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Proactive Management of Ebola Virus Disease Outbreaks in Africa

Ebola virus disease has caused devastating losses in Africa, and the ecology of the virus is still not fully understood. Since the first outbreak occurred in 1976, knowledge of the molecular biology and epidemiology of the *Ebolavirus* genus has greatly increased. However, the evolution and ecology still have knowledge gaps which have created obstacles related to managing the disease (Judson et al. 2016). The prominent limiting factor that hinders the understanding of Ebola virus disease outbreaks is that the natural reservoir host or hosts are unknown (Marí Saéz et al. 2015). Ebola virus is a zoonotic disease, which means that it spreads from animals to humans, and these instances of transmission are termed spillover events (Judson et al. 2016). With regards to control and management of the disease, it is especially difficult to determine which methods would have the greatest outcomes when the original source causing outbreaks is unknown.

What is known is that Ebola virus disease case fatality rates are usually 60-70%, but can be as high as 90% in humans. Human infection can occur from contact with an infected animal or person's blood or bodily fluids. Ebola virus can be fatal in humans and primates, like gorillas and chimpanzees (Pigott et al. 2014). Five distinct members of the *Filoviridae* family include: *Zaire ebolavirus* (EBOV), *Sudan ebolavirus* (SUDV), *Taï Forest virus* (TAFV), *Bundibugyo ebolavirus* (BDBV), and *Reston ebolavirus* (RESTV) (Muyembe-Tamfum et al. 2012; Judson et al. 2016). These are the causative agents for Ebola haemorrhagic fever, which is now known more commonly as Ebola virus disease. Most of the human outbreaks are caused by ZEBOV, SEBOV, and BEBOV, while the other two typically infect nonhuman primates and other animals (Muyembe-Tamfum et al. 2012).

In this paper, I will discuss proactive mechanisms that can be implemented to reduce or eliminate the risk of Ebola virus disease spillover events. Because resources for control of infectious diseases are limited, it is important to identify areas that are more at risk for spillover occurrences (Pigott et al. 2017). In order to do this while lacking the knowledge of a reservoir species, studies have combined factors that increase spillover risk and have analyzed the patterns associated with different Ebola virus disease outbreaks (Muyembe-Tamfum et al. 2012; Pigott et al. 2014, 2017; Judson et al. 2016; Oliviero et al. 2017; Schmidt et al. 2017; Reed Hranac et al. 2019). Once the regions at risk are determined, management resources can be distributed to these areas first in an attempt to stop or slow transmission at the human-animal interface (Pigott et al. 2017). Some risk factors that contribute to higher chances of Ebola virus disease outbreaks include seasonal changes of temperature and precipitation, spatiotemporal patterns related to vegetation, anthropogenic factors such as urbanization, deforestation, human population growth, and settlement changes, bat birthing cycles, and cultural factors such as hunting and consuming wild animals (Muyembe-Tamfum et al. 2012; Pigott et al. 2014, 2017; Judson et al. 2016; Oliviero et al. 2017; Schmidt et al. 2017; Reed Hranac et al. 2019). After regions have been identified, they should be targeted to receive management resources. Some proactive control resources that will be discussed include surveillance, ecological interventions, and vaccines (Kelly et al. 2017; Levy et al. 2018; Sokolow et al. 2019).

Outbreak Patterns and Risk Factors

In order to determine effective spillover control methods, it is important to understand where, when, and why Ebola virus disease spillovers occur. Identifying disease patterns and regions with higher risk for outbreaks can be used as a starting point to then allocate resources to areas that are most susceptible. From 1976 to 2014, 34 human index cases were identified, each complicating the patterns associated with Ebola virus outbreaks, or lack thereof. Index cases are the initial human cases that are confirmed either from a clinical setting or from

laboratory testing and formations of transmission chains, and the 34 cases have been poorly characterized. The limiting factor in studying the ecology of Ebola virus disease is that the natural reservoir host of the virus remains unknown. This increases the difficulties surrounding identification of wildlife to human transmission risks since the source of these spillovers has not been defined. There may even be intermediate hosts which then can transmit the virus to humans. Fruit bats are suspected of being reservoir hosts. Additionally, potential intermediate hosts or species able to be infected by the reservoir include duikers, gorillas, chimpanzees, and multiple rodents which have presented with positive tests of Ebola virus RNA. Although these unknowns make it difficult, researchers have determined many ecological factors that increase the risk of Ebola virus disease emergence at the human-animal interface, which is very useful for implementing preventative measures prior to future outbreak occurrences (Judson et al. 2016).

Using ecological niche models, the conditions and habitats of all known Ebola virus index cases from 1976 to 2014 were characterized by species and location of each of the spillover events. Each of the *Ebolavirus* species - *Zaire ebolavirus* (EBOV), *Sudan ebolavirus* (SUDV), *Bundibugyo ebolavirus* (BDBV), and *Taï Forest ebolavirus* (TAFV) - exhibited distinct ecological relationships based on different outbreak patterns, demonstrating that more than one *Ebolavirus* can cause Ebola virus disease outbreaks (Judson et al. 2016). In the past, outbreaks have typically occurred in the Congo and Nile basins. The first outbreaks were in Sudan and the Democratic Republic of the Congo (DRC) at almost the same time in 1976, but by different viral species, EBOV and SUDV (Muyembe-Tamfum et al. 2012). Spillovers of EBOV were identified between latitudes of -5.3° and 8.6°, whereas SUDV spillovers were clustered between 0.64° and 4.6° (Judson et al. 2016). The mean elevation for spillover events of SUDV were significantly higher than elevation of EBOV spillovers. EBOV spillover events also had a higher association with evergreen broadleaf forests and SUDV spillover events were associated with woodland vegetation. Suitable habitats for spillover events of EBOV and SUDV were derived from the

