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# OUTBREAKS REVEAL DEFICIENCIES IN BIOTECH R&D FOR EMERGING DISEASES

A Thesis
Presented to
The Academic Faculty

by

Rebecca Byler

In Partial Fulfillment
of the Requirements for the Degree
Master of Public Health in the
Department of Epidemiology of Microbial Diseases

Yale School of Public Health
May 2016

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# OUTBREAKS REVEAL DEFICIENCIES IN BIOTECH R&D FOR EMERGING DISEASES

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# ABSTRACT

The absence of commercial diagnostics, therapeutics, and vaccines hindered control efforts during the recent Zika and Ebola epidemics. This study evaluates the connectivity and productivity of both viruses' R&D networks before, during, and after the epidemics to ascertain the ability of current R&D practices to support the development of crucial biotechnologies. Both network maps exhibited low baseline connectivity with emergent collaborative R&D practices during the identified outbreak period that correlated with increased research productivity. It is argued that formally establishing permanent collaborative, open R&D practices prior to epidemics can enhance scientific knowledge and innovation capabilities to more effectively advance commercial availability of diagnostics, therapies, and vaccines for emerging diseases.



**Keywords:** Zika; Ebola; Open Access; Data Sharing; Emerging Diseases

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| | |
|---|---|
| R&D | Research and Development |
| WHO | World Health Organization |

# CHAPTER 1

# INTRODUCTION

The recent emergence of Zika virus—a flu-like illness that was originally thought to only produce mild symptoms—has triggered widespread global panic due to a recently discovered causative association with birth defects in infants and neurological disorders in adults[1,2]. As the international community scrambles to effectively manage and control this emerging outbreak in the Americas[3,4], predominately relying on traditional public health prevention measures and vector-control strategies[5,6], the international research community has focused on the fact that, despite first identifying Zika nearly 70 years ago, the current scientific understanding of the neglected disease is lackluster[7,8] and, perhaps most importantly, commercial diagnostics, therapies, and vaccines are nonexistent[3]. While this wasn't inherently poor practice, as there exists no endogenous market incentives for neglected disease R&D[9] and Zika previously only caused begin symptoms[10], this dearth became significant given the unpredictability of the epidemic and associated high global burden of disease[11].

As we have become increasingly aware, there is a conspicuous gap between the global burden of all neglected diseases, including Zika, and the amount of research and policy focus received: despite representing 12% of the global disease burden, neglected diseases received only 1% of all R&D expenditures[12]. This is even lower for emerging neglected diseases. Indeed, as emerging infections that primarily affect low- and middle-income countries, both Zika and Ebola faced institutionalized neglect in both public and

private R&D efforts prior to the initiation of their respective global outbreaks in 2013/2014. Absent from even the World Health Organization's list of seventeen neglected diseases[13], Ebola and Zika were largely scientifically ignored until reaching epidemic potential: the international community did not pledge significant research funds nor attempt to fast track the development of commercial biotechnologies until after each disease was declared a "public health emergency of international concern"[4,7]. In order to successfully control and, possibly, eliminate diseases of epidemic potential, whether Zika, Ebola, or a still unknown emerging pathogen, a robust, global R&D capacity to more effectively innovate, develop, and commercialize biotechnologies for neglected diseases is paramount[13,14].

Cross-disciplinary, collaborative research strategies have emerged as a viable, nontraditional R&D approach to combat financial and human resource shortages while also advancing the ability to innovate[15–17]. Although there are many strategies to promote innovation and productivity in biotechnology R&D, networks that promote open knowledge exchange through exploitation of a collaborative environment—including open access, open data repository, and co-creation strategies—have been found to be highly successful in generating and supporting new biotechnologies[18–20]. Whereas rapid, reactionary responses to public health emergencies usually belie root causes and challenge existing infrastructure[21], long-term biotechnology R&D facilitated by a collaborative approach can encourage the development of a multifaceted biomedical strategy for disease prevention and treatment[9]. In fact, based on social network and interaction theories, collaborative, open R&D strategies overtly bolster existing

knowledge exchange and innovation efforts, as well as facilitate advanced co-creation activities[22,23]. Consequently, open R&D networks can be an attractive long-term strategy for neglected and emerging disease R&D since they directly advance scientific understanding via collaborative data exchange and diversify new technology development via enriched innovation capacity[24,25].

