

**Lessons From Ebola and Zika: The Role of Economic Incentives in Drug Development  
and Public Health**

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The Zika virus has gone from an obscure tropical disease to an international public health concern. It is spread primarily via the *Aedes aegypti* mosquito, which is the aggressive, primary animal vector in the current Zika epidemic. The Zika virus is considered to have “explosive pandemic potential”, with outbreaks now in Africa, the Pacific Islands, Southeast Asia, and the Americas (Fauci & Morens, 2016). As of November 2016, there have been a total of 4,575 confirmed Zika cases in the United States alone and 33,838 cases in the United States Territories of American Samoa, Puerto Rico, and the U.S. Virgin Islands (CDC, 2016). The disease usually causes mild illness such as fever, rash, muscle/joint pain, and conjunctivitis, or may be asymptomatic altogether. However, a growing number of severe clinical manifestations such as Guillain-Barré syndrome (a nervous system disorder that can lead to life-threatening paralysis) and microcephaly (a birth defect where a baby’s brain is not developed properly) led the World Health Organization (WHO) to declare Zika a Public Health Emergency of International Concern (PHEIC) in February 2016 (Heymann et al., 2016).

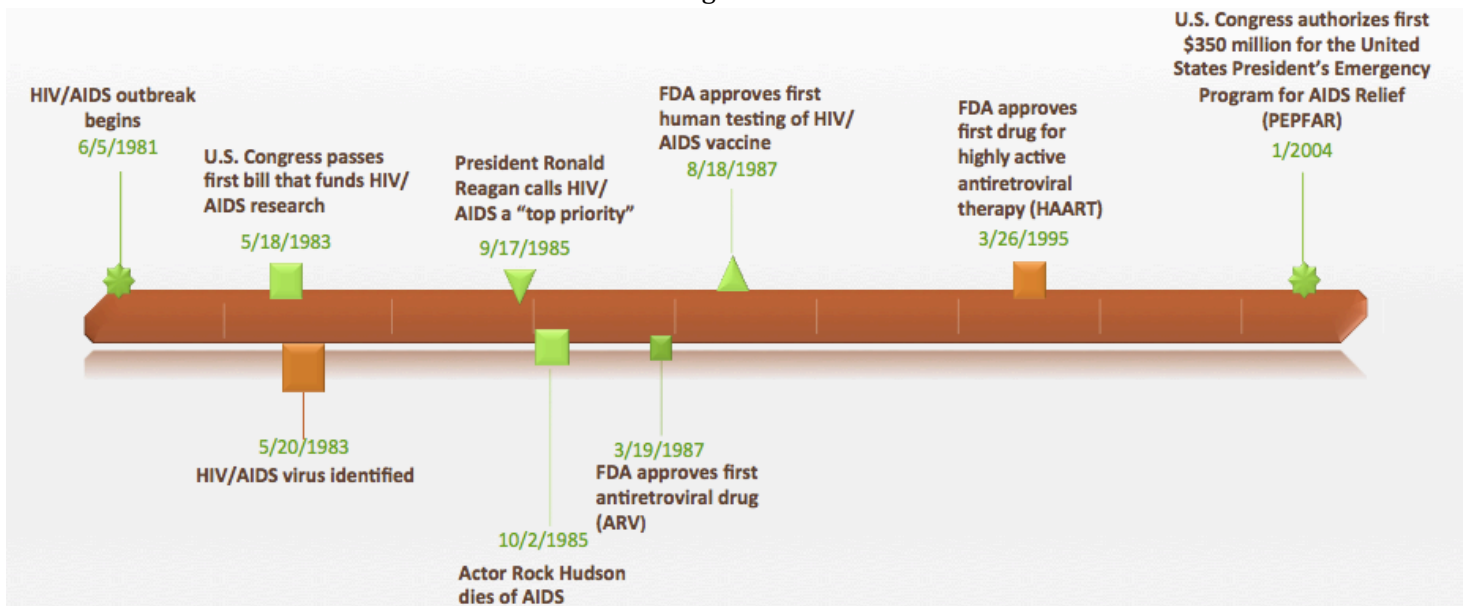
The last time WHO declared a PHEIC was just one and a half years earlier, in August 2014. This was for the Ebola virus, believed to have been first transmitted from an infected fruit bat or chimpanzee to a young boy in Guinea, before it spread rapidly through West Africa via human-to-human contact (World Health Organization, 2015). Although cases were confirmed in Nigeria, Senegal, Mali, the Congo, and the United States, the countries of Sierra Leone, Liberia, and Guinea were by far the most severely affected. These three affected countries have extremely weak health systems; lack human and infrastructural resources; and have only recently emerged from long periods of conflict and instability. The Ebola virus’s treatable symptoms of fever, headache, muscle pain, fatigue, diarrhea, and vomiting, and, at times, unexplained hemorrhaging, resulted in 11,340 deaths and 28,601 confirmed illnesses altogether in Guinea, Sierra Leone, and Liberia as of the end of the epidemic in January 2016 (Medicins Sans Frontieres, 2016).