ecological niche models using locations of index cases and environmental covariates. EBOV spillover events were most likely to occur in West Africa and Central Africa. East Africa and areas in Central Africa were habitats suitable for SUDV spillover. Most of these predictions were supported by serological evidence of antibodies in humans or animals (Judson et al. 2016). Regions included in the moderate to high risk category based on a different spatiotemporal model included East Africa, Madagascar, south central Africa, and a substantial portion of West Africa. Compared to past Ebola virus disease outbreaks, these results show an expansion of the geographical scope of potential spillover locations in tropical Africa, showing that areas characterized as being in tropical or subtropical forests and woodlands in Angola, Ethiopia, Zambia, East Africa, and Madagascar were at risk (Schmidt et al. 2017). The geographic scope is vast for the distribution of *Ebolaviruses* and their hosts, with substantial amounts of suitable habitats for spillover of EBOV and SUDV. The ecological contexts of spillover events are variable based on habitats, dispersal of animals, and human behaviors and activities, with distinct conditions for both EBOV and SUDV (Judson et al. 2016).

Schmidt et al. (2017) drew some conclusions that paralleled those from Judson et al. (2016), along with some in opposition. Since the patterns of outbreaks have been seemingly inconsistent, they aimed to address two questions: does Ebola virus disease follow a seasonal pattern, and are there geographic areas at risk for outbreaks that have not experienced previous outbreaks? This model of spillover intensity combined spatial data on the dynamics of human population density and distribution over four decades, monthly rainfall estimates from satellites, and climate summaries to assess the factors associated with timing of previous Ebola virus spillovers. They identified all known Ebola epizootics and outbreaks in human populations, which were used to isolate the time and place of the origins of different spillover events. Environmental factors incorporated into the model included an enhanced vegetation index and variation in climate and land cover for areas in Africa with over 500 mm of annual rainfall.

The model shows that over the past three decades, there have been seasonal shifts of Ebola virus disease outbreak risk due to environmental factors (Schmidt et al. 2017). This contradicts the model by Judson et al. (2016), which did not find any seasonal associations of precipitation or temperature in the months when spillover events occurred. They found that EBOV spillover events occurred throughout the year in wet and dry seasons, however SUDV spillover events occurred mainly during the wet season. The less prevalent *Ebolaviruses*, BDBV and TAFV, both exhibited spillover events during the wet season as well (Judson et al. 2016). Schmidt et al. (2017) reported a substantial seasonal fluctuation of spillover intensity patterns geographically. A high enhanced vegetation index in the wettest areas of tropical Africa was associated with the highest mean Ebola virus disease spillover intensity, which is a measurement of risk proportional to the likelihood of spillover occurrences and changes with respect to environmental contexts. Most often the areas in the humid tropics had the lowest spillover intensity in dry months when the rainfall was below 50 mm. Months with rainfall at intermediate levels between 100 and 250 mm typically had spillover intensities equal to or more than high rainfall months with greater than 250 mm of rainfall. Generally constant spillover intensity was observed in central Africa near the equator throughout the year. Southern Africa's spillover intensity varied highly with seasonal patterns, and West Africa had slight variation as well. Spillover intensity was highest at the point when areas that typically exhibited more rainfall transitioned to or from periods of dryness, peaking most in moderately dry months and least in the driest months (Schmidt et al. 2017).

Spatiotemporal variation of Ebola virus disease spillovers can be attributed to increased human population and settlement pattern changes. Although climate and seasonal variation have a larger impact, spillover intensity is still affected by human population density. Some hypotheses of these drivers are seasonal impacts on the availability of resources, frequency of host animal-human contact, and changes in human behavior. Human behavioral changes could be different hunting efforts, amount of hunted meat consumed, or the frequency of wild animal

contact, since these have all been related to prior Ebola virus disease index cases. Between 1975 and 2015, large shifts in spillover intensity appeared to be from increases in human population. For example, population growth from intermediate to high densities in a particular region, like West Africa or the areas near Lake Victoria, has predicted increased spillover intensity. Spillover intensity has increased in some isolated regions with populations that have subsided over time, because of people moving toward areas in central Africa. These data interpretations for spatiotemporal patterns and spillover intensity risks can be used as a public health resource to guide surveillance efforts and designs to increase readiness of future outbreaks, as well as for distribution of management resources to regions with the highest levels of risk (Schmidt et al. 2017).

Despite the many Ebola virus disease outbreaks that have occurred, the reservoir and intermediate hosts, as well as spillover mechanism, are not well understood. Using a mechanistic approach, the impacts of how bat birthing cycles affect spatiotemporal spillover occurrences of Ebola virus disease were investigated. Tree roosting bat species that have lower colony densities than Egyptian fruit bats are suspected reservoirs for Ebola virus disease. Three groups of bat species used in this model were African fruit bats, molossid bats, and non-molossid microbats. Ecological niche models were made across a subset of Subsaharan Africa which, using the suggestions from Schmidt et al. (2017), were restricted to mainland areas with greater than 500 mL of annual precipitation. They found that there was a correlation between African fruit bath births and Ebola virus disease outbreaks in both humans and non-human spillover hosts. Bat birthing could facilitate transmission of Ebola virus into non-human mammals, with significance for fruit bats and non-molossid microbats (Reed Hranac et al. 2019).