Recently, the World Health Organization (WHO) recognized the power of collaborative scientific R&D, specifically open access and data sharing, when it announced the need to improve data dissemination practices in September 2015[7]. However, the WHO's final recommendation only explicitly endorsed and supported data sharing and open access during identified public health emergencies[26]. While this is a laudable initial policy, the precise organization and practices of current emerging disease R&D networks is not known. As such, the effect of this reactionary open R&D approach is uncertain, particularly with respect to its ability to diminish an epidemic's impact and to successfully develop commercial biotechnologies. Using network connectivity analysis and evaluation of research and commercial outputs, this paper ascertains the extent to which open access and data sharing practices presently occur in emerging disease research networks, using Zika and Ebola as case studies, and discusses the effect of reactionary R&D practices on the availability of crucial biotechnologies for emerging diseases prior to epidemics.

# CHAPTER 2

# METHODOLOGY

This study seeks to understand current R&D practices for two emerging diseases, Zika and Ebola, by comparing R&D network connectivity and productivity before (five years), during, and after their largest outbreaks. Using this as a basis for understanding current R&D practices for emerging diseases, the relevance of WHO's recommendation for short-term open access and data sharing is evaluated and potential strategies to improve precautionary, sustained R&D of vital biotechnologies for Zika, Ebola, and other emerging diseases are discussed.

## Identification of Outbreak Stages

Identifying an outbreak is inherently variable with high heterogeneity in explicitly defining the exact point at which an outbreak begins and ends[27]. This is particularly true of emerging diseases, as illness by more common pathogens is usually rejected before alternative hypotheses are considered. As such, widespread knowledge about the start of an epidemic might not emerge until several months after an outbreak truly begins; nevertheless, some individuals may respond to an outbreak before pervasive global reaction, especially if the pathogen is rare, such as in the case of Ebola and Zika[5]. For this reason, a lag time corresponding with the first outbreak-specific publication (one month for Ebola and three months for Zika) was used to distinguish the "pre-outbreak" and "outbreak" stages. Since the Zika outbreak is still ongoing, only Ebola has a defined "post-outbreak" stage, which was determined by comparing the number of new cases to WHO's assessment of the outbreak's progression. As such, for the purpose of this study,

January 1, 2014-March 1, 2016 (most recent data available) represents the Zika outbreak period and January 1, 2014-December 31, 2015 represents the Ebola outbreak period. Months prior to this date represent the pre-outbreak period and subsequent months (Ebola only) represent the post-outbreak period. Although a lag time inherently exists with patents and publication dates, the range is highly variable and it is an aim of this study to evaluate how a network's connectivity might have modulated productivity at the onset of an epidemic. Thus, no further lag time was used when assessing network productivity.

## Network Selection and Mapping

Research collaborations were reconstructed using institutions listed on journal publications. As only current R&D knowledge networks for Zika and Ebola viruses were desired, since the aim of this study is to optimize current, existing research collaborations, only recent publications between January 1, 2009 and March 1, 2016 were used for network analysis. Biotechnology-related Ebola and Zika publications were identified via SCOPUS using the terms "Zika" and "Ebola" within its life sciences, health sciences, and physical sciences databases. Publications were reviewed for duplications and to ensure relevancy to the fields of diagnostics, therapeutics, and vaccines. Specifically, patient case studies, policy briefs, and publications that only reported epidemic-specific data were excluded. Of those initially identified by SCOPUS, 52/79 (66%) listed publications for Zika and 1437/2601 (55%) listed publications for Ebola fulfilled inclusion criteria. All affiliated institutes listed on each publication were manually extracted and codified for subsequent network analysis. Network maps were generated and analyzed using a Fruchterman-Reingold force-directed algorithm via standard mapping software (Gephi 0.9.1).

