Give it a shot: Seven lessons learned from the Ebola virus disease for public-private vaccine development collaboration in response to future neglected disease outbreaks

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Introduction

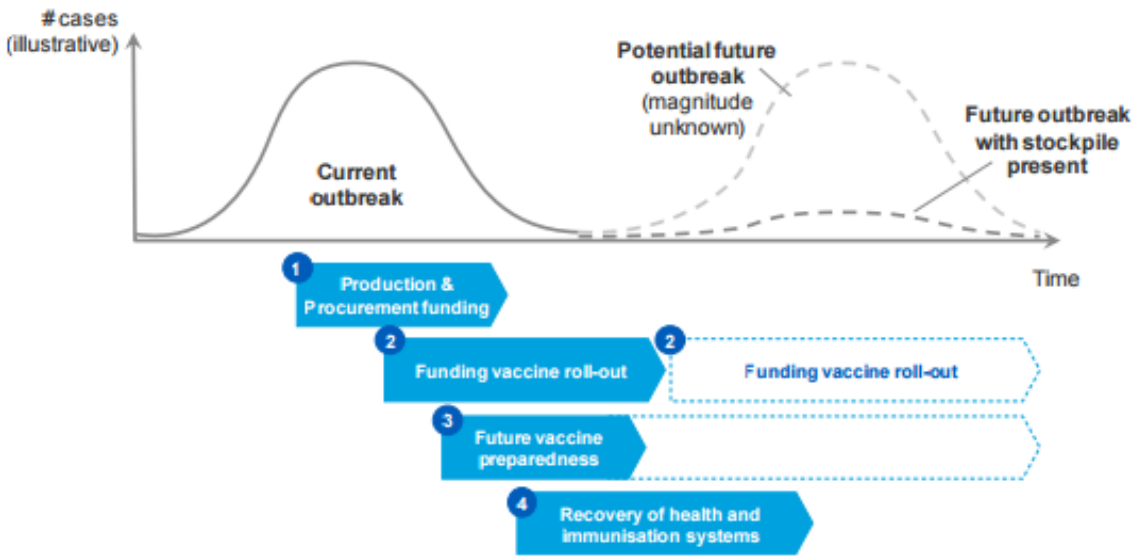
In one intervention to address the 2014/2015 Ebola crisis in West Africa a variety of private and public actors came together to successfully execute a vaccine development program on an extremely tight timeline. Processes that normally take about a decade were concluded in a matter of months, as a result of unprecedented cooperation between industry, national and supra-national government bodies, the scientific community, and private-public funding mechanisms. The Ebola pandemic was eventually overcome through non-immunization means – but the vaccine program still warrants careful examination in order to distill takeaways and best practices for vaccine development in future neglected disease outbreaks.

The Ebola outbreak in West Africa, which killed more than 11,000 people and infected at least 28,000, was "a stark reminder of the fragility of health security in an interdependent world"[1]. The pandemic caused unimaginable human suffering and pain, with the Word Health Organization (WHO) declaring it "the most severe acute public health emergency seen in modern times"[2]. Never before in recorded history has a biosafety level four pathogen – a pathogen of the highest threat level – infected so many people so quickly, over such a broad geographical area, for so long. In addition to the loss of human lives and the trauma inflicted upon survivors and their families, the Ebola virus disease outbreak decimated economic, social, and public health infrastructures in some of the poorest and least developed countries in Sub-Saharan Africa. In March 2015, the UN Development Group estimated that Ebola would cost West Africa $14.7-$19.7 billion between 2014 and 2017[3] (Liberia, for reference, had a 2014 GDP of ~$2 billion[4] with 64% of its population living under the national poverty line). Ebola thus reminds us of how health touches and impacts so many facets of our lives, and of the dramatic implications health emergencies often trigger. The 2013/2014 Ebola pandemic has been overcome, yet it did not take long for the next health crisis to emerge. The ongoing Zika outbreak in Brazil provides just one glimpse at the frequency and severity of neglected disease

[1] The Lancet. "Ebola: Lessons for future pandemics". The Lancet 386.10009 (Nov 28, 2015): 2118.
[2] World Health Organization. "Experimental therapies: growing interest in the use of whole blood or plasma from recovered Ebola patients (convalescent therapies)." Geneva: World Health Organization (2014).
[3] The Lancet. "Timeline of Ebola virus disease progress in West Africa". 2015. Available online at: www.thelancet.com/infographics/ebola-timeline (accessed on 7/28/2016).
[4] *The World Bank Open Data.* Available online at: http://data.worldbank.org/indicator/SI.POV.NAHC/countries/LR?display=graph (accessed on 7/28/2016).

outbreaks the global community will be battling going forward, as a result of climate change, population growth, and increasing human-wildlife interaction. In light of the "unpredictable nature of outbreaks and other health crisis, and the mounting scale of ecological changes that may trigger them"[5], the identification of processes and structures facilitating effective collaboration of all relevant Global Health actors is critical to enable adequate and timely responses to future outbreaks of neglected disease and thus prevent the extensive suffering and tragedy caused by the 2014/2015 Ebola crisis in West Africa.

(Potential) impact of an efficacious vaccine on disease case load in EVD outbreak vs future neglected disease outbreaks



Source: Brooks, Alan and Alex de Jonquieres, Eliane Furrer, Stefano Malvolti, Patience Musanhu, Aurélia Nguyen. "ACCELERATING ACCESS TO EBOLA VACCINES AND COUNTRY PERSPECTIVE". GAVI. Report to the board. Dec 2014.

This case study intends to diagnose the key attributes and mechanisms that made public-private cooperation in the Ebola vaccine program so successful, through numerous interviews conducted with actors from a variety of groups and institutions that were part of the public-

[5] World Health Organization. "Report of the Ebola Interim Assessment Panel." (2015). 9.

private universe contributing to the vaccine effort, as well as careful study of the scientific literature. At the outset of my research in the summer of 2015, very few studies examining the Ebola vaccine development had been published. As we leave the 2014/2015 crisis further behind and begin to assess it through the rear-view mirror, more work similar to mine is being undertaken and my case study is only one humble contribution to the growing body of literature, by no means exhaustive. Rather, it is meant as an invitation to spark discussion on how the private and the public spheres can collaborate more closely going forward to improve global health equity and what international governance structure can best facilitate such collaboration.

My work identified seven essential lessons learned from the Ebola program that will enable public-private collaboration in vaccine development in response to similar, future neglected disease outbreaks:

1. Rigorous ongoing risk assessment
2. Translation of assessment in expanded public-private research efforts
3. Transfer of public-private IP to appropriate manufacturers
4. Testing and implementation coordination by the WHO
5. Discussion and articulation of ethics guidelines in emergency response
6. Harmonization of regulatory approval and indemnity architecture
7. Development of a sound emergency funding structure under GAVI

Public-private collaboration in Global Health – a perspective

The rise and proliferation of non-governmental actors over the past 15-20 years has substantially transformed the global health landscape, resulting in numerous cross-sector initiatives or Public-Private-Partnerships (PPPs). Born out of the understanding that "few successful international initiatives in public health can rely on a single organization"[6], PPPs facilitate the coordination of efforts by government and public health agency bodies, International Organizations (IOs), private health providers, commercial actors, philanthropic

[6] Burci, Gian Luca. "Public/private partnerships in the public health sector."International Organizations Law Review 6.2 (2009): 360.

foundations, NGOs, civil society, and people living with disease. *GAVI, The Global Fund to fight AIDS, Tuberculosis, and Malaria*, and the *Rollback Malaria Initiative*, provide three prominent – and rather successful – examples of such collaboration. Strikingly, the advent of collaborative efforts between public and private actors coincides with the dramatic spike in the availability of funding for global health interventions that marked the first decade of the 21st century, often labeled the 'golden age for health development'[7]. As Kent Buse and Andrew Harmer note, growing public-private collaboration efforts also reflected increasing 'vilification of the public sector'[8] and 'feeling of ill-will' towards the WHO in particular. Lastly, the increase in the number and prominence of PPPs in the Global Health field reflect advocacy by a number of economist, and notably the World Bank[9], for the increased privatization of health service delivery in developing countries in response to inefficient delivery through government means.

PPPs in the realm of global health distinguish themselves from orthodox actors through their innovative approach to joint decision-making, often reflecting an inclination to "skip the step of cautious philanthropy"[10] and plunge directly into accelerated, highly outcome-oriented problem-solving endeavors. Buse and Harmer observe that many Health PPPs have been "remarkably speedy out the starting blocks, particularly when compared with the time it has taken to establish other international initiatives"[11]. Their focus on quick, measurable impact is informed by and aligns with the urgency of the issues they aim to address, in the context of infectious diseases response or intervention time and lives saved tend to be strongly correlated. In their analysis of the merits and drawbacks of collaboration between public and private actors through PPPs, Buse and Harmer identify seven meaningful contributions these PPPs have made to tackling neglected diseases: a) getting specific health issues onto national international agendas by allocating proportionally more resources to advocacy and communications than conventional international health organizations; b) mobilizing additional funds for these issues;

[7] Chan, Margaret. "Best days for public health are ahead of us, says WHO Director-General." Geneva, Switzerland: Address to the 65th World Health Assembly (2012).
[8] Buse, Kent, and Andrew M. Harmer. "Seven habits of highly effective global public–private health partnerships: practice and potential." Social science & medicine 64, no. 2 (2007): 259-271.
[9] Birdsall, Nancy, and Estelle James. "Health, government, and the poor: the case for the private sector." Policy and Planning Implications of the Epidemiological Transition (1993): 229-51.
[10] Ramiah, Ilavenil, and Michael R. Reich. "Building effective public–private partnerships: Experiences and lessons from the African Comprehensive HIV/AIDS Partnerships (ACHAP)." Social Science & Medicine 63, no. 2 (2006): 397-408.
[11] Buse, Harmer.

c) stimulating research and development through the application of innovative financing models; d) improving access to cost-effective health care interventions among populations with limited ability to pay; e) strengthening national health policy processes and content; f) augmenting health service delivery capacity; and g) establishing international norms and standards. The impact these characteristics delivered – at least through a subset of the numerous global health-focused PPPs – has been impressive, and global health focused PPPs have proven to be 'remarkably effective'[12] in procuring and supplying underserved communities with free or cost-reduced, quality assured medicines and vaccines. The Global Fund, one example of a PPP that delivers cutting-edge mechanisms for transforming access to medicine in developing countries, self-reportedly saved more than 17 million lives since 2002 through the programs it supports[13]. Currently, it claims, to save more than 2 million lives each year, projecting to have supported countries in saving more than 22 million lives by the end of 2016. GAVI, the vaccine alliance, is another example of the extraordinary impact delivered by some PPPs, and its role in the delivery of vaccines to impoverished populations will be explored in subsequent chapters.

Yet despite their impact on and promise for the future of global health, the increasing number and popularity of PPPs in the health space creates a host of new challenges[14] that involved actors must tackle. Among these are defining an appropriate and meaningful role for the private sector actors, implementing sound governance structures, overcoming their inherent democracy or legitimacy deficit, facilitating representation of recipient country and non-for-profit actors, identifying and avoiding conflicts of interest, articulating and following rigorous ethics, maneuvering an inadequate global health governance system, overcoming the mutual prejudices and reservations of actors towards each other, and coping with insufficient and ill-developed funding mechanisms. The difficulty in assessing the effectiveness of PPPs compared to conventional intervention or delivery mechanisms lies in the very nature of the setup that makes them so apparently successful in the first place: their rather narrow focus and mission. By design, health-focused PPPs pursue issue-specific goals. They thus struggle to align with other, parallel efforts of health delivery, which they often end up competing – in some cases, destructively. The 2005 Paris Declaration on Aid Effectiveness calls for 'increasing alignment of

[12] Buse, Harmer.
[13] The Global Fund. Available online at: http://www.theglobalfund.org/en/impact/ (accessed 7/28/2016).
[14] *See* Burci, Gian Luca. "Public/private partnerships in the public health sector."International Organizations Law Review 6.2 (2009): 359-382.

aid with partner countries' priorities, systems and procedures'[15] and PPPs often find it "difficult to fully embrace the Paris agenda"[16]. Their focus on quick results complicates their collaboration with mechanisms already present in recipient countries.

In addition to the above complications, Buse and Harmer point to the "danger that some GHPs [Public-Private Health Partnerships] will simply collapse because of lack of financial support"[17]. Analyzing funding requirements and commitments for 11 GHPs, they find that only one, GAVI, had more than 70% of its total required funding secured by commitments. This gap between required funding to fuel the PPPs ambitious goals and the funding they have secured reflects, for one, unmet expectations for contributions from the private sector which have "not generally met the initial, and perhaps naïve, expectations that it would become the principal patron of these initiatives"[18]. It also reflects the reliance on one major source of funding supporting a host of PPPs: the Bill and Melinda Gates Foundation. The foundation is at the center of a number of PPPs and the leading financier of numerous public-private health-delivery mechanisms. Seven of the PPPs examined by Buse and Harmer relied entirely on Gates funding and at least nine list Gates as the single largest donor. This reliance on a single benefactor not only introduces significant risk should that one source dry up but also enables one single private organization to heavily influence and determine the direction of a host of global health initiatives.