Humans can be infected by animals when they come into contact with tissues and fluids from infected wildlife, with an emphasis on nonhuman primates and bats (Muyembe-Tamfum et al. 2012; Marí Saéz et al. 2014). Evidence that bats could be a reservoir for EBOV includes that

some fruit and insectivorous bats have been found to survive infection in experiments, and fruit bats have shown possible active infections with detection of RNA from EBOV in three different species. Antibodies for EBOV have also been detected in those three species and six additional ones. Many bats, but especially fruit bats, are often hunted and eaten, offering further possibilities of direct infection (Marí Saéz et al. 2014). Handling of infected animal carcasses is a way that humans can become infected, which can lead to human-to-human transmission from the original case (Muyembe-Tamfum et al. 2012). Since the exact reservoir is unknown, two hypotheses for modes of Ebola virus disease zoonotic transmission include either direct contact with a reservoir host or contact to other animals that are able to be infected from the reservoir (Marí Saéz et al. 2014). A list of all of the index cases from 1976 to 2014 with the potential source of their associated spillover events included sources like insectivorous bats, rodents, antelopes, monkey meat, as well as carcasses of chimpanzees, duikers, gorillas, and fruit bats (Table 1) (Judson et al. 2016). Culturally, wild meat, known as bushmeat, involves hunting and consuming animals such as nonhuman primates, duikers, bats, and antelopes (Bonwitt et al. 2018). Spillover events of EBOV have had a higher association with bushmeat exposure compared to SUDV spillovers (Judson et al. 2016). The World Health Organization has attempted to outlaw the acts of hunting and eating some wild animals as part of Ebola virus disease prevention campaigns (Bonwitt et al. 2018).

Along with hunting and consuming bushmeat, forest ecosystems have changed significantly in tropical Africa, which is related to increases in Ebola outbreaks due to human invasion. This increases the likelihood of interaction with a natural Ebola virus reservoir. Human index cases involving hunters, gold miners, and farmers have been associated with working in shared locations with animal hosts, possibly as a result of contact with the reservoir in their natural habitat (Muyembe-Tamfum et al. 2012). Anthropogenic factors of urbanization, farming, and deforestation become more prevalent along with human population and forest takeover, and increase the chances of infection from a potential reservoir of the virus. Forest clearance effects

on Ebola virus disease outbreaks were investigated in Central and West Africa. Results showed that outbreaks along the outsides of the rainforest were associated with diminished forest area from the previous two years, with the strongest association for closed forests. Based on these results, it was suggested that the likelihood of future outbreaks could be lowered with the reduction of deforestation, as well as by reducing human access and proximity to forests that have been damaged within the past two years (Olivero et al. 2017).

Outbreak Stages

Viral hemorrhagic fevers, like Ebola virus disease, are of particularly high risk in places that have a low capacity for rapid diagnostic disease testing, occurring in both endemic and non-endemic locations. This is largely due to the similarity of clinical presentations of hemorrhagic fevers to other pathogens, supporting the importance of rapid diagnostic testing. A framework of three stages was used to identify where to focus existing pathogen countermeasures. Stage 1 is the index case potential with animal-human transmission from zoonotic reservoirs to the initial case in any potential epidemic. This stage was built upon existing environmental suitability models for viral transmission from environmental sources into human populations in order to identify risk areas for spillover events. Geographic index case information and detection of the pathogen in animals was used to create spillover risk maps, visually highlighting areas with the highest possibility of spillover. Stage 2 is the outbreak potential, which characterizes the human-to-human transmission after the initial zoonotic transmission event. This tends to be located near areas where care is given, including homes and healthcare settings and in the surrounding areas (Pigott et al. 2017). Although this stage occurs after a spillover, it is still important to mention since many areas may have a high spillover risk, but a lower risk of human-to-human transmission. Therefore, said region would be less of a priority for resource allocation compared to a region with higher human-to-human transmission, conceivably leading to a much larger disease burden if more people are affected.

This stage paired stage 1 information with outbreak receptivity factors to identify areas that were more likely to experience human-to-human spread. The factors included governance, communications, isolation, infrastructure, and health care, which are used to reflect a location's susceptibility to further spread following the index case on the basis of the resident population and response infrastructure in place.

The results of stage 1 indicated that Ebola virus disease had the highest potential for index cases due to spillover events in western Africa, including Macenta, Guinea and Foya, and Liberia, as well as middle Africa, including Woleu, Gabon and Haut-Uele, and the Democratic Republic of the Congo (Figure 1a). Stage 2 demonstrated that susceptibility for human-to-human transmission of Ebola virus disease was the greatest in Angola, the Central African Republic, and South Sudan. Those are areas that should be targeted for prompt interventions to minimize the scale of local outbreaks (Figure 1b). Areas that had higher likelihood of spillover events in stage 1 with lower likelihood of human-to-human transmission included areas in Côte d'Ivoire and Uganda.

The possibility of Ebola virus disease spillover events occurring in both endemic and non-endemic locations were underlined by the results from stage 1. An area typically considered to be non-endemic is the Central African Republic, however this is an area at risk for zoonotic transmission. One method to control spillovers is proactive surveillance of animal populations to assess potential emergence threats. Another is providing adequate diagnostic capacity to locations ranked as high risk so that they are able to diagnose the infected patients quickly and accurately. Areas ranked highest in stage 2 should be focused on in terms of resource allocation for strengthening of health systems. This would begin with healthcare worker awareness of possible index case presentations to reduce the possibility of human-to-human spread. Also, the regions with the highest need for vaccine distribution can be determined by these results. Because this framework is independent from an outbreak, it can be used to develop proactive plans for public health measures. It allows for control measures to be prepared in vulnerable

areas prior to an outbreak's occurrence. In order to implement informed prevention and control protocols, it is critical to understand where these outbreaks have the potential to occur and be sustained with secondary transmission. These results add value to the conversation of where to focus the limited resources available to prepare for an outbreak of Ebola virus disease (Pigott et al. 2017).