## Network Connectivity

The innovation capacity of a network is directly proportional to its size, degree of interconnectivity of groups ("nodes"), and strength of association between connections ("links")[28]. Thus, the structure of Zika and Ebola's R&D networks was visually compared and quantified on the basis of connectivity, or degree of collaboration, via comparison of the location and size of nodes in the network and the presence of distinctive sub-networks. Using standard network mapping software (Gephi 0.9.1), the total number of nodes and links, maximum number of connected nodes, and average degree (i.e. the number of links per node) were directly calculated; network diameter and average link length were calculated using a relative "graph-distance" unit. Gephi also generated quantitative statistics describing the visual trends of the mapped network, namely graph density, average clustering coefficient, and modularity. A high centrality of nodes with saturated links indicates high collaboration, while a sparsely populated or dispersed network indicates a trend towards isolationist practices. Specifically, network diameter and link length indicate degree of closeness and betweenness centrality, while the clustering coefficient and graph density indicate the amount of network saturation. Additionally, network modularity measures how well a network decomposes into sub-networks; a high modularity score indicates sophisticated internal structure and greater innovation capacity. This correlation operates under the assumption that the collective knowledge, tacit expertise, and ideas of nodes are continually created, shared, and iterated in tandem across each link[29]. Given this, a successful open R&D network should visually display a large number of highly connected nodes of similar sizes and numerically indicate a high graph density, clustering coefficient, and network modularity.

## Network Productivity

Network productivity was measured by analyzing three research and commercial outputs: journal publications, patents, and available commercial products. Publications and patents are commonly used as indicators of current scientific and technological productivity and are accepted measures of innovation and future R&D potential[30]. The methods for identifying relevant publications were previously described (n=52 for Zika and n=1437 for Ebola). In addition, US patents were identified using the United States Patent and Trademark Office (USTPO) patent full-text database. In particular, patents were included if the terms "Zika" or "Ebola" were included in a patent's "Title", "Claim(s)" and/or "Description/Specification" sections. Only patents with initial application dates between January 1, 2009 and March 1, 2016 were included (n=62 for Zika and n=1082 for Ebola). Finally, the US Food and Drug Association (FDA) databases for medical devices and drugs were used to identify all approved commercial diagnostics, therapeutics, and vaccines for Zika and Ebola using the terms "Zika" and "Ebola". Only one commercial product total met the search criteria (n=0 for Zika and n=1 for Ebola). Lastly, timelines of R&D and outbreak-specific events during the Ebola and Zika epidemics were constructed to ascertain and compare the biotechnology response to each global outbreak.

# CHAPTER 3

# RESULTS

It was found that both the Ebola and Zika R&D network maps exhibited low connectivity during the pre-outbreak period with enhanced connectivity during the identified outbreak period [Table 1]. The outbreak period also correlated with an increase in network productivity, as seen by a temporary increase in publications and patents. Nevertheless, only one commercial product is available.

| | EBOLA | | | ZIKA | |
|---|---|---|---|---|---|
| | Before Outbreak | During Outbreak | After Outbreak | Before Outbreak | During Outbreak |
| Total Number of Nodes | 602 | 777 | 347 | 31 | 176 |
| Total Number of Links | 923 | 1115 | 400 | 20 | 156 |
| Network Diameter | 10 | 11 | 9 | 3 | 6 |
| Average Link Length | 3.99 | 4.25 | 3.29 | 1.41 | 2.09 |
| Maximum Connected Components | 95 | 122 | 42 | 12 | 37 |
| Graph Density | 0.003 | 0.002 | 0.003 | 0.022 | 0.005 |
| Average Clustering Coefficient | 0.06 | 0.05 | 0.03 | 0.000 | 0.03 |
| Average Degree (Links per Node) | 3.06 | 2.87 | 2.31 | 1.29 | 1.77 |
| Modularity | 0.60 | 0.66 | 0.74 | 0.70 | 0.87 |

