where the scientific experts are and the NIH has a big budget. Yet NIH’s core competency is not product development. The DoD’s capabilities are being overlooked—a quarter of vaccines approved by the FDA in the last century have been developed with DoD participation.¹⁵¹

Stakeholders argued that DoD’s medical R&D does not get the recognition that it deserves, and is dwarfed by higher profile defense projects. The core mission of DoD—the provision of the military forces needed to deter war and to protect US security—has no direct link to global health research, and some (though not all) members of Congress believes the department should stay focused on its core defense responsibilities rather than extending itself. Senior medical military leadership is more focused on treatment needs and the crisis of the day, such as access to medical care for veterans, traumatic brain injury, and post-traumatic stress disorder and suicide, rather than R&D. Additionally, while DoD policy and budgeting have a well-oiled machine to secure additional funding from appropriators and

Strengthening the United States Government's Role in Product Development for Global Health

committee staff for defense projects, that kind of machine does not exist on the medical side. And while global health challenges have recently been framed through a security lens, as seen with the GHSA, global health is still seen as “low politics” within the national security world compared with other threats. As a result, global health research experts may not command as much attention from senior leadership as national security experts.

Historically, WRAIR, which predated the NIH, was the place to go in the federal government for translational medical research, whether it was for the first flu vaccine, meningococcal vaccine, a cure for typhoid, typhus therapy in refugees after WWII, and more.¹⁵² But as HHS and NIH grew, the contribution of WRAIR and its research work got eclipsed.

Inadequate incentive structures

There was widespread agreement among key informants that the current incentive mechanisms for global health R&D are inadequate; newer mechanisms are needed that would provide larger, more reliable, longer-term financing. Ongoing market failures highlight the inadequacy of the current incentive structures to promote product innovation and discovery in the areas of AMR, EIDs, and NTDs. In addition, it is difficult to predict in the abstract what will be needed in the future. For instance, recent outbreaks such as Ebola and Zika were never anticipated and the existing structures were not easily adaptable to meet these outbreaks.

No clear mechanism to track USG funding for global health R&D

There is no common, standard working definition of R&D across the executive agencies and no clear mechanism to track R&D funding flows (e.g., there are no clear budget lines for global health R&D). This inconsistency prevents OMB from adequately tracking global health R&D across multiple executive branches and limits conversations about coordination that might otherwise have been triggered.

Section 6. Perspectives from Industry, Product Development Partnerships, and Foundations

In this section we briefly summarize perspectives of two groups of key informants from outside government—one group comprising senior representatives from six companies that conduct global health R&D, and the other made up of senior representatives from eight NGOs, PDPs, and foundations (Table 3). To avoid repetition and redundancy, we focus on ways in which their perspectives were distinct from those of the USG key informants. One aim of this section is to explore what it is like for private sector actors (both for-profit and non-profit) to partner with the USG on global health R&D.

PERSPECTIVES FROM INDUSTRY

Industry stakeholders indicated a significant commitment to developing innovations to address the unmet needs of vulnerable populations, based on social responsibility and the vision of their leadership, despite the challenges presented by the limited return on investment. When their scientists identified innovative opportunities within their library of assets, they felt an obligation to make them widely available to both developed and developing countries. In some cases, commitment and, consequently, funding were susceptible to changes in leadership. When possible, companies try to invest in products that have multi-market potential to address similar needs in both low and higher income populations, improving expected returns. Some companies have established institutes dedicated to nonprofit missions, or have looked at spinning out a portion of their portfolio into a foundation to eliminate investor concerns about return on investment.

Despite this commitment, industry scientists face significant pressure to create a cost neutral development environment by securing funding from nontraditional sources. While it is helpful for companies to establish internal ring-fenced budgets to prevent global health projects from having to compete internally against other more profitable mainstream projects, they still rely on external funds for global health R&D. Funding opportunities can come from partnerships with other pharmaceutical companies, academia, foundations, USG, WHO, or PDPs. Some companies are exploring innovative financing sources, such as:

- *Social impact bonds*: social investors take on the risk, which is linked to the successful development of a product (success metrics are pre-defined); if the metrics are achieved, investors are paid a premium by guarantors such as BMGF.
- *Venture philanthropy funds*: in this mechanism, returns are based on the health value created (e.g., DALYs averted) rather than being linked to a specific product's development.

Industry stakeholders described funding and “go/no-go” decisions as complex processes contingent upon (a) innovative scientific opportunity and impact, (b) burden of disease and unmet medical need, and (c) market conditions, such as the distribution network, the purchasing power of the patient and/or government, the regulatory landscape, and the return on investment. Industry stakeholders thought the industry was well positioned to address most of these issues, but was struggling to overcome the barriers of high risk investment in the absence of adequate market return.

Strengthening the United States Government's Role in Product Development for Global Health

Push and pull mechanisms—including those offered by the USG, such as research funding (push) the PRV (pull), and orphan drug designation (push and pull)—are important to industry but not the key driver in their decision-making, in part because the incentives only account for a fraction of the total cost of developing a product. Industry stakeholders view the PRV and orphan drug designation as part of the solution, but not the whole solution. Given (a) investment decisions for product development have at least a ten-year time horizon, (b) the attrition of successful molecules, and (c) diminished value of money over time, the PRV is seen as being insufficient to encourage early stage investment all by itself. Industry indicated there is a huge need for seed funding, such as that provided by the Wellcome Trust, or advanced market commitments, such as those provided by the USG for biodefense projects, to jump start early discovery work at the outset.

Industry stakeholders also suggested that market incentives are not as readily available for diagnostics as they were for vaccines and drugs. However, this perception is likely to be due to low awareness of such incentives among the industry key informants; there are more prizes for diagnostic development than there are for developing drugs and vaccines, and there are also major diagnostic procurement programs (e.g., through the Global Fund, UNITAID, the President's Malaria Initiative, and the Clinton Health Access Initiative) that help to create a *de facto* market incentive.

Critical factors considered early on by industry key informants when making investment decisions are knowing the downstream plans for marketing, who will purchase the product, and how it will be distributed. These key informants noted that if there is not some type of commitment by funding agencies, foundations, or local governments to procure the products, then the effort just goes to waste, discouraging future investment.

Industry stakeholders experience significant barriers to partnering with USG. These include bureaucratic processes, complex reporting requirements, slow FDA approval systems, limited levels of translational funding, and overall lack of political will to partner. Of these, the two most important are:

- *The FDA approval system.* Some stakeholders avoid seeking FDA approval for products intended for use outside the US, though others believe there is significant value in going through the stringent FDA approval process as it assures high medical standards to different regulatory bodies worldwide and so expedites approval into other markets. Some believe FDA lacks the requisite expertise for neglected disease submissions and are inclined not to pursue FDA approval if the product is only intended to be used in just a few countries. Stakeholders viewed the European Medicines Agency approval process as better suited to global health needs and, if secured, as a means to expedite approval by the FDA. While some industry key informants argued that the WHO prequalification process is relatively easy and flexible, others commented that it was getting more cumbersome and not an easy way out. Device companies were more likely to seek CE Mark certification, an indication that a product meets all of the safety requirements of the European Union, as it was considered much simpler than the FDA approval process.¹⁵³
- *Low levels of translational funding from the USG.* The amounts of funding on the table for translational research are rarely at the level needed to incentivize industry. Or, as one key informant put it: “the pay lines are worse than ever and the funding is miniscule—the NIH spreads the stuff so thin you can’t even taste the peanut butter.” One individual indicated that the Defense Threat Reduction Agency provided a flexible funding mechanism that provided “real” money for drug discovery (e.g., against biological threats), but it would need to be expanded beyond biodefense to have a real impact on global health R&D.¹⁵⁴ Stakeholders thought the USG could transform itself to be a real player in global health innovation by changing its model completely, to approach innovation in the way that the Department of Energy did during the early days of the

Strengthening the United States Government's Role in Product Development for Global Health

Obama administration to advance renewable energy technology. As part of the 2009 American Recovery and Reinvestment Act, large market incentives (loan, guarantees, advanced market commitments) were offered for the development of “new or significantly improved technologies.”¹⁵⁵ The incentives were coupled with technical support from experts in the Department of Energy to help new technologies overcome the barriers to commercialization (the “valley of death”). Hundreds of submissions were received during the window for new applications. There is evidence that the program helped to bring down the cost of electricity produce by wind turbines, boost vehicle fuel efficiency standards, and expand solar energy production.

Industry engages with PDPs and PPPs to leverage expertise and financing not available within the parent company. Partnerships typically evolve after the parent company has done some preliminary discovery work either internally or in partnership with academia and has generated sufficient data to allow them to develop a credible proposal for funding. PDPs enable smaller companies to develop new skills in cross-sector collaborations that they can apply in fast growing markets such as India and China. Other companies engage directly with US military hospitals so they can do animal testing or eventually purchase medications for stockpiles.

Despite the benefits of collaboration, some stakeholders consider partnerships to be more difficult to manage than going it alone because goals are not always aligned. One criticism was that academic partners were more interested in rapidly publishing while industry was more cautious about when they would disclose information and give up their intellectual property (IP). Many stakeholders believed their companies already had end-to-end capabilities and supporting functions such as regulatory, finance, legal, toxicology, manufacturing, and distribution teams that could facilitate product delivery and registration, which is lost when the work is shifted outside of the parent company.

Some industry stakeholders favored technology transfer as an equally viable model for product development. They were willing to waive their IP rights to pre-qualified partners almost immediately upon FDA approval, transferring the technology to generic manufacturers with the right to produce and sell products. To minimize abuse of the IP, companies negotiated a price-ceiling agreement up front to ensure that the price of a product stayed within the affordable range for a consumer. One interviewee commented that Indian generic manufacturers were the best at high volume, low margin production. And even though the parent company recouped a small royalty from sales, they indicated they were not making much money in these geographies.

R&D needs to be coupled with improved models to expand access to innovations; these models, argued industry key informants, need to include local government engagement and increasing domestic commitment to health financing. Greater leadership from the USG, and from WHO and other multilateral organizations, to persuade local governments to more actively participate in advanced market commitments and overcoming regulatory hurdles could be instrumental in securing industry's ongoing R&D efforts. One example given was hepatitis C, which now has curative—but very expensive—drug treatments (called “direct acting antivirals”).¹⁵⁶ One key informant argued that middle-income countries will need to contribute domestic financing to scale up hepatitis C control programs.