Proactive Control Methods

Surveillance

Because of continued pathogen emergence and spread within at-risk populations, a focus on proactive management rather than simply responsive activities to emerging infectious disease outbreaks is of utmost importance. The practice of responding to the outbreaks once they occur is not only cost-prohibitive, but also unsustainable. Optimal surveillance, preventive strategies, and treatment use, resources for a proactive approach, are limited and must be prioritized to areas that need them most (Pigott et al. 2017). The West African Ebola virus disease epidemic highlighted the need for better forecasting methods for emergence in new regions because of its sheer size and geographic area covered. In order to improve surveillance and responses to future spillovers, it is necessary to identify the environmental factors that contribute to higher outbreak risk (Schmidt et al. 2017). Surveillance has been widely recognized as a tool that could benefit the study of Ebola virus disease outbreaks. If the surveillance system is able to detect early Ebola cases, it could serve as an avenue to study animal reservoirs synchronously which has previously been difficult to accomplish in remote African forests (Muyembe-Tamfum et al. 2012). Through building the understanding of the spatial distribution of the zoonotic niche for Ebola virus, surveillance capabilities can be improved (Pigott et al. 2014). Areas characterized as high-risk for spillover should be allotted appropriate surveillance resources to reduce the outbreak potential. Evaluation of emerging disease threats through proactive surveillance of animal populations can be especially helpful

for areas with high spillover potential such as the Central African Republic, which is a non-endemic region (Pigott et al. 2017). Schmidt et al. (2017) suggested that surveillance be implemented and extended to areas other than just central and West Africa. Improved design for forecasting, surveillance, and rapid response preparation can be informed by the spatiotemporal factors that have helped to identify geographically widespread regions and dynamic seasons of higher Ebola spillover intensity. The savannah and humid tropical regions of Africa were specified as having dynamic seasonality of spillover risk, and should be targeted for proactive surveillance (Schmidt et al. 2017).

One Health is a transdisciplinary, proactive method for prevention and preparedness of disease emergence. It aims to reduce the impacts of future emergence by identifying viruses early at their source so that interventions can be implemented before a spillover occurs. The One Health approach was applied by the PREDICT project consortium, which was led by the US Department for International Development. Since human, animal, and environmental health are interconnected, PREDICT supports public health measures that pull from different disciplines to provide a well-rounded view of emerging infectious diseases with a focus on prevention. Five One Health strategies for improving early detection and response to pathogen threats include strengthening or building detection capabilities for zoonotic pathogens, developing diagnostic lab and outbreak response capacities, identifying high risk animal-human interfaces, optimizing models that predict emergence and spread, and providing information management and communication tools for sharing zoonotic virus surveillance globally. Understanding the underlying causes for emergence and drivers of spread is crucial for outbreak prevention.

PREDICT focused on surveying wildlife with evidence for Ebola virus spillover to humans. Healthy suspected reservoirs were sampled to gather more information regarding which species can carry Ebola virus. They contributed to advancements of a noninvasive method of antibody detection in gorilla feces to determine whether this species had been

previously infected with Ebola virus. Surveillance methods for early virus detection may also benefit wild ape populations that are susceptible to Ebola virus disease. Ebola outbreaks in humans helped provide evidence for surveillance recommendations, which resulted in a focus on animal sampling strategies. These included limited resource response efforts, target species, and rapid screening diagnostic prioritization for viral detection in animals that are potential reservoirs or secondary hosts.

Digital surveillance platforms developed by the consortium have the ability to identify the times and places with higher risk of disease emergence. This platform would alert public health officials, who could then implement active surveillance methods and interventions before a spillover occurs. Additionally, local media was implemented for surveillance enhancement and early detection of infectious diseases. This was valuable in that it provided localized information, which was used as a supplement to digital surveillance data. In areas that are less capable of developing disease detection and response technologies, local media surveillance along with active digital surveillance could be substantial. PREDICT highlights the importance of inclusion of diverse disciplines to provide a range of perspectives on emerging disease outbreaks. Through the detection of Ebola virus at the wildlife-human interface, these strategies would be very helpful in pushing toward a proactive approach to outbreak prevention and control, rather than the current, unfavorable reactive approach (Kelly et al. 2017).

Ecological Interventions

Control interventions that target the ecological context of a pathogen spillover can be used to complement conventional approaches. Conventional control methods for humans and domestic animals include vaccination, clinical treatment, disinfection, and control with chemicals. However, this category of control methods does not consider the more complex ecological interactions. These approaches are often met with consequences and may be difficult and costly to implement. Although some conventional methods are successful, ecological

interventions can also have positive effects by taking a different approach and focusing on the ecology of spillovers. Through these methods, it may be possible to produce new, actionable solutions to control and minimize spillovers in an unconventional way.

A spillover event can be defined as a set of barriers that a pathogen must get through to move from its original reservoir into a new host at a specific place and time. Reduction or prevention of pathogen movement across a barrier will therefore prevent or reduce the risk of spillover occurrence. Ecological interventions have the ability to address multiple layers or systems in the ecology of a pathogen. The dissemblance between conventional and ecological interventions is the way in which the two different approaches modify transmission. Conventional methods usually involve shifts in the amount of susceptible, infected, and recovered individuals, but must be sustained or else the effects will dwindle. Consequences of conventional solutions include damage to the environment, evolution of resistance, unexpected effects outside of the targeted host or pathogen, and tendencies to be complicated and challenging to put in place (Sokolow et al. 2019).

