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Ebola Response and Mitigation in Central and Western Africa: A Literature Review

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Abstract

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By Paige Gannon

Background Since 1976, Ebola has plagued Central and Western Africa causing twenty-two separate outbreaks resulting in over 15,000 deaths. Ebola, while a rare disease, has an average mortality rate of 50% however has been as high as 90%. Only in the last few years have there been major improvements in vaccine and therapeutic development. However, despite these improvements, Ebola outbreaks have continued. Since 2014, there have been nine separate outbreaks including both the longest and the deadliest on record. Fighting Ebola in Central and Western Africa must identify and address challenges to improve their response to this deadly disease.

Methods A narrative review of peer-reviewed and gray literature was conducted utilizing electronic databases PubMed, Embase, and Google Scholar and published after January 1st, 2016. Articles were screened to include geographical countries in Central and Western Africa and Ebola response related terms such as vaccine, surveillance, transmission, and diagnostics.

Results 55 total sources were included for review. These sources included 43 peer reviewed articles and 12 sources from government and NGO documents. The literature showed various challenges Central and Western Africa face in addressing Ebola. These challenges include weak health infrastructures that lead to decreased vaccination, treatment, and diagnostic testing, interruptions to contact tracing and surveillance due to civil unrest, new concerns of sexual transmission of the virus months after initial infection, and distrust towards local governments among the population.

Conclusion The literature highlighted several challenges that need to be addressed to improve Ebola response in Central and Western Africa, including strengthening the overall health infrastructure of Ebola affected countries, further improve vaccine and therapeutic development and distribution, and address perceptions and mistrust of the public.

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Table of Contents

Acronyms and Abbreviations

ADF	Ugandan Allied Democratic Forces
ALIMA	Alliance for International Medical Action
DRC	Democratic Republic of Congo
EVD	Ebola Virus Disease
INFS	Type 1 Interferons
MAPK	Mitogen-Activated Protein Kinase Inhibitors
MSF	Médecins Sans Frontières
PPE	Personal Protective Equipment
RDTs	Rapid Diagnostic Tests
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SOPs	Standard Operating Procedures
UNICEF	United Nations Children's Fund

Introduction

Background

In 1976, a case of hemorrhagic fever of unknown origin appeared in a village along the Ebola River in Zaire, or modern-day Democratic Republic of the Congo (DRC). This novel disease was later identified as the species *Zaire ebolavirus* classified under the genus *Ebolavirus*.[1] Since then, six different species of *Ebolavirus* have been identified, four of which have been known to cause disease in humans: *Zaire ebolavirus*, *Sudan ebolavirus*, *Taï Forest ebolavirus*, and *Bundibugyo ebolavirus.*[1] Of these four species, the most common and deadliest has been the originally discovered *Zaire ebolavirus*, a strain causing Ebola Virus Disease. Henceforth, *Zaire ebolavirus* will be referred to as Ebola. At the time of this writing, there have been twenty-two outbreaks of Ebola across Central and Western Africa, thirteen of which have occurred in or affected the Democratic Republic of the Congo (DRC).[2]

Ebola is a highly infectious disease spread through direct contact with bodily fluids of a person who is infected with the disease. Researchers suspect that exposure to bush meat leads to transmission from non-human primates to humans.[3] Ebola is believed to be zoonotic in origin, with bats being the most likely reservoir host, however this has yet to be confirmed.[2] Ebola, while a rare disease, has an average case fatality rate around 50% but this has varied from 25% to 90% across outbreaks and has resulted in approximately 15,000 suspected and laboratory confirmed deaths.[2] The incubation period of Ebola is 2 to 21 days and a person cannot spread the disease until they begin to develop symptoms.[2] It has also been shown that the disease may spread after the death of an individual and even from Ebola survivors several months after treatment. For survivors of Ebola, there is a risk of developing chronic symptoms that emulate autoimmune or inflammatory diseases such as systemic lupus erythematosus (lupus) or arthritis.

These morbidities can be debilitating and may lead to stigma and isolation from the community.[3]

Rapid identification and diagnosis are difficult due to Ebola's similar presentation to other endemic infectious diseases in Africa such as malaria and typhoid fever. The most common symptoms are fever, anorexia, headache, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea.[4] The World Health Organization (WHO) has released case definition recommendations that call for immediate notification to local public health officials of any patient who presents with onset of fever whose symptoms do not resolve from treatment for another disease and at least one of the following: bloody diarrhea, bleeding gums, purpura, or bleeding into the eyes or urine.[5] This specific case definition was put in place to help differentiate potential Ebola cases from other diseases and ensure immediate response to a potential Ebola outbreak.