Although focused on PPPs in particular, the above analysis offers a number of insights into the benefits and complications of public-private collaboration in global health in general. Many of the highlighted opportunities and problems played out in the effort to develop and bring to market the Ebola vaccine. The urgent nature of the Ebola pandemic called for a quick, impactful response. Time is an important factor in any response to humanitarian emergencies. It is particularly important in the context of infectious disease emergencies. The proven advantage public-private efforts have in responding quickly and in an outcome-oriented manner, made a collaboration of public and private actors the obvious mode of operation in developing a vaccine.

[15] Organisation for Economic Co-operation and Development. "The Paris declaration on aid effectiveness and the Accra agenda for action." (2005).
[16] Buse, Harmer.
[17] Ibid.
[18] Ibid.

The 2014/2015 Ebola outbreak – the power of the exponential curve

Over the course of eight months the Ebola virus disease transformed from a largely ignored outbreak of an opaque disease in a remote, severely impoverished region of West Africa, into a large-scale pandemic that eventually triggered an unprecedented global response. Researchers have traced the outbreak back to Emile Ouamouno, a then 2-year old toddler living in a rainforest village in southern Guinea. In December 2013 Emile experienced fever, black stools, and vomiting. On December 6th, four days after showing these symptoms, he passed away. From Emile, the Ebola virus began to spread throughout Guinea and into neighboring Liberia. The spreading disease didn't go unnoticed, yet it triggered few alarms. Referencing past outbreaks, the WHO tweeted on March 25th, 2014 that "Ebola has always remained a very localized event"[19]. Throughout the spring of 2014, it was only the NGO 'Medicines Sans Frontiers' (MSF) that appreciated and articulated the threat and challenge Ebola posed warning of an "epidemic of a magnitude never seen before"[20].

MSF's dire forecast soon turned into reality. In late May Ebola was confirmed in Sierra Leone and by mid-June over 100 cases were being reported each week. The disease's death toll breached the 1,000 person mark on August 11th and by mid-September the number of new weekly cases reported had exploded to 700. While the case load had been increasing steadily throughout the spring of 2014, it wasn't until the summer that policy makers and the wider public outside of West Africa started paying attention. In July Ebola had spread beyond the Guinea-Liberia-Sierra Leone region into Nigeria; in August a Guinean national with Ebola symptoms arrived in Senegal; and in September Thomas Eric Duncan arrived in Dallas, TX after contracting the virus in Liberia, later infecting two nurses who treated him. By the time the world started paying attention to the humanitarian catastrophe unfolding in West Africa, virus transmission in the impacted countries had accelerated dramatically and researchers were struggling to predict spread patterns and the growth in case loads. Alessandro Vespignani, a scientist at Boston's Northeastern University, was one of those who quantified transmission with the help of computer models; in mid-September he issued the warning that "in our modeling, by

[19] The Lancet. "Timeline of Ebola virus disease progress in West Africa".
[20] Ibid.

mid-October, we're already between 10,000 to 25,000 cases,"[21] pointing to the exponential curve that indicated the doubling of cases every three to four weeks. On September 23rd the US CDC warned of up to 1-4 million cases by January 20th, 2015.

It was this shockingly bleak prognosis that informed the response and policy decisions that transpired throughout August and September 2014. On August 8th WHO Director-General Dr. Margaret Chan declared Ebola a 'Public Health Emergency of International Concern' (PHEIC) as defined by the International Health Regulations (IHR), the international legal framework governing Public Health. Since the regulations' revision in 2005, Ebola was only the third PHEIC declared by the WHO after the H1N1 Influenza in 2009 and Polio in 2014[22]. The WHO's initial Ebola response has been heavily attacked, and while it points to the complexities of the Global Health architecture and governance system as well as neglected responsibilities under the IHR by numerous countries, the organization largely acknowledges the criticism. The report of the Ebola Interim Assessment Panel found: "Although WHO has a considerable number of policies and procedures in place, they were activated late because of the judgments relating to the declaration of a PHEIC. It is clear that early warnings about the outbreak […] did not result in an effective and adequate response."[23]

In light of the dramatic increase in caseload in Guinea, Liberia, and Sierra Leone, and WHO's obvious ill-preparedness for large scale crisis response, UN Secretary-General Ban Ki-moon made Ebola an executive matter of the UN secretariat. Following the passage of General Assembly resolution 69/1 and the adoption of Security Council Resolution 2177 – co-sponsored by a record-setting 134 countries, one of three resolutions in the history of the Council to address a global health concern, and the first to declare a health issue to be a threat to international peace and security – he established the UN Mission for Ebola Emergency Response (UNMEER). The mission was charged with "the core objective of scaling up the response on the ground and

[21] News@Northeastern. "Why the math of the Ebola epidemic is so scary". September 2014. Available online at: http://www.northeastern.edu/news/in-the-news/why-the-math-of-the-ebola-epidemic-is-so-scary/ (accessed 7/28/2016).
[22] Center for Disease Control and Prevention. "Global Health Security: International Health Regulations (IHR)". Available online at: http://www.cdc.gov/globalhealth/healthprotection/ghs/ihr/ (accessed 7/28/2016).
[23] World Health Organization. "Report of the Ebola Interim Assessment Panel." 12.

establishing unity of purpose among responders in support of the nationally led efforts"[24]. The WHO "welcomed the move"[25] having clearly been overwhelmed by the heavy logistical burdens that were impeding the response. UNMEER quickly established an air bridge delivering staff, materials, vehicles and essential medicines to West Africa; the previous lack of personal protective kits was only one example of the absence of even basic resources for intervention. Although UNMEER coordinated the comprehensive on-the-ground response, the WHO remained in charge of the overall health strategy within UNMEER and implemented its Ebola Response roadmap, aiming from August 2014 to "reverse the trend in new cases and infected areas within 3 months, stop transmission in capital cities and major ports, and stop all residual transmission with 6-9 months"[26].

In order to achieve these targets, the WHO issued a number of recommendations under the IHR to prevent international spread, such as exit screenings at international airports, seaports and land crossings; the alignment of international airline carriers practices with national travel policy; and the prohibition of travel of all Ebola case contacts with the exception of medical evacuations. More important however, were the measures implemented on the ground in the affected countries, the so-called "Ebola intervention package"[27]. The package outlined the procedures for managing cases, starting with case diagnosis by a WHO-recognized laboratory, with positive diagnosis then leading to referral to a primary health care facility and/or referral/isolation centre complemented by contact tracing and monitoring, and finally concluding in supervised burials executed by dedicated expert burial teams. This case management chain was complemented by a public crisis risk communications plan to facilitate case identification, contact tracing and risk education.

At the time of the outbreak, no approved medicine to treat Ebola, such as an antiviral drug, was available, although experimental drugs were being researched like "ZMapp" which was developed by California-based *Mapp Biopharmaceuticals*. Such drugs were initially

[24] UN Mission for Ebola Emergency Response (UNMEER). "UNMEER, the first-ever UN emergency health mission, was established on 19 September 2014 and closed on 31 July 2015, having achieved its core objective of scaling up the response on the ground." Available online at: http://ebolaresponse.un.org/un-mission-ebola-emergency-response-unmeer (accessed 7/28/2016)
[25] World Health Organization. "Key events in the WHO response to the Ebola outbreak". January 2015. Available online at: https://who.int/csr/disease/ebola/one-year-report/who-response/en
[26] World Health Organization. "Ebola Response Roadmap". August 2014. 7.
[27] Ibid.

developed in response to the post 9/11 anthrax scare and concerns by the defense community over the potential threat of future attacks involving biological weapon agents and happened to be applicable in the treatment of the EVD. The few existing doses of the experimental drugs that were available for treatment use were exhausted quickly and manufacturers were unable to resupply the drugs, as their efficacy had not been established, the drugs had not undergone adequate testing, and the drug manufacturers were lacking large-scale production capacities. Given this absence of proven, tested, and available treatment, case isolation proved the most obvious and effective immediate intervention to halt virus transmission.

While the actors on the ground, under WHO guidance, pursued isolation and safe burial efforts to contain virus spread and reduce disease prevalence, the WHO also orchestrated efforts to develop and bring to market a number of Ebola vaccines. Various public-private and private actors for years had been researching technologies that lent themselves to an Ebola vaccine, and coordinated efforts were undertaken in the fall of 2014 to streamline testing and large-scale production of these vaccines in order to employ them in the fight against the ongoing pandemic.

Vaccines – the health intervention of choice

Since Edward Jenners demonstrated 320 years ago that deliberate infection of the cowpox virus into humans could prevent smallpox, thus developing the first vaccine, the practice of artificially inducing immunity through the administration of a vaccine has dramatically transformed human health. With Jenners' work paving the way – his discovery eventually resulted in the eradication of smallpox in 1977 (the WHO declared the world smallpox free in 1980) through a global immunization campaign that marked one of the most significant public health achievements in history – further innovation led to the development of the Rabies vaccine by Louis Pasteur in 1885 and the creation of the first killed vaccine in 1886 when Salmon and Smith produced the hog cholera vaccine. Innovation in vaccinology has generated such transformative health outcomes that Barry Bloom suggests "Vaccination […] has been and continues to be one of the most important public health interventions in history"[28]. Brian

[28] Bloom, Barry R., and Paul-Henri Lambert, eds. The vaccine book. Academic Press, 2002. 3.

Greenwood et al. claim that "vaccination has probably saved as many lives as any other public health innovation with the possible exception of improvements in sanitation and water safety"[29].

The advent of tissues culture, the growth of tissues or cells separate from organisms, in the 1940s marked another significant breakthrough in the vaccine success story, as it enabled large-scale vaccine production. In 1974 the WHO initiated the Expanded Programme on Immunization (EPI) with the objective of providing children worldwide with minimum vaccine coverage for diseases such as diphtheria, whooping cough, and measles. In 1984, the WHO further refined the program introducing a standardized vaccination schedule and adding new vaccines to the list as they become available. Since the start of EPI the proportion of children who received their basic vaccines has increased from 15% in 1974 to about 90% currently[30]. Childhood vaccination has decreased disability-adjusted life year (DALY) – a health gap measure equaling one year of healthy life lost or expressing the years of life lost to premature death (YYL) and the years lived with disability (YLD) – attributable to communicable diseases in the developed world to as little as over 4% in 1990. Given the remarkable impact on the reduction of infectious diseases, vaccine development has been shifting in focus from the prevention of the classic infections to the development of agents for use in particular geographic regions, for example, dengue fever or malaria, or high-risk groups such as surgical patients or the immune comprised. With Malaria and improved tuberculosis vaccines within reach and vaccination against the human immunodeficiency virus (HIV) a realistic possibility, the challenge researchers are now tackling is the use of therapeutic vaccine technologies for the treatment of cancer and other non-communicable diseases such as hypertension or diabetes.

As rosy as the outlook seems, however, both Greenwood and Bloom emphasize that the success story of vaccines varies dramatically between the developed and developing world. Infectious and parasitic diseases still accounted for nearly 30% of the global disease burden in 2000, and the situation was particularly bleak in Africa where the share of infectious diseases and parasitic diseases of the total diseases burden was 60%[31]. HIV/AIDS was the major driver behind that score but it does not explain the score entirely. Bloom finds that among the top ten

[29] Greenwood, Brian, David Salisbury, and Adrian VS Hill. "Vaccines and global health." Philosophical Transactions of the Royal Society of London B: Biological Sciences 366, no. 1579 (2011): 2733-2742.
[30] Ibid.
[31] Bloom. 2.

leading causes of DALYs worldwide in the year 2000, four were infectious diseases other than HIV (lower respiratory infections, diarrheal diseases, malaria, and tuberculosis). In order to close the existing gap in coverage between rich and poor nations and address the plateauing global vaccine coverage, the World Health Assembly in 2012 endorsed the WHO's Global Vaccine Action Plan (GVAP), a framework for preventing 20 million of deaths by 2020 through more equitable access to existing vaccines for people in all communities.

In 2000, even before the creation of the GVAP, the WHO, the United Nations Children's Fund (UNICEF), the World Bank and the Bill and Melinda Gates Foundation created GAVI, the Vaccine Alliance to address the discrepancy in access to vaccines between the developed and developing world. GAVI, set up as a Public-Private Partnership headquartered in Geneva, was charged with pooling knowledge and leveraging financial resources from both public and private actors to make vaccines more affordable and available in countries with an average national per capita income of less than $1,000. By covering the difference between the contribution from the national vaccination programs and the costs charged by manufacturers, GAVI reached a self-reported 500 million additional children from its inception to 2015, thereby preventing more than 7 million deaths[32]. GAVI's success in making a greater share of vaccines accessible to impoverished communities, thus reducing global health inequity partly rests on its implementation of innovative financing mechanisms: "The GAVI model assumes that by mobilizing significant finance and generating predictable and measurable demand from developing countries, markets can be 'shaped' not only through GAVI's global purchasing power and the impact of new entrants to the market (notably emerging market manufacturers able to compete at a global scale on quality and price), but also through other innovative financial instruments such as the advance market commitment (AMC)."[33] The AMC binds future donor obligations or pledges to incentivize industry to develop and/or produce a vaccine and deliver it at affordable prices. Through the AMC, GAVI 'creates a market' that de-risks development for the manufacturer, enabling industry to offer its product at a lower, risk-adjusted price point.