Strengthening the United States Government's Role in Product Development for Global Health

Industry stakeholders highlighted novel access models that work to overcome the confluence of logistical barriers that impede market access. Stakeholders suggested the following examples: (a) providing microcredits and loans for medication procurement, (b) technology transfer to generic manufacturers, and (c) health worker education and training to address challenges of weak health systems. Two programs were cited as examples of such new models:

- *The Medicines Patent Pool (MPP)*, which aims to increase the accessibility of quality-assured generic products in LMICs.¹⁵⁷ One company noted that by placing its antiretroviral drug in the pool, it was able to sell the drug in 112 countries. So far the MPP has signed agreements with seven patent holders for 12 ARVs and for one hepatitis C direct-acting antiviral.
- *Patents for Humanity*, a voluntary prize competition run by the United States Patent and Trademark Office, which provides a certificate for expedited processing of patents working on humanitarian products.¹⁵⁸ The prize competition is based on the PRV program, but is less commercially valuable because prioritized examination can be purchased at the USPTO for just thousands of dollars.

Stakeholders also indicated the importance of harmonization initiatives, such as the work of the International Federation of Pharmaceutical Manufacturers (IFPMA) to promote regulatory harmonization.¹⁵⁹ BMGF has also spearheaded a CEO Forum on regulatory harmonization, particularly for the South African Development Community (SADC) where economic agreements are already in place; the forum is called the African Medicines Harmonization Program (AMRH).¹⁶⁰⁻¹⁶¹ It is hoped that there could be a NAFTA-type agreement for drugs that would allow for easier access across the entire African Union, not just limited to SADC.

PERSPECTIVES FROM NGOS, PDPS, AND FOUNDATIONS

Key informants from NGOs, PDPs, and Foundations shared industry's view that there are practical hurdles preventing collaboration with USG. It can be challenging, they argued, to work with the USG's piecemeal programs, disease-specific approach, and agency-centered R&D activities. Key informants co-fund R&D based on common goals with the US agencies, but the process is messy, with multiple bilateral MOUs with various US agencies, or with the same agency, on various diseases. "Walking the path of split collaborations" has been challenging and financially inefficient, and leads to duplication of efforts.

Stakeholders from this sector feel that the USG's funding for global health R&D is being hindered by the lack of an explicit priority setting process. Without such a process, congressional and US diplomatic priorities largely determine these investments, in terms of priority countries and diseases as well as budget allocations. USAID prioritizes countries of strategic importance and US military presence is another determinant of which diseases and regions are prioritized—an approach that can work against funding for R&D for certain diseases or countries. Within each government agency, R&D priorities are influenced greatly by reports from the National Academies as well as by advisory boards and task force committees. As such, influencing prioritization would mean penetrating the bureaucracy to reach various actors in these agency advisory panels as well as administrative and executive offices. Agencies like the President's Council of Advisors on Science and Technology (PCAST) are "heavyweights" in terms of their expertise and influence on priority setting; the growing focus on AMR is a result of the great push on this challenge from PCAST.¹⁶²

Strengthening the United States Government’s Role in Product Development for Global Health

NGOs who work on advocacy for increased global health R&D find the USG’s long, complex budget and appropriations process a major barrier. The rigidity of the system and the length of the process make it rare to see an immediate impact of any advocacy efforts. Budgetary increases may not guarantee additional R&D funding because of the interlinkage of the various agency budgets and because there are not direct R&D funding lines. For example, if funding is increased under the Labor, Education, HHS funding bill, the increment may not necessarily accrue to NIH, because more funds for NIH means less elsewhere. Informants also complained about the non-transparent “backroom deals” that fund certain offices such as BARDA.

While there is significant USG funding for global health translational research, key informants argued that there remains an imbalance, given that USG funding for global health R&D is concentrated at two ends of the spectrum—upstream basic science and downstream operational research. Stakeholders argued that with NIH focused mostly on basic science and early clinical trials, and USAID focused on implementation and operational research, there is an ongoing gap in the funding of translational and diagnostics research and product development platforms that are key to developing drugs, vaccines and technologies. Academic institutions, a major recipient of NIH’s extramural funding, have limited opportunities for securing additional funding for translational research. The void in product development funding is reflected in the relative lack of USG funding for PDPs compared with funding from European governments. For example, 14 percent of MMV’s total funding (received or pledged, from 1999–2020) has come from UK DFID, and only four percent from US agencies like USAID and NIH.¹⁶³ Most of MMV’s funding (60 percent) has come from BMGF, the dominant US funder of PDPs. Key informants argued that Europe has a more reliable support and funding system for PDPs and understands the PDP model better.

Key informants had mixed views on the PRV, but felt it was too early to judge its impact and its potential may not yet have been reached. They praised the FDA for playing a crucial role in popularizing this incentive and trying to bring more partners and resources to neglected disease R&D. Since the PRV is a commercial instrument, information on which products are being developed lives within the companies themselves and may not be publicly available—which makes it hard for people see the full impact of the PRV on drug development. Nevertheless, several key informants pointed out that PRVs have had only a short track record of success and can have unintended consequences. Expanding PRVs too much would make them less valuable on the market. There is also some concern that the PRV scheme does not guarantee access to products, especially by the populations who need it the most.

Stakeholders had positive views on their experiences working with industry and generally saw benefits from greater USG-industry collaboration. While some work with industry on early stage research, tech transfers, knowledge sharing, and drug and vaccine development, others concentrate more on the delivery side to ensure access and affordability of medicines. One example cited was the public-private WIPO Re:Search consortium, which provides access to IP, including pharmaceutical compounds, technologies, know-how, and data for global health R&D.^{164,165} By the end of 2014, the initiative had facilitated 70 research agreements between consortium members. Most key informants argued that while criticism of industry is sometimes warranted for its genuine profit-mongering practices, constant attacks on the sector could overshadow its efforts to develop drugs and vaccines and to aid technology transfers.

Strengthening the United States Government's Role in Product Development for Global Health

BMGF is an influential funder of global health R&D, and most NGOs and PDPs interviewed received funding from the foundation. The result is that R&D prioritization within these organizations is greatly influenced by the priorities of BMGF. This influence can have benefits, argued the key informants, as long as the priorities help in making advancements in a field where investments are highly risky. However, concerns were also expressed about BMGF's changing priorities, the seriousness of its commitment to funding PDPs, and the recent shift in its focus away from vaccine development through PDPs towards industry players. This shift may have resulted from the high risks and costs involved in funding translational research and vaccine development and the Foundation's experience with the RTS,S malaria and TB vaccines, which proved to be quite expensive (\$200 million was provided by BMGF for RTS,S).¹⁶⁶ Some key informants believed that part of this shift may be due the fact that the Global Health Division is now led by someone who came from industry, which may have resulted in more grants shifting towards industry and away from PDPs. While the WHO's Product Development for Vaccines Advisory Committee (PDVAC) could create momentum to support PDPs, key informants stated that it is receiving some pushback from BMGF.¹⁶⁷

Improving the USG's poor coordination with the WHO would be helpful to the USG's global health R&D efforts. Some key informants argued that the US does not recognize the significance and reputation enjoyed by the WHO in developing countries in Asia and Africa. Due to the lack of coordination with the WHO, USG processes differ from the WHO's processes, creating unnecessary and time consuming bureaucratic hurdles.

Section 7. Stakeholders' Suggestions for Reform Recommendations

In this section, we summarize the six main suggestions given by key informants for reforms that could improve the way in which the USG supports global health R&D.

1. The USG should implement strategies to support leadership and collaboration at the Agency level

USG stakeholders recommended a “Manhattan project” type program for global health R&D targeted to leaders (not necessarily at the Secretary level) to improve key competencies in USG agencies and overcome the challenge of maintaining individual agency mission while working collaboratively. This approach was one of the reasons for the success of PEPFAR, with each group making compromises to increase impact. USG stakeholders emphasized that senior leaders should drive and take responsibility for such an initiative, otherwise progress will be incremental. Some USG stakeholders argued that leadership needs to come from the White House or Congress, otherwise it will be difficult to bring all relevant agencies to the table, though others worried that this kind of forced, “top-down” collaboration would be a mistake. USG stakeholders noted that Congress or the White House should provide new resources, clearly defined goals, and budgetary authority for this kind of “Manhattan Project” type program.

USG stakeholders expressed a need for more joint stakeholder meetings to ensure alignment of priorities to expedite product development and to facilitate hand-offs to avoid gaps in the development cycle (they noted that cancer has done more of this than other disease areas). Key informants from USG believe that many of the challenges are practical problems related to access, financing, and delivery of the products that are “intervention ready.” They cautioned against developing a prescriptive framework, noting the importance of diversity and flexibility. Non-USG actors also noted that greater flexibility of funding would improve the investment environment and promote the free exchange of ideas. One USG stakeholder suggested that an outside partner or advocacy group could play a convening role.

The USG should create a taxonomy of global health R&D and clearly define R&D to better track resource allocations, which would allow OMB to better track resources across the board. OSTP was mentioned as the group most likely to engage in this type of effort. Such tracking could also help to align different research activities across USG agencies; avoid duplicative efforts; increase cost effectiveness; and potentially drive a more integrated, streamlined approach in targeting funding. While USG reporting mechanisms are cumbersome, stakeholders were quick to point out that the agencies are answerable to Congress and taxpayers to make sure that public funds are used wisely, so reporting requirements are essential. But streamlining reporting requirements could be a helpful innovation.

A new forum or blue ribbon task force in the NIH could be established to help with global health R&D priority setting. This task force could incorporate lessons from other sectors, such as from PCAST or the American Energy Innovation Council.¹⁶⁸

2. The USG should invest in R&D capacity building in LMICs

USG stakeholders believe that more funding should be invested in developing foreign investigator expertise, research capacity within LMIC countries, and regulatory science so that solutions become sustainable. One avenue to achieve this would be to properly fund the Fogarty Center to support in-country capacity building. The World Bank and the National Academy of Medicine could be two key partners for this work, as they are well positioned to forecast where the most significant health problems will unfold. The US Science Envoy Program is advocating for in-country R&D capacity building, and this advocacy should be matched with USG funding. For example, the program is advocating for

Strengthening the United States Government's Role in Product Development for Global Health

vaccine R&D capacity building in the Middle East and North Africa (MENA) region and the establishment of a vaccine research institute in Saudi Arabia, but funds will come from MENA government investments and not the US.¹⁶⁹ Bolstering local national regulatory systems to attract manufacturing capacity and create infrastructure to ensure the safety and quality of products could also help sustain investment for key programs, such as PEPFAR.

3. The USG should step up its efforts on collaboration and knowledge exchange with outside partners, both domestically and internationally, to help inform global health R&D prioritization and improve R&D efficiency

The USG should work more closely with the WHO, which is well placed to lead the prioritization of global health R&D and to support regulatory systems around the world. As the WHO commands international respect in the field, USG should collaborate more closely with the organization to develop new R&D strategies, guidelines, regulations, and operational tools. For example, the USG could develop a partnership with the WHO to strengthen the WHO Global Observatory on Health Research and Development or to harmonize regulation across the WHO and FDA.¹⁷⁰ Non-USG actors also noted that the European governments support the WHO, which is generally understaffed and underfunded, by seconding government personnel to the organization. This builds working relationships and helps align priorities in the country of origin.