Within the last 5 years, significant advancements in vaccine and pharmacological treatment have offered a potential solution for improving Ebola response in Central and Western Africa. However, despite these medical advancements, Central and Western Africa are still reporting Ebola outbreaks. In 2021 alone, three separate outbreaks occurred.[6] One of these outbreaks occurred in Guinea and two in the DRC. These outbreaks had the added challenge of co-occurring with the COVID-19 pandemic. In recent years, an increase in armed militia violence, particularly in the DRC, have hindered efforts to carry out mass vaccination and contact tracing, resulting in an increased risk of transmission of Ebola. Armed militia groups have been documented attacking health facilities and healthcare workers assigned to carry out surveillance.[7] Furthermore, distrust of the local government among the population has aided in decreasing compliance with vaccination and case reporting to local health facilities.[7] These challenges and other potential barriers need to be identified and addressed to successfully combat

Ebola.

Problem Statement

In the last few years, Africa has seen two of the longest and most fatal outbreaks of Ebola. Between 2014 and 2016 a total of 28,616 cases and 11,310 deaths were reported in Guinea, Liberia, and Sierra Leone.[1] A few years later, between 2018 and 2020, the DRC suffered 2,287 deaths and 3,470 total cases.[1] These two outbreaks alone account for nearly 90% of all deaths caused by the *Zaire ebolavirus* since it was first detected in 1976. Despite the advancements in technology and medical care, Ebola outbreaks are still occurring and with high case fatality rates. Due to the numerous changes in Ebola response, an in-depth look at current practices is needed to identify potential gaps so they may be addressed to strengthen surveillance and response.

Purpose Statement

This literature review is designed to explore challenges that are currently being faced in central and west Africa's ability to detect and respond to Ebola outbreaks. The aims of this literature review are to:

1. Explore potential barriers and logistical challenges currently faced in Ebola outbreak response within central and western Africa.
2. Discuss lessons learned in previous outbreaks and their implications for future response.
3. Identify potential solutions and make recommendations for public health interventions.

Significance Statement

The findings from this review of current barriers and challenges in addressing Ebola outbreaks in Central and Western Africa will be used to provide valuable information for the improvement of surveillance, prevention, and treatment of Ebola. Even with the development of both vaccines and medications, Ebola outbreaks are continuing to stress an already fragile healthcare infrastructure. Efficient and practical recommendations are needed to address these gaps and barriers to aid in the current fight against Ebola to prevent this deadly disease from continually wreaking havoc on society.

IRB Considerations

This is a literature review, and classified as not human subjects research, therefore no IRB review is needed.