**Table 1.** Summary of Network Analysis Results for Ebola and Zika Viruses

## Network Connectivity

Ebola

Similar to the trend of increased publications during the Ebola outbreak from 2014-2015, the R&D network size swelled from 602 nodes and 923 links before the outbreak to 777 nodes and 1115 links during the outbreak [Figure 1]. This correlates with an increase in the maximum number of connected nodes (95 to 122). Although this alone does not definitively indicate a more open R&D network, it should be noted that while

the network diameter remained relatively constant before and during the outbreak (10 and 11 graph-distances, respectively), there was a slight increase in the average length between nodes (3.99 and 4.25 graph-distances) and a similar average degree of node connectivity (3.06 and 2.87 links), graph density (0.003 and 0.002), and Watts-Strogatz clustering coefficient (0.06 and 0.05). However, following the conclusion of the outbreak, this connectivity diminished. Specifically, although the post-outbreak network diameter (9 graph-distances) remains analogous before and during the Ebola outbreak, the post-epidemic network displayed reduced connectivity via declines in the average link length (3.29 graph-distances), clustering coefficient (0.03), average links per node (2.31), and the maximum number of connected components (42). The modularity increased across all intervals from 0.60 before the outbreak, 0.66 during the outbreak, and 0.74 after the outbreak. Three primary nodes coordinated virtually all Ebola biotechnology research: the University of Texas at Galveston (UT Galveston), the US National Institute of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID), and the US Army Medical Research Institute of Infectious Diseases (USAMRIID). These nodes had particularly strong links with universities and research institutes, including Makerere University, Institut Pasteur, and KU Leuven, as well as with various ministries of health in endemic countries and larger coordinating agencies like the WHO.

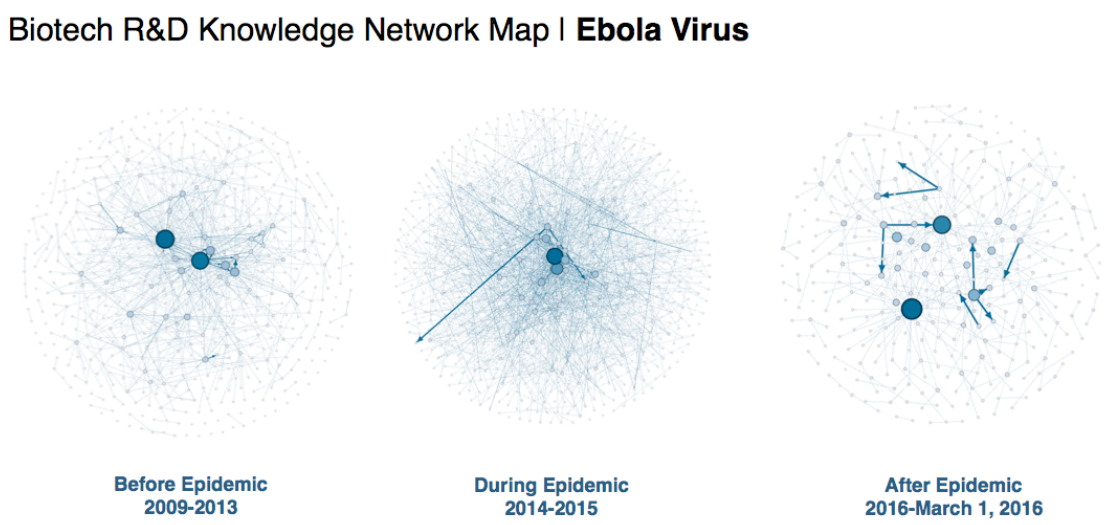


**Figure 1.** R&D Network Map of Ebola Before, During, and After Outbreak

Zika

Given its small network size, with only 31 nodes and 20 links before the current outbreak (2009-2013) and 176 nodes and 156 links during the outbreak (as of March 1, 2016) it is clear that this R&D network is still being established [Figure 2]. This is confirmed by the fact that the network diameter for Zika biotechnology R&D has doubled (3 to 6 graph-distances) and the link length increased from 1.41 to 2.09 graph-distances since the outbreak began in 2014, also indicating enhanced closeness and betweenness centrality. Moreover, the network has experienced a proliferation in its clustering coefficient (0.00 to 0.03) with the average number of links per node increasing from 1.29 to 1.77 graph-distances. As the clustering coefficient and link length indicate the degree of network saturation, this demonstrates movement from isolation to collaboration in R&D practices. Modularity increased from 0.70 to 0.87, which demonstrates the presence of an increased number of nodes with relatively similar high collaboration practices. The two most active nodes were Institut Louis Malard and

Institut Pasteur, which tended to form strong links with universities, particularly the University of Sao Paulo, and large national and international research institutes including the US Centers for Disease Control and Prevention (US CDC) and the German Centre for Infection Research (DZIF).