Industry stakeholders recommend greater collaborative leadership from two USG partners—BMGF and WHO—as a way to stimulate more rapid innovation. Priorities should be established based upon an unbiased outlook, driven by science and need, and not by overarching political and economic parameters. Speed is of the essence to maximize R&D impact and without synergistic oversight of the entire global health portfolio, there will be continued development delays and wasted expenditure on products of limited use.

The USG should better engage with industry and nongovernment actors to share knowledge and create economies of scale. To increase interaction with industry, the USG can use PDPs that specialize in such interaction. One example given of such a platform was the Anacor/MMV collaboration, a successful drug development partnership for malaria.¹⁷¹ Another valuable knowledge platform would be a global repository of data on negative trials. The single largest “black hole,” said the industry key informants, is not having access to data and information on trials across the industry that were negative. Significant lessons can potentially be drawn from such negative trials, which would be valuable when similar products are being developed. This lack of transparency often leads to duplication of cost-intensive trials. Creating a repository of this information that would be available either in the public domain or accessible with certain permissions could significantly benefit early-stage R&D.

There are valuable lessons for the USG to learn from Europe's successes in creating an infrastructure to fund global health R&D. For example, key informants argued that European governments are more willing to fund PDPs and have mechanisms to do so via foreign ministries. The USG could adopt a similar mechanism to provide funding through foreign assistance organizations (such as PMI or PEPFAR). There was widespread support among key informants for the USG to step up its funding for PDPs, including PDPs housed in US universities. One key informant, who works in a PDP housed at a university, argued that housing PDPs in academic institutions has several advantages—for example, it can save costs since labs are already in place, the PDP benefits from having academic faculty deeply engaged, and universities have independence from outside agendas and priorities. Another example that key informants cited of a successful European approach is the EMA's development of Article 58 in partnership with the WHO, allowing EMA to offer a scientific opinion on products that will not be used

Strengthening the United States Government's Role in Product Development for Global Health

in the European market.^{172,173} Since its introduction in 2004, seven medical products have received a positive scientific opinion, which include antimalarial, hepatitis and postpartum hemorrhage drugs.¹⁷⁴ Article 58 offers a potential lesson for USG: it could be valuable to expand the remit of the existing FDA initiative on providing tentative approval for HIV drugs for use by PEPFAR to include additional global health diseases and conditions.

4. The USG should allocate funding more strategically to address gaps in product development

All stakeholders believed that there should be an increase in USG funding for global health R&D, including providing better incentive mechanisms or innovative and additional financing mechanisms. Funding should strategically address the gaps in product development, especially conducting clinical trials and in manufacturing, and should better support high-impact, breakthrough technologies. This strategic effort could be guided by the Office of Global Affairs in HHS, the WHO, and WHO's expert advisory groups. Non-USG actors suggested that the federal government could increase its support for industry research directly, noting the SBIR has mainly benefitted small players and that the government has experimented with this model to develop clean energy technologies.^{175,176}

OMB is in favor of setting evidenced-based targets for R&D funding and disease-specific priorities in the budgeting process, but other USG agencies are concerned that targets would be harmful. For example, targets might underestimate the spending that is already there and inadvertently reduce R&D funding. Given the annual US budget cycle, it would be difficult to plan and to proscriptively implement a budget with R&D targets. USG stakeholders outside OMB argued that more flexibility and clearer prioritization would be better than earmarking funds. They also cited concern about too much transparency in R&D allocations because it creates an easy target for people who want to strike out certain investments (e.g., for reproductive health). Targets may also bias funding towards R&D products with an immediate impact, undercutting R&D products with longer development periods.

Some stakeholders both inside and outside the USG believe that the government should participate in an international pooled fund for global health R&D, but many government stakeholders are strongly opposed to this proposal. The WHO's Consultative Expert Working Group and many global health advocates have called for each country to contribute at least 0.01% of its gross domestic product (GDP) to global health R&D, with 20-50% of the funding going to a pooled fund.¹⁷⁷ Some key informants believe that a sustainable and constant funding stream such as this one is necessary to achieve long term goals and recommended that the G7 establish the fund to be managed by a public-private stakeholder board accountable for a portfolio of products.¹⁷⁸ This streamlining and explicit decision making mechanism could help in strengthening the value chain of global health R&D from early stage clinical trials to country level implementation. While product development is not a key WHO strength, they argued, the WHO could serve as the arbiter and facilitator for setting R&D priorities. But many other stakeholders strongly opposed the idea of USG supporting such a pooled fund. As the largest funder of global health R&D, they argued, the USG has little interest in relinquishing its authority to a group that may have poorly defined objectives. USG spending is based on mandates and authorities within its law; it is not possible to suspend current law and divert funding from designated areas to a fund over which USG has no control. In addition, while these stakeholders recognized that there are inefficiencies and disconnects in bringing products to market, there have been many positive results in recent years. They did not accept the notion that global health R&D lacked funding or that funding was allocated inappropriately and felt that these notions were not based on sound evidence.

Strengthening the United States Government's Role in Product Development for Global Health

Creative and innovative approaches to R&D financing should be tried. Suggested examples were:

- Explore ways in which USG could support European institutions that are conducting global health R&D, and European governments could support US institutions conducting this type of research;
- Support blended financing mechanisms to bring together public, private, and philanthropic funding;
- Create a new fund, supported by the G20 countries, modeled on Japan's Global Health Innovative Technology Fund, which brings Japanese and non-Japanese organizations together to spur innovation.¹⁷⁹

5. The USG's push and pull incentive mechanisms should be refined to improve their impact

Refining existing mechanisms could improve the odds of new products reaching patients who need them the most. For example, the PRV could be redesigned to include commitments to register the drug and make it available and affordable to patients and treatment providers. Another stakeholder suggested commissioning of requests for applications (RFAs) and requests for proposals (RFPs) targeted directly at PDPs, noting that while the WIPO Re:Search consortium has been a positive addition, it will not sustain industry engagement. There was widespread interest and excitement about BARDA's recent launch of CARB-X, which is seen as a potentially important PPP arrangement to incentivize anti-bacterial drug development.¹⁸⁰

Industry actors believe that the USG, WHO, and other organizations should be more creative in developing models and incentives that are substantial enough to keep the private sector engaged in the face of high risk and limited market return. Academic partners and small startup companies benefit the most from NIH funding and while they may be valuable partners, they often have a steep learning curve and may never be successful in getting products to market. Current market incentives such as the PRV are helpful, but there needs to be far more funding available throughout the development continuum. The BARDA and DARPA models are both frameworks that should be expanded beyond biodefense.

6. Scaled up and more strategic advocacy efforts could help improve USG support for global health R&D

Strategic advocacy and "good story telling" could help to improve funding and prioritization of global health R&D. Stakeholders indicated that while it can get routine for advocacy groups to push their messages out on an ongoing basis, they should be "primed" with critical facts and good success stories that can capitalize on situational events to propel policy initiatives forward. Building relationships with the NIH, OMB, agency heads, and expert committee members can be crucial in building support before major decisions are made on advocacy efforts. Linking people working on global health issues, whether industry or NGOs, with legislators is also important for impactful advocacy. Advocacy groups *can* help to boost R&D funding. For example, NIH funding doubled over the period FY1998 to FY2003 from \$13.7 billion to \$27.1 billion, in part through NIH Director Harold Varmus's efforts to engage outside advocacy groups to influence Congress as well as individual institutional leaders pushing for more funding.¹⁸¹ Rotary and BMGF have successfully lobbied for supplemental funding for polio.

Creative approaches to advocacy are needed, such as showcasing the economic benefits of global health R&D and its potential to create jobs. These approaches could potentially help generate more interest than talking about global health R&D itself. MMV adopted a similar approach in which its researchers showed that funds invested by the UK and Australia into the PDP were being reinvested back in their own countries in terms of publications, PhD student enrollment, and grants. This framing is a counter-argument to the notion that development aid—a common source of funding for PDPs—just goes into a black box.

Strengthening the United States Government's Role in Product Development for Global Health

Influencing key legislation, such as the End Neglected Tropical Diseases Act (Bill HR 1797), which is currently stalled in Congress, is also important. This act aims to “extend the USAID’s NTD Program to target more diseases and better integrate programs, direct the US Department of Health and Human Services to research the impact of NTDs in the US and require US policymakers to advocate for increased NTDs efforts among international institutions such as the World Bank and United Nations. The bill will also create one or more NTD centers of excellence and establish a panel on intestinal worm infections to encourage increased R&D for tools to diagnose, prevent, treat and control NTDs.”^{182,183} Like the PRV, the provisions of this bill could be instrumental in supporting global health R&D. Another legislative example is the Global Development Lab Act of 2016 (HR 3924), which passed the House in September, 2016.¹⁸⁴ This Act establishes key duties for the Lab related to the application of innovation to addressing extreme poverty; the discovery, testing, and scaling of development innovations; forging partnerships across sectors; using “innovation-driven competitions to expand the number and diversity of solutions to challenges of development”; and “supporting USAID missions and bureaus in applying science, technology, innovation, and partnership approaches to decision-making, obtainment and program design according to the legislation.”

Advocacy efforts should include pushing for regulatory review processes for global health products to be harmonized across countries, especially at the regional level, to facilitate clinical development and maximize the impact of investments. A uniform technical dossier across regions, for example, would allow for easier operations of pharmaceutical companies. Streamlining regulations should be complemented with fast track approvals where appropriate, based on a risk to benefit ratio approach. Stringent approval is still necessary, but, as shown by the FDA’s approval of bedaquiline for MDR-TB, if a condition has a high mortality rate, this should be factored into the review process.

Many stakeholders believe that FDA can play an important mentoring role in the harmonization of regulatory processes while also building capacity by providing training on regulatory processes to other countries. This global coordination could help in establishing a more global regulatory framework and in finding the right regulatory balance. Developing this framework and finding this balance could be achieved through information sharing and bringing together regulators from multiple countries and agencies, including the WHO, as was seen in the case of the Ebola clinical trials. Some stakeholders suggested that if more funding becomes available for global health R&D, staffing should be ramped up at the FDA to deal with the time-consuming processes.

Conclusions and Recommendations

Our review of the literature combined with interviews with a diverse array of stakeholders across the public and private sectors has shown that the USG clearly plays a vital role in supporting global health R&D. Its outsized impact and influence is reflected in the fact that it is by far the most significant funder of global health R&D globally, especially among government funders. This dominance in funding is coupled with many other spheres of influence upon the global health R&D landscape. These include its innovative mechanisms to rapidly marshal attention and resources towards product development in tackling global crises (as seen with the Ebola and Zika Grand Challenges and BARDA's support of Ebola and Zika countermeasures) and its world-renowned research and technical agencies that help fuel global health innovation, including NIH and CDC.