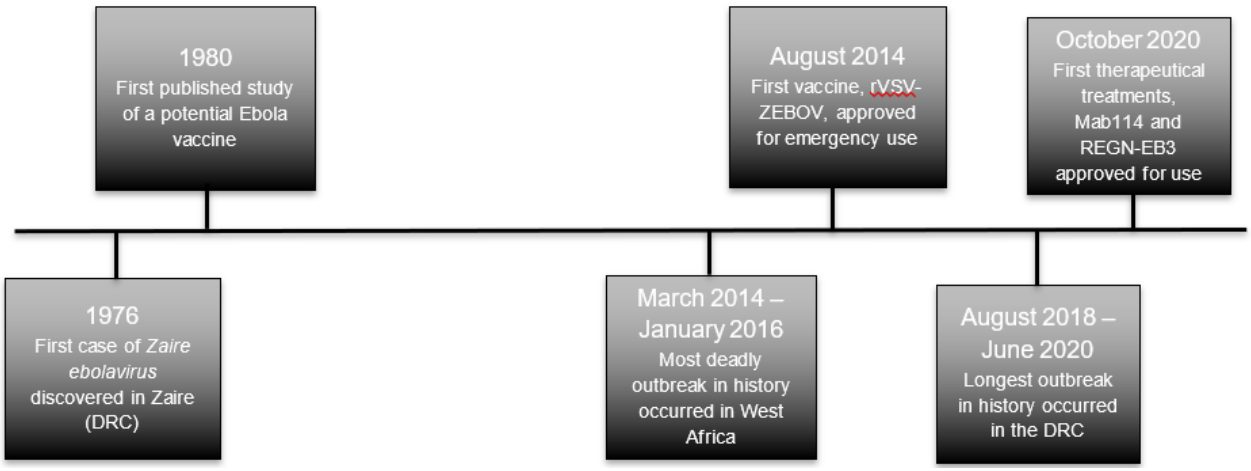
Methods

We conducted a narrative review of peer-reviewed and gray literature to gather information relating to the current Ebola response methods. PubMed, Embase, and Google Scholar were searched using the following location-based ("Democratic Republic of the Congo", "DRC", "Sierra Leone", "Liberia", "Guinea", "Africa", "West Africa", "Central Africa"), disease-focused ("Ebola" OR "Ebola Virus Disease") and response-related terms ("vaccine", "vaccine hesitancy", "treatment", "therapy", "refugee", "diagnostic", "case reporting", "surveillance", "response", "violence", "COVID-19"). A priori search terms focused on surveillance, transmission, diagnostic, and vaccine and evolved from topics discovered in the literature. Resources from the official websites from the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and Ministries of Health of the DRC and Sierra Leone were reviewed to provide additional information about current Ebola practices.

Article inclusion criteria include publication on or after January 1st, 2016, with full-text available, and published in English. 55 resources were reviewed and Zotero was used to manage references and citations.