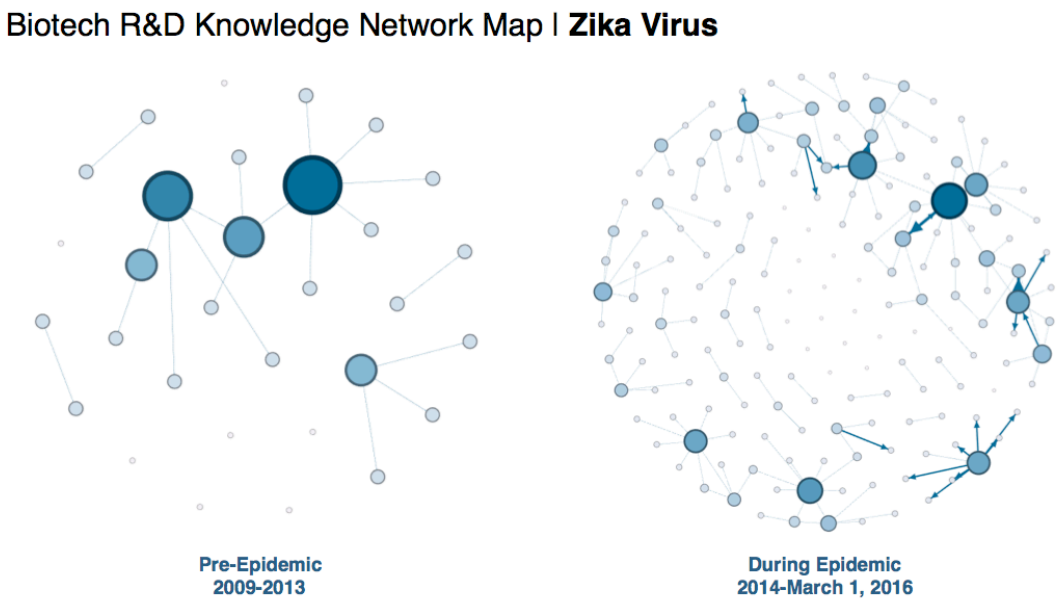


**Figure 2.** R&D Network Map of Zika Before, During, and After Outbreak

## Network Productivity

Prior to their outbreaks, there was a mean of 123 ± 28 Ebola journal publications and 2 ± 1 Zika journal publications from 2009-2013 [Figure 3]. However, during the outbreak period, this number doubled each year of the Ebola outbreak from 233 publications in 2014 to 493 publications in 2015. Similarly, the number of Zika publications increased ten-fold to 13 in 2014 and 19 in 2015. The number of Zika publications in 2016 is already set to break this annual record given its eight biotechnology publications during the first quarter. No patent applications that solely

targeted Zika virus were identified using the "Title" search criteria; however, an average of 9 ± 5 patents that included Zika in its "Claim(s)" and/or "Description/Specification" were identified from 2009-2014. No patent applications were submitted in 2015 or 2016; thus, no period comparison could be conducted. As previously stated, there is only one FDA-approved biotechnology product for either Zika or Ebola: ReEBOV Antigen Rapid Test Kit (Corgenix, USA) for Ebola diagnosis.