Nevertheless, our study has also highlighted several areas of concern and ways in which the USG's role in global health R&D is being weakened or even threatened. These include funding levels that are in decline, under-use of potentially important agencies, an ongoing core challenge in improving communication, collaboration, and alignment within and between different agencies, and missed opportunities to better engage with the WHO and other international actors.

We end our report by drawing nine main conclusions related to ways in which USG support for global health R&D could be strengthened. We have linked each of these conclusions with our recommendations on policy proposals, solutions, or next steps.

Conclusion 1: There is an ongoing struggle to find the correct balance between USG agency autonomy and greater inter-agency coordination

Coordination is often associated with centralized control, though it can simply mean more information sharing. The challenge of coordination has been an ongoing concern, as highlighted, for example, by GHTC's seventh annual policy report published in April, 2016, which noted that "US efforts can be hampered by the fractured nature of the US health R&D infrastructure."¹⁸⁵ We heard many case studies from stakeholders of the negative consequences of this fracturing—from microbial samples not being shared across agencies to the near-impossibility of setting up contractual relationships that would allow investigators at different agencies to work on a shared project.

The "positive consequences" of the fractured USG infrastructure for global health R&D has received less attention. It is clear from our study that several high level USG stakeholders, including those who are investigators themselves, believe passionately that there is great value in letting agencies operate autonomously. Different agencies have their own mandates and missions, their unique expertise, and their own ways of doing business. "Letting a million flowers bloom" in this way may well be an approach that generates more innovative ideas than trying to have all agencies in lock-step.

Recommendations: Informing the debate on how best to facilitate coordination to better leverage USG funding and build efficiencies will require careful analysis of the problems and robust evidence on which solutions will work best. The failure of the GHI to gain traction shows the limits of attempting to force inter-agency collaboration. But is there a better mechanism for improving the architectural arrangements within the USG to avoid duplicative efforts and maximize synergies? Answering this question could have profound benefits, but will require in-depth analysis of the current arrangements and the development, piloting, and evaluation of new inter-agency coordination mechanisms. Such an analysis should also learn lessons from the success of mechanisms such as PACCARB and PHEMCE.

Strengthening the United States Government's Role in Product Development for Global Health

Conclusion 2: The USG is missing opportunities to strengthen its collaboration with other actors in the global health R&D space

Industry, NGOs, foundations, and PDPs want the USG to step up its collaborations with them. An important conclusion from our study is that there seems to be a real hunger for the USG to become a much more serious participant in and funder of public-private PDPs. This would require a shift in thinking—it might mean, for example, that the NIH model of sending nearly all research dollars to academia would evolve to one in which a portion of funding goes instead to the highest-impact PDPs. One of the disconnects in USG support for global health R&D, which is seen in other donor countries, is that funding is dominated by its biomedical science agency (NIH) rather than its development agency (USAID). This matters because science funding and development agency funding have different priorities, as shown by our study. As Mary Moran, Executive Director of Policy Cures, has argued, “science funding is shaped by biomedical research paradigms rather than global health paradigms” and it is often “investigator driven, rather than being linked to development priorities and strategies—for instance, while new tools for post-partum haemorrhage (PPH) are a development priority, they receive very little science funding.”¹²

Recommendations: While we acknowledge that NIH’s basic science, investigator-driven, and university-dominated funding approach has been an extraordinary engine of discovery, we believe there is scope for NIH to support more downstream translational research without straying too far from its core mandate. Increased USG funding to PDPs would both increase opportunities to collaborate with a broad array of global health R&D actors from the public, private, and philanthropic sectors and would provide more support for translational and late-stage product development. USAID could play an expanded role in support of PDPs, including developing new reproductive health technologies, such as tools for PPH. The role would be a natural fit for USAID’s core mission. Robert Clay, USAID’s deputy assistant administrator in the Bureau for Global Health, coined the term “bold endgames” in global health, referring to outcomes such as an AIDS-free generation and an end to avertable child mortality.¹⁸⁶ These outcomes will only be possible with the development of new health technologies, and so it would make sense for USAID to match its “bold endgames” rhetoric with scaled up support for product development.¹⁸⁷ If support from foundations for PDPs is at risk of declining in the future, as suggested by our study, we believe USG should position itself to fill this void.

Improving USG’s collaborative efforts with the WHO is low hanging fruit that could have a large payoff. Our study suggested that there is a frostiness in the USG-WHO relationship, which has unfortunate consequences. Despite WHO’s weaknesses, which were on full display at the start of the West African Ebola outbreak, the organization is still the most important global body for setting norms and standards in global health. The USG’s global health R&D efforts, including its in-country trials and other studies, could be facilitated by closer working with the WHO.

Conclusion 3: The declining USG funding for R&D, including global health R&D, is an existential threat to the USG’s impact, influence, and credibility within the R&D landscape and jeopardizes the USG’s reputation as a global leader in innovation

It is no exaggeration to say that the falling R&D funding levels represent an existential crisis in US support for innovation writ broad, hamstringing agency efforts, and sending a signal to the world that the US may be relinquishing its leadership role. The 2015 surge in funding for R&D for Ebola and other African VHF gives a falsely reassuring picture—in fact, the surge hid a decline in overall funding for global health R&D other than Ebola and other VHF. This decline is already being felt at the agency level, particularly at the CDC, and there is evidence that it is slowing down innovation across the spectrum of

Strengthening the United States Government's Role in Product Development for Global Health

neglected diseases and conditions. As one stakeholder noted, there is a limit to one's ability to "rob Peter to pay Paul." The USG has shown that it can mobilize R&D funds for time-bound emergencies, but this is little consolation when it comes to the lack of sustained funding needed to tackle "non-emerging" conditions of poverty that primarily affect populations outside of the US—such as African sleeping sickness, Chagas disease, and MDR-TB.

Recommendations: There has never been a more important time for the advocacy community to make the public health, economic, business, and moral case for USG support for global health R&D. This is particularly true given that the incoming Administration has not made any clear pronouncements about its commitment to global health funding. A December 19, 2016 analysis by the *New York Times* of the global health positions of the new Administration noted that "advocates for the poor, health experts and government officials admit that they have no idea what direction the incoming Trump administration is going to take."¹⁸⁸ The analysis suggested that the Trump administration will pursue an "America first" approach to global health. Given the early indications that economic and business interests will dominate, there is a time-critical need to document and demonstrate to the new administration the extraordinary returns to investing in global health R&D. For example, a forthcoming analysis by GHTC and Policy Cures Research estimates that out of every dollar that USG invests in global health R&D, around 89 cents goes to supporting U.S.-based researchers and product developers and building, improving U.S. research and technological capacity, and providing a direct investment into the US economy.¹⁸⁹ An analysis by Policy Cures and DSW, an international health NGO, found that every Euro invested by European governments into R&D for poverty-related neglected diseases and conditions brought an additional 1.47 Euros in investment from outside into Europe.¹⁹⁰

Conclusion 4: BARDA's ecosystem of push and pull mechanisms and the Other Transaction Authority used by BARDA and DARPA to establish long term partnerships with industry have been successful incentive mechanisms

BARDA's integrated model of push and pull mechanisms, which requires significant funding, has been effective in addressing market failures for a number of conditions. There has been enough flexibility to allow its mandate to be expanded to include AMR, which may have opened the door to finding ways to include additional global health challenges. Our study has suggested that long term portfolio partnerships established through OTA has been a "game changer," for example in incentivizing companies to develop antimicrobials. While it would be hard to make the case that the PRV has had a similar effect, we believe it is much too early to write it off. Outside of this study, companies have told us that the PRV is the reason that they entered the neglected disease space. At a presentation given at Duke University in 2013, for example, Eugene Seymour, CEO of NanoViricides discussed how the PRV had incentivized his company to start working on dengue.⁴⁴

Recommendations: These successful incentive mechanisms should be expanded to other diseases and replicated by other agencies and offices. Not all market failures have the same causes, and a BARDA-type model used for different obstacles may need refinement to make it specific to the actual challenge. For example, while incentivizing molecule discovery may be one obstacle, incentivizing manufacturing of sufficient quantities of vaccine at an affordable price may be a very different one.

Conclusion 5: Better leveraging of what is working well is a principle that can also be applied when it comes to the under-use of effective agencies

An important finding of our study is that there are some key resources, such as the DoD's medical research capabilities, that are under-recognized and under-used. The DoD's overseas labs have greatly under-used potential for global health R&D, including for vaccine development.

Strengthening the United States Government's Role in Product Development for Global Health

Recommendations: The new Administration has pledged a huge increase in defense spending, perhaps by as much as \$500 billion.¹⁹¹ While there are certainly risks in the “securitization” of global health (e.g., it can be dangerous to conflate the principles of public health with those of national security), this increase may represent an avenue to boost USG support for global health R&D if some of it can be directed to DoD’s global health research.

Conclusion 6: Although the USG is generally seen as a behemoth—a giant, inflexible bureaucracy—it has the ability to expand its global health R&D remit

We found an encouraging number of examples of legislative and bureaucratic flexibility. Legislation has been adopted to broaden USG’s role in global health R&D. Agency mandates have been revised to include additional diseases or conditions.

Recommendations: Important lessons could be learned from an analysis of how these shifts happened—for example, who were the key actors involved and what were the levers that allowed change to happen? These lessons could potentially be applied to find other valuable ways for the USG to support additional R&D efforts. To give one example, there may be a route by which PHEMCE could take on additional global health conditions or diseases.

Conclusion 7: There is no standard definition of what constitutes global health R&D used uniformly across USG agencies, including OMB.

USG needs a clear definition of what constitutes global health R&D, which will allow better tracking of funding flows and help drive more explicit prioritization

Recommendations: A definition and typology should be urgently developed, which would go a long way to enhancing the efforts of researchers, advocacy groups, and the government itself to track funding levels, distributions, and trends. This in itself could have knock-on benefits, including helping to align R&D across agencies and even to drive the kind of explicit R&D prioritization process that many stakeholders called for. The timing is right for agreeing on such a definition, given that the Organization for Economic Cooperation and Development-Development Assistance Committee (OECD-DAC), a forum of 29 donors, has (a) recognized the increasing importance of donor support for global public goods (GPGs) such as global health R&D, and (b) started a process to develop improved and more comprehensive measures of official development assistance (ODA) that include funding for such GPGs.¹⁹² As part of this process, OECD is currently working on a new statistical measure, the Total Official Support for Sustainable Development (TOSSD), which aims to enhance international accountability by increasing transparency and rigor in reporting on development finance beyond ODA.¹⁹³ TOSSD is likely to include funding for GPGs, including global health R&D, making it important that USG investments in such research can be properly captured.