Understanding the complex ecological context of pathogen transmission is the key to ecological interventions, which aim to control reservoir density, spread, or infectiousness, environmental survival or spread of pathogens, or spillover host risk of contact, susceptibility, or treatment effectiveness. Since different reservoirs have different ecologies, not all ecological interventions will work to the same extent for all emerging or re-emerging infectious diseases. However, interventions can provide clues that point toward which reservoir components are most influential to spillover events. This is relevant in the case of Ebola virus disease since the natural reservoir species are presently unknown. One possible intervention that may contribute to limiting risk for Ebola spillover could be limiting access to habitats like forests, that are home to many wild animals that are potential Ebola virus reservoirs (Sokolow et al. 2019). Suspected reservoirs are mainly tree roosting bat species, since African fruit bat species have contributed to recent EBOV evolution based on phylogenetic analyses. Species that have been found to

harbor RNA viral fragments of *ebolaviruses* include the Hammer-headed bat (*Hypsignathus monstrosus*), Franquet's epauletted fruit bat (*Epomops franqueti*), and the Little collared fruit bat (*Myonycteris torquata*), which are all African fruit bats (Reed Hranac et al. 2019). The potential spillover source of the 2013 outbreak in Guinea was an insectivorous bat (*Mops condylurus*), which was also suspected to be the potential source of the 1976 and 1979 South Sudan outbreaks (Judson et al. 2016). Human outbreaks are not exclusively because of direct exposure to bats, so other non-human species should not be discounted for these ecological interventions since they are part of the disease transmission chains (Reed Hranac et al. 2019).

An example of this type of ecological intervention limiting access at times when human or non-human secondary hosts comes from Hendra virus, which is transmitted from bats to horses. Blocking access to trees where bats roost overnight was implemented to prevent transmission by delaying the time of contact between horses and grasses contaminated with bat urine. This would reduce the likelihood of horses coming into contact with live Hendra virus secreted in the urine (Sokolow et al. 2019). An ecological intervention like this should be considered, since many index cases of different Ebola virus disease outbreaks have been hunters, butchers, and other people who have reported potential wildlife spillover sources of chimpanzee, duiker, and baboon carcasses (Judson et al. 2016). If access is restricted to forests with dense aggregations of animal host populations at key times of bat and other animal activity, it could help to reduce the risk of spillover.

Using a model of a hypothetical bat-human spillover for a virus with high human-to-human transmission, like Ebola virus, different types of interventions were evaluated based on the numbers of susceptible, infectious, and recovered individuals. This model involves donor hosts, also known as the reservoir, and recipient hosts, which would be a human. In the heat map presented in Figure 1, the threshold effects of the different interventions are shown with respect to the number of recipient cases at different intensities of intervention application. The types of interventions that had the best results based on the model are recipient behavior

modification, recipient treatment, and recipient vaccination, which each require around or less than 50% intensity. Effective at a higher intensity would be donor treatment, which almost eliminates the disease in recipients at over 99% intensity and biosecurity measures at the bat-human interface with closer to 99.9% intensity. These two interventions with great reduction of disease in recipients at such a high level of intensity would likely be unfeasible, however the three interventions at or below 50% intensity could be implemented to see how effective they are in an actual disease setting (Sokolow et al. 2019).

Vaccines

The 2013-2016 outbreak in Guinea, Liberia, and Sierra Leone was controlled effectively with coordinated public health measures including rapid case identification, isolation of cases and contacts, and contract tracing (Levy et al. 2018). Although that outbreak was controlled, the outbreaks in the Democratic Republic of the Congo in 2017, 2018, and 2020 emphasize that there is still a risk for re-emergence of Ebola virus disease (Levy et al. 2018; WHO 2020). As of June 18, 2018, there were 36 completed vaccine trials, seven non-recruiting active studies, and seven recruited vaccine studies registered. The Ebola Ça Suffit vaccination trial in Guinea was said to have 100% vaccine efficacy, however that efficacy extent is debatable (Levy et al. 2018). Another study confirmed that the rVSV-ZEBOV vaccine had about 100% efficacy, with 75.1% effectiveness at the cluster level, which included herd immunity of cluster members who were unvaccinated (Gsell et al. 2017). This was determined by investigation of the effectiveness of the vaccine in case contacts, with randomized clusters of contacts given immediate or delayed vaccination. It is a recombinant, replication-competent, vesicular stomatitis virus-based vaccine that expresses the *Zaire Ebolavirus* glycoprotein. According to the US National Academies of Sciences, Engineering, and Medicine, the vaccine was likely to provide some protection, and possibly even ‘substantial protection’ (Levy et al. 2018).