Public health emergencies are becoming familiar occurrences with dire human and economic consequences. Infectious disease outbreaks have sparked international concerns due to the large number of people impacted and lack of effective strategies to contain these diseases at the time of the outbreaks. In response to political pressure and economic incentives, billions of U.S. dollars have been invested in research for illnesses like HIV/AIDS and influenza. However, very limited resources have been dedicated to Ebola and Zika. There remains no Food and Drug Administration (FDA)-approved medicine to treat either, despite the fact that they have been infecting populations for decades (Zeitvogel, 2016). Ebola and Zika historically affect poorer populations that lack the political clout and economic ability to demand treatments. The result is little incentive for governments or pharmaceutical companies to invest in developing medicines for these marginalized communities, which poses a risk to everyone in our increasingly globalized society (Fauci & Morens, 2016; World Health Organization, 2015). The question then becomes: is the lack of drug development for Ebola and Zika due to lack of economic incentives rather than lack of incidence?

The drug discovery and development process requires costly investments over a long period of time and is subject to high levels of risk and uncertainty. In fact, the cost of developing a new drug is estimated to be more than \$1 billion (Wizemann, Robinson, & Griffin, 2009). Development of this scale necessitates several financing mechanisms and involves multiple stakeholders throughout the process. Incentives for organizations to invest in this capital-intensive business can be defined under three categories: pharmaceutical companies, governments and academia, and extreme measures. The most visible drug developers are large pharmaceutical companies driven by the promise of hefty profits to invest heavily in research and development. Perhaps of even greater importance are governments and academic institutions, which invest taxpayer and tuition money for research and development. These are often motivated by the possibility of scientific advancement and can lead to new drugs.

The emergence of HIV/AIDS is a case study in the push factors that led to rapid drug development for one of the most destructive infectious diseases in public health history. The lessons learned from this epidemic give relevant context for the recent Ebola and Zika outbreaks, as HIV/AIDS reveals how public activism promotes drug production and innovation, while the wealthy are often able to obtain life-saving treatments before the poor. Figure 1 is a timeline of major events of the HIV/AIDS outbreak that follow the process of drug development and accessibility.

Figure 1



Source: HHS website and AVERT website

Soon after the virus's discovery, HIV/AIDS patients, advocacy groups, and other supporters protest to fast-track drug development, notably in San Francisco, New York, and Washington, D.C. By the end of 1986, the disease's cumulative known death tolls climb to 16,301 (amfAR, 2016). Amid growing pressures by public activism and media coverage, the FDA prioritizes drug development for HIV/AIDS and administers a clinical trial of Azidothymidine (AZT), the first drug to prove effective against the rapidly replicating HIV virus. Originally a chemotherapy drug, AZT works so well during its human trials that the FDA stopped the trial on the grounds that it would be unethical to further administer placebos and deprive those patients of the actual drug. As a result,