Literature Review

Figure 1. Timeline of Major Ebola Events

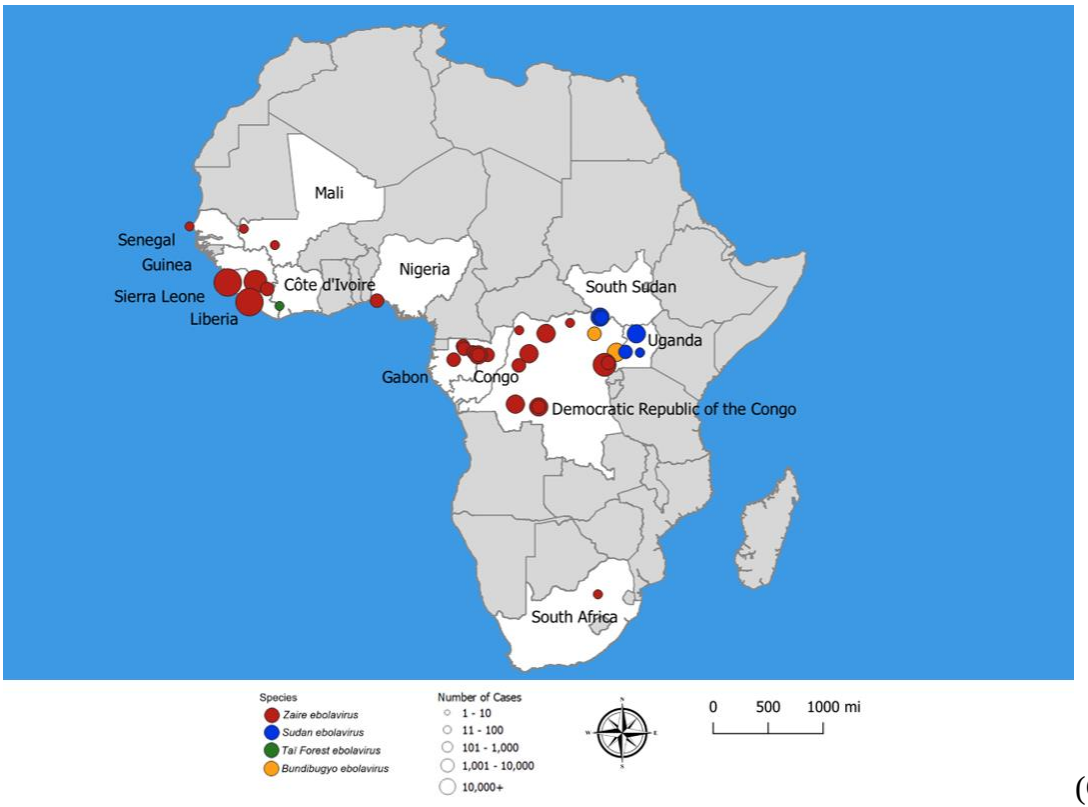


Ever since Ebola (*Zaire ebolavirus)* was first identified in 1976 in Zaire, modern day Democratic Republic of the Congo (DRC), this rare but often fatal disease has plagued much of Central and Western Africa. At the time of writing, twenty-two documented outbreaks of Ebola (Figure 2) in Central and Western Africa have occurred, totaling over 33,000 suspected or laboratory confirmed cases of Ebola resulting in approximately 15,000 deaths (Table 1).[1] Since 2014, nine outbreaks have occurred including two of the longest and deadliest on record. The 2014-2016 outbreak in West Africa, primarily affecting Guinea, Sierra Leone, and Liberia, resulted in 28,616 total cases with a case fatality rate of nearly 40%.[1] Isolated travel-associated cases were also identified in Europe and Asia.[8] This outbreak, characterized by its length and high case numbers, brought the Ebola crisis in Africa to a global scale and demonstrated the need for a stronger and more effective plan to fight Ebola. Two years later, the 2018-2020 outbreak in

the Democratic Republic of the Congo and Uganda reported 3,470 and a case fatality rate of 66%.[1] The Democratic Republic of the Congo in particular has been severely affected, with thirteen total outbreaks, nine of which in the last eight years.[1]

Only in the last few years have there been new and important developments in the fight against Ebola. The introduction of a vaccine and ongoing therapeutic trials have proved vital in containing Ebola. However, despite these improvements, Ebola outbreaks have continued, and case fatalities remain high. To allow us to address and evaluate the current situation, numerous factors must first be analyzed to determine the strengths and limitations in the current Ebola plan. These factors include disease surveillance and diagnostics, treatment, vaccinations, population perceptions, current health infrastructures, militia violence, and population migration, and recently, the ongoing COVID-19 pandemic.

Figure 2. Map of Ebola Outbreaks



(CDC, 2021)

Table 1. List of all Ebola Outbreaks with Total Case and Death Totals

Dates	Location	Total Cases	Total Deaths
September - October 1976	DRC (Zaire)	318	280
December 1994 - February 1995	Gabon	51	31
December 1994 - March 1995	Gabon	60	45
May - July 1995	DRC (Zaire)	315	254
January 1996 - April 1996	Gabon	31	21
July 1996 - March 1997	Gabon	60	45
October 2001 - July 2002	Gabon	65	53
October 2001 - July 2002	Republic of the Congo	59	44
December 2002 - April 2003	Republic of the Congo	143	128
November - December 2003	Republic of the Congo	35	29
April - May 2005	Republic of the Congo	12	10
August - November 2007	DRC	264	187
December 2008 - February 2009	DRC	32	15
March 2014 - January 2016	Liberia, Sierra Leone, and Guinea	28,616	11,308
August - November 2014	DRC	69	49
May - July 2017	DRC	8	4
May - July 2018	DRC	54	33
August 2018 - June 2020	DRC	3,470	2,287
June - November 2020	DRC	130	55
February - May 2021	DRC	12	6
February - June 2021	Guinea	23	12
October - December 2021	DRC	11	6

Adapted from WHO, 2022

Transmission

Ebola is a highly transmissible disease that spreads through direct contact with the bodily fluids of those who are symptomatic or indirect contact with contaminated surfaces. Ebola has been detected in bodily fluids such as blood, sputum, urine, sweat, semen, and breastmilk.[9] It has also been shown that the Ebola virus can survive outside the body on dry surfaces for several

hours, leading to a risk of transmission without proper use of disinfectants and cleaning protocols.[10] Despite Ebola being considered a zoonotic disease, a specific reservoir is unknown. The most likely candidate is the African fruit bats.[9] It is believed that these fruit bats infect non-human primates that in turn become bushmeat to be handled and sold, leading to spill-over into the human population.[11] Numerous animal surveillance studies have been conducted on bats native to the area, however none of them have been able to detect the Ebola virus in the wild.[12] The identification of this reservoir is needed to better understand the transmission cycle of Ebola to help inform preventative spillover measures.