Another study by the Partnership for Research on Ebola Vaccines in Liberia I (PREVAIL I) tested the same vaccine, rVSV-ZEBOV, for its safety and immunogenicity. This was tested along with the chimpanzee adenovirus type 3-vectored vaccine for Ebola virus, chAd3-EBO-Z, in a group of 1500 adults. There were more symptoms reported in both of the vaccine groups compared to the placebo group. These symptoms were mild and included headache, muscle achiness, fever, and fatigue for the week after the injection. Upon followup at 1 month, the immunogenicity data showed that 71% of the chAd3-EBO-Z recipients, and 84% of the rVSV-ZEBOV recipients had antibody responses. This was the maximum amount of antibody responses recorded over the time of the trial. After 12 months, these responses dropped to 64% in the chAd3-EBO-Z and 80% in the rVSV-ZEBOV groups. Throughout the 12 month period, many patients also experienced serious adverse events. This included 8% of the chAd3-EBO-Z group and 9% of the rVSV-ZEBOV group, and of these, 71% of the adverse events were due to malaria. A collection of data from the STRIVE study on over 8000 healthcare and frontline workers in Sierra Leone and Guinea, as well as eight phase 1 trials and one phase 3 trial in North America, Europe, and Africa for the rVSV-ZEBOV vaccine indicated that the safety profile is acceptable. The vaccine induces immunity that persists for at least 24 months in adults. The rVSV-ZEBOV vaccine has been used through emergency authorization for Ebola virus epidemics (Levy et al. 2018). More than 43,000 people, including almost 9,000 healthcare workers, received the rVSV-ZEBOV vaccine in response to the outbreak from 1 June to 18 November, 2020 in the Democratic Republic of the Congo (WHOb 2020). This vaccine has been licensed in four countries in Africa, including the Democratic Republic of the Congo, Burundi, Ghana, and Zambia, as of February, 2020. It is called Ervebo, manufactured by Merck, and more recent studies have shown 97.5% efficacy of the vaccine (WHOa 2020).

Another vaccine candidate with promising results utilized a different technology than the rVSV-ZEBOV vaccine. It was an adenovirus type 26-vectored vaccine that encoded Ebola virus glycoprotein Ad26.ZEBOV. This was boosted with a modified vaccinia Ankara-vectored vaccine

encoding for *Ebola, Sudan, and Marburg virus* glycoproteins and the nucleoprotein for *Taï Forest virus*, MVA-BN-Filo. The results of this trial in phase 1 were very promising. Of the 87 patients, seroconversion frequencies of 79-89% were noted as soon as two weeks following the initial Ad26.ZEBOV vaccine. The specific immunity had sustained elevation after the MVA-BN-Filo booster. It was concluded that this combination of vaccines resulted in immunity for at least 360 days, and had a good safety profile. The chAd3-EBO-Z vaccine with a MVA-BN-Filo booster resulted in B-cell and T-cell immune responses superior to the single-dose chAd3-EBO-Z vaccine. After 6 months, the antibody responses were still positive (Levy et al. 2018).

Data is scarce regarding the effectiveness of vaccines in children. This is an important factor to investigate because in the west Africa epidemic in 2013-2016, 21% of the patients with Ebola virus disease were aged 16 years or younger, and children 5 or younger had a case fatality rate that was greater than 80%. Also, the index case of this epidemic in particular was a 2-year-old patient. This stresses the huge importance in generating a vaccine that is effective in children, since they were disproportionately affected in this outbreak (Levy et al. 2018). The rVSV-ZEBOV vaccine trial tested the effects in 6-17 year olds. None of the participants experienced secondary Ebola virus disease infections from the vaccine. Adverse symptoms were reported as mild in 17% of the 6-17 year olds. 36% of adults older than 18 years also experienced adverse symptoms from the vaccine, however 98% of which were mild (Gsell et al. 2017). Another important group with no data acquired is pregnant women. They have been excluded from all vaccine trials, however they are a very vulnerable group. Of the vulnerable groups, children as young as 1 year old were vaccinated during the 2018 outbreak in the Democratic Republic of the Congo, pregnant women were not vaccinated, and high-risk immune-compromised individuals, especially those with HIV, were underrepresented in one trial that resulted in 48% and 62% showing antibody responses for the chAd3-EBO-Z and rVSV-ZEBOV groups, respectively. This was lower than the antibody responses in the healthy

adults tested. Additionally, there is also little information regarding the vaccine's effectiveness in elderly populations (Levy et al. 2018).

PREVAC conducted a trial of the three vaccine strategies in adults and children over 1 year of age. These strategies included the rVSV-ZEBOV prime without a booster, rVSV-ZEBOV prime with a rVSV-ZEBOV booster, and Ad26.ZEBOV prime with a MVA-BN-Filo booster shot. There were over 2350 participants recruited as of June 2018, and they expected to add 2500 more. The purpose of this controlled trial was to research Ebola activities to prevent or effectively respond to future Ebola outbreaks. Strategies that are important to more effectively respond to future outbreaks include contact and post-exposure vaccination, targeted preventive vaccination, and widespread preventive vaccination of populations that are at higher risk of infection like healthcare workers and people living in areas that have experienced repeated outbreaks (Levy et al. 2018).

Discussion

The severity of Ebola virus disease warrants the need for an improvement of control methods. This research provides a framework for determining which areas have the highest risk of outbreaks, and therefore those areas should be the first to receive the limited disease management resources. Until the reservoir host is pinpointed, the factors associated with spillover risk should be considered when making decisions regarding distribution of resources. A proactive approach to controlling outbreaks at the human-animal interface is essential, since responding to outbreaks once they have occurred has been largely unsuccessful, as well as cost-prohibitive and unsustainable for long-term control (Pigott et al. 2017). Further studies should be conducted on these control measures in the future. The success of the Ervebo vaccine shows hope for the future of Ebola virus disease outbreaks, since it helped immensely in the Democratic Republic of the Congo, as over 8000 healthcare workers were vaccinated, and none were infected over the course of the outbreak (WHOc 2020). A combination of

improved proactive surveillance, diagnostics, ecological interventions, and vaccination should hopefully improve the outcomes of future Ebola virus disease outbreaks in the especially vulnerable regions in Africa.

Tables and Figures

Table 1: (Judson et al. 2016)

Table 1. Ebolavirus index cases and associated spillover events 1976–2014.