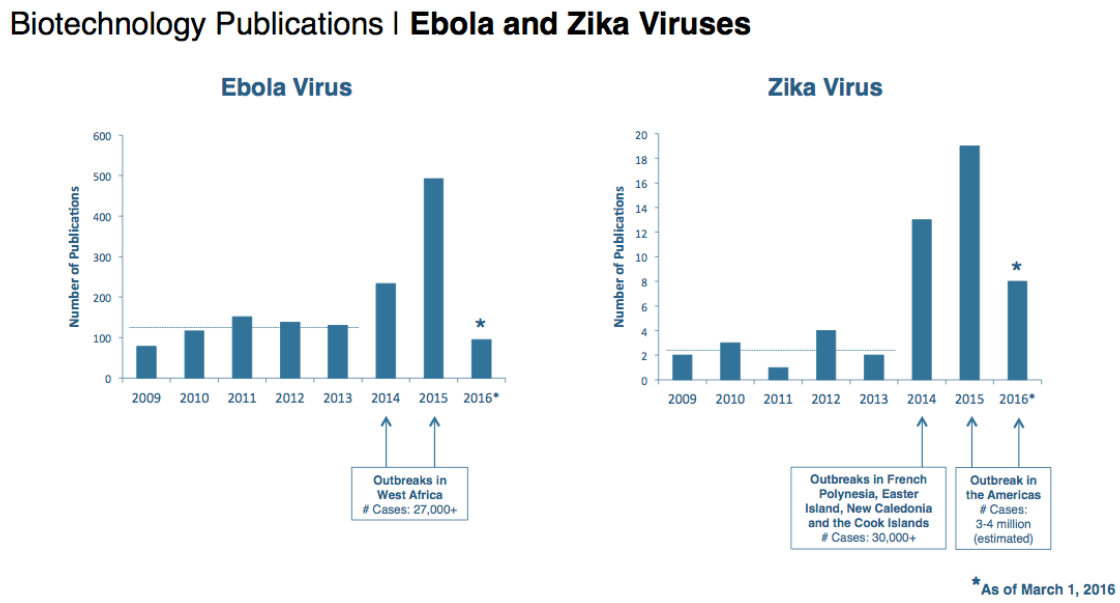


**Figure 3.** Biotechnology Publications of Zika and Ebola (2009-2016)

## Limitations

There exist several limitations regarding the interpretation of network analysis statistics and the generalizability of results. This is largely due to the fact that such statistics are highly dependent on the availability and quality of inputted source information. In this study, published literature was used as the basis for network mapping; as such, it is possible that some current research teams and collaborations were

excluded. Nevertheless, as this study ultimately seeks to identify productive R&D collaborations that advance future commercial development of biotechnologies, it is unlikely that a research group that contributed meaningful scientific and technological knowledge from 2009-2016 was missing from the database. Finally, a network analysis does not explore or explain potentially interfering external factors, such as national R&D policies, variances in protection of intellectual property rights, and different cultural paradigms regarding openness. Thus, network analyses should be interpreted with caution due to limitations in the existing knowledge base regarding inherent heterogeneity among nodes and their ability to form links. Nevertheless, meaningful interpretations about the global state of biotechnology R&D for Zika and Ebola viruses were made by analyzing the entire R&D network—not just individual nodes— attempting to overcome this nuanced framework. Finally, it is known that bibliometric and patent data offer an incomplete measure of innovation since a publication does not guarantee a patent or commercial product and there is no method to differentiate between incremental and disruptive innovation. Still, as multiple standard indicators were used as a proxy for scientific, technological, and commercial productivity and innovation, it is improbable that this altered the resultant trend, but it might have overestimated the magnitude. Given the low productivity of the current Ebola and Zika networks, this only serves to further support the study's findings of deficient biotechnology R&D practices.

# CHAPTER 4

# DISCUSSION

The Zika epidemic draws several parallels to the Ebola pandemic, particularly with regard to the gradual global response and comparable absence of commercial diagnostics, therapies, and vaccines [Figure 4]. Prior to the two large outbreaks, there were no obvious scientific barriers to the development of either an Ebola or Zika vaccine, rapid diagnostic test, or treatment[5,6]. Yet, no measures were taken to rectify this technology dearth until five months after the Ebola outbreak began in West Africa and nine months after Brazil first detected Zika virus [Figure 4].