A new and emerging concern out of the 2014-2016 outbreak was prolonged and recurrent infections caused by persistently infected survivors. Evidence from this outbreak demonstrated the virus could be detected in bodily fluids such as semen and vaginal secretions and remain transmissible up to 18 months after the onset of symptoms.[13] The possibility of Ebola transmission months after initial clinical presentation poses the risk for breakthrough cases after an outbreak has been declared over. The four most recent outbreaks, those in the DRC and Guinea, have all been suspected to be the result of persistent infection in an Ebola survivor or new infections transmitted sexually.[1]

Ebola cases in pregnant and postpartum women have demonstrated devastating results for both mother and infant. While limited studies have been conducted in this population, current data associates high rates of infant mortality whose mothers had Ebola either during pregnancy or the months following delivery. Ebolavirus has been demonstrated to transmit from mother to infant in utero, during delivery, or through breast milk months after maternal infection.[14,15] Pregnant women with Ebola are at high risk for preterm labor, spontaneous abortion, and still-birth. For neonates born preterm to mothers with Ebola, rates of survival have been poor. For

mothers currently breastfeeding, it is recommended that those who have suspected or confirmed cases of Ebola, cease breastfeeding and seek alternative nutrient sources for their infant for at least 6 months after onset of symptoms.[16] This poses nutritional and food security challenges where it is common for prolonged breast feeding to occur.

A major contributor to Ebola transmission is the use of traditional burial practices. These practices often include washing of the body, touching of the face, wrapping of the body, and in some cases, laying over the body.[17] The close contact with the deceased and potential contact with bodily fluids can lead to transmission of the virus. The WHO has provided guidelines for safe burial practices for those who have died of Ebola. These guidelines attempt to limit potential exposure for bodily fluids post-mortem as patients remain contagious for several days after death. These guidelines encourage post-mortem preparation of the body occurring in health facilities by trained staff and the restriction of familial viewing of the body.[18] However, it is estimated that between 28% and 43% of deaths occur outside of health facilities where families may choose to perform these burial practices without proper precautions. The challenge of these guidelines is to properly respect local rituals and cultures while also ensuring the lowest risk of transmission to the community. Organizations such as the Red Cross have assisted local communities in performing safe, yet dignified burials.[18]

Nosocomial infections, or infections that occur within health facilities, have been an ongoing concern since the first discovery of Ebola. Nosocomial infections were reported in patients seeking treatment for another ailment, patient visitors, and healthcare workers. Healthcare workers are among those most at risk for exposure and subsequent infection of Ebola due to close and prolonged contact with infected patients. During the 2018-2020 outbreak in the DRC, 579 of the 3481 (16.6%) confirmed cases were nosocomial in origin with a case fatality

rate of nearly 62%.[11] High rates of nosocomial infections have been in part to poor infection control practices and scarce personal protective equipment, especially in more rural and remote villages.[19] Among healthcare workers, lapses in infection control practices were demonstrated by limited handwashing and disinfectant facilities as well as the lack of standard operating procedures for facilities receiving and caring for suspected and confirmed Ebola cases.

Surveillance

Early presentation of Ebola is often nondescript and mimics that of other diseases endemic to the area such as malaria or dengue fever. These symptoms often result in a delay in identification of potential Ebola cases. Furthermore, clinical presentation may also be altered or masked by comorbidities such as HIV or Tuberculosis. The incubation period of Ebola ranges from 2-21days with an average time of 12 days.[20] Symptoms typically begins with non-specific symptoms such as fever, malaise, fatigue, and body aches. Within a few days, symptoms typically progress with gastrointestinal symptoms including nausea, vomiting, and diarrhea, as well as respiratory symptoms such as cough and dyspnea. In more severe cases, hemorrhagic bleeding, shock, organ failure, and sudden death can occur.[20]

In 1999, the WHO issued its first case definition for Ebola that included the following criteria: “body temperature greater than or equal to 38.3 degrees Celsius, or 101 degrees Fahrenheit, severe illness with no predisposing factors for hemorrhagic manifestations, no established alternative diagnosis, and at least two of the following symptoms: hemorrhagic symptoms that presents as a purple rash, epistaxis, hematemesis, hemoptysis, rectal bleeding or blood in stools, or other signs of bleeding”.[9] This definition was standard use until 2014, when WHO revised the Ebola case definition to be: “fever with no response to treatment of usual causes of fever in the area, and at least one of the following: bloody diarrhea, bleeding from

gums or skin, or bleeding into the eyes or urine."[5] This broader definition was introduced due to estimation of only 58% of Ebola patients meeting the previous case definition.[9]

Timely and accurate contact tracing is imperative for effective Ebola surveillance and response. The WHO guidelines for contact tracing strongly recommend that all contacts of suspected and confirmed cases of Ebola be put under surveillance for 21 days.[21] However, actual contact tracing efforts demonstrate a lapse in implementation. During the first year of the 2018-2020 DRC outbreak, only 12,777 of the more than 88,000 identified contacts were under current surveillance. However, follow-up rates of these contacts were around 80%. Difficulties in contact tracing lie in poor record-keeping at community clinics, distrust among the community and their reluctance to cooperate with local health officials, and a highly mobile population caused by displacement.[22]