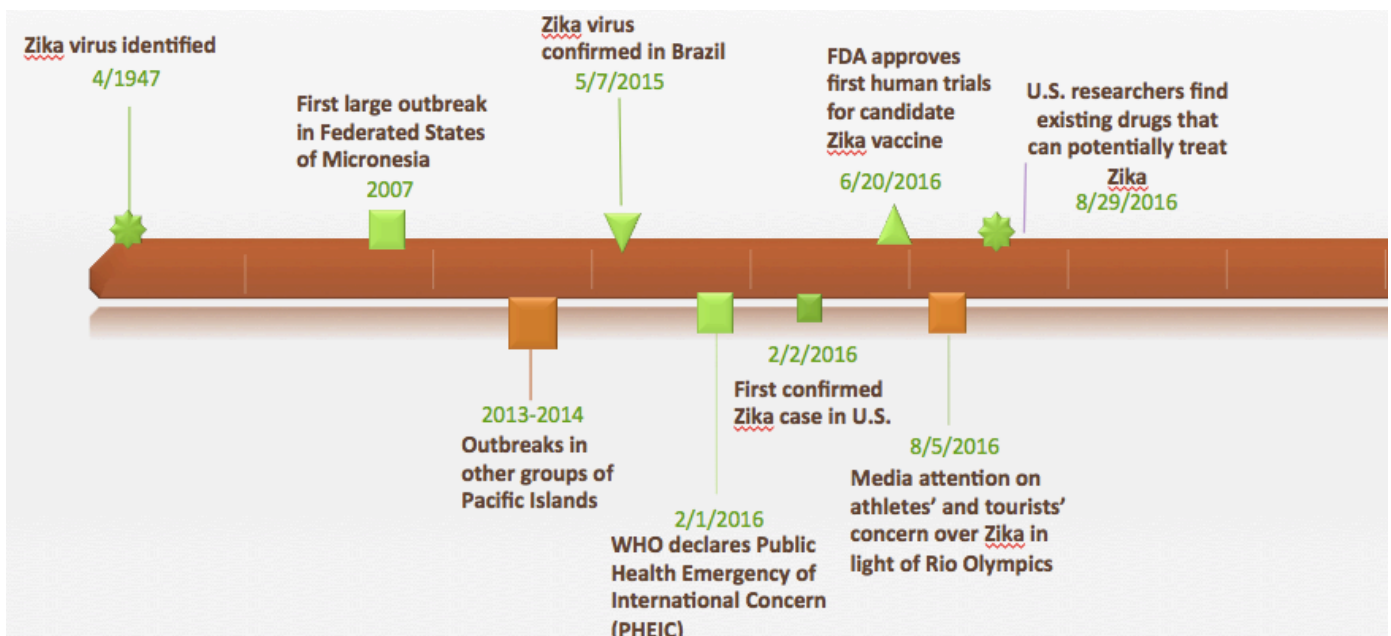
AZT is the first drug for antiretroviral therapy (ART) approved by the FDA on March 19, 1987 (FDA, 2014). On the same day, the U.S. Congress approves \$30 million in emergency funding for states to make AZT available to HIV/AIDS patients, laying the groundwork for the AIDS Drug Assistance Program (ADAP).

The race for treatments continues to move quickly, and on August 18, 1987, the FDA approves the first human testing of a candidate HIV vaccine. However, even with the ongoing mobilization of resources directed at vaccine development, researchers have still yet to discover an effective HIV vaccine due to complexities of the HIV virus (amfAR, 2016). The most recent promising vaccine, called SAV001, is slated to begin human testing on 600 volunteers in 2017 (MacDonald, 2016). Going back to the emergence of the disease, March 26, 1995 ushers in a new era of highly active antiretroviral therapy (HAART), with the FDA approval of the first protease inhibitor. Protease inhibitors bind to sections of the HIV virus to prevent viral replication, and HAART becomes indispensable in treating HIV to turn it from a “death sentence” to a chronic disease (AIDS.gov, 2011).

At the end of 2012, The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports approximately 34.5 million people infected with HIV worldwide, with an estimated 1.2 million of them being Americans (UNAIDS, 2012). India has over 3 million people living with HIV, and South Africa (home to the largest number of people living with HIV) has 6.8 million HIV/AIDS patients (AVERT, 2016). The effects are far worse in Sub-Saharan Africa, where the region accounts for over half of global HIV/AIDS cases, and this ratio has barely improved since 1997 (UNAIDS, 2004). It is not until January 28, 2003 – almost 16 years after the FDA approved the first ARV drug – that President George W. Bush announces the creation of the United States President’s Emergency Plan For AIDS Relief (PEPFAR), a \$15 billion, 5-year plan to combat AIDS in countries with a high burden of infections. An estimated 700,000 patients are reached by the end of 2004 (AIDS.gov, 2011).