Conclusion 8: The future of USG support for global health R&D must include a transition to greater support for developing in-country R&D and regulatory capacity

To tackle future global health challenges, development assistance for health—including from USG—must include increasing support for in-country R&D. The Commission on Investing in Health made the case that the entire world, and particularly high-poverty regions, is left vulnerable by the under-funding of product development for global health, including for pandemic preparedness and tackling AMR.¹⁹²

Recommendations: In the SDGs era, an increasing proportion of DAH that is directed to individual countries should be spent on developing domestic R&D capabilities. Fogarty would be ideally placed to provide leadership for such a strategy.

Strengthening the United States Government’s Role in Product Development for Global Health

Conclusion 9: Advocacy for global health R&D has an impressive history of success and will have a particularly important role in the years ahead.

There is an urgent need to continue developing, testing, and refining advocacy efforts to influence major decision makers such as the Congress. Advocacy efforts have been crucial in pushing forward important legislation and past global health initiatives.

Recommendations: Building an evidence base on “what works” in mobilizing USG support for global health R&D—for example, whether it is emphasizing the number of lives saved or the boost to the US economy—has gained increasing importance given how little is known about the next Administration’s global health commitment. One strategy to consider is to focus on the link between adequate investment in R&D as a critical precursor for the USG to maintain its preeminent position as a global innovator.

References

1. United Nations International Children's Fund. Levels & Trends in Child Mortality. http://www.childmortality.org/files_v20/download/igme%20report%202015%20child%20mortality%20final.pdf. Published September 2015. Accessed January 20, 2017.
2. Jamison DT, Summers LH, Alleyne G, et al. Global health 2035: a world converging within a generation. *Lancet*. 2013;382(9908):1898-1955. doi: 10.1016/S0140-6736(13)62105-4
3. Murray CJ, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9947):1005-1070. doi: 10.1016/S0140-6736(14)60844-8
4. World Health Organization. Global Health Estimates (GHE). http://www.who.int/healthinfo/global_burden_disease/en/. Accessed February 16, 2017.
5. Houweling T, Karim-Kos H, Kulic M, et al. Socioeconomic inequalities in neglected tropical diseases: a systematic review. *PLoS Neglected Tropical Diseases*. 2016;12(10(5)):e0004546. doi:10.1371/journal.pntd.0004546
6. Fenwick A. The global burden of neglected tropical diseases. *Public Health*. 2012;126:233-236. doi: 10.1016/j.puhe.2011.11.015
7. Policy Cures. Saving Lives and Creating Impact: Why Investing in Global Health Research Works. <http://www.policycures.org/downloads/Saving%20lives%20and%20creating%20impact.pdf>. Published 2012. Accessed December 7, 2016.
8. Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. *The Lancet*. 2002;360(9337):2188-2194. doi: 10.1016/S0140-6736(02)09096-7
9. Pedrique B, Strub-Wourgaft N, Some C, et al. The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment. *Lancet Global Health*. 2013;1(6):e371-e379. doi: 10.1016/S2214-109X(13)70078-0
10. Cohen J, Dibner MS, Wilson A. Development of and Access to Products for Neglected Diseases. *PLoS* 2010;5(5). doi: 10.1371/journal.pone.0010610
11. Cohen J, Sturgeon G, Cohen A. Measuring progress in neglected disease drug development. *Clin Ther*. 2014;36(7):1037-1042. doi: 10.1016/j.clinthera.2014.05.004
12. Moran M. The Grand Convergence: Closing the Divide between Public Health Funding and Global Health Needs. *PLoS Biol*. 2016;14(3). doi: 10.1371/journal.pbio.1002439
13. Wexler A, Valentine A, Kates J. The U.S. Global Health Budget: Analysis of Appropriations for Fiscal Year 2016. Kaiser Family Foundation. <http://kff.org/global-health-policy/issue-brief/the-u-s-global-health-budget-analysis-of-appropriations-for-fiscal-year-2016/>. Published January, 20 2016. Accessed December 5, 2016.
14. Moran M, Chapman N, Abela-Oversteegen L, et al. Neglected Disease Research and Development: The Ebola Effect. Policy Cures. <http://policycures.org/downloads/Y8%20GFINDER%20full%20report%20web.pdf>. Published 2015. Accessed January 17, 2017.
15. Moran M, Guzman J, Chapman N, et al. Reproductive Health: R&D for the Developing World. Policy Cures. <http://www.policycures.org/downloads/RH%20full%20report.pdf>. Published 2014. Accessed February 16, 2017.

Strengthening the United States Government's Role in Product Development for Global Health

16. Moran M, Chapman N, Abela-Oversteegen L, et al. Neglected Disease Research and Development: The Ebola Effect. Policy Cures. <http://policycures.org/downloads/Y8%20GFINDER%20full%20report%20web.pdf>. Published 2015. Accessed February 16, 2017.
17. G-FINDER Public Search Tool FAQ. Policy Cures website. <http://gfinder.policycures.org/PublicSearchTool/faq>. Published 2014. Accessed August 23, 2016.
18. Enhancing the Work of the Department of Health and Human Services National Vaccine Program in Global Immunization: Recommendations of the National Vaccine Advisory Committee: Approved by the National Vaccine Advisory Committee on September 12, 2013. Public Health Reports. 2014;129(Suppl 3):12-85. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4121882/>. Accessed February 16, 2017.
19. 2010 National Vaccine Plan. U.S. Department of Health and Human Services website. https://www.hhs.gov/sites/default/files/nvpo/vacc_plan/2010-Plan/nationalvaccineplan.pdf. Published 2010. Accessed February 16, 2017.
20. SMART Vaccines: Strategic Multi-Attribute Ranking Tool for Vaccines. The National Academies Press website. <https://www.nap.edu/smartvaccines/>. Accessed November 29, 2016.
21. Office of Global Affairs. AIDS website. <https://www.aids.gov/federal-resources/federal-agencies/hhs/office-of-global-affairs/index.html>. Updated June 19, 2012. Accessed October 3, 2016.
22. Consultative Expert Working Group on Research and Development: Financing and Coordination. World Health Organization website. <http://www.who.int/phi/cewg/en/>. Updated May 16, 2016. Accessed October 5, 2016.
23. Transatlantic Task Force on Antimicrobial Resistance (TATFAR). Centers for Disease Control and Prevention website. <http://www.cdc.gov/drugresistance/tatfar/>. Updated June 24, 2016. Accessed October 5, 2016.
24. BARDA'S Vision, Mission, and Values. Public Health Emergency website. <http://www.phe.gov/about/barda/stratplan/Pages/barda-vision-mission-and-values.aspx>. Updated February 16, 2017. Accessed February 16, 2017.
25. Division of Chemical, Biological, Radiological and Nuclear Medical Countermeasures. Public Health Emergency website. <http://www.phe.gov/about/barda/Pages/cbrn.aspx>. Updated September 12, 2014. Accessed February 16, 2017.
26. U.S. Department of Health and Human Services Assistant Secretary for Preparedness and Response. FY 2016 Budget in Brief: An Overview of ASPR's Budget Request and Strategic Priorities. <http://www.phe.gov/about/ofpa/Documents/bib-2016.pdf>. Published August, 2015. Accessed 27 October, 2016.
27. U.S. Department of Health and Human Services. Biomedical Advanced Research and Development Authority. 2016; <http://www.phe.gov/about/BARDA/Pages/default.aspx>. Accessed September 26, 2016.
28. U.S. Department of Health and Human Services. BARDA Strategic Plan 2011-2016. <https://www.phe.gov/about/barda/Documents/barda-strategic-plan.pdf>. Published October 4, 2011. Accessed February 16, 2017.
29. BARDA Strategic Plan 2011 – 2016: Introduction. Public Health Emergency website. <http://www.phe.gov/about/barda/stratplan/Pages/introduction.aspx>. Updated August 19, 2013. Accessed 27 October, 2016.
30. HHS enhances nation's health preparedness for radiological threats [news release]. U.S. Department of Health and Human Services website. <https://www.hhs.gov/about/news/2016/10/06/hhs-enhances-nation-s-health-preparedness-radiological-threats.html>. Published October 6, 2016. Accessed October 12, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

31. Robinson RA. Written Statement to the U.S. Senate Committee on Health, Education, Labor, and Pensions. *BARDA's Role in Medical and Public Health Preparedness and Response*. <http://www.help.senate.gov/imo/media/doc/Robinson2.pdf>. Published February 26, 2015. Accessed February 16, 2017.
32. Project BioShield. Medical Countermeasures website. <https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/>. Updated October 18, 2016. Accessed February 16, 2017.
33. Gottron F. *The Project BioShield Act: Issues for the 112th Congress*. R42349. U.S. Congressional Research Service. <https://fas.org/sgp/crs/terror/R42349.pdf>. Published October 12, 2012. Accessed December 20, 2016.
34. PHEMCE Mission Components. Public Health Emergency website. <http://www.phe.gov/Preparedness/mcm/phemce/Pages/mission.aspx>. Updated February 27, 2015. Accessed October 5, 2016.
35. Tarbet EB, Dorward JT, Day CW, Rashid KA. Vaccine production training to develop the workforce of foreign institutions supported by the BARDA influenza vaccine capacity building program. *Vaccine*. 2013;31(12):1646-1649. doi: 10.1016/j.vaccine.2012.06.041
36. Xccerating Global Antibacterial Innovation. CARB-X website. <http://www.carb-x.org>. Accessed October 12, 2016.
37. CARB-X: Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. Public Health Emergency website. <http://www.phe.gov/about/barda/CARB-X/Pages/default.aspx>. Updated July 28, 2016. Accessed October 27, 2016.
38. NIH Organization. National Institutes of Health website. <https://www.nih.gov/about-nih/what-we-do/nih-almanac/nih-organization>. Updated October 25, 2016. Accessed November 16, 2016
39. National Institutes of Health. *Biennial Report of the Director, Fiscal Years 2012 & 2013*. https://report.nih.gov/pdf/NIH_Biennial_Report_2012.pdf. Published 2012. Accessed February 17, 2017.
40. National Institutes of Health. *Congressional Justification of the NIH Fiscal Year 2017 Budget Request*. <https://officeofbudget.od.nih.gov/pdfs/FY17/31-Overview.pdf>. Accessed November 16, 2016.
41. NIAID Role in Research. National Institute of Allergy and Infectious Diseases website. <https://www.niaid.nih.gov/research/role>. Accessed November 16, 2016.
42. *HHS FY2016 Budget in Brief*. U.S. Department of Health and Human Services website. <http://www.hhs.gov/about/budget/budget-in-brief/nih/index.html>. Published February 2, 2015. Accessed November 29, 2016.
43. Our Mission and Vision. Fogarty International Center website. <https://www.fic.nih.gov/About/Pages/mission-vision.aspx>. Accessed November 16, 2016.
44. Congressional Justification for Fiscal Year 2017. Fogarty International Center website. <https://www.fic.nih.gov/About/Budget/Pages/2017.aspx#orgchart>. Accessed November 16, 2016.
45. National Center for Advancing Translational Sciences. FY2017 Budget Request. <https://ncats.nih.gov/files/FY17-justification.pdf>. Accessed November 16, 2016.
46. Reardon S, Tollefson J. Obama's top scientist talks shrinking budgets, Donald Trump, and his biggest regret. *Nature*. 2016;535:15-16. doi: 10.1038/535015a. Published July 6, 2016. Accessed November 10, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