The AMC thus adds to and advances the already appealing economics of vaccines in comparison to other health interventions. Vaccines are widely accepted as the best use of scarce

[32] GAVI. Available online at: http://www.gavi.org/about/mission/ (accessed 7/28/2016).
[33] Lob-Levyt, Julian. "Contribution of the GAVI Alliance to improving health and reducing poverty." Philosophical Transactions of the Royal Society of London B: Biological Sciences 366, no. 1579 (2011): 2743-2747.

health care dollars because once developed, they are inexpensive to produce. As they deliver safe and highly effective prevention of diseases that would otherwise be expensive to treat, their benefits tend to far outweigh their financial costs. Bloom estimates the cost-effectiveness ratio of vaccines to be at about $15-$25 per life year gained compared to hundreds or even thousands of dollars per life year gained for many common healthcare interventions[34]. "[…] Unlike virtually all other health interventions, routine childhood immunization is so cheap and so effective that it is cost-saving to society."[35] The compelling, superior economics of vaccines are one of the main reasons for the Gates Foundation's $750 million seed pledge to GAVI. The foundation's own roots can be traced back to Bill and Melinda Gates' realization, in the late 1990s, of the devastating impact of the rotavirus, which was killing half a million children every year and which drove them to set up their foundation. Vaccines have been the foundation's biggest investment ever since.

Amplifying the appealing economics of vaccination are their indirect 'herd immunity' effects. Herd immunity refers to the idea that "the risk of infection among susceptible individuals in a population is reduced by the presence and proximity of immune individuals"[36], meaning that once immunization rates pass a certain threshold ($R < 1$) even unprotected or non-vaccinated individuals are safe from infection by the defense wall erected around them by vaccinated community members. The concept of herd immunity played a vital role in the considerations informing the Ebola vaccine development and delivery effort, as it carried important implications for the goal of containing or eliminating[37] the Ebola virus disease.

[34] Bloom. 26.
[35] Ibid.
[36] Fine, Paul, Ken Eames, and David L. Heymann. ""Herd immunity": a rough guide." Clinical infectious diseases 52, no. 7 (2011): 911-916.
[37] *For a detailed discussion of the sophisticated mathematical models than can simulate disease transmission and the differences between disease containment, elimination, and eradication see Bloom p. 42 (Elizabeth Miller, "Potential and Existing Impact of Vaccines on Disease Epidemiology").*

The Ebola vaccine effort: Chance meets a shaky system

After the WHO had declared the Ebola outbreak a Public Health Emergency of International Concern (PHEIC) on August 8th, 2014 and the number of reported new cases of the Ebola Virus disease overpowered orthodox public health and medical interventions, the WHO convened an international meeting from September 4th-5th, comprised of more than 200 global experts to review available Ebola therapies and preventive options. The need for an Ebola vaccine had become an urgent international priority and its development required a collaborative effort of global health organizations and funding mechanisms: the WHO, pharmaceutical companies, regulatory agencies, and NGOs. The various actors convened hoping they would able to pool resources and accelerate the development of existing, promising vaccine technologies so they could be used to combat the rapidly spreading crisis. "Delivering an effective, safe vaccine to West African populations in time to help extinguish the current epidemic presented a global challenge that required not only considerable resources and expertise, but also an unprecedented degree of determination, transparency, trust and cooperation."[38]

The effort that followed that first meeting provides an outstanding example for what is possible when all actors in the complex net of global health come together, overcome organizational restraints and interests, stretch their mandates and collaborate effectively. However, the vaccine development program that unfolded over the fall and winter of 2014 wasn't born out of one single WHO meeting. Rather, the various actors coming together in Geneva were able to leverage the science that had been developed by a number of small research and development teams over decades – sometimes with the intention to develop an Ebola intervention, sometimes with other non-Ebola aims – in various corners of the world. Without the legwork that was done, deliberately or unwittingly, far in advance of the 2013/2014 pandemic, there would have been no science to build a vaccine development effort on top of in response to the crisis.

[38] Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota and the Wellcome Trust. "Recommendations for Accelerating the Development of Ebola Vaccines". February 2015. 8.

The vaccine development effort of 2014 was largely an ad-hoc undertaking. In almost all interviews informing this case study, that precise wording – 'ad hoc' – was used by the various actors in their reflection on how the program got underway and progressed. Where actors disagreed, though, was on the question of whether the effort was the result of chance or good luck, or whether it was the logical result of a global public health infrastructure that had been built internationally and on various national levels over the past decades.

The 'chance' hypothesis:

Those arguing that the various Ebola vaccine programs were, for the most part, a result of good luck, point to the numerous different platforms that the industry happened to be working on prior to the crisis – and into which Ebola was able to be plugged into. Ebola, they note, was by no means the intended application of these platforms. Rather, researchers pursued therapeutic goals (for example, cancer) and the underlying technology also happened to work for Ebola. This view is expressed primarily by industry and IO actors. They warn that affected countries and the international community might not get as 'lucky' once the next pandemic occurs.

Furthermore, collaboration in the development effort was largely driven by a small number of key decision makers within the various organizations from which the vaccine program stemmed. These individuals supported the undertaking because they were able to comprehend the severity of the crisis as a result of their unique backgrounds and training. Jeremy Farrar, Director of the Wellcome Trust, was Director of the Oxford University Clinical Research Unit in Vietnam before joining the Trust. His research interests there were infectious diseases, tropical health and emerging infections. Similarly, Seth Berkley, the CEO of GAVI since August 2011, is a medical doctor specializing in infectious disease epidemiology. It was these leaders' particular backgrounds and resultant understanding of infectious disease that enabled them to comprehend the severity of the crisis in West Africa and instruct their organizations to take swift action. A different set of leaders, argue the supporters of the 'chance' hypothesis, might not have been able to recognize the need for a large scale response or the potential for a vaccine response, and therefore might have been ineffective in orchestrating a collaborative effort.

The 'System delivered' hypothesis:

In contrast, government actors, insist that 'chance' played a very small role in the vaccine development and suggest instead that the effort was the product of a functioning system. The institutions that led the response were in existence pre-crisis and their ability to act and collaborate was less a function of their leaders than their effective and powerful setup. Those who expressed this view in their interviews acknowledge individuals like Farrar and Berkley but maintain that they weren't crucial to the effort, claiming that under different leadership, the outcome would have been similar. The actors that hold this view oftentimes point to the *Biomedical Advanced Research and Development Authority* (BARDA), operating within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, and charged with providing an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies, as evidence of a robust, well-structured system set up to anticipate and respond to public health emergencies and thus avoid random or chance-driven responses. BARDA's existence, they argue, reflects the wisdom informing the global health governance setup and represents a key assurance of global health emergency preparedness.

This divergence in views and perceptions should not surprise, as one could hardly expect government officials to reference 'chance' as a decisive variable driving the response to a major global health crisis. Whether their expressed faith in the system is sincere or merely political speak, a closer examination of the history of the three major vaccine candidates that emerged throughout the response effort of 2014 may help clarify the role 'chance' really played in the vaccine development effort.

Although a number of different vaccine candidates have been and continue to be researched and tested, three candidates quickly emerged as carrying the most promise for efficacy, safety and speedy manufacturing:

cAd2-EBO: a live-virus replication-defective monovalent (Zaire) or biovalent (Zaire and Sudan) recombinant chimpanzee-derived adenoviral vaccine manufactured by GSK. This candidate was co-developed by the US National Institute of Allergy and Infectious Diseases (NIAID) and Okairos, an Italy-based private biotechnology company acquired by GSK in 2013 for EUR 250

million. Although clinical development of the Okairos vaccine began in 2011 and the company was collaborating with US partners, it took the resources of a pharmaceutical giant like GSK to fast-track development and to accelerate the vaccine's entry into clinical trials in response to the West Africa Ebola epidemic. Ripley Ballou, head of GSK's Ebola program, estimated in an August 2014 "back of the envelope" calculation based mainly on personnel expenses, that GSK could produce up to half a million doses for $25 million."[39] Furthermore, significant capital investment would be required in order to develop production capacity sufficient to deliver up to millions of doses. Okairos in its original setup would have been ill-prepared to respond to the Ebola crisis; it took the shared capabilities of GSK to dedicate a team and fast-track delivery.

rVSV-ZEBOV: a single-dose, live-virus replication-component movovalent recombinant vaccine based on an attenuated vesicular stomatitis virus (VSV) platform. The rVSV-ZEBOV vaccine was developed by the Public Health Agency of Canada under the leadership of Gary Kobinger and funded as a bio-security project. When asked why he had dedicated himself to Ebola, Kobinger responded in 2012: "You take the biggest and the toughest and you try to bring it down, with the rationale that if it works against Ebola, it'll work against other things."[40] rVSV-ZEBOV and the underlying technology were licensed to BioProtection Systems (BPS), a wholly owned subsidiary of NewLink Genetics (NLG). In order to fast-track development in response to the EVD in November 2014, Merck Vaccines established an exclusive licensing and collaboration agreement with BPS-NLG for the research, development, manufacture, and distribution of the vaccine, paying $50 million plus a provision for royalties in certain markets.

Ad26.ZEBOV/MVA-BN-Filo: a monovalent, live-virus replication-defective adenovirus-vector vaccine expressing GP from the Zaire Ebola virus (Ad16.ZEBOV) applied in a heterologous prime-boost strategy with MVA-BN-Filo, a booster vaccine. Ad26.ZEBOV is manufactured by Janssen Pharmaceuticals, a subsidiary of J&J. MVA-BN-Filo is a recombinant multivalent replication-defective MVA booster vaccine containing the GP from Zaire Ebola virus, Sudan virus, and Marburg virus. MVA-BN-Filo is manufactured by Bavarian Nordic. Crucell

[39] Cohen, Jon, and Kai Kupferschmidt. "Push to gamble big on mass production of Ebola vaccines". *Science Magazine*. October 2014. Available online at: http://www.sciencemag.org/news/2014/10/push-gamble-big-mass-production-ebola-vaccines (accessed 7/28/2016).

[40] Anna Mehler Paperny. "Canadian doctor zeroes in on vaccine for Ebola virus". *The Global and Mail*. May 2012. Available online at: http://www.theglobeandmail.com/news/national/canadian-doctor-zeroes-in-on-vaccine-for-ebola-virus/article4104896/ (accessed 7/28/2016)

Holland BV, one the Jansen Pharmaceutical Companies of J&J, licensed the MVA-BN-Filo booster from Bavarian Nordic for use with the Ad26.ZEBOV vaccine. In January 2015 J&J received more than EUR 100 million from the EU-backed Innovative Medicines Initiative to support development and manufacturing of vaccines and diagnostic tools for Ebola[41].

The commonalities in the cAd2-EBO and rVSV-ZEBOV efforts are striking. In both cases, it took a private-public research effort to develop the science and platform. The private components in both cases were rather small pharma outfits with limited financial firepower or infrastructure. It then took one of the world's large pharmaceutical companies to step in and support the development efforts once merit for a large-scale, fast-pace effort had been established with the outbreak in West Africa. It is at this point that the two cases diverge. GSK bought Okiros for strategic reasons, eager to acquire a complementary platform enriching its vaccine franchise. Merck established its collaboration with Newlink only after the Ebola pandemic occurred, likely considering "the pressure from various bodies to speed up vaccine development"[42] rather than commercial factors. Nevertheless however, in the cases of both GSK and Merck, it took their acquisition of a rather insignificant industry player to facilitate development. J&J's case differs somewhat. Instead of relying on partial public funding early on in the R&D process, J&J's efforts received public money once the crisis was underway and the need for a vaccine had been established.

In all three major Ebola vaccine programs, it took the interplay of private and public efforts to develop the technology underlying potential large-scale development. The GSK and Merck cases in particular demonstrate the reliance on public-private mechanisms in the initial research stages: Public agencies guided by public health or national security policy collaborating with small biopharmaceutical companies that delivered promising platforms. Such public-private labs are one cornerstone of my seven-lessons-playbook.

The playbook developed out of numerous interviews with actors from all groups involved in the vaccine development effort. All individuals and groups involved brought a set of

[41] Ward, Andrew. "J & J Receives EUR 100m EU Injection for Ebola Vaccine Development." FT.com (2015) ProQuest. Web. 28 July 2016.
[42] Trefis Team. "Merck's Ebola Vaccine Won't Move The Needle". Forbes Magazine. August 2015. Available online at: http://www.forbes.com/sites/greatspeculations/2015/08/24/mercks-ebola-vaccine-wont-move-the-needle/#5e853103437a (accessed 7/28/216)

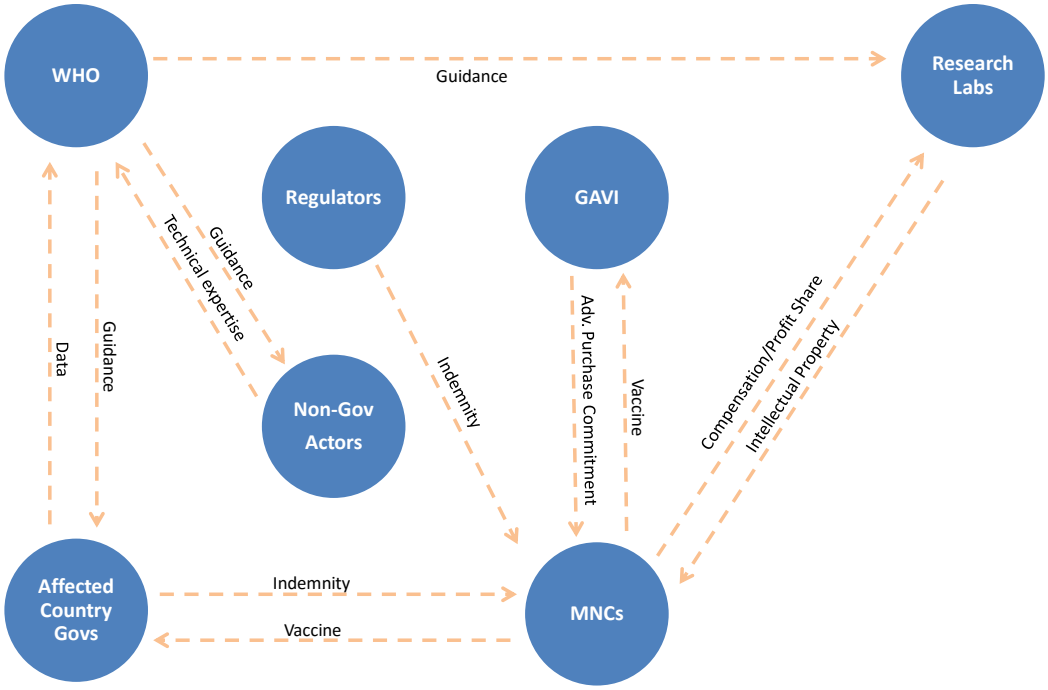
assets and capabilities – often unique – to the table, and at the same time required the resources possessed or offered by others. This setup created a complex net of interdependencies illustrated below and provides the basis for the high-level examination of the network underpinning my seven-lessons-playbook.