The emergence of HIV/AIDS is a prime case of economic incentive and political clout influencing the course of drug development and access. The timeline for HIV/AIDS is useful to compare with the timeline for Zika and Ebola to establish patterns linking economic incentives with treatment availability. Although Zika was not an international health concern until 2016, scientists had already identified the Zika virus since 1947 in Uganda (WHO, 2016). G. W. A Dick published findings on its pathogenicity and physical properties in the Transactions of the Royal Society of Tropical Medicine & Hygiene Journal in 1952, and studies in the 1960s-1980s consistently indicate widespread human exposure to the virus. Despite scientists' early discovery and understanding of the Zika virus, there remains no effective treatment for Zika even today. Figure 2 is a timeline of major Zika outbreaks and events that can help explain this deficiency.

Figure 2



Source: WHO website

After its discovery in Uganda, the virus moves from Uganda to western Africa and Asia in the first half of the 20<sup>th</sup> century. Human cases are confirmed through blood tests, and symptoms are reported as “mild,” with no deaths or hospitalizations (Haddow et al., 2012). The first large Zika outbreak occurs in 2007 in the Pacific Island of Yap in the Federated States of Micronesia. Before

this, there had been no outbreaks and only 14 human cases of Zika documented in the world. 73% of Yap residents are infected with Zika virus, but the world does not take notice of this outbreak that is occurring in a relatively isolated island with a GDP per capita of just \$2,107 (World Bank, 2015). Major outbreaks occur again from 2013-2014, this time in four other Pacific island nations: French Polynesia, Easter Island, the Cook Islands, and New Caledonia. Thousands of infections in French Polynesia reveal possible links between Zika infection and congenital malformations and neurological and autoimmune complications (WHO, 2016). However, Zika maintains the status of a neglected tropical disease due to the modest economic standing of affected countries.

On May 7, 2015, Brazil confirms that the Zika virus is circulating the country. WHO releases an epidemiological alert for possible infection in Brazil, and it recommends that countries establish Zika virus infection management guidelines to fight its spread. By the end of November 2015, Zika is also confirmed in Suriname, El Salvador, Guatemala, Mexico, Paraguay, and The Bolivarian Republic of Venezuela (WHO, 2016). In addition to these countries representing growing economies, they are also in close geographic proximity to the United States. WHO's Weekly Epidemiological Record highlights the affect that Zika outbreaks in Latin and South America have on the U.S. and the global economy: "Recent outbreaks of ZIKV infection in different regions of the world underscore the potential for the virus to spread further in the Americas and beyond, wherever the vector is present" (WHO, 2015). By December 2015, Panama, Honduras, French Guiana, Martinique, and Puerto Rico all report confirmed cases of Zika infection. Although the Zika virus had swept through Africa, western Asia, and groups of Pacific islands decades earlier, it is not until it affects the Americas and threatens the U.S. that it is considered a serious threat. On February 1, 2016, WHO declares Zika a Public Health Emergency of International Concern (PHEIC) and catalyzes an international response to the disease (WHO, 2016).

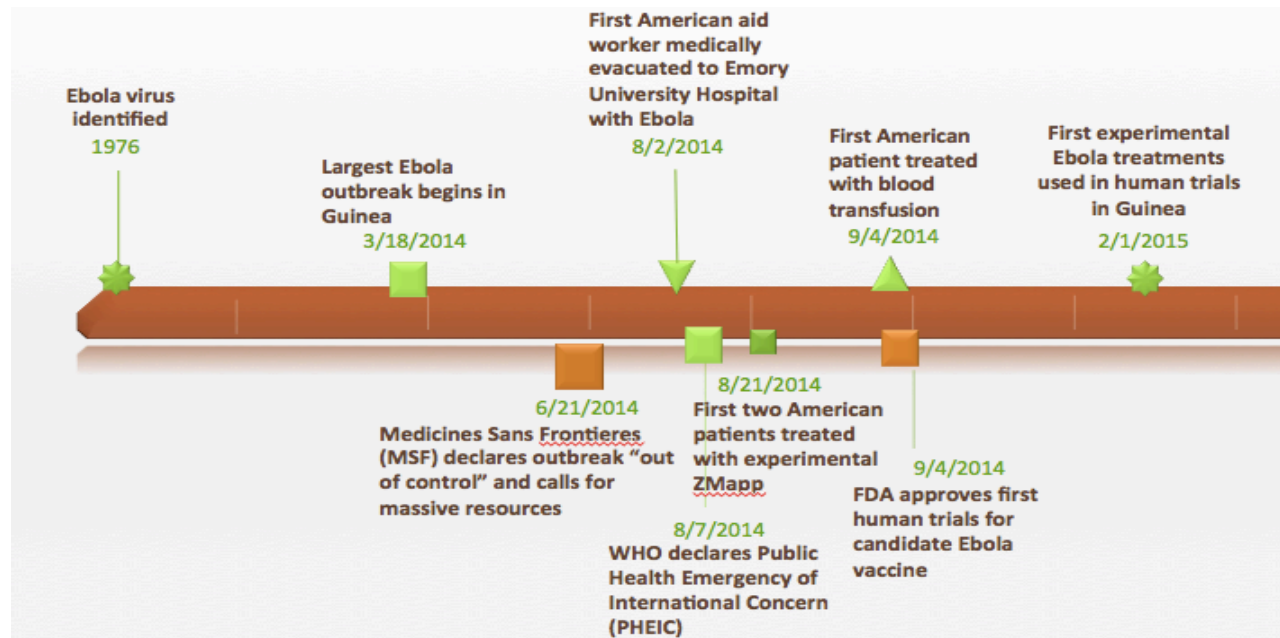
Just one day later, the U.S. reports its first case of Zika infection in the country. Within the month, President Obama petitions Congress for \$1.9 billion to combat Zika, and the FDA approves