Country	Location	Index case date*	Index patient	Potential source of spillover	Season†	Ebolavirus	Lat	Long	Reference
South Sudan	Nzara	6/27/1976	male, textile worker	insectivorous bats (*M. condylurus*), rodents (*Rattus rattus*)	Wet	SUDV	4.63912	28.25115	[30, 38]
DRC	Yambuku	9/1/1976	44 y/o male, teacher	antelope, monkey meat	Wet	EBOV	2.82535	22.22567	[52]
DRC	Bonduni village	June/1977	9 y/o female		Wet	EBOV	2.88874	19.22384	[53]
South Sudan	Nzara	7/31/1979	male, textile worker	insectivorous bats (*M. condylurus*), rodents (*Rattus rattus*)	Wet	SUDV	4.63912	28.25115	[54]
Gabon	Mekouka, Andock mining camps	11/13/1994	gold miner		Wet	EBOV	1.44201	12.92929	[55]
Cote d'Ivoire	Tai National Park	11/16/1994	34 y/o female ethologist	chimpanzee (*Pan troglodytes*) carcass	Dry	TAFV	5.86442	-7.31794	[39, 56]
DRC	Mwembe, Kitwit	1/6/1995	42 y/o male farmer, charcoal pit worker		Wet‡	EBOV	-3.951	18.115	[57]
Gabon	Mayibout 2	1/31/1996	butcher	chimpanzee carcass	Lesser dry	EBOV	1.11667	13.1	[39, 55]
Gabon	Logging camp near Boue	7/13/1996	hunter	chimpanzee carcass	Dry	EBOV	0.1	11.95	[39, 55]
Gabon	Logging camp near Boue	8/24/1996	hunter	chimpanzee carcass	Dry	EBOV	0.1	11.95	[39, 55]
Uganda	Rwot-Obilo village, Gulu	8/30/2000			Wet	SUDV	2.94998	32.19997	[41, 58]
Gabon	Mendemba	Oct/2001		duiker (*Cephalophus* sp.) or gorilla (*Gorilla gorilla*) carcass	Wet	EBOV	0.70055	14.15543	[39, 41]
Gabon	Mendemba	10/25/2001		duiker or gorilla carcass	Wet	EBOV	0.70055	14.15543	[40, 41]
Gabon	Ekata	11/28/2001		duiker carcass	Wet	EBOV	0.67705	14.28902	[40, 41]
Gabon & RoC	Olloba	12/1/2001		gorilla carcass	Lesser dry	EBOV	0.62049	14.37774	[40, 41]
Gabon	Ekata	12/22/2001			Lesser dry	EBOV	0.67705	14.28902	[40, 41]
Gabon	Etakangaye	12/29/2001		chimpanzee carcass	Lesser dry	EBOV	1.0166	13.966	[40, 41]
RoC	Entsiami	Jan/2002			Dry	EBOV	0.09141	14.21818	[40, 41]
Gabon & RoC	Olloba	5/17/2002		chimpanzee carcass, pangolin	Wet	EBOV	0.62049	14.37774	[40, 59]
Gabon	Grand Etoumbi	4/27/2002	hunter	gorilla carcass	Wet	EBOV	1.30411	14.17743	[39]
RoC	Yembelangoye village	12/21/2002		gorilla carcass	Lesser dry	EBOV	0.13418	14.20981	[39, 60]
RoC	Mvoula	1/1/2003		chimpanzee carcass	Wet‡	EBOV	0.06823	14.41997	[39, 60]
RoC	Mbandza village	10/11/2003		monkey carcass (*Cercopithecus nictitans*)	Wet	EBOV	0.56015	14.65732	[39, 61]
South Sudan	Forests bordering Yambio	4/15/2004	hunter	baboon carcass (*Papio* sp.)	Wet	SUDV	4.43149	28.7054	[39]
RoC	Parc d'Odzala	4/18/2005	hunter	duiker or gorilla carcass	Wet	EBOV	1.12508	14.9158	[39, 60]
DRC	Bamoukamba 2	5/15/2007	butcher	fruit bat carcass (*H. monstrosus*, *E. franqueti*)	Dry	EBOV	-5.25956	21.40954	[39, 62]
Uganda	Kabango village	8/20/2007	26 y/o female		Wet	BDBV	0.7706	30.13041	[39, 63]
DRC	Luebo	11/27/2008	18 y/o pregnant female		Wet	EBOV	-5.35063	21.41646	[62, 64]
Uganda	Nakisamata village	5/1/2011	12 y/o female		Wet	SUDV	0.641297	32.71896	[65]
DRC	Isiro	June/2012			Wet	BDBV	2.772236	27.60828	[38, 66]

Table 1. (*Continued*)

Country	Location	Index case date*	Index patient	Potential source of spillover	Season†	Ebolavirus	Lat	Long	Reference
Uganda	Nyanswiga (Kibaale)	6/11/2012			Dry	SUDV	0.86599	30.92654	[39, 66]
Uganda	Luwero district	11/13/2012			Wet	SUDV	0.83175	32.58253	[39, 66]
Guinea	Meliandou	12/2/2013	2 y/o male	insectivorous bats (*M. condylurus*)	Dry	EBOV	8.616067	-10.0612	[38, 67]
DRC	Boende	7/26/2014	pregnant female butcher	monkey carcass	Wet	EBOV	0.284286	20.88509	[38, 68]

*Month shown for index cases without exact date

† Dry season = monthly precipitation < 60 mm, Lesser dry = 60 mm < monthly precip. <120 mm, Wet = monthly precip. >120 mm

‡Actual month was atypically wet or dry compared to long-term monthly mean

Figure 1a: Results of Stage 1 (Pigott et al. 2017)