Resources and needs: The network of actors

The different phases of vaccine development each require a distinct set of resources and capabilities that no one actor is set up to provide or can muster alone. The Ebola vaccine example demonstrates how preliminary, basic research is most productive in small public-private lab settings but it then takes a larger pharmaceutical company to turn a promising technology into a finished product. Vaccine trials only generate sound data if they are conducted in large enough populations of persons exposed to the disease the vaccine is supposed to protect against and the example of the Ebola vaccine shows how the countries most prone to outbreaks of neglected diseases thus lending themselves to host vaccine trials, oftentimes suffer a lack of adequate regulatory capabilities to oversee trials and approve interventions; they look to partner countries in the developed world and IOs to provide assistance. Pharmaceutical companies have the resources for large-scale vaccine manufacturing but the production of a vaccine only relevant in emergency settings and to be deployed primarily in developing countries, offers very little financial incentive for these companies to pull resources from existing commercial platforms and rededicate them for the temporary production on an emergency vaccine. These companies thus look to international financing mechanisms like GAVI to provide procurement guarantees in order to manage their commercial risk.

The development of vaccines in response to outbreaks of neglected disease – as illustrated by the Ebola vaccine – creates a complex net of interdependencies and needs. A sound understanding of these needs, expectations, and the relationships between the various actors involved in the vaccine development process is a pre-requisite for sound analysis of the public-private collaboration that resulted from these mutual dependencies and it is the foundation for the following seven-lessons framework.

The interplay of resources and needs: The network of interdependencies triggering the unprecedented public-private collaboration of the Ebola vaccine effort



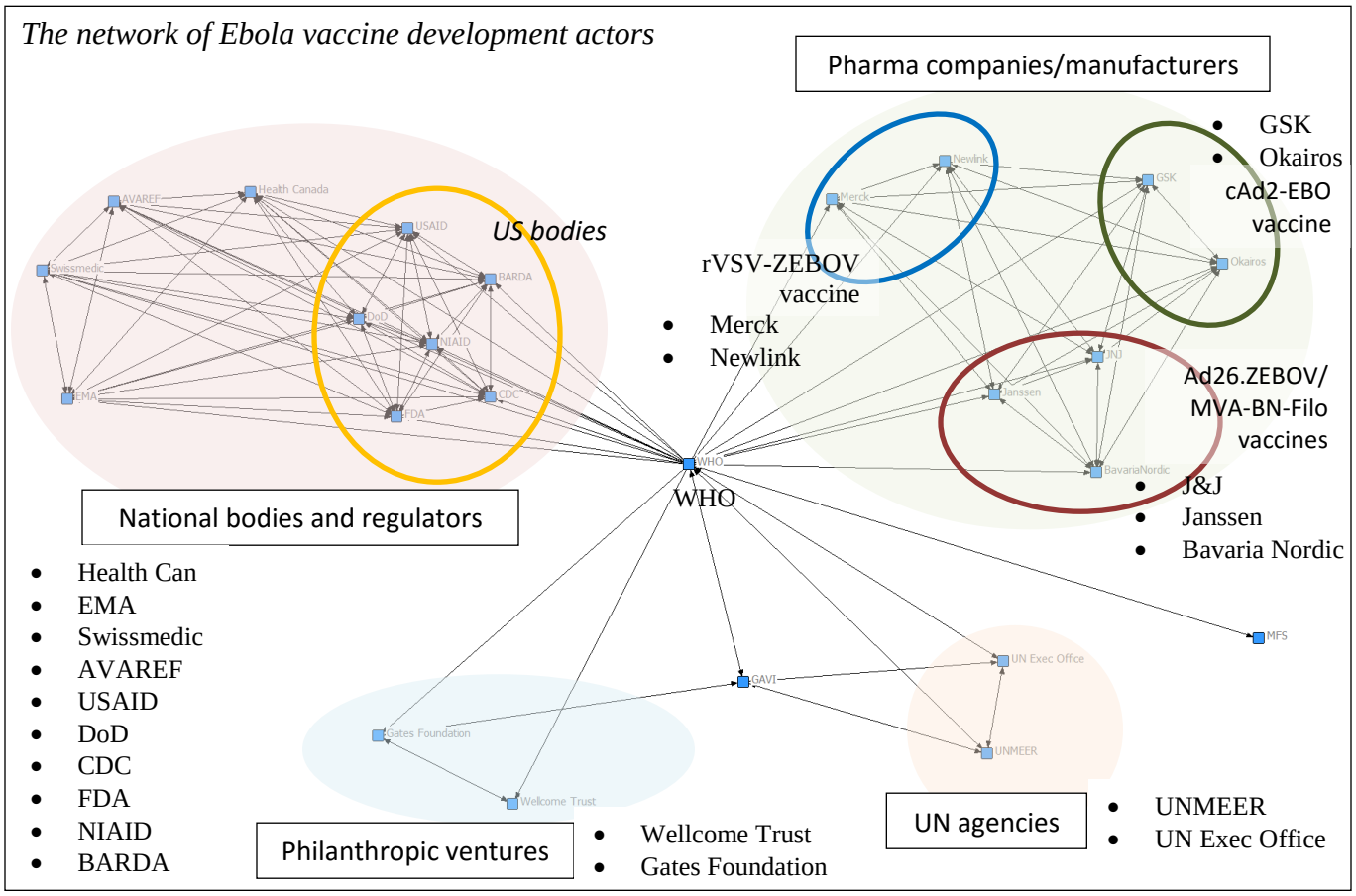
The above illustration offers a simplified, high-level overview of the resources and capabilities exchanged between the various actors involved in the Ebola vaccine effort. In actuality, fare more resources moved between far more nodes creating a complex flow of material and non-material assets under the tremendous external pressure of a developing global health crisis. The following seven-lessons framework explores the processes that facilitated this exchange of resources and highlights opportunities to improve processes and setups in similar, future efforts.

For the sake of simplicity, the broad network of actors involved in the Ebola vaccine development effort can be broken down into four major groups: (1) national governmental or regulatory organizations, (2) international organizations and agencies, (3) the private pharmaceutical industry, and (4) philanthropic, donor, and non-for profits groups. In reality,

segmenting actors into distinct groups is oftentimes challenging. Many organizations do not fit into one distinct category and operate on the intersection of one or many groups. GAVI, as a public-private partnership, is a case in point. Therefore, the purpose of the below network illustration is merely to provide a rough map to illustrate the diversity of the actors and groups that came together in response to the EVD to fast-track the development of the three major vaccines.

Again, the network is simplified and doesn't include all actors that were part of the effort. However, it includes most of the organizations relevant for the following seven-lessons framework and offers itself as a reference for visualizing the divisions that the various actors crossed in order to move the vaccine candidates out of preliminary R&D into production.

The network of Ebola vaccine development actors

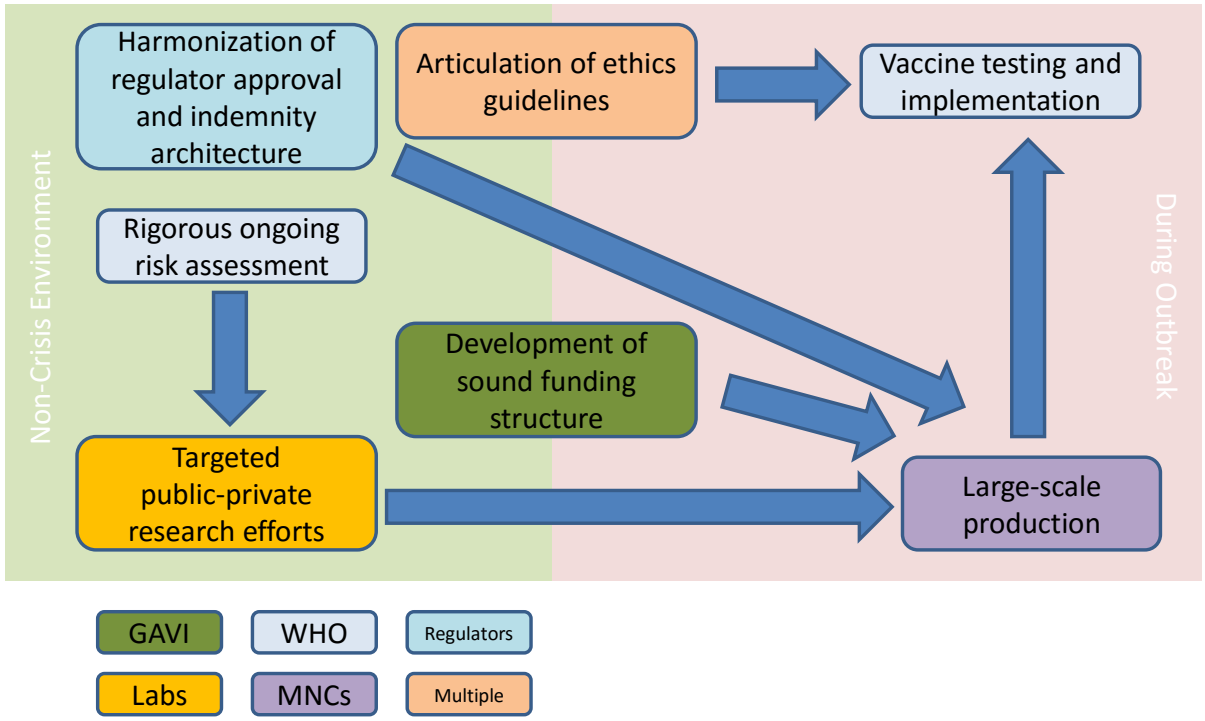


Unsurprisingly, the WHO as the normative international body for health and health regulation sits at the center of this network of actors. The WHO's role in the Ebola response has been heavily criticized and its actions and inactions demand careful examination and, when

appropriate, reform. However, its unique position at the heart of the above network provide a substantial asset that played a key role in the Ebola vaccine development effort and must continue to be leveraged in similar vaccine development efforts in the future.

Seven lessons learned: The framework

The seven-lessons framework



A detailed understanding of what worked in the Ebola vaccine program, and why it worked, will prove critical to replication efforts in future outbreaks of neglected disease. Thus, the distillation of the processes and dynamics that played out in the Ebola program can inform a playbook to be relied upon in the preparation for and actual response to such future outbreaks. The seven-lesson model is a first attempt at developing such a playbook and is by no means

exhaustive. It distinguishes two phases of vaccine development for neglected diseases: A non-crisis or pre-crisis environment marked by the absence of a health emergency; and an outbreak or crisis phase marked by the development or escalation of a serious public health emergency.

The seven lessons that my research identified as crucial either apply to one stage, non-crisis or outbreak, or they are part of both stages. While three of the seven lessons must be applied immediately to lay the groundwork onto which a response to an actual crisis can be built, two apply in particular during the time of a crisis. This doesn't mean that the actors driving the crisis-relevant lessons should sit back and merely wait until the next health crisis emerges. Rather they must build and maintain relationships with those partners with whom they share or exchange resources. Furthermore, their dialogue will generate important understanding, ideally even guidelines, informing crisis collaboration – the principles for the transfer of Intellectual Property from small public-private labs to Multi National Pharmaceutical Producers being one example. Lastly, two of the seven lessons must be applied throughout both non-crisis and outbreak environments. Actors behind these two lessons must come together now and begin discussions for how to implement these lessons. At the same time, not every detail of these lessons can be achieved in a non-crisis setting; it takes the specific contexts, needs, and constraints of a unique crisis to inform these lessons, and so, while initial conversations and planning must get underway now, modifications will occur once actual crisis strikes.