47. Advisory Committee to the Director. National Institutes of Health website. <http://acd.od.nih.gov/>. Updated December 28, 2016. Accessed February 17, 2017.
48. Sizemore CF, Schleif AC, Bernstein JB, Heilman CA. The role of biomedical research in global tuberculosis control: gaps and challenges: A perspective from the US National Institute of Allergy and Infectious Diseases, National Institutes of Health. *Emerging Microbes & Infections*. 2012;1(7):e9-. doi:10.1038/emi.2012.21
49. About the NICBR. National Interagency Confederation for Biological Research website. <http://www.nicbr.mil/>. Updated November 30, 2016. Accessed February 14, 2017.
50. CRADAS Overview. National Institutes of Health, Office of Technology Transfer website. <https://www.ott.nih.gov/cradas>. Accessed October 14, 2016.
51. Mission, Role and Pledge. Centers for Disease Control and Prevention website. <http://www.cdc.gov/about/organization/mission.htm#>. Updated April 14, 2014. Accessed November 16, 2016.
52. Centers for Disease Control and Prevention. CDC Global Health Strategy 2012 - 2015. <http://www.cdc.gov/globalhealth/strategy/pdf/cdc-globalhealthstrategy.pdf>. Published June 29, 2012. Accessed September 26, 2016.
53. National Center for Emerging and Zoonotic Infectious Diseases. NCEZID Strategic Plan 2012 – 2017. CS234429-A. https://www.cdc.gov/ncezid/pdf/strategicplan_ncezid.pdf. Accessed February 17, 2017.
54. Uniting to Combat Neglected Tropical Diseases. London Declaration on Neglected Tropical Diseases. http://unitingtocombatntds.org/sites/default/files/resource_file/london_declaration_on_ntds.pdf. Published 2014. Accessed February 17, 2017.
55. U.S. Agency for International Development. President's Malaria Initiative Strategy 2015–2020. https://www.pmi.gov/docs/default-source/default-document-library/pmi-reports/pmi_strategy_2015-2020.pdf. Published April, 2015. Accessed December 1, 2016.
56. World Health Organization. Global Technical Strategy for Malaria 2016–2030. http://apps.who.int/iris/bitstream/10665/176712/1/9789241564991_eng.pdf?ua=1. Published 2015. Accessed October 20, 2016.
57. Board of Scientific Counselors, OI. Centers for Disease Control and Prevention website. <http://www.cdc.gov/oid/bsc.html>. Updated June 13, 2016. Accessed September 26, 2016.
58. Global Health - CDC and the Global Health Security Agenda. Centers for Disease Control and Prevention website. <https://www.cdc.gov/globalhealth/security/>. Updated February 11, 2016. Accessed October 7, 2016.
59. About Global Health Security Agenda. Global Health Security Agenda website. <https://www.ghsagenda.org/about>. Accessed 16 November, 2016.
60. Small Business Innovation Research. National Institutes of Health, Small Business Innovation Research website. <https://sbir.nih.gov/>. Accessed September 26, 2016.
61. Office of the Associate Director for Science: Technology Transfer Office. Centers for Disease Control and Prevention website. <http://www.cdc.gov/od/science/technology/techtransfer/>. Updated October 14, 2016. Accessed February 17, 2017.
62. The Task Force for Global Health. The Task Force for Global Health website. <http://www.taskforce.org/>. Accessed September 8, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

63. 2015 COR-NTD Meeting. Neglected Tropical Diseases Support Center website. <http://www.ntdsupport.org/news/2015-cor-ntd-meeting>. Published July 30, 2015. Accessed September 26, 2016.
64. Qvarnstrom Y, Wei-Pridgeon Y, Li W, et al. Draft Genome Sequences from *Cyclospora cayetanensis* Oocysts Purified from a Human Stool Sample. *Genome Announcements*. 2015;3(6):e01324–01315. doi: 10.1128/genomeA.01324-15
65. Developing a meningococcal A conjugate vaccine. Meningitis Vaccine Project. <http://www.meningvax.org/developing-conjugate-vaccine.php>. Accessed November 15, 2016.
66. What We Do. U.S. Food and Drug Administration website. <http://www.fda.gov/AboutFDA/WhatWeDo/default.htm>. Updated October 24, 2016. Accessed October 27, 2016.
67. FDA Organization. U.S. Food and Drug Administration website. <http://www.fda.gov/AboutFDA/CentersOffices/default.htm>. Updated September 9, 2015. Accessed October 27, 2016.
68. U.S. Food and Drug Administration. Justification of Estimates for Appropriations Committees Fiscal Year 2017. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM485237.pdf>. Accessed February 17, 2017.
69. Office of Global Regulatory Operations and Policy. U.S. Food and Drug Administration website. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/default.htm>. Updated January 24, 2017. Accessed February 17, 2017.
70. FDA awards nearly \$3 million for TB research [news release]. U.S. Food and Drug Administration website. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm228250.htm>. Published October 4, 2010. Accessed October 5, 2016.
71. Critical Path 2010 Update: Q's and A's. U.S. Food and Drug Administration website. <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm204289.htm>. Updated April 7, 2011. Accessed August 1, 2016.
72. Ridley DB, Grabowski HG, Moe JL. Developing Drugs For Developing Countries. *Health Aff (Millwood)*. 2006;25(2):313-324. doi: 10.1377/hlthaff.25.2.313
73. Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff (Millwood)*. 2016;35(5):776-783. doi: 10.1377/hlthaff.2015.1314
74. International Medical Device Regulators Forum. International Medical Device Regulators Forum website. <http://www.imdrf.org/>. Accessed October 12, 2016.
75. Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan. U.S. Food and Drug Administration website. <http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm>. Updated January 18, 2017. Accessed February 17, 2017.
76. Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act. Final order. *Fed Regist*. 2015;80(161):50559-50564.
77. Administration USFaD. Centers of Excellence in Regulatory Science and Innovation. <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm>. Accessed 27 October, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

78. U.S. Food and Drug Administration. Food and Drug Administration Broad Agency Announcement for the Advanced Research and Development of Regulatory Science. FDABAA-16-00122. <https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=f526e63aa7e70f2c79f1ada43e7147ef&cview=0>. Published February 23, 2016. Accessed 27 October, 2016.
79. About MDIC. Medical Device Innovation Consortium website. <http://mdic.org/about-us/>. Accessed 27 October, 2016.
80. Bureau for Global Health. U.S. Agency for International Development website. <https://www.usaid.gov/who-we-are/organization/bureaus/bureau-global-health>. Updated September 26, 2016. Accessed November 18, 2016.
81. U.S. Agency for International Development. FY 2016 Development and Humanitarian Assistance Budget Factsheet. https://www.usaid.gov/sites/default/files/documents/1869/FY2016DevelopmentBudget_FactSheet.pdf. Accessed 27 October, 2016.
82. U.S. Department of State. Congressional Budget Justification: Department of State, Foreign Operations, and Related Programs Fiscal Year 2017. <https://www.usaid.gov/sites/default/files/documents/9276/252179.pdf>. Published February 9, 2016. Accessed 27 October, 2016.
83. Center for Accelerating Innovation and Impact. U.S. Agency for International Development website. <https://www.usaid.gov/cii>. Updated January 12, 2017. Accessed February 17, 2017.
84. U.S. Global Development Lab. U.S. Agency for International Development website. <https://www.usaid.gov/who-we-are/organization/bureaus/us-global-development-lab>. Updated January 19, 2017. Accessed February 17, 2017.
85. Grand Challenges for Development. U.S. Agency for International Development website. <https://www.usaid.gov/grandchallenges>. Updated October 27, 2016. Accessed October 27, 2016.
86. U.S. Agency for International Development, Bureau for Global Health. USAID Health-Related Research and Development Progress Report. https://www.usaid.gov/sites/default/files/documents/1864/Health-Research-Report-2016-508_0.pdf. Published 2015. Accessed October 6, 2016.
87. U.S. Agency for International Development. Report To Congress: Health-Related Research and Development Strategy 2011–2015. http://pdf.usaid.gov/pdf_docs/pdacw525.pdf. Published December, 2012. Accessed October 27, 2016.
88. Global Funding of Innovation for Neglected Diseases. Sydney, Australia: Policy Cures Research; 2015. <https://gfinder.policycures.org/PublicSearchTool/>. Accessed October 11, 2016.
89. Center for Accelerating Innovation and Impact. U.S. Agency for International Development website. <https://www.usaid.gov/cii>. Updated January 12, 2017. Accessed February 17, 2017.
90. USAID HIV Vaccine Research and Development. U.S. Agency for International Development website. <https://www.usaid.gov/what-we-do/global-health/hiv-and-aids/technical-areas/hiv-vaccine-research-development>. Updated February 23, 2016. Accessed 27 October, 2016.
91. About the Department of Defense. U.S. Department of Defense website. <http://www.defense.gov/About-DoD>. Updated January 27, 2017. Accessed February 17, 2017.
92. Ashton B. Carter, Former Secretary of Defense. U.S. Department of Defense website. <http://www.defense.gov/About-DoD/Biographies/Biography-View/Article/602689/ashton-b-carter>. Accessed February 17, 2017.