the first human trials of a candidate Zika vaccine on June 20, 2016 (Branswell, 2016). All this goes on while media reports spur controversy over tourists' fears and athletes' outcries over Zika during the Rio Olympics in August 2016. And after seven months of partisan bickering, the U.S. Congress finally agrees to allocate \$1.1 billion to help fight the Zika virus (WHO, 2016). In the meantime, American researchers are already making progress in finding a vaccine. On August 29, 2016, Nature Medicine Journal publishes the work of teams from Johns Hopkins University School of Medicine, Florida State University, and NIH, who have identified several compounds that show the ability to stop the Zika virus in-vitro. According to Dr. Hongjun Song, Director of the Stem Cell Program in the Institute of Cell Engineering at Johns Hopkins, "It takes years if not decades to develop a new drug. In this sort of global health emergency, we don't have that kind of time" (Johns Hopkins Medicine, 2016). In November 2016, federal scientists launch human testing of the most recent promising vaccine called ZPIV that has already proved effective in targeting a virus similar to Zika. This research is being funded by the Department of Defense and the National Institute of Allergy and Infectious Diseases (NIAID). The head of NIAID, Dr. Anthony Fauci, states, "We urgently need a safe and effective vaccine to protect people from Zika virus infection, as the virus continues to spread and cause serious public health consequences, particularly for pregnant women and their babies" (Harris, 2016). It is clear that WHO's PHEIC declaration has directed much-needed attention and resources toward Zika drug development.

Similar to Zika, Ebola also has discreet beginnings in central Africa. However, the Ebola outbreak mainly affected three impoverished West African countries. Figure 3 shows a timeline of events for the worst Ebola outbreak in history. These events may reveal economic and political incentives that drive global response to a disease.



Figure 3



Source: CDC website and UN website

In 1976, scientists discover the Ebola virus in what is now the Democratic Republic of the Congo (WHO, 1978). Since then, small outbreaks have appeared sporadically in rural parts of Central Africa, but they come and go without drawing international attention. Decades later on March 18, 2014, the largest Ebola outbreak in history according to the CDC begins in Guinea, and the Ministry of Health notifies WHO of 49 cases of the illness, including 29 deaths from it (CDC, 2016). It rapidly spreads over the next several months through Guinea, Liberia, and Sierra Leone, three of the world's poorest countries. Jeremy Farrar and Peter Piot in the *New England Journal of Medicine* describe it as "likely to be a result of the combination of dysfunctional health systems, international indifference, high population mobility, local customs, densely populated capitals, and lack of trust in authorities after years of armed conflict" (Farrar & Piot, 2014). The affected countries in West Africa have weak capacity and infrastructures for disease preparedness and response. Before the Ebola outbreak even begins, they are already struggling with poverty, so they are in no position to mobilize additional resources for new Ebola treatments.