Compared to other analyses of the various responses to the Ebola crisis, one major difference of this seven-lessons approach is that it aims to improve future responses without creating new organizations or centers. In the wake of the Ebola crisis, there have been ongoing discussions between the African union and United States Centers for Disease Control and Prevention to establish an African Centre for Disease Control[43]; similarly the report of the *Harvard-LSHTM Independent Panel on the Global Response to Ebola* suggests the creation of a unified WHO Centre for Emergency Preparedness and Response[44]. The challenge these proposal create is that "establishing a new agency takes time and requires substantial new resources in

[43] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 11.
[44] Moon, Suerie, Devi Sridhar, Muhammad A. Pate, Ashish K. Jha, Chelsea Clinton, Sophie Delaunay, Valnora Edwin et al. "Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola." The Lancet386, no. 10009 (2015): 2204-2221. 8.

order to set up administrative systems and capacity"[45]. Estimates based on recently established agencies place the one-off costs for establishing a new agency at $100 million and the annual overhead expenses of a secretariat at another $100 million. These costs are exclusive of any programming expenses. In addition, the establishment of any new agency requires substantial political will of numerous heads of governments and the time-consuming establishment of consensus-seeking working groups. To avoid these numerous hurdles, the seven-lessons plan seeks instead to leverage existing institutions and frameworks, aiming for a) better coordination and communication between the various actors, b) reconfiguration of existing agencies where necessary, and c) the articulation and establishment of clear protocols for action in future disease outbreaks. The wealth of discussions with practitioners that informed this plan, revealed that the necessary building blocks or agencies necessary for successful crisis response already exist; they are simply not setup and utilized in a manner that allows for effective crisis response. Therefore, this plan deems the creation of a new agency – whether at the UN-level, the WHO-level, or an inter-institutions-level – unnecessary. Furthermore, considering the speed with which Ebola has moved into the rear-view mirror of the international community, one must doubt whether the political will to create a new agency exists in the current non-crisis environment.

Lesson #1: Rigorous ongoing risk assessment

The ad-hoc response to the 2014/2015 Ebola crisis has clearly demonstrated the lack of preparedness of the health systems of the affected countries as well as of the institutions and system in place on a global stage. The scale of the outbreak took actors by surprise. The absence of coordinated action until well into the summer of 2015 reveals the need for a reform of the WHO setup and its escalation mechanism. This need has been well established and the organization is undertaking steps to initiate such reforms. Reform efforts of the WHO architecture are to be supported and will shorten response times in future outbreaks. However, such reforms will do little to address the absence of suitable pharmaceuticals and immunizations required in an effective crisis response. The typical lead time for the development of both medications and vaccines far outlasts the response time available to control a crisis. Waiting for

[45] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 15.

the occurrence of a crisis to trigger targeted vaccine development in response to the challenge at hand will prove ineffective.

Given the nature of neglected diseases, one should also not expect the industry to pursue the development of vaccines as part of its business-driven R&D processes. As the major vaccine manufacturers are profit-driven, they inherently lack the incentive to pursue the development of vaccines for which there is no market, or an undeveloped market, even if the opportunity for development presented itself. The Ebola vaccine case demonstrated that the motor for the development of appropriate vaccine technology was public-private cooperation. Such public-private efforts must be prioritized. The work of institutions such as the Canadian National Microbiology Lab in Winnipeg must be strengthened and built out as the primary sources of novel vaccine research. At the same time, that work must be guided. The main reason that several public-private labs, particularly in North America, were engaged in research that led itself to applications facilitating an Ebola vaccine was a push from the defense community to develop means to counter military or terrorism attacks delivered through biological agents. In 2007, the Defense Threat Reduction Agency awarded several vaccine contracts with a total value of $1.5 billion under a program designed to protect against genetically engineered biological weapons, focused on defenses against intracellular bacterial pathogens and hemorrhagic fever in particular[46]. It was this defense-driven initial research and defense funding that the vaccine development effort in response to the West Africa crisis was able to be built upon. In the next outbreak of a neglected disease, scientists may not be able to fall back on similar defense-funded basic research. Threat assessment guided by defense or national security considerations will prove inadequate in accounting for emerging pathogens, particularly those that are unstable or aren't easily transportable and thus unfit to serve as biological weaponry. What's needed is a system of holistic threat assessment on the international level that incorporates the findings of various disciplines and national agencies.

The WHO took a first step towards creating such a holistic threat assessment infrastructure when it convened experts in virology, microbiology, immunology, public health, clinical medicine, mathematical and computational modeling, product development, and

[46] Wagner, Breanne. "Government Contracts Focus on Vaccines, Emergency Response." *National Defense* 91.643 (2007): 44-5. ProQuest. Web. 28 July 2016.

respiratory and severe emerging infections in Geneva in early December 2015 to prepare a process for prioritization of pathogens for accelerated R&D for severe emerging diseases with the potential to generate a public health emergency. The prioritization exercise was part of a larger 'R&D Blueprint' initiative agreed upon by the World Health Assembly (WHA) in response to the Ebola virus disease outbreak. Workshop participants identified nine elements[47] guiding their prioritization exercise:

1. Human transmissibility (including population immunity, behavioral factors, etc)
2. Severity or case fatality rate
3. Spillover potential
4. Evolutionary potential
5. Available countermeasures
6. Difficulty of detection or control
7. Public health context of the affected area(s)
8. Potential scope of outbreak (risk of international spread)
9. Potential societal impacts

Based on these criteria, the participating experts developed a list of seven diseases requiring urgent R&D: Crimean-Congo hemorrhagic fever, Filovirus Disease (eg, EVD & Marburg), Highly pathogenic emerging Coronaviruses relevant to humans (MERS Co-V & SARS), Lassa Fever, Nipah, Rift Valley Fever, and – rather vaguely – 'R&D preparedness for a new disease'[48]. The meeting concluded with the agreement to revisit the priority list 'on a regular basis' and rerun the prioritization processes 'within a year'[49].

The priority list of the 'R&D Blueprint' provides a helpful starting point, but the informal structure of the expert panel convened to design it and the lose timeframe for follow-up are inadequate to provide a solid basis for threat assessment or even R&D guidance. What is needed is a formal, permanent international body fully dedicated to updating and further developing the

[47] World Health Organization. "Blueprint for R&D preparedness and response to public health emergencies due to highly infectious pathogens". *Workshop on Prioritization of Pathogens*. December 2015. Available online at: http://www.who.int/csr/research-and-development/meeting-report-prioritization.pdf (accessed 7/28/2016). 2.
[48] World Health Organization. "Blueprint for R&D preparedness and response to public health emergencies due to highly infectious pathogens". 1.
[49] Ibid. 4.

priority list, and to screening for new threats on a continuous basis. In-line with the premise of this seven-lessons framework, no new agency is needed to accommodate such a permanent panel. The WHO already operates the 'Strategic Health Operations Centre' (SHOC) charged with information sharing and response coordination to public health risks of potential international concern[50]. The SHOC currently focuses on emergency monitoring and response support; growing this existing centre by a more long-term focused threat assessment team would be a natural, complementary expansion allowing for ongoing cross-fertilization. Expanding the SHOC by a long-term surveillance function would create the most efficient and effective mechanism for long-term threat assessment through the leverage of existing infrastructure and competencies.

While it is housed within the WHO, the SHOC must collaborate with the health agencies of national governments such as the US CDC, non-governmental actors such as the Wellcome Trust, or relief organizations such as Medicines Sans Frontiers, as well as the academic community. Furthermore, its staff must reflect the numerous disciplines informing our knowledge of disease and Global Health, well beyond the established contributions from the fields of medicine and epidemiology. As the linkages between disease and climate change are becoming more evident, along with the health impact of the increase of global migration and rise of human-wildlife conflict, disciplines such as anthropology and environmental studies inform our understanding of disease and disease spread in ever more prominent ways.

While this report recommends the utilization of existing facilities and resources, others have suggested the creation of new centers and agencies. The report of the *Harvard-LSHTM Independent Panel on the Global Response to Ebola* suggests the formation of a dedicated centre for outbreak response. The report recommends that "the centre should merge the outbreak risk assessment and response capacities that reside in the Global Alert and Response Network with WHO's humanitarian teams, which presently respond to natural disasters, refugee crises, and other large catastrophes"[51]. Somewhat similarly, the *Ebola Interim Assessment Panel* convened

[50] The World Health Organization. "International Health Regulations – Strategic Health Operations Centre (SHOC)". Available online at: http://www.who.int/ihr/about/IHR_Strategic_Health_Operations_Centre_SHOC_respond.pdf (accessed 7/28/2016).
[51] Moon et al. 8.

by the WHO recommends the establishment of a "WHO Centre for Emergency Preparedness and Response"[52]. Both ideas are ambitious and likely to encounter significant stumbling blocks. Crisis anticipation – or risk monitoring – and crisis response demand significantly different skill sets. Risk assessment in a public health context is a highly theoretical exercise; emergency response, on the other hand, is a highly practical one. The pooling of risk assessment and humanitarian emergency response capabilities, as intuitive as it may seem on the surface, is ill-informed: "One of the difficulties to understanding is that the risk assessment of public health emergencies and so-called humanitarian emergencies differs, because of uncertainty in assessing the likelihood of disease spread"[53].

Instead of creating a new center or agency interface and overloading it with incompatible functions, the international community is best served by leveraging existing resources. The expansion of SHOC by an independent, long-term threat assessment capability will serve as a reliable guide to national governments on how to prioritize research efforts and allocate spare R&D resources.

Lesson #2: Translation of risk assessment in expanded public-private research efforts

This study previously highlighted that all three major vaccine candidates originated in public-private research settings: cAd3-EBOZ was co-developed by the US National Institute of Allergy and Infectious Disease and Italian-based Okairos; rVSV-ZEBOV originated in Gary Kobinger's National Microbiology Laboratoryin Winnipeg with funding from the Public Health Agency of Canada, its technology was licensed at a later stage to BioProtection Systems (BPS) which is wholly owned by US-based Newlink Genetics (NLG); and Ad26.ZEBOV and MVA-BN Filo received development support from the NIAID and Europe's Innovative Medicines Initiative. The close collaboration between public and private entities in the development of the technology that eventually supported the Ebola vaccine reflects the tightly knit partnerships between public agencies, public and private research and academic institutions, and private

[52] World Health Organization. "Report of the Ebola Interim Assessment Panel". 7.
[53] Ibid. 23.

industry that have supported vaccine development for decades. The US National Vaccine Advisory Committee, housed by the Department of Health & Human Services, estimates that two thirds of all new vaccines provided worldwide have been produced by a US network of independent industrial, governmental, and academic partners[54].

The NIH supports most of the basic research that eventually facilitates vaccine development, using both in-house scientists and external researchers, often funding academic institutions. Once the basic technology has been identified, it is then usually licensed to private industry actors if those private entities had not been part of the experimental development phase to begin with: "Expertise in process development resides almost exclusively in the large companies; there is no other resource for such development."[55] Other government actors with the capacity to support vaccine development are the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Department of Defense (DOD), the US Agency for International Development (USAID), as well as the state governments of Michigan and Massachusetts[56].

This "fragile"[57] interplay between public, academic, and private actors which had slowly evolved in the second half of the 20th century, prepared the groundwork for tremendous scientific breakthroughs and game-changing vaccine candidates, yet despite the successful collaboration it nurtured, the current setup is feeble due to its reliance on funding by political bodies and its lack of a holistic strategy. As highlighted earlier, the basic research informing the technology which facilitated the development of at least one of the three major Ebola vaccines was conducted with the help of national defense funding. It was the post-9/11 and post-Anthrax environment that triggered the desire to develop capabilities to protect Western populations from the threats posed by biological weapons. While a sound consideration from a national security perspective, this national security approach to vaccine development offered no consideration for the needs of populations that were naturally exposed to hemorrhagic fevers and whose governments lack the resources to engage in and support basic primary drug and vaccine development research themselves.

[54] National Vaccine Advisory Committee. "United States vaccine research: a delicate fabric of public and private collaboration." Pediatrics 100, no. 6 (1997): 1015-1020. 1.
[55] Ibid. 5.
[56] Ibid. 1.
[57] Ibid.

What is needed then from a global health perspective is a fluent translation of the priority threats identified by the WHO's risk assessment, as outlined in Lesson #1, into research priorities on a national level within the existing public-private-academic partnership setting. Naturally, national bodies will amend the WHO priorities by their own domestic research and capability development agenda while the WHO assessment will provide hard-to-ignore guidance that ensures that the interests and needs of all populations are covered by the research initiatives carried out in the developed world. And again, the infrastructure to conduct this basic research already exists. No new agencies or labs need to be formed – the Ebola effort demonstrated the ingenuity of the current tightly-knit partnership setup. All that is needed now is the linkage of that research network into a global risk assessment.

The Ebola virus disease outbreak offered a strong rationale for why governments of countries not directly exposed to neglected disease outbreaks have an incentive to invest R&D addressing these diseases – apart from defense or development considerations. The rapid uptick in case loads throughout West Africa over the summer of 2014 and the realistic fear of the aggressive spread not only to neighboring African countries but globally, demonstrated the toxic threat infectious disease pathogens pose not only to the populations in disease-affected countries but to the interconnected world as a whole. It is thus in the interest of developed countries to protect global travel, commerce and ultimately their domestic populations through investment into research with the potential to protect against or cure these diseases.

The past success of the research networks examined above, provides a strong case for conducting R&D on a national level instead of trying to replicate existing structures internationally. As a consequence, the translation of an international risk assessment into national research initiatives will inherently lead to some duplication in efforts. Nationally sponsored R&D might compete with research efforts on the same disease elsewhere. Countries are thus encouraged to collaborate closely and frequently exchange research priorities and plans amongst themselves to minimize possible duplication of efforts. Most importantly, such inter-country exchanges must ensure that at least one country is sponsoring research on every disease on the priority list to make sure every identified disease threat is addressed. The risk of one disease attracting insufficient attention looms much larger than the threat of duplication. Some level of duplication is even desirable. The Ebola vaccine effort demonstrated that it takes a multitude of

research efforts to generate a small number of effective vaccines. In an ideal world, one would want to have numerous candidate interventions at hand in the case of an emergency.