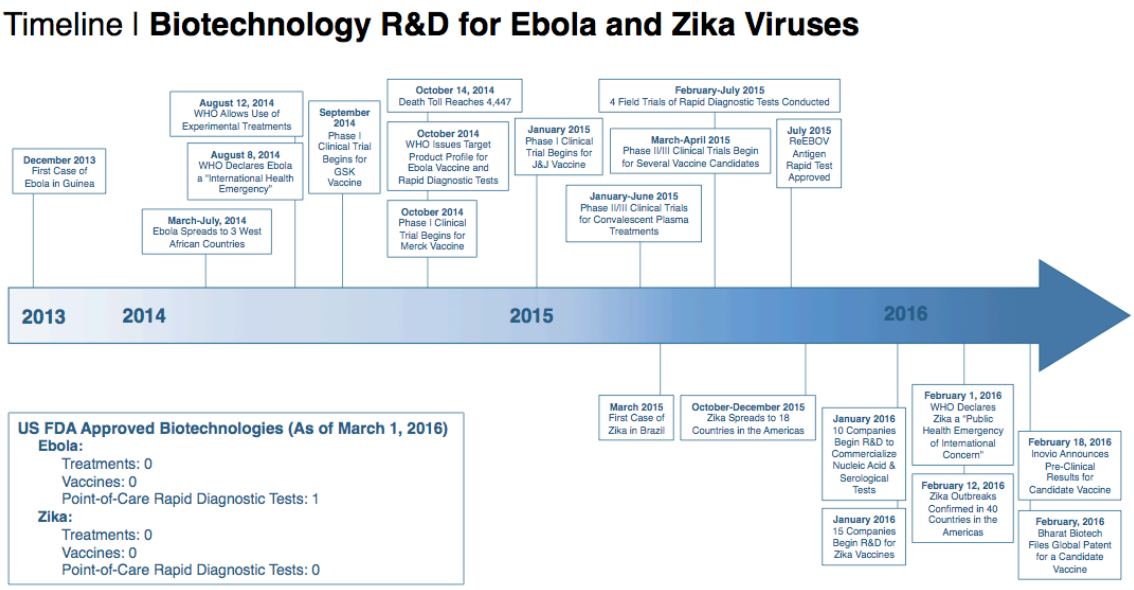


**Figure 4.** Timeline of Ebola and Zika Biotechnology R&D Milestones

This reactive, sluggish global response to both outbreaks demonstrates that external factors, such as political will and public outcry, currently decide if, when, and how current R&D networks develop biotechnologies for an emerging disease. Given the

proliferation of clinical trials that emerged over the course of each epidemic, it is clear that the R&D networks for Zika, Ebola, and other emerging pathogens currently wait for a public health emergency to initiate or accelerate commercial biotechnologies for neglected diseases. That is, current R&D practices are primarily reactionary in response to an outbreak rather than precautionary or proactive. While this isn't inherently poor practice, as there exists no endogenous market incentives for neglected diseases and biomedical R&D is an expensive process, this dichotomy becomes significant given that we were unable to predict either the Zika or Ebola epidemic[27].

Studies have shown that better, more complex solutions are developed via collaboration and teamwork than by individuals alone[28]. However, there simply aren't enough researchers tackling emerging diseases globally prior to a large-scale outbreak [Figures 1 and 2] and, of those that do exist pre-outbreak, virtually all operate under an isolated R&D approach rather than one that promotes open collaboration. In fact, not only do the pre-outbreak biotechnology R&D networks of Ebola and Zika contain a low overall number of nodes, the majority of which are small in size, but the networks are also highly fragmented with only a few nodes dominating the entire R&D space while the remaining nodes have very minimal connectivity. As such, the pre-outbreak Zika and Ebola R&D networks underperformed with respect to scientific and technological productivity. Particularly, each network only relied on a few number of institutes to coordinate and conduct the majority of precautionary biomedical research. It follows that the number of publications, patents, and commercial products would also be modicum [Figures 3 and 4].