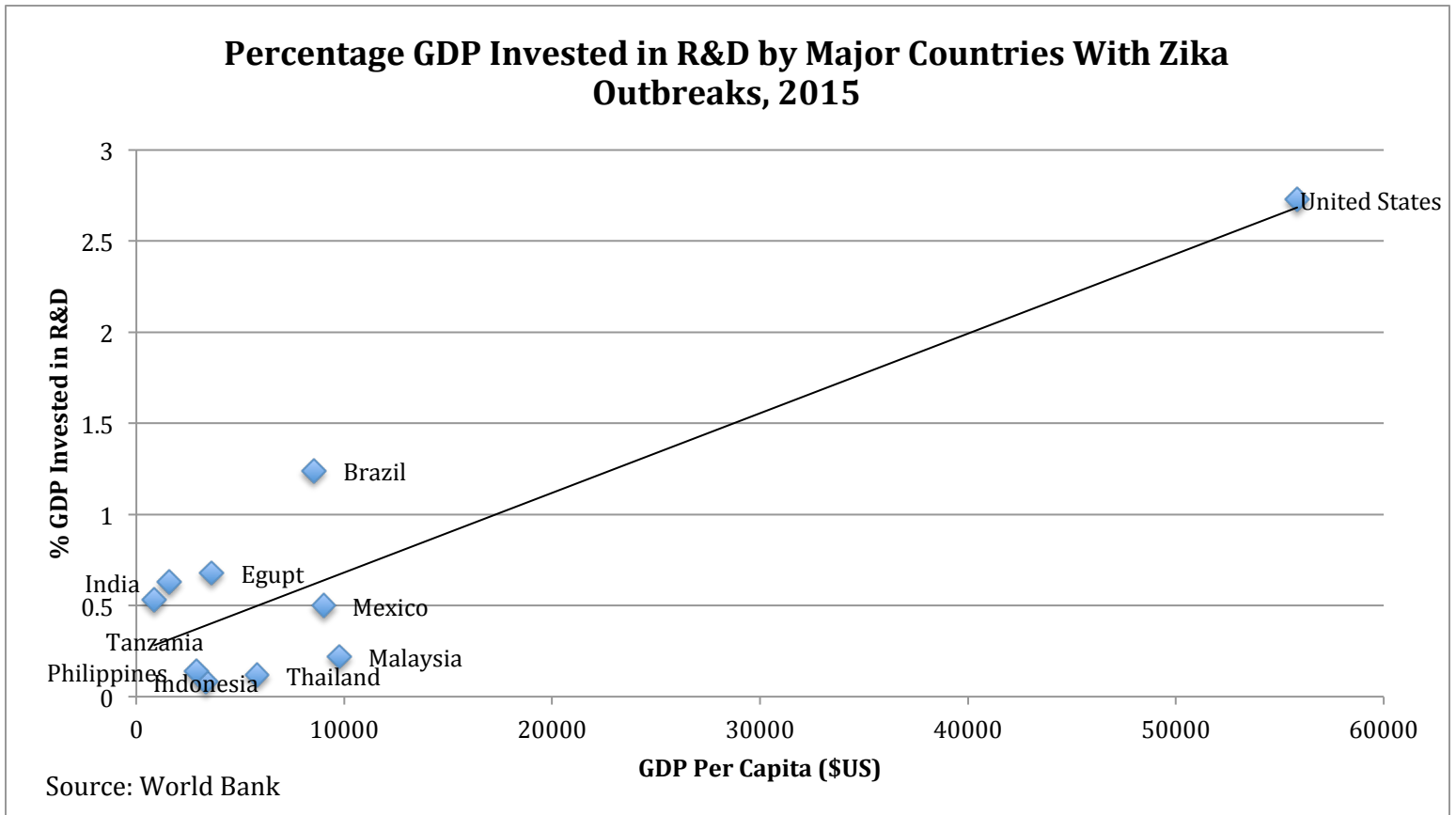
By June 21, 2014, the French medical organization Medecins Sans Frontieres (MSF), declares the outbreak “out of control.” Ebola is confirmed in 60 locations across Guinea, Liberia, and Sierra Leone, with cases exponentially increasing and health workers dying in alarming numbers. In a public statement, MSF’s Director of Operations, Bart Janssens warns, “The WHO, the affected countries and their neighboring countries must deploy the resources necessary for an epidemic of this scale. Ebola is no longer a public health issue limited to Guinea. It is affecting the whole of West Africa” (MSF, 2014). This is a clear call to action coming from the world’s first-responders, yet the international community does not take significant action until four and a half months after the first international spread. WHO declares a PHEIC on August 7, 2014 – five days after the first American aid worker is medically evacuated with Ebola to Emory University Hospital (Gostin, L., & Friedman, E., 2015). Although the PHEIC announcement comes quickly after the first American aid workers are evacuated, it comes almost two months after MSF’s clear warning that this Ebola outbreak necessitated a global response. With the PHEIC declaration, WHO eventually asks the international community to contribute \$988 million in September 2014 for Ebola response. Donations finally begin to flow, with the World Bank and U.S. contributing the most (Gostin, L., & Friedman, E., 2015).