Lesson #3: Transfer of public-private IP to appropriate manufacturers

Lesson #2 and Lesson #3 addressed necessary changes to be implemented immediately, absent any new disease emergency. They provide for ongoing, holistic risk assessment and prioritization and the translation of the risk assessment findings into national public-private research efforts charged with developing the basic technology which can be leveraged in case of an actual disease outbreak. The previous chapter illustrated the established dynamics facilitating basic R&D, oftentimes resulting in the licensure of public-privately developed IP to private companies at some stage in the research process. The example of the rVSV-ZEBOV Ebola vaccine is an illustrative case in point: Developed by a research lab of the Public Health Agency of Canada (PHAC), the agency granted marketing rights in 2010 for the experimental vaccine to Newlink Genetics' BioProtection Systems with the expectation that the private company would get the vaccine through testing, regulatory approval, and ultimately into production.

Once a disease emergency hits however, the setup of these public-private collaborations becomes inadequate. Ebola demonstrated how a crisis imposes time urgency and resource demands that overwhelm the public-private R&D eco system. As outlined earlier, in the case of the rVSV-ZEBOV vaccine, it took pharmaceutical giant Merck to step in and push vaccine development forward by leveraging its vastly superior resources relative to the infrastructure Newlink was able to fall back upon. Similar dynamics also played out in the development of the other two major Ebola vaccine candidates: GSK pressed ahead with the development of the cAd3-EBOZ vaccine that had been jointly developed by the NIAID and Okairos which GSK had acquired in 2013; and J&J took the lead in the development of the Ad26.ZEBOV and MVA-BN Filo vaccines that had been in development at its Janssen Pharmaceutical subsidiaries, and at Bavarian Nordic, in which J&J subsequently took a 5% equity stake.

All three pathways from basic R&D in rather small public-private lab settings to accelerated development by a multi-national pharmaceutical company differ somewhat. GSK's development of the cAd3-EBOZ vaccine seems most straight-forward as the transfer of ownership from Okairos into the GSK parent entity occurred in-house. At the same time, the development of the vaccine took up significant internal resources. Scientists had to be pulled from other vaccine programs, a new in-house development team had to be assembled, and production facilities had to be re-assigned. Multiple external interviewees applauded the determination of GSK's CEO Andrew Witty, who personally pushed the Ebola program internally. Witty is said to have felt a moral obligation to deliver GSK's capabilities and resources despite uncertain testing and approval outcomes and no assurance of final product uptake. Witty's conviction that "big pharmas have to be more in step with the needs of the global society"[58] is well documented, and the Ebola virus disease outbreak offered an opportunity to put GSK's money where Witty's mouth was.

Merck and J&J came to develop their vaccines in a different manner. Merck paid Newlink $50 million plus royalties exchange for worldwide commercial rights to the rVSV-ZEBOV vaccine. Newlink itself had paid a "milestone payment" of a mere $205,000 to the Canadian government in exchange for exclusive commercial licensing rights in 2010. It had invested very little into the vaccine development since and "moved at what some critics call an agonizingly slow pace"[59]. It remains nebulous what made the Canadian government sell-off the rights to the vaccine for a bargain in 2010, and it also remains somewhat unclear what led Merck to pay a significant premium for the rights in 2015. Analysts reckon that Merck approached the deal "from a humanitarian perspective rather than a commercial endeavor"[60] yet the deal dynamics warrant close examination as similar rights transfers will constitute a key building block of future vaccine development efforts in disease emergencies. In those future outbreaks, counting on the good-will of big pharma might not be good enough.

[58] Cohen, Jon. "GSK to make cancer drugs more accessible in poor countries". *Science Magazine*. March 2016. Available online at: http://www.sciencemag.org/news/2016/03/gsk-make-cancer-drugs-more-accessible-poor-countries (accessed 7/28/2016).
[59] Thomas Walkom. "The strange tale of Canada's Ebola vaccine". *Toronto Star*. Nov 2014. Available online at: https://www.thestar.com/news/canada/2014/11/25/the_strange_tale_of_canadas_ebola_vaccine_walkom.html (accessed 7/28/2016).
[60] Trefis Team. "Merck's Ebola Vaccine Won't Move The Needle".

Rather, public and private actors must come together and articulate clear guidelines for the transfer of Intellectual Property and commercial rights that satisfy both the public's interest in access to a speedily-developed, affordable intervention and the private company's interest in generating a financial return. Antony Taubman stresses the importance of considering the entire drug or vaccine development value chain from rudimentary R&D, over the licensure of certain IP and the eventual large-scale manufacturing, when negotiating rights transfers. He finds that "both development and downstream distribution issues need to be considered, both as distinct sets of issues, but also as integrated elements of an overall longer-term partnership"[61]. It appears that the Canadian government in the case of the rVSV-ZEBOV neglected this advice and its rights transfer to Newlink neither led to significant development progress nor allowed for Canada to participate in any financial upside upon resale of the commercial rights to Merck.

The articulation of detailed guidelines for rights transfers in vaccine development would go beyond the capacity of this study. Taubman and the health-innovation-focused non-for-profit PATH[62] offer a number of recommendations for guiding IP transfers. PATH considers the principles of 'Availability', 'Accessibility', and 'Affordability' to be of particular importance. The Ebola vaccine experience demonstrated that any negotiated agreement must consider the potential need for emergency scale-up which can only be properly undertaken by a large multi-national. Agreements, therefore, must accommodate a multi-state rights transfer and be structured in a way that satisfies the needs of both public and private R&D and development partners as well as guarantees reasonable transfer terms from one private actor to another in case of a disease emergency. Public and private actors must come together now, in a non-emergency environment, and discuss terms of IP transfer in future emergencies.

[61] Taubman, Antony. "Public-Private Management of Intellectual Property for Public Health Outcomes in the Developing World: The Lessons of Access Conditions in Research and Development Agreements." Operational Issues on Health Public-Private Partnerships (2004). 12.

[62] Brooke, S., C. M. Harner-Jay, H. Lasher, E. Jacoby, A. Krattiger, R. T. Mahoney, L. Nelsen et al. "How public-private partnerships handle intellectual property: the PATH experience." Intellectual property management in health and agricultural innovation: a handbook of best practices, Volumes 1 and 2(2007): 1755-1763.

Lesson #4: Testing and implementation coordination by WHO

The very nature of neglected diseases – their rare and oftentimes isolated occurrence – presents a unique and hard-to-solve challenge for vaccine development: sound, rigorous testing is impossible in the absence of an affected population. Any meaningful testing for efficacy must therefore be undertaken in the context of an evolving crisis, forcing policy makers to strike a delicate balance between scientific and ethical considerations. Lesson #4 focuses mainly on the technical challenges of vaccine testing during a disease outbreak while Lesson #5 revolves around ethical considerations. Yet at times one cannot be discussed without touching upon the other, and thus this chapter will periodically also refer to the ethics of vaccine testing.

As GSK, Merck, and J&J took charge of the development of the three major vaccine candidates, none of the vaccines had been tested in humans. All had shown promising results when tested in primates and, in the fall of 2014, became ready to enter clinical trials, the major hurdle to be overcome prior to regulatory approval and application [Appendix 1]. Clinical trials in vaccine development typically break down into three separate, defined phases: Phase 1 marks the first time the vaccine is introduced into a study population of healthy adult volunteers who do not have preexisting acquired immunity to the disease the vaccine is designed to prevent[63]. Phase 1 studies typically enroll less than 50 subjects[64] and are designed "to determine whether a vaccine has an acceptable margin of safety and induces sufficiently robust and appropriate responses to justify the considerable time and expense required to conduct further clinical trials"[65]. If both conditions are met following a usual follow-up phase of at least six months[66], testing progresses to Phase 2. In the second testing phase the vaccine gets introduced to a larger, more diverse population of typically several hundred subjects in order to extend and refine the Phase 1 data and conduct additional studies of dose-response, different formulations, schedule optimization, and lot consistency[67]. Only after Phase 1 and 2 trials yield satisfactory results, can

[63] Bloom. 87.
[64] Ibid.
[65] Ibid. 88.
[66] Ibid. 90.
[67] Ibid.

a vaccine candidate move into the decisive Phase 3. Phase 3 studies are meant to generate rigorous evidence about vaccine protection and are designed as experiments with a clear hypothesis. The randomized, controlled clinical trial (RCT) is regarded as the gold-standard design to provide scientifically credible evidence about the clinical performance of vaccines[68]. Thus, for RCT study purposes, Phase 3 trials must be conducted in a population that normally experiences the diseases against which the vaccine is supposed to protect with half the population being treated with the vaccine and the other half – the control group – being treated with a placebo.

Industry, policymakers, and funders faced myriad challenges as they adjusted the orthodox vaccine testing procedures to the realities of the Ebola crisis. For one, they had to reconcile the urgency of getting a vaccine candidate into manufacturing and ultimately into the affected populations, with the need for proper safety and efficacy testing. While all actors were interested in the quick delivery of a final product, they also stressed that "any Ebola vaccine candidate will require rigorous demonstration of safety"[69]. In the effort to strike this delicate balance, one possible approach for reducing the duration of the overall trial stage was to conduct Phase 1 and 2 trials simultaneously. Ethical hesitations over safety were manageable under this approach as both trial phases enrolled volunteers who knowingly agreed to a possibly unsafe intervention. And yet, while the simultaneous run of Phase 1 and 2 trials saved time, it created some problems down the road as it generated insufficient information on formulation and made it a struggle for vaccine manufacturers to get Phase 3 trials under way as scheduled in December of 2014, as they didn't have a clear understanding of what dose would be needed[70].

A more promising option for speeding up the duration of trails while ensuring a safe and efficient process would be combining Phase 1 and Phase 2 trials into one single Phase. Such a solution would save time, and by testing the vaccine candidate in a larger population, more typical of a Phase 2 trial, testing would also generate the necessary information to move forward into Phase 3 should safety and efficacy standards be met. While some observers critique this idea

[68] Bloom. 96.
[69] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 18.
[70] Mohammadi, Dara. "Ebola Vaccine Trials Back on Track." The Lancet 385.9964 (2015): 214-5. ProQuest. Web. 28 July 2016.

as an "extraordinary gamble"[71], it is a gamble justified by the extreme threat posed by highly-fatal diseases like Ebola.

Another major point of contention in the testing of the three vaccine candidates became the design of the Phase 3 trials. While representatives of the industry pushed hard for a RCT design, representatives from humanitarian organization – most notably Medecines Sans Frontier – claimed it would be irresponsible to not immunize study participants in the control group, all of whom would be continuously exposed to Ebola in their daily lives, if such immunization was available. One compromise proposed was a so-called "stepped wedge" design in which all study participants would receive the immunization, only with time delays between different groups. Representatives of industry and the scientific community insisted that such a compromise would generate insufficient efficacy evidence and any useful data that would come out of such a study design would take longer to generate than the data extracted from a RCT. Scientists estimated the power to detect a 90% effective vaccine to be between 49% and 89% for an RCT, and between 6% and 26% for a stepped-wedged cluster trial if conducted in early 2015[72]. To reconcile both camps, some industry representatives suggested moving ahead with a RCT but to utilize an active control, for example against hepatitis B, instead of placebo. At a meeting in Geneva, GSK's Ripley Ballou argued this study design "offers the fastest, most acceptable route to determining whether a vaccine is safe and effective, and thus would potentially save the most lives"[73].

The arguments over study design were "tense"[74]. Despite the good intentions of all actors involved in the vaccine development effort, the study design discussion revealed most clearly the varying interests of the different parties engaging in the vaccine development exercise. For the WHO, the vaccine program was an opportunity to show leadership and push ahead with a promising intervention to a crisis which it was initially very slow to respond to. For the industry, the outbreak presented a unique opportunity to test technologies and vaccine candidates that,

[71] Cohen, Jon, and Kai Kupferschmidt. "Ebola vaccine trials raise ethical issues." Science 346, no. 6207 (2014): 289-290.
[72] Bellan, Steven E., Juliet RC Pulliam, Carl AB Pearson, David Champredon, Spencer J. Fox, Laura Skrip, Alison P. Galvani et al. "Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis." The Lancet Infectious Diseases 15, no. 6 (2015): 703-710.
[73] Cohen, Jon, and Kai Kupferschmidt. "Ebola vaccine trials raise ethical issues."
[74] Ibid.

absent a large outbreak, would be extremely difficult to validate. As efficacy testing can only be undertaken during disease outbreaks, all involved parties must come together now post-crisis and continue their discussions over appropriate trial designs in order to articulate best practices for testing of future vaccine candidates during disease emergencies. There are no simple answers to the difficult questions discussed above and the Ebola vaccine case offers an opportunity to develop parameters that are acceptable under both ethical and scientific standards. These discussions are better had during a time of non-crisis than after disaster has already struck.

The discussions over best practices must also consider the difficult question of who should get to participate in trials. During the initial discussions over the Ebola vaccine trials, WHO consultants recommended that efficacy trials first recruit health care workers, as they are at high risk and provide a critical service[75]. This language was later amended to 'front-line caregivers' which referred to a much larger population including janitors, gravediggers, and care-giving family members of patients. The question of who gets to participate in vaccine trials raises obvious ethical as well as scientific concerns: It seems reasonable to first protect those health workers who sustain a very strained health infrastructure which surely would collapse in their absence or death. On the other hand, focusing on health workers who are also likely to share characteristics other than their profession, might introduce bias into any trial design and lead to unsatisfactory testing outcomes. These questions must be carefully examined and clear protocols on participation should become part of any study design guidelines.