Diagnostic Testing

At the start of the 2014-2016 outbreak in West Africa, there were no official guidelines for an approved method of diagnostic testing.[23] This meant that the majority of cases were initially diagnosed solely based on clinical presentation. This outbreak highlighted the need for standardization of reliable diagnostic tools. Due to the sporadic and unpredictable nature of Ebola outbreaks, the challenge with developing these diagnostic tests is the limited amount of time and cases to conduct diagnostic trials.[23] Currently, there are two types of diagnostic tests for Ebola. The current gold standard for diagnostic testing is the Reverse Transcription Polymerase Chain Reaction (RT-PCR) test.[24] However, these tests require highly specialized equipment that are currently limited to only a few laboratories in Central and Western Africa. The need for these samples to be transported to a different facility further delays identification and treatment of cases. Additional challenges with RT-PCR tests stem from storage and shipping requirements of

the assays used in tests. These assays require variable storage temperatures that may be hard to regulate in areas without consistent electricity or proper cold-chain storage.

Alternatively, the antigen-based rapid diagnostic tests (RDT) may offer a solution to this delay in diagnosis. These tests only require a small drop of blood, obtained via fingerstick. The tests allow for more widespread use as they require little training to perform and operate. These tests are often used in more rural and remote communities due to the quick turnaround time and the limited amount of equipment and training needed. These types of tests are also less prone to storage challenges compared to traditional RT-PCR testing. However, these rapid tests have demonstrated lower sensitivity compared to RT-PCR tests. The sensitivity of RDTs range from 65% to 84% and specificities 98% to 100% when using whole blood samples.[24] These tests are primarily utilized to help rule out cases or triage cases for the potential need for further diagnostic testing via PCR testing.

Treatment

Before the 2014-2016 outbreak in West Africa, there were no approved therapeutic treatments for Ebola and there were limited clinical care trials to determine the efficacy of investigational therapies.[24] The 2018-2020 outbreak in the DRC laid the groundwork for field trials of therapies including the antiviral drug Remdesivir, and three monoclonal antibodies drugs, MAb114, ZMapp, and REGN-EB3.[24] The results of these therapies showed that the MAb114 and REGN-EB3 therapies demonstrated lower 28-day mortality rates with 35.1% and 33.5% respectively compared to 49.7% of ZMapp and 53.1% from Remdesivir.[24,26] Of note, most of the deaths occurred within 10 days of treatment, prompting the success of these agents dependent on finishing the treatment course. Neither of these studies reported mortality rates for those who did not receive treatment with one of these agents. These results yield promising

results, but further trials are needed to identify a standardized course of treatment. Outside of these field trialed therapies, another candidate is currently awaiting approval to conduct phase III trials. Favipiravir, a T-705 molecule, is a broad-spectrum antiviral that has been shown to reduce viral load in infected patients, however these results have been limited and need further trials to understand efficacy of this treatment.[27]

A small trial in Liberia and Guinea aimed to observe the effects Remdesivir had on persistent seminal Ebola RNA, a current problem in addressing recurrent Ebola infections. This study demonstrated that completing a 5-day course of Remdesivir may reduce the presence of Ebola RNA in the semen of Ebola survivors months after treatment.[25] The results are promising in helping to address the growing concern of case breakthrough from sexual transmission of the disease months later.

Supplemental therapy is important to treat or correct abnormalities caused by disease progression. A major complication seen in patients during recent outbreaks have been renal injury and metabolic imbalance, both of which require intensive and often resource heavy therapy to correct.[24] Other therapies include hydration either intravenously or orally to prevent dehydration, correction of electrolyte abnormalities, supplemental oxygen administration, intravenous vasoactive medications for severe hypotension, and nutritional supplementation.[22]

Beyond these field trialed therapies, other immunotherapeutic options have been explored. Used for broad spectrum antiviral therapy, type 1 interferons (INFs), have demonstrated the ability to delay mortality, in Ebola infected nonhuman primates.[28] This discovery may prove useful as an adjunct therapy to prolong the time available for treatment but further research is needed to understand its exact mechanism in treating Ebola. Another investigation that was pursued was the use of specific antibodies to target T-cell immunoglobulin

to prevent the entry of the Ebola virus into the cells, disrupting the infectious process. However, there have currently been no significant studies demonstrating this effect.[28] Lastly, mitogen-activated protein kinase inhibitors (MAPK) have been shown to block Ebola virus replication within human antigen presenting cells.[27] Unfortunately, none of these approaches have led to a viable clinical trial leaving the future of Ebola treatment in need of further research.