Strengthening the United States Government's Role in Product Development for Global Health

93. About the Military Health System. Military Health System website. <http://www.health.mil/About-MHS>. Accessed November 16, 2016.
94. Defense Health Agency. Military Health System website. <http://www.health.mil/About-MHS/Defense-Health-Agency>. Accessed November 16, 2016.
95. Global Health Technologies Coalition. From idea to impact: How the US government can improve coordination of global health research and development. <http://www.ghtcoalition.org/pdf/From-idea-to-impact-how-the-US-government-can-improve-coordination-of-global-health-research-and-development.pdf>. Published November, 2014. Accessed September 10, 2016.
96. Michaud J, Moss K, Kates J. U.S. Global Health Policy: The U.S. Department of Defense and Global Health. Kaiser Family Foundation. <http://kff.org/global-health-policy/report/the-u-s-department-of-defense-global/>. Published September 29, 2012. Accessed November 16, 2016.
97. Mission. Walter Reed Army Institute of Research website. <http://www.wrair.army.mil/AboutWRAIR.aspx>. Updated February 17, 2017. Accessed February 17, 2017.
98. Translational Medicine. Walter Reed Army Institute of Research website. http://www.wrair.army.mil/ReAndDevelop_InfectDisRe_TranslationalMed.aspx. Updated February 17, 2017. Accessed February 17, 2017.
99. WRAIR Research and Development. Walter Reed Army Institute of Research website. <http://www.wrair.army.mil/WRAIRResearchAndDevelopment.aspx>. Updated February 17, 2017. Accessed February 17, 2017.
100. Naval Medical Research Center. Naval Medical Research and Development website. <http://www.med.navy.mil/sites/nmrc/NMRC/Pages/NMRC.aspx>. Accessed February 17, 2017.
101. Infectious Diseases. Naval Medical Research and Development website. http://www.med.navy.mil/sites/nmrc/NMRC/NMRC_Offices/Pages/IDD.aspx. Accessed February 17, 2017.
102. Prophecy (Pathogen Defeat). Defense Advanced Research Projects Agency website. <http://www.darpa.mil/program/prophecy-pathogen-defeat>. Accessed October 27, 2016.
103. Prabhakar A. Statement to U.S. Senate Subcommittee on Emerging Threats and Capabilities Armed Services Committee. *Strategy and Implementation of the Department of Defense's Technology Offsets Initiative in Review of the Defense Authorization Request for Fiscal Year 2017 and the Future Years Defense Program*. <http://www.darpa.mil/attachments/DARPA2016SASCTestimony4-1-2016.pdf>. Published April 12, 2016. Accessed October 27, 2016.
104. Salaam-Blyther T. *U.S. Global Health Assistance: Background and Issues for the 113th Congress*. R43115. U.S. Congressional Research Service. <https://fas.org/sgp/crs/row/R43115.pdf>. Published June 21, 2013. Accessed November 16, 2016.
105. Serafino N. *The Department of Defense Role in Foreign Assistance: Background, Major Issues, and Options for Congress*. RL34639. U.S. Congressional Research Service. <https://fas.org/sgp/crs/natsec/RL34639.pdf>. Published December 9, 2008. Accessed November 16, 2016.
106. National Defense Authorization Act. U.S. House Committee on Armed Services website. <https://armedservices.house.gov/hearings-and-legislation/ndaa-national-defense-authorization-act>. Accessed October 12, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

107. U.S. Department of Defense, Under Secretary of Defense (Comptroller). Defense Health Program: Fiscal Year (FY) 2017 Budget Estimates.
http://comptroller.defense.gov/Portals/45/Documents/defbudget/FY2017/budget_justification/pdfs/09_Defense_Health_Program/DHP_PB17_Vol_I-II.pdf. Published February, 2016. Accessed October 13, 2016.
108. The Mission and Structure of the Office of Management and Budget. The Office of Management and Budget website. https://www.whitehouse.gov/omb/organization_mission. Accessed October 8, 2016.
109. Executive Office of the President. The White House Administration website.
<https://www.whitehouse.gov/administration/eop>. Accessed October 8, 2016.
110. The Office of Management and Budget. The Office of Management and Budget Strategic Plan.
<https://www.whitehouse.gov/sites/default/files/omb/organization/omb-strategic-plan.pdf>. Published 2014. Accessed October 8, 2016.
111. Hourihan M. The Federal Budget Process 101. American Association for the Advancement of Science.
<https://www.aaas.org/news/federal-budget-process-101>. Updated February 2, 2016. Accessed October 8, 2016.
112. Pasachoff E. The President's Budget as a Source of Agency Policy Control. *The Yale Law Journal*. 2016;125(8):2182-2555. <http://www.yalelawjournal.org/article/the-presidents-budget-as-a-source-of-agency-policy-control>. Accessed November 16, 2016.
113. The White House Administration. National Action Plan for Combating Antibiotic-Resistant Bacteria.
https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf. Published March, 2015. Accessed February 10, 2017.
114. The National Security Council. The White House Administration website.
<https://www.whitehouse.gov/administration/eop/nsc>. Accessed October 8, 2016.
115. The Office of Science and Technology Policy. The White House Administration website.
<https://www.whitehouse.gov/administration/eop/ostp/about>. Accessed October 8, 2016.
116. Saturno JV, Heniff B, Lynch MS. *The Congressional Appropriations Process: An Introduction*. R42388. U.S. Congressional Research Service. <https://fas.org/sgp/crs/misc/R42388.pdf>. Published November 30, 2016. Accessed December 16, 2016.
117. "Fiscal Year," 31 U.S. Code, §1102. U.S. Government Publishing Office.
<https://www.gpo.gov/fdsys/pkg/USCODE-2012-title31/pdf/USCODE-2012-title31-subtitleII-chap11-sec1104.pdf>. Accessed November 20, 2016.
118. Christensen MD. *The President's Budget: Overview of Structure and Timing of Submission to Congress*. R43163. U.S. Congressional Research Service. <https://fas.org/sgp/crs/misc/R43163.pdf>. Published July 25, 2013. Accessed November 16, 2016.
119. Streeter S. *The Congressional Appropriations Process: An Introduction*. 97-684. U.S. Congressional Research Service. <https://www.merkley.senate.gov/imo/media/doc/appropriations.pdf>. Published December 2, 2008. Accessed November 16, 2016.
120. Heniff B. *Overview of the Authorization Appropriations Process*. RS20371. U.S. Congressional Research Service. http://www.aacn.nche.edu/downloads/sgl/Overview_of_the_Authorization-Appropriations_Process.pdf. Published November 29, 2010. Accessed November 16, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

121. Kates J, Fischer J, Lief E. The U.S. Government's Global Health Police and Architecture: Structure, Programs, and Funding. Kaiser Family Foundation.
<https://kaiserfamilyfoundation.files.wordpress.com/2013/01/7881.pdf>. Published April, 2009. Accessed November 10, 2016.
122. Moss K, Kates J. The U.S. Congress and Global Health: A Primer. Kaiser Family Foundation.
<http://files.kff.org/attachment/report-the-u-s-congress-and-global-health-a-primer>. Published January 15, 2016. Accessed August 15, 2016.
123. Ritz B. Can Congress Deliver Appropriations Bills On Time? Bipartisan Policy Center website.
<http://bipartisanpolicy.org/blog/can-congress-deliver-appropriations-bills-on-time/>. Published May 16, 2016. Accessed February 10, 2017.
124. PEPFAR Stewardship and Oversight Act of 2013 (enacted). S. 1545. 113th Congress.
<https://www.govtrack.us/congress/bills/113/s1545>. Accessed February 17, 2017.
125. Congressional Budget Office. Unauthorized Appropriations and Expiring Authorizations. 51131.
<https://www.cbo.gov/sites/default/files/114th-congress-2015-2016/reports/51131-uaea-appropriations2.pdf>. Published January 15, 2016. Accessed November 16, 2016.
126. Salam RA. *USAID Global Health Programs: FY2001-FY2012 Request*. RS22913. U.S. Congressional Research Service.
http://pdf.usaid.gov/pdf_docs/pcaac428.pdf. Published June 30, 2011. Accessed November 20, 2016.
127. Vaccine Research Center. National Institute of Allergy and Infectious Diseases website.
<https://www.niaid.nih.gov/about/vrc>. Updated June 3, 2016. Accessed October 12, 2016.
128. HIV/AIDS Clinical Trials Networks. National Institute of Allergy and Infectious Diseases website.
<https://www.niaid.nih.gov/research/hivaids-clinical-trials-networks>. Updated July 15, 2016. Accessed September 23, 2016.
129. CHAVI-ID. The Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery website.
<https://chavi-id-duke.org/>. Accessed October 12, 2016.
130. History of the ACTG: Staff Reflect on Network's Milestones. Aids Clinical Trials Group website.
<https://actgnetwork.org/History>. Accessed October 12, 2016.
131. U.S. Agency for International Development. USAID Development Innovation Accelerator Broad Agency Announcement for Fighting Ebola: A Grand Challenge for Development. BAA-EBOLA-2014.
http://pdf.usaid.gov/pdf_docs/PBAAB273.pdf. Accessed November 16, 2016.
132. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. Office of the Assistant Secretary for Health website.
<http://www.hhs.gov/ash/advisory-committees/paccarb/about-paccarb/index.html>. Updated September 15, 2015. Accessed October 8, 2016.
133. National Vaccine Advisory Committee. U.S. Department of Health and Human Services, National Vaccine Program Office website.
<https://www.hhs.gov/nvpo/nvac/>. Updated August 18, 2015. Accessed October 12, 2016.
134. National Science and Technology Council. The White House Administration website.
<https://www.whitehouse.gov/administration/eop/ostp/nstc>. Accessed October 7, 2016.
135. Other Transactions for Advanced Research. Public Health Emergency website.
<http://www.phe.gov/about/amcg/otar/pages/default.aspx>. Updated December 7, 2015. Accessed October 12, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

136. Federal Acquisition Regulation. U. S. General Services Administration, Acquisition website. <https://www.acquisition.gov/?q=browsefar>. Updated January 19, 2017. Accessed February 12, 2017.
137. Carroll J. Inspired by \$220M in BARDA funding, AstraZeneca steps up antibiotics R&D. FierceBiotech. <http://www.fiercebiotech.com/r-d/inspired-by-220m-barda-funding-astrazeneca-steps-up-antibiotics-r-d>. Published September 17, 2015. Accessed November 21, 2016.
138. Priority Review Voucher. Priority Review Voucher website. <http://priorityreviewvoucher.org/>. Accessed October 13, 2016.
139. National Vaccine Injury Compensation Program. U.S Department of Health and Human Services, Hosue Resources and Services Administration website. <https://www.hrsa.gov/vaccinecompensation/>. Updated February, 2016. Accessed October 12, 2016.
140. Countermeasures Injury Compensation Program. *Morbidity and Mortality Weekly Report*. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5925a5.htm>. 59(25);780. Published July 2, 2010. Accessed November 21, 2017.
141. Cox E, Laessig K. FDA Approval of Bedaquiline — The Benefit–Risk Balance for Drug-Resistant Tuberculosis. *N Engl J Med*. 2014;371(8):689-691. doi: 10.1056/NEJMp1314385
142. FDA News Release. U.S. Food and Drug Administration website. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm>. Published December 31, 2012. Accessed December 27, 2016.
143. Emergency Use Authorization. U.S. Food and Drug Administration website. <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>. Published January 26, 2017. Accessed February 18, 2017.
144. The Kaiser Family Foundation. The U.S. Global Health Initiative. <https://kaiserfamilyfoundation.files.wordpress.com/2013/01/8116.pdf>. Published December, 2011. Accessed November 20, 2016.
145. U.S. Department of State. Leading Through Civilian Power: The First Quadrennial Diplomacy and Development Review. <https://www.state.gov/documents/organization/153108.pdf>. Published 2010. Accessed December 20, 2016.
146. Shah R, Goosby E, Frieden T, Quam L. Officials Chart Next Steps for U.S. Global Health Initiative. Global Health Initiative Official Blog. <http://iipdigital.usembassy.gov/st/english/article/2012/07/201207058538.html>. Published July 3, 2012. Accessed December 20, 2016.
147. Oomman N, Silverman R. GHI Mid-Term Review and a Way Forward: A Report of the Rethinking U.S. Foreign Assistance Program. Center for Global Development. https://www.cgdev.org/sites/default/files/1425914_file_NO_RS_GHI_FINAL_0.pdf. Published January 30, 2012. Accessed February 18, 2017.
148. U.S. Government Global Health Initiative. The United States Government Global Health Initiative Strategy. <http://www.pepfar.gov/documents/organization/136504.pdf>. Accessed October 12, 2016.
149. Budget Control Act of 2011 (enacted). S.365. 112th Congress. <https://www.congress.gov/bill/112th-congress/senate-bill/365>. Accessed November 20, 2016.
150. Sanders K. Stephanie Cutter: Ebola vaccine research was cut in half, and more cuts are coming. PunditFact. <http://www.politifact.com/punditfact/statements/2014/oct/24/stephanie-cutter/stephanie-cutter-ebola-vaccine-research-was-cut-ha/>. Published October 24, 2014. Accessed December 27, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