Ultimately, any guidelines on vaccine trials during times of an acute disease outbreak need to have some degree of flexibility. Future outbreaks will differ from Ebola and occur in different geographies, posing new, unique challenges that any recommendations derived from the Ebola response would be unable to anticipate. "Designs of efficacy trials should, to the extent possible, permit adaptive decisions to add participants or increase follow-up time in response to patterns of incidence that were not anticipated in the original study design, such as declining incidence or occurrence of localized outbreaks."[76] Declines in the incidence of the disease throughout the various Phase 3 trials posed a particular challenge in the Ebola vaccine testing: As the disease incidence had dropped markedly throughout 2015, the clinical trials suffered from

[75] Cohen, Jon, and Kai Kupferschmidt. "Ebola vaccine trials raise ethical issues."
[76] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 24.

a lack of statistical power to demonstrate efficacy, which made it nearly impossible to perform direct comparisons of vaccines under similar field conditions. "If the incidence does continue to fall, then it's great news but it might make the trials more difficult"[77], said John Edmunds, an infectious disease modeler from the London School of Hygiene & Tropical Medicine (LSHTM) at the time of the Ebola trials.

It is the responsibility of the WHO to re-convene all parties who were involved in the discussion around the Ebola vaccine trials and ensure an ongoing dialogue over best practices in future trials in an emergency environment. Only the WHO has the convening authority to bring together this diverse set of actors and the deep relationships with the governments that would ultimately host Phase 3 trials, exposing their populations to somewhat comprised and potentially risky trials. Furthermore, as the WHO is the international organization with the normative power to approve or recommend any vaccine product through its prequalification process, it only makes sense that it also remains at the centre of any discussions over efficacy and safety trials.

Lesson #5: Discussion and articulation of ethics guidelines in emergency response

Ethics considerations have historically featured prominently in vaccine development, more so than in non-immunization drug development. "For example, the U.S. Food and Drug Administration (FDA) maintains that safety standards have to be set higher for vaccines than for other products because they are administered to healthy subjects."[78] This chapter will highlight the even more complex role ethics play in vaccine development during disease emergencies, building on some of the ethical hurdles already alluded to in the previous chapter on the Ebola vaccine trials.

A central ethical debate throughout discussions over trial designs was the issue of access: actors discussed at great length the question of who should get to participate in the vaccine trials,

[77] Mohammadi.
[78] Bloom. 120.

considering the life saving potential of the vaccine. Some claimed that healthcare workers should get priority in vaccine trials as they were the primary population exposed to the disease and critical for the upkeep of the health infrastructure in the disease affected region. Others argued that "because healthcare workers are likely to be financially secure and have ties to the healthcare system, they may enjoy a privilege not afforded people who provide care but are not trained as health professionals"[79]. Ethical questions well beyond access remained throughout the trials. "If one vaccine shows convincing efficacy ahead of the others, it may be difficult to continue other trials if sufficient supplies of the efficacious vaccine are available for widespread use. In this situation, continuing other trials would raise issues that may need to be addressed by in-country ethics committees."[80] The halt of other trials, however, may turn out problematic in the long-term as the vaccines whose trials were aborted could actually end up being superior to the vaccine showing efficacy mostly quickly, for example with regards to manufacturing, changing tolerability, early waning immunity, or higher efficacy. The Wellcome authors warn: "Choosing only one vaccine would lead to a single point of vulnerability and could limit vaccine choices in the future."[81]

Furthermore, given the severity of the Ebola threat, researchers and policy makers struggled to define a tolerable risk-benefit ratio to determine if the vaccine safety profile coming out of the various trials was acceptable for eventual deployment of the vaccine for disease control. In the past, in a number of situations, low levels of serious adverse events had been associated with vaccines, but their occurrence had been accepted because such serious adverse events were rare and the overall risk-benefit ratio for vaccination remained favorable. Related to the conundrum over an appropriate risk-benefit ratio is the open question regarding vaccine-related adverse events post-crisis. "It is unclear […] how potential adverse events related to the post-licensure administration of vaccines will be handled, who is accountable for oversight, and how reparations will be made."[82]

Although it features prominently in the wider discussions over vaccine policy, the issue of moral hazard was barely raised in the Ebola case. Moral hazard in the context of vaccines

[79] Rid, Annette, and Ezekiel J. Emanuel. "Ethical considerations of experimental interventions in the Ebola outbreak." The Lancet 384, no. 9957 (2014): 1896-1899.
[80] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 22.
[81] Ibid. 22.
[82] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 37.

arises through "the ironic prospect"[83] that vacinees may be placed at a higher risk of acquiring the disease against which the vaccine is supposed to protect them because they "believe the vaccine will be successful in preventing infections, resulting in their tendency to engage in risky behavior or a failure to reduce risks they might otherwise seek to avoid"[84]. The moral hazard dilemma is particularly relevant to vaccines in the trial stage where efficacy has not yet been fully established. The challenge of moral hazard could potentially be mitigated through appropriate emphasis of proper community engagement. "Lessons learned from past vaccine campaigns in Africa indicate that success pivots on authentic CE (community engagement) that instills and maintains trust."[85] The lack of sufficient community engagement in the early phase of the Ebola crisis response has been well documented[86] and reflects inadequate African representation in crucial coordinating bodies on the international level, including, for example, the discussions over clinical trial designs, causing observers to warn: "The urgency and speed of vaccine development and delivery must not be allowed to trump the imperative that African stakeholders are positioned at the forefront of decisions that affect the safety, well-being, and resilience of the populations hardest hit by EVD."[87]

This pyramid of ethical issues yet to be resolved demonstrates the need for profound ethical review and oversight. However, the global community currently lacks the capacity to facilitate such ethics discussions. Throughout the Ebola outbreak, the WHO has attempted to provide preliminary ethical guidance, emphasizing the need for transparency and the use of the three traditional ethical principles of distributive justice (fairness between countries and among populations within countries), reciprocity (placing priority on people who put their lives at risk to cure others) and social usefulness (targeting people who are instrumental to controlling the outbreak, those who perform burial services, and relatives who provide care to patients) for making prioritization decisions[88]. Yet it would be careless to automatically rely on the WHO to host discussions on ethics going forward, as the agency lacks the expertise and appropriately

[83] Bloom. 121.
[84] Ibid.
[85] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 35.
[86] Shrivastava, Saurabh R., Prateek S. Shrivastava, and Jegadeesh Ramasamy. "Public health strategies to ensure optimal community participation in the Ebola outbreak in West-Africa." Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 20, no. 3 (2015): 318.
[87] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 38.
[88] World Health Organization. "Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO." (2014).

trained personal. Given that ethics considerations have featured prominently in a number of health and non-health related global humanitarian initiatives, the absence of a supra-national normative organization to facilitate and guide ethics discussions is somewhat surprising. To fill this void, the Ethics Work Group of the 'Recommendations for Accelerating the Development of Ebola Vaccines' suggests a "need for a kind of 'Ethicists Without Boarders' organization that would be akin to the well-funded relief organizations that deploy healthcare workers as volunteers"[89]. While this seven-lessons framework is generally skeptical of the merits and feasibility of creating new institutions in order to facilitate future vaccine development efforts, preferring to urge actors to leverage existing resources instead, the absence of adequate resources to address the ethics of such efforts warrants the creation of a new supra-national agency or committee. As detailed above, the creation of a new agency in the international arena takes time and significant resources. Given the urgency of exploring the various ethical issues inherent in vaccine development during disease emergencies, the creation of such an ethics committee must be prioritized and sponsored by the various UN agencies involved in humanitarian response. Alternatively, an ethics agency could be administered independently by a well-established and reputable non-governmental funder in order to "avoid conflicts of interest"[90].

Lesson #6: Harmonization and acceleration of regulatory approval and indemnity architecture

The delivery of an Ebola vaccine in West Africa ultimately depended on regulatory approval or authorization by the regulators of the affected countries in accordance with local pharmaceutical law. Given "notable deficiencies"[91] of the regional regulatory regimes, "approval by a national regulatory authority (NRA) such as the FDA, the European Medicines Authority

[89] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 37.
[90] Ibid. 37
[91] East African Community Secretariat. "East African Community Regional Pharmaceutical Manufacturing Plan of Action: 2012-2016". Available online at: https://www.unido.org/fileadmin/user_media_upgrade/What_we_do/Topics/Business__investment_and_technology_services/CUP/Pharma/Literature/EAC_Regional_Pharmaceutical_Manufacturing_Plan_of_Action.pdf (accessed 7/28/2016). 24.

(EMA), Health Canada (HC), or Swissmedic could facilitate West African NRA's regulatory processes"[92]. Throughout the vaccine development effort, in tandem with its efforts to facilitate appropriate vaccine trial designs, the WHO played an active role in bringing together the various national regulators. Representatives of the vaccine manufacturing companies, the African Vaccine Regulators Forum (AVAREF), and the NRAs, including the FDA, the EMA, HC, and Swissmedic focused in particular on developing procedures for joint regulatory reviews, the harmonization of regulatory requirements, and – most importantly – potential pathways for accelerated approval.

In a 2011 guidance document[93], the FDA highlighted accelerated approval in emergency environments as one of two US licensing options for a vaccine that has been studies for safety and efficacy and provides meaningful therapeutic benefits over existing interventions. Approval could be withdrawn later on if post-marketing studies failed to verify the clinical benefit. The other option offered by the FDA – which was "not be applicable if a vaccine could be approved through accelerated approvals pathways"[94] – was the so-called 'animal rule', which stipulates that when definitive human efficacy studies are not ethical or feasible, it is sufficient to rely on evidence generated through adequate and well-controlled studies in animals. In addition to these two FDA emergency licensing options, US law allows access to investigational (non-licensed) products under certain circumstances when no acceptable alternative exists. This Emergency Use Authorization (EUA) requires the declaration of a public health emergency by the Secretary of the Department of Health and Human Services (HHS) and was leveraged for the authorization of five Ebola diagnostic tests. Equivalent measures issued by the EMA, are the 'Conditional Marketing Authorization', which requires demonstration of a positive benefit-risk ratio based on scientific data and is issued for one year, and the related 'Marketing Authorization Under Exceptional Circumstances', which applies when comprehensive data cannot be generated. As the need for regulatory approval subsided with the diminishing EVD case load in early 2015, harmonization efforts between the various national regulators stalled.

[92] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 28.
[93] U.S. Department of Health and Human Services. "Guidance of industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Disease". December 2011. Available online at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM282995.pdf (accessed 7/28/2016).
[94] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 29.

Going forward, the WHO should leverage its convening power to facilitate ongoing harmonization efforts and oversee the development of a blueprint for accelerated approval during disease emergencies. The creation of a sound indemnity architecture – ideally facilitated by a permanent WHO regulatory fast-track facility – will support such harmonization efforts. Thus, the two must go hand in hand. Ongoing WHO-led discussions on accelerated approval pathways must also include the WHO's own Prequalification Program (PQP), which is the single point of reference used by international aid organizations, such as UNICEF or GAVI, for the procurement of medicines and vaccines. The absence of an "international mechanism […] to prequalify unapproved vaccines available under emergency authorization"[95], demonstrates the need to harmonize policies not only between national governments but also between national governments and the WHO.

Parallel to exploring accelerated regulatory pathways, industry and government actors also wrestled with the challenge of legal liability in the case of an Ebola vaccine causing immediate or delayed damage. GSK Chief Executive Andrew Witty called for indemnity on the basis of the unique situation in which companies are being urged by the WHO to fast-track the supply of novel vaccines in a matter of months rather than years[96], a view supported by many experts such as Brian Greenwood, a professor of clinical tropical medicine at the London School of Hygiene and Tropical Medicine, who agreed that drug companies should not have to shoulder all the risk[97]. Indemnity is a crucial building block of a successful vaccine development program during a disease emergency as "worries about litigation and liability have delayed the availability of vaccines, even as other parts of the emergency response have been hastened"[98]. The 2009 H1N1 outbreak stands as a prominent example for a disease emergency in which vaccine development and regulatory approval was fast-tracked yet legal uncertainty ultimately caused

[95] Center for Infectious Disease Research and Policy (CIDRAP), Wellcome Trust. 31.
[96] Nebehay, Stephanie and Hirschler, Ben. "Drugmakers may need indemnity for fast-tracked Ebola vaccines". Reuters. October 2014. Available online at: http://www.reuters.com/article/us-health-ebola-vaccine-idUSKCN0IC0TZ20141023 (accessed 7/28/2016).
[97] Ibid.
[98] Attaran, Amir, and Kumanan Wilson. "The Ebola vaccine, iatrogenic injuries, and legal liability." PLoS Med 12, no. 12 (2015): e1001911.

significant delays and caused some countries to receive vaccines after the peak of the epidemic had passed[99].