On August 21, 2014, the first two American Ebola patients receive the experimental ZMapp drug while being treated in the U.S. ZMapp supplies are scarce, and public controversy arises over the morality of Americans receiving these therapies before any West Africans. On September 4, 2014, the third medically evacuated American case receives a blood transfusion from the first successfully recovered American patient (Besser, 2014). A panel of experts from WHO considers blood transfusions an immediate priority among all experimental therapies, because effective antibodies produced in the blood of Ebola survivors may help a newly infected person survive the disease. WHO also calls for countries to help affected West African countries to build capacity to safely draw blood and carry out blood transfusions (Gostin, L., & Friedman, E., 2015). As FDA approves the first human trials in the U.S. for a candidate Ebola vaccine, it is clear that patients in

West Africa will have to wait to receive treatments when developed countries produce a larger supply of experimental drugs and take steps to help developing countries build blood transfusion (and overall healthcare) capacity. The first experimental Ebola treatments are not used for human trials in Guinea until February 1, 2015. More than 21 months from the first confirmed case in Guinea, the total number of reported deaths from Ebola (WHO admits it is an underestimate) is 11,315 people (WHO, 2015). Only one of these deaths occurred in the U.S., with the rest almost all taking place in Guinea, Liberia, and Sierra Leone. Most of these deaths resulted from simple dehydration due to a lack of basic health infrastructure in affected communities that lack running water. After the relatively recent global response, a number of potential Ebola treatments are being tested, but no effective vaccines or targeted drugs have yet been approved.

From the timelines of HIV/AIDS, Zika, and Ebola, drug development seems to be driven in large part by the economic power of affected countries. Figure 4 compares the GDP per capita (as an approximate indicator of economic wealth) to the % GDP invested in research and development (as a rough estimation of investments in health research) for major countries affected by Zika outbreaks. The countries affected by Zika can be compared to the countries affected by Ebola, for which there is no graph because World Bank data on % GDP invested in research and development is unavailable for the African countries affected by Ebola. These countries are struggling to emerge as post-conflict nations and lack the infrastructure to collect this data (World Bank, 2015). The relatively swift global response to Zika can be attributed to the relative wealth of countries directly affected by the Zika virus, as compared to the relative poverty of those directly affected by the Ebola virus.