151. History and Achievements. Military Infectious Diseases Research Program website. <https://midrp.amedd.army.mil/info/HAchieve.jsp>. Accessed November 22, 2016.
152. Collins C. Walter Reed Army Institute of Research: A Brief History. Defense Media Network. <http://www.defensemmedianetwork.com/stories/walter-reed-army-institute-of-research-a-brief-history/>. Published April 28, 2014. Accessed January 12, 2017.
153. CE marking. European Commission website. https://ec.europa.eu/growth/single-market/ce-marking_en. Updated October 13, 2016. Accessed October 13, 2016.
154. Defense Threat Reduction Agency. Defense Threat Reduction Agency website. <http://www.dtra.mil/>. Accessed October 13, 2016.
155. Biello D. Obama Has Done More for Clean Energy Than You Think. *Scientific American*. <https://www.scientificamerican.com/article/obama-has-done-more-for-clean-energy-than-you-think/>. Published September 8, 2015. Accessed December 27, 2016.
156. Wapner J. We Now Have the Cure for Hepatitis C, but Can We Afford It? *Scientific American*. <https://www.scientificamerican.com/article/we-now-have-the-cure-for-hepatitis-c-but-can-we-afford-it/>. Published September 1, 2014. Accessed December 27, 2016.
157. Medicines Patent Pool. Medicines Patent Pool website. <http://www.medicinespatentpool.org/>. Accessed October 12, 2016.
158. USPTO Patents for Humanity. United States Patent and Trademark Office website. <http://patentsforhumanity.devpost.com/>. Accessed October 12, 2016.
159. International Federation of Pharmaceutical Manufacturers & Associations. International Federation of Pharmaceutical Manufacturers & Associations website. <http://www.ifpma.org/>. Accessed October 13, 2016.
160. South African Development Community. Southern African Development Community website. <http://www.sadc.int/>. Accessed October 13, 2016.
161. African Medicines Regulatory Harmonisation. New Partnership for Africa's Development website. <http://www.nepad.org/content/african-medicines-regulatory-harmonisation-armh-programs>. Accessed October 13, 2016.
162. President's Council of Advisors on Science and Technology. The White House Administration website. <https://www.whitehouse.gov/administration/eop/ostp/pcast>. Accessed October 13, 2016.
163. Medicines for Malaria Venture. Annual Report 2015. http://www.mmv.org/sites/default/files/uploads/docs/publications/MMV_Annual_Report_2015.pdf. Accessed November 30, 2016.
164. World Intellectual Property Organization. WIPO Re:Search Sharing Innovation in the Fight Against Neglected Tropical Diseases. http://www.wipo.int/export/sites/www/research/docs/guiding_principles.pdf. Published June 8, 2011. Accessed November 28, 2016.
165. Ramamoorthi R, Graef KM, Dent J. WIPO Re:Search: Accelerating anthelmintic development through cross-sector partnerships. *International Journal for Parasitology: Drugs and Drug Resistance*. 2014;4(3):220-225. doi:10.1016/j.ijpddr.2014.09.002.
166. Malaria Vaccine Initiative. Frequently Asked Questions. <http://www.malariavaccine.org/files/MVI-GSK-FAQ-FINAL-web.pdf>. Accessed November 27, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

167. Product Development for Vaccines Advisory Committee : Meetings, terms of reference and composition. World Health Organization website. <http://www.who.int/immunization/research/committees/pdvac/en/>. Accessed November 27, 2016.
168. Our Mission. American Energy Innovation Council website. <http://americanenergyinnovation.org/our-mission/>. Accessed October 12, 2016.
169. Announcement of U.S. Science Envoys. U.S. Department of State website. <http://www.state.gov/r/pa/prs/ps/2014/12/234682.htm>. Accessed October 20, 2016.
170. World Health Organization. Global Observatory on Health Research and Development. http://www.who.int/research-observatory/onepager_20160607.pdf?ua=1. Accessed October 12, 2016.
171. Anacor Pharmaceuticals and MMV sign agreement to pursue promising compound for malaria (press release). Medicines for Malaria Venture. <http://www.mmv.org/newsroom/press-releases/anacor-pharmaceuticals-and-mmv-sign-agreement-pursue-promising-compound>. Published March 18, 2011. Accessed October 12, 2016.
172. Article 58 applications: Regulatory and procedural guidance. European Medicines Agency website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp. Accessed October 12, 2016.
173. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003883.pdf. Published November 17, 2005. Accessed January 20, 2017.
174. Brennan Z. Article 58: How EMA Helps Increase Access to Drugs in Low- and Middle-Income Countries. Regulatory Affairs Professionals Society. <http://www.raps.org/Regulatory-Focus/News/2016/04/26/24825/Article-58-How-EMA-Helps-Increase-Access-to-Drugs-in-Low--and-Middle-Income-Countries/#sthash.lKcKmfi.dpuf>. Published April 26, 2016. Accessed October 12, 2016.
175. The White House Administration. Obama Administration Announces More Than \$4 Billion in Private Sector Commitments and Executive Actions to Scale up Investment in Clean Energy Innovation (press release). <https://www.whitehouse.gov/the-press-office/2015/06/16/fact-sheet-obama-administration-announces-more-4-billion-private-sector>. Published June 16, 2015. Accessed October 12, 2016.
176. The White House Administration. President Obama Announces New Investments to Combat Climate Change and Assist Remote Alaskan Communities (press release). <https://www.whitehouse.gov/the-press-office/2015/09/02/fact-sheet-president-obama-announces-new-investments-combat-climate>. Published September 2, 2015. Accessed October 12, 2016.
177. World Health Organization. Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. http://www.who.int/phi/CEWG_Report_5_April_2012.pdf. Published April 5, 2012. Accessed October 12, 2016.
178. Laub Z. The Group of Eight (G8) Industrialized Nations. Council on Foreign Relations. <http://www.cfr.org/international-organizations-and-alliances/group-eight-g8-industrialized-nations/p10647>. Updated March 3, 2014. Accessed October 12, 2016.
179. Founding Principles. Global Health Innovation Technology Fund website. <https://www.ghitfund.org/hww/principles>. Accessed October 12, 2016.
180. Scope. CARB-X website. <http://www.carb-x.org/scope>. Accessed October 12, 2016.

Strengthening the United States Government's Role in Product Development for Global Health

181. Johnson JA. *Brief History of NIH Funding: Fact Sheet*. R43341. U.S. Congressional Research Service. <https://fas.org/sgp/crs/misc/R43341.pdf>. Published December 23, 2013. Accessed November 27, 2016.
182. End Neglected Tropical Diseases Act (introduced). H.R. 1979. 114th Congress. <https://www.congress.gov/bill/114th-congress/house-bill/1797>. Accessed January 20, 2017.
183. Gunderson D. Breaking Now on Capitol Hill: Introducing the End Neglected Tropical Diseases Act. END7. <http://endtheneglect.org/2014/06/breaking-now-on-capitol-hill-introducing-the-end-neglected-tropical-diseases-act/>. Published June 13, 2014. Accessed October 14, 2016.
184. Global Development Lab Act of 2016 (introduced). H.R.3924. 114th Congress. <https://www.congress.gov/bill/114th-congress/house-bill/3924>. Accessed September 20, 2016.
185. Chmiola M, Carson C, Kelley K, Morton EW, Robinson M. Achieving a bold vision for global health: Policy solutions to advance global health R&D. Global Health Technologies Coalition. <http://www.ghtcoalition.org/pdf/Achieving-a-bold-vision-for-global-health-Policy-solutions-to-advance-global-health-R-D.pdf>. Published 2016. Accessed November 30, 2016.
186. Christoph M. Imagining “Bold Endgames” In Global Health. InterAction. <https://www.interaction.org/blog/imagining-%E2%80%9Cbald-endgames%E2%80%9D-global-health>. Published April 12, 2013. Accessed November 22, 2016.
187. Yamey G, Morel C. Investing in Health Innovation: A Cornerstone to Achieving Global Health Convergence. *PLoS Biol.* 2016;14(3):e1002389. doi: 10.1371/journal.pbio.1002389
188. McNeil, DG. Trump Administration Puts the U.S. at a Crossroad for Global Health Aid. *New York Times*. <http://www.nytimes.com/2016/12/19/health/donald-trump-foreign-aid-global-health.html>. Published December 19, 2016. Accessed December 27, 2016.
189. Global Health Technologies Coalition. Making the case for US Government investment in poverty-related neglected disease research and development. March 2017 (in press).
190. Walsh E. Why invest in R&D for HIV, TB and Malaria? Because it's good for global health, and good for Europe. Deutsche Stiftung Weltbevölkerung. <http://www.dsw.org/en/2014/09/invest-for-hiv-tb-malaria-good-for-global-health-good-for-europe/>. Published September 4, 2014. Accessed December 27, 2016.
191. Tiefer C. President Trump Is Likely To Boost U.S. Military Spending By \$500 Billion To \$1 Trillion. *Forbes*. <http://www.forbes.com/sites/charlestiefer/2016/11/09/president-trump-is-likely-to-boost-u-s-military-spending-by-500-billion-to-1-trillion/#10000a1c4108>. Published November 9, 2016. Accessed November 22, 2016.
192. Jamison DT, Summers LH, Alleyne G, et al. Global health 2035: a world converging within a generation. *The Lancet*. 2013;382(9908):1898-1955. doi: 10.1016/S0140-6736(13)62105-4
193. What is total official support for sustainable development (TOSSD)? Organisation for Economic Co-operation and Development. <http://www.oecd.org/dac/financing-sustainable-development/tossd.htm>. Accessed November 20, 2016.