In order to avoid a similar holdup in the Ebola response, on December 3rd, 2014, the US government issued a declaration under the Public Readiness and Emergency Preparedness (PREP) Act that extended a two-year liability protection in the US for companies involved in the production and distribution of the three major Ebola vaccine candidates being evaluated in clinical trials. The PREP Act declaration did not, however, offer protection from liability for claims arising under non-US law or brought in a non-US court. While the PREP Act offered a way forward in the absence of better, more holistic options, the current non-disease emergency environment offers the opportunity to develop a more sustainable indemnity architecture. The "recognized options"[100] for such an architecture include the following: (1) the country experiencing the public health emergency indemnifies the vaccine supplier; (2) the United Nations uses its immunity from lawsuit to shield the vaccine supplier; (3) the international community establishes a no-fault compensation fund to fairly redress vaccine injuries.

While all three of these options are practical and have been tried and implemented in various forms, the third – the establishment of an international no-fault compensation fund – has crystallized as the vastly preferred one[101]. The challenge with indemnity granted by countries that are experiencing a health emergency is that such indemnity requires complex national legislation that most developing countries lack. Furthermore, indemnity doesn't fully remove the potential for lengthy and costly civil and criminal legal battles which individuals might carry out despite their slim chances of success. Immunity under the UN shield provides one alternative to indemnity and has been used in the response to the H1N1 pandemic. It was again used during the Haiti earthquake of 2010. However, Haiti's poor experience with the immunity arrangement after UN peacekeepers introduced a virulent cholera bacteria that caused ~7,500 deaths makes it unlikely other developing countries will accept a similar legal template in the future.

[99] World Health Organization. "Main operational lessons learnt from the WHO pandemic influenza A (H1N1) vaccine deployment initiative". *A report of a WHO meeting held in Geneva, Switzerland 13–15 December 2010.* Available online at: http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiaitve_moll.pdf (accessed 7/28/2016)

[100] Attaran, Kumanan.

[101] Ibid.

On the other hand, the no-fault compensation model is being utilized successfully in a number of countries and such compensation funds "provide rapid, equitable compensation for injuries causally related to vaccination, without resort to damaging litigation"[102]. In the developed world such funds are oftentimes funded through a vaccines tax, a mechanism that does not lend itself to experimental vaccines developed for disease emergencies. Instead, the World Bank could facilitate the creation of an insurance backed fund with premiums paid for by donor countries. As the bank "already has appropriate mechanisms at hand"[103] such a fund should be fairly easily implemented. Given the World Bank's existing resources, it is in a much better position to house the indemnity mechanism than other agencies, such as GAVI, that are experts in vaccine procurement funding but have historically not concerned themselves with indemnity questions due to their focus on established, proven product. As the next chapter will show, GAVI must play the key role in the procurement of any eventual finished vaccines; however, procurement financing and the coverage of legal no-fault liabilities should be separated in order to avoid needlessly building up expertise that already exists in the World Bank.

Lesson #7: Development of a sound emergency funding structure under GAVI

Created in 2002 "to improve access to new and underused vaccines for children living in the world's poorest countries"[104], GAVI acts as a principal funding mechanism to enable the procurement of vaccines and the provision of technical support for their delivery to patients in countries with the greatest needs. Given its mission and technical expertise, GAVI was a logical partner in the quest to bring an Ebola vaccine to West Africa and help contain the impact of the Ebola virus disease on the region's populations. And yet, like many other actors, the GAVI team initially struggled with its exact role in the development effort. Its CEO, Seth Berkeley, was keen for the organization to play a key role, and charged his team – supported by the Boston Consulting Group – with developing a detailed board report laying out the options for GAVI's involvement. The report, delivered in December 2014, suggests the provision of $390M for

[102] Attaran, Kumanan.
[103] Ibid.
[104] GAVI. Available online at: http://www.gavi.org/about/mission/ (accessed 7/28/2016).

vaccine procurement ($300M), rollout ($45M) and the support of the recovery of health systems and immunization services ($45M)[105].

GAVI's commitment was a crucial signal to the industry actors, assuring them that there would be a market for the vaccines under development. This dynamic, referred to by GAVI as 'market shaping', is one the Alliance's key functions, and GAVI's experience in this area makes it a logical player in the provision of funding facilities for future vaccine development efforts in the response of neglected disease outbreaks. However, despite its deep expertise, GAVI was initially ill-prepared to take on the Ebola financing effort. One obvious limitation it faced was personnel. The GAVI team quickly realized the tremendous effort required and feared overstretching itself, becoming unable to meet its responsibilities – both from a financial and human-resources perspective – to its existing vaccine programs. The December 2014 board report finds that GAVI "is not set up as an emergency response organization"[106]. The Alliance feared not only that the Ebola commitment would cannibalize other, long-established vaccine initiatives, but also that it would expose the organization to reputational risk by "negotiating agreements with manufacturers that are later revealed to be sub-optimal"[107].

In particular, GAVI was concerned that its involvement in the development effort would facilitate non-Ebola related industry interests. As the various vaccine platforms offered themselves to a variety of therapeutic goals other than Ebola, the Ebola virus outbreak offered the industry a unique opportunity to test platforms that otherwise would have taken much longer to access. GAVI was thus prudent in defining and articulating the boundaries of its involvement, and negotiated accordingly with industry actors. These negotiations were delicate because despite GAVI's numerous concerns and limitations – for example, that it was unable to financially support vaccine development and could only step in to fund procurement of the fully developed product – the Alliance had a strong interest in having multiple drug companies on board so it wouldn't depend on one supplier alone. Despite its intention, GAVI ultimately wasn't

[105] Brooks, Alan and Alex de Jonquieres, Eliane Furrer, Stefano Malvolti, Patience Musanhu, Aurélia Nguyen. "ACCELERATING ACCESS TO EBOLA VACCINES AND COUNTRY PERSPECTIVE". GAVI. Repor to the board. December 2014. Available online at: file:///T:/05%20-%20Accelerating%20access%20to%20Ebola%20vaccines%20and%20country%20perspective.pdf (accessed 7/28/2016). 3.
[106] Ibid. 6.
[107] Ibid.

able to avoid the one-supplier scenario. As it turned out, Merck was the only industry actor willing to accept GAVI's proposal to provide its Ebola vaccine to the world's poorest countries at the lowest possible, not-for-profit access price. In January 2016 at the World Economic Forum in Davos, GAVI signed a $5M advance purchase commitment to buy Merck's VSV-ZEBOV live attenuated Ebola Zaire vaccine to protect vulnerable populations against future outbreaks of the deadly Ebola virus. GAVI said the agreement would help the U.S. drugmaker take the experimental Ebola vaccine through late-stage clinical trials to licensing and then through pre-qualification by the WHO[108].

GAVI found that the risk of inaction outweighed its concerns and ended up playing a crucial role in the Ebola vaccine effort. Its involvement proved that the Alliance has a role to play in the responses to disease emergencies in which vaccines have the potential to alleviate suffering. The GAVI board, aware of the necessity of reviewing the Alliance's capacity and capabilities for future crisis response, is undergoing considerable soul searching trying to formulate its role in future emergencies. The board needs to clarify the flexibility of the Alliance's mandate when facing a disease emergency in which its resources and experience can be of considerable value-add. At the same time, a high degree of flexibility can only be part of the answer. GAVI has proven core competencies and relationships that make it indispensable in any emergency response involving immunization. It must put into place clear procedures for crisis response and definitely assign responsibilities within the organization. The offices of the 'Deputy CEO' or of the 'Chief of Staff' lend themselves to taking on a coordinating role for GAVI's involvement in future emergency responses and should develop a detailed roadmap for the allocation of personnel and funding that ensures minimal impact on the operation of existing, ongoing priorities.

The use of Advance Purchase Commitments (APCs) has proven extremely effective in creating a market for vaccines for which there ordinarily would be demand but insufficient purchasing power as the vaccine recipients or the governments of the countries they reside in lack the financial resources to purchase these vaccines. Ebola provides an example for how the use of APCs remains relevant even under emergency circumstances, and the financing model

[108] Hirschler, Ben and Kelland, Kate. "Vaccine alliance signs $5 million advance deal for Merck's Ebola shot". Reuters. January 2016. Available online at: http://www.reuters.com/article/us-health-ebola-vaccine-idUSKCN0UY0OT (accessed 7/28/2016).

thus suggests itself for use in future vaccine-supported health emergencies. The GAVI board must now collaborate closely with its partners and funders to secure commitments to fund a facility for the financing of emergency APCs so that the scramble to secure or re-allocate funds will not obstruct an effective response in future emergencies. Given the broad coalition that formed in the response to the Ebola crisis and the emergence of new, non-traditional financiers such the African Development Bank or the government of China, GAVI must use the opportunities created by Ebola to approach donors that currently are not supporting its operations yet have a strong interest in a designated emergency-response facility.

The creation of such a finance facility would close the circle of necessary steps in the vaccine development and realization effort that transpired throughout the Ebola pandemic. Only the guarantee of final product uptake will facilitate the necessary R&D, testing, and development of manufacturing capacities. In conjunction with the nationally, public-privately funded research labs suggested in Lesson #2 and a sound mechanism for the transfer of IP to able manufacturers as outlined in Lesson #3, an established funding mechanism under GAVI's direction would make unnecessary other more complex funding schemes such as the global financing facilitated by the Harvard-LSHTM panel. In its recommendations, the panel suggests the creation of an integrated financing scheme supporting both R&D and manufacturing for drugs, vaccines and diagnostics[109]. Such a scheme would be extraordinarily difficult to set up considering how many different actors and interests it would have to accommodate if it aimed to span the entire value chain from R&D through to procurement. Instead of reinventing the wheel, the Global Health community should rely on its existing strengths, and GAVI stands out as a core asset when it comes to vaccine financing. This asset must be leveraged and will prove indispensable in future emergencies once appropriately re-configured and funded.

Conclusion

The Ebola virus disease outbreak highlighted the inadequacies of the current setup of the international health infrastructure as well as the possibilities and potential of close collaboration of a diverse set of actors. No aspect of the crisis illustrates this potential better than the Ebola

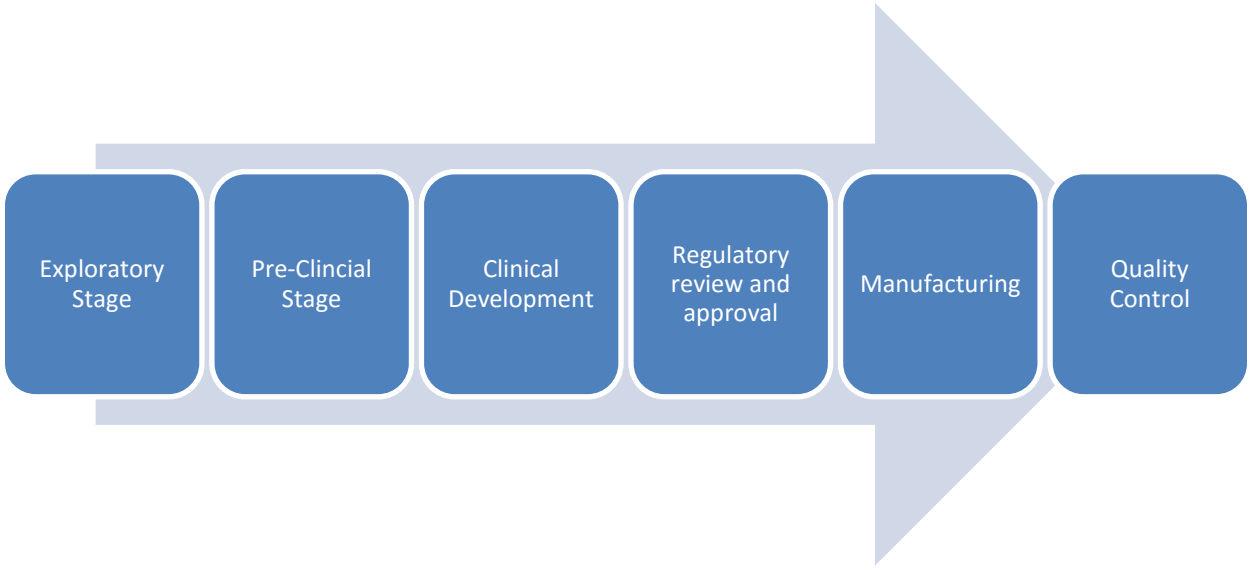
[109] Moon. 11.

vaccine development program. As various international agencies and programs increasingly stress the necessity for closer public-private cooperation, the Ebola vaccine effort is a handy case study for how such collaboration can play out in practice and a reminder of the structures necessary to facilitate effective cooperation. This study investigated the various facets of these structures in an effort to tease out and preserve the aspects that worked in the Ebola vaccine development, thus creating a playbook to be relied upon in future outbreaks of neglected disease. In the midst of the destruction and suffering brought about by the Ebola outbreak, this study attempts to provide a glimmer of hope by arguing that similar catastrophe may be avoided – or at least minimized – in the future if all involved actors come together and apply the lessons laid out rather than continuing to rely on ad-hoc efforts.

This analysis is only one of an increasing number of studies evaluating the experiences, actions and inactions in response to the Ebola outbreak. It builds on the work of others and equally invites the further development of the ideas presented here. The attention Ebola drew to Global Health and the momentum that resulted from that global interest has already contracted significantly. There is a very real probability that the learnings from Ebola will be neglected – that the system will revert to the status quo and be forced to scramble again in its response to a future crisis. Only sound analysis and passionate advocacy can prevent such an unfortunate outcome, and this study shall constitute one contribution to this vital effort to learn from the Ebola experience.

APPENDIX

[APPENDIX 1]: The six major steps of vaccine development



Source: http://www.cdc.gov/vaccines/basics/test-approve.html

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