However, it should be noted that both the Zika and Ebola networks systemically changed formation during their outbreaks as seen by the transition to more dense, centralized networks [Figures 1 and 2]. As each network gained not just more nodes, but more interconnected nodes, R&D productivity increased correspondingly [Figure 3]. Consequently, it appears that the current trend of Zika and Ebola R&D practices—even prior to the WHO's new recommendation—is to instinctively shift towards greater connectivity and co-creation during highly publicized public health emergencies and epidemics. As such, WHO's current open access and data sharing provision merely supports naturally-occurring open R&D practices rather than stimulates more proactive, improved data dissemination practices. Yet, it is because of these current pre-outbreak R&D deficiencies that diagnostics, therapeutics, and vaccines were not developed for Zika and Ebola. This is critical since, in the case of Ebola, the post-outbreak R&D network map indicates a natural reversion to a less connected state with a reduced number of nodes [Figure 1] and is associated with a decrease in R&D productivity [Figure 3]. Since the current reactionary open R&D practices do not translate to long-term R&D productivity (and subsequent commercial development), WHO should have bolstered a strategy that not only addresses pre-outbreak R&D deficiencies but also extends the permanence of open, collaborative R&D practices beyond the acute crisis.

As such, the ability of WHO's September 2015 recommendation to reduce the impact of future epidemics is limited by its inherently reactionary and short-term R&D response to an epidemic. This is imprudent since open access, data sharing, and co-

creation prior to an outbreak has the potential to more quickly reduce the burden of disease since proactive sharing can increase the quantity and quality of data accumulated, while also pooling risk[22]. Moreover, the endorsed strategy only mimics the endogenous behavior already exhibited by current R&D networks during public health crises and it does not address the lack of vital long-term support for maintaining these collaborative, open data access and data sharing practices. Instead, WHO implicitly allows these hyper-productive, highly connected R&D networks during public health crises to regress to non-collaborative R&D practices post-outbreak. The position does not support the essential continuation of preliminary scientific and technological progress made via open R&D during an outbreak once political will, public outcry, and funding mechanisms decline. This is paramount to avoid complacency between outbreaks on unfinished biotechnology R&D.

# CHAPTER 5

# CONCLUSIONS

Current R&D efforts for emerging diseases remain primarily reactionary in response to debilitating disease outbreaks rather than proactive. As the Zika outbreak is still ongoing, a similar natural trend of reversibility in collaborative R&D practices following the conclusion of its epidemic cannot yet be determined, but we must preemptively ensure it does not occur. Collaboration begets innovation, and, when the majority of existing R&D networks only seek a high level of collaboration during times of public health crises and revert to traditional strategies once an outbreak is contained, the effectiveness and benefit of an open R&D strategy, even one endorsed by WHO, is squelched by its ephemeral applicability and limited use. As such, although the WHO's recommendation is laudable, it fails to recognize that open R&D practices presently occur endogenously during emerging disease pandemics. The endorsement does not improve current emerging disease networks' long-term ability to advance scientific knowledge and develop commercial biotechnologies. If not revised, the same deficient, reactionary R&D practices that failed to develop commercial diagnostics, therapeutics, and vaccines prior to the Zika and Ebola outbreaks will remain and it is uncertain if other emerging disease R&D networks will be able to overcome these systemic R&D deficiencies prior to an outbreak.

The acceleration of existing scientific and technological knowledge should not be dependent on a catastrophic event, especially when WHO's established best practice to

quickly advance the development of therapeutics, diagnostics, and vaccines during crises is through the exploitation of open collaboration and access. As such, WHO should update its recommendation to endorse and support permanent data sharing and open access for all emerging diseases regardless of its status as a "public health emergency of international concern". If actively utilized before a pathogen can cause an outbreak, formally organizing and managing long-term open R&D networks has the potential to vastly improve global vaccine, diagnostic, and treatment development efforts for emerging diseases. If WHO wishes to prevent a similar paucity of available biotechnologies at the onset of the next emerging disease epidemic, enhanced research collaboration prior to outbreaks is requisite and regulated strategic innovation practices must be employed globally. Although there is no single guaranteed strategy for success, shifting the research paradigm is crucial to overcoming the existing systemic R&D barriers for emerging diseases. As the international research community cannot definitively predict the next epidemic, adjusting current R&D practices to encompass long-term open, collaborative R&D strategies offers the potential to more effectively mitigate both the global health and economic burdens associated with emerging diseases of epidemic potential.

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