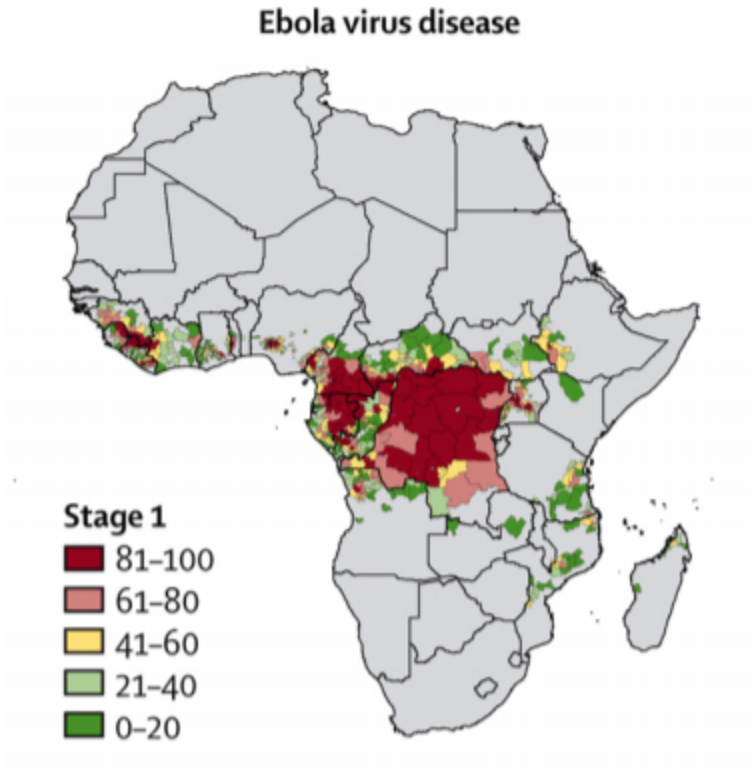


Figure 1b: Results of Stage 2 (Pigott et al. 2017)

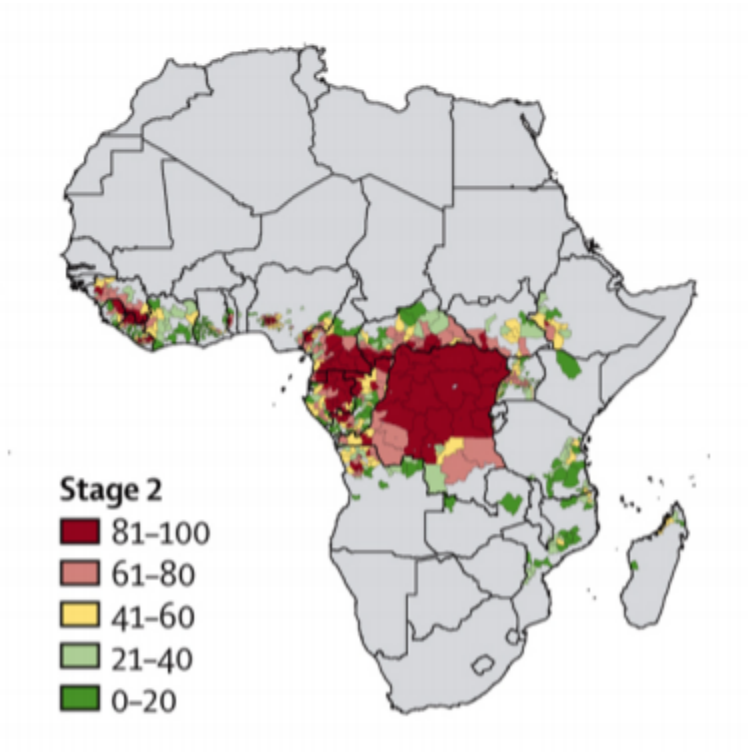
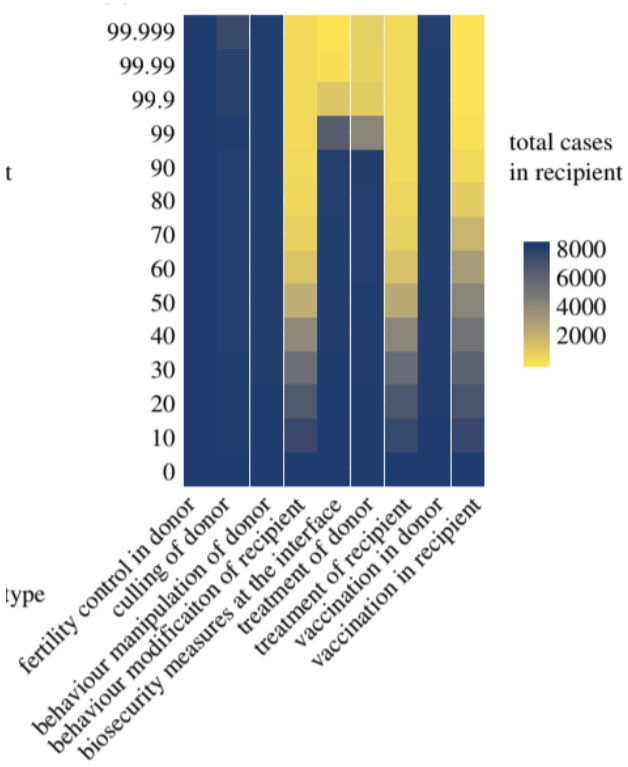


Figure 2: Heat map of the effects of different intervention intensities on total cases in the recipient (Sokolow et al. 2019)



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