Figure 4

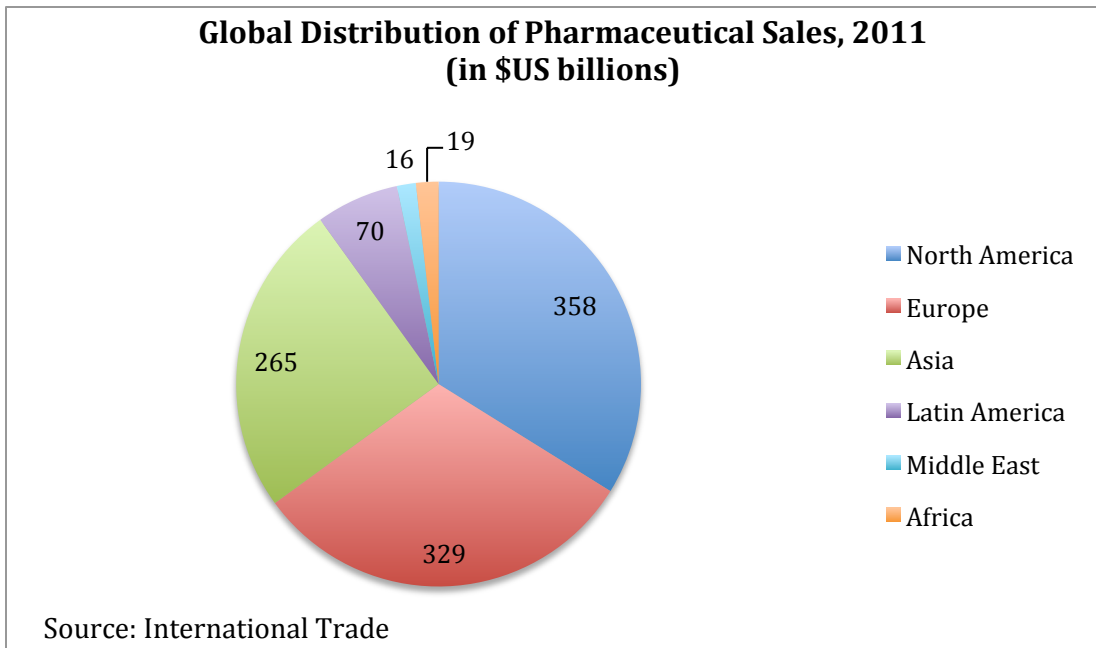


There is a strong correlation between the relative wealth (GDP per capita) of a country affected by Zika and the proportion of this wealth that is invested into research and development. These investments are crucial for drug development, as massive amounts of resources and funding go into making a new treatment. Richer countries invest a higher percentage of its already great resources towards research and development. While this may not be an exact indicator of drug development specifically, research and development is crucial for creating new treatments and can indicate approximate trends in resources devoted to this area. For countries affected by Ebola (namely Guinea, Liberia, and Sierra Leone) GDP per capita hovers around just \$500, much less than major countries affected by Zika such as Brazil (\$8,539) and the U.S. (\$55,837) (World Bank, 2015). It can be deduced from the lack of available data and Guinea, Liberia, and Sierra Leone’s political and

economic situations that these countries invest little, if any, portion of their GDP towards pharmaceutical drug development.

A small market for pharmaceutical drugs in countries with Zika and Ebola may also have delayed drug development for these diseases. The global distribution of pharmaceutical sales can be seen in Figure 5. This pie chart clearly illustrates large discrepancies in pharmaceutical consumption between geographic regions. North America, with \$358 billion in pharmaceutical sales in 2011, is the largest, most lucrative market for pharmaceuticals in the world. North America, Europe, and Asia comprise the regions with the top three total sales by a wide margin. On the other hand, Latin America, Africa, and the Middle East are regions with the smallest numbers of pharmaceutical sales that, combined, do not even add up to half of total sales in the third largest pharmaceutical market, Asia. Africa and the Middle East are the regions with the least pharmaceutical sales, \$19 billion and \$16 billion, respectively (International Trade Administration, 2011).

Figure 5



Since economic incentives drive pharmaceutical development, the relatively tiny market for Ebola drugs that treat people in Africa is a significant barrier to innovation. Likewise for Zika, few resources were invested in research on the disease while it spread through small, tropical islands. Only once the virus arrived in Brazil and threatened the large economies of the Americas, did countries mobilize significant resources for Zika research.

Economic incentives seem to determine drug development and availability of treatments for diseases, with significant public health impact. In the wake of the recent Ebola and Zika outbreaks, the world still lacks a proven vaccine or treatment targeted at the Ebola and Zika viruses. The emergence of HIV/AIDS showed how political pressures and the economic status of affected stakeholders spurred great innovations in HIV/AIDS treatments in a short amount of time. Even then there was and continues to be a lag in treatment accessibility for patients in developing countries. This can be applied to the Ebola outbreak, where the rest of the world was slow to respond as thousands died in poor West African countries. Outbreaks of Zika were also ignored until they arrived in Brazil and spread through other parts of the Americas, including the U.S. Although more funding is still needed to fight Zika, the global response to this outbreak, which affected wealthier countries, was quicker than Ebola's (Hoyt & Hatchett, 2016). The course of drug development for HIV/AIDS, Zika, and Ebola indicates that the wealthy are able to get what they need, while the poor lack or need to go through extraordinary measures to obtain treatment.

Pooling funds from industry, governments, and philanthropic organizations is just the first step in addressing infectious disease outbreaks like Zika and Ebola. Practical recommendations by a report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola urge WHO to develop a framework of rules to “enable, govern, and ensure access to the benefits of research;” and “establish a global facility to finance, accelerate, and prioritize research and development” (Moon et al., 2015). The framework’s goal would be to guide countries in providing access to data and samples to accelerate research in the event of disease outbreak; designate ethical standards for

research and development to involve affected populations; and set standards for equitable access to the benefits of research. A clearer framework by WHO would hold countries accountable and guide research and development for pathogens that affect developing countries.

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