Vaccines

During the 2018-2020 Ebola outbreak in the DRC, the first wide-scale use of a vaccine outside of clinical trials was used. The rVSV-ZEBOV vaccine manufactured by Merck is a single dose, live-attenuated, recombinant vaccine that has demonstrated variable, yet successful, protection in individuals both pre- and post- Ebola exposure. This vaccine was administered to all eligible adults in the DRC, including pregnant and lactating women, as well as to children aged 6 months and older. During this outbreak, over 303,000 people were vaccinated. Estimated vaccine efficacy for preventing infection and transmission is 97.5%.[29] Post-vaccination studies estimate antibody titers are detected up to one to two years later.[30] This finding has prompted the possibility of a second dose or booster to enhance immunity. This vaccine was administered in a "ring vaccination" technique that involved vaccination of the primary infected person, vaccination of secondary contacts, or those who had had direct contact with the infected person, and vaccination of persons in contact with the secondary contacts.[4] The success of this technique requires accurate and efficient contact tracing to ensure that enough people are vaccinated to interrupt the transmission of Ebola. Conversely, the ring vaccination technique can strengthen contact tracing efforts by providing a method for identifying potential cases.

To help supplement the Merck vaccine, the DRC's Ministry of Health announced that a second vaccine would be authorized for investigational use during the 2018-2020 outbreak. The

two dose Ad26-EBOV/MVA-BN-Filo vaccine, manufactured by Janssen was primarily utilized prophylactically vaccinate healthcare workers in areas that did not have active Ebola transmission.[30] This vaccine was approved for use in persons older than 1 year of age. The challenge with this vaccine is the requirement of two doses to achieve adequate immunity. This vaccine begins with one dose of the Ad26-EBOV with the MVA-BN-Filo administered 60 days later. While the first dose does offer some protection, it wanes quickly, resulting in the need for the second dose to boost immunity and offer protection for at least a year. This may pose a problem for highly transient or mobile populations. For these populations, such as refugees or migrant workers, it may be difficult to receive the second dose due to relocating where the vaccine is not available.

The results from clinical trials and the investigational use during the 2018-2020 outbreak has led to the Merck vaccine being approved and registered for use by national health authorities in the DRC, Burundi, Ghana, and Zambia.[31] Currently, both of these vaccines are only used during outbreak response and not as a routine measure.[32] Currently, mass vaccination of the entire population at risk is currently not feasible due to limited vaccine supply and limited healthcare workers to deliver the vaccines. The ring vaccination technique has raised ethical concerns over the selectivity of who is eligible for vaccination. One argument in favor of the ring vaccine technique, especially early on, was that it served similarly to a placebo study with unvaccinated people as the control group to measure the effectiveness of the vaccine.[52] Additionally, since people are not infectious until they are symptomatic, the ring vaccination technique provides an opportunity to interrupt transmission by vaccinating contacts before they develop symptoms.

Health Infrastructure

Many Ebola affected countries, most notably the DRC, Sierra Leone, Guinea, and Liberia, rank among the lowest in multiple healthcare quality measures. Until recently, these countries did not have any recommended Ebola infection control practices leading to varying, and often negligible, protection. Due to this lack of guidance, WHO and CDC worked with national Ministries of Health to create recommendations including proper PPE use, the separation and isolation of positive Ebola patients, and other infection control practices.[33] Local medical facilities are often ill equipped to appropriately address potential and confirmed Ebola cases. During the 2014-2016 outbreak in West Africa, medical supplies and PPE quickly ran out due the combination of high case load and lack of an established supply chain. Other health services such as maternal care was interrupted due to health facilities priority in addressing Ebola. Further, the sheer number of cases during this outbreak quickly over run medical facilities ability to house and isolate Ebola cases.[34,35] In outbreak situations, these countries rely heavily on external aid from organizations such as Médecins Sans Frontières (MSF), UNICEF, or the Red Cross to provide funding, infrastructure, and workforce.

A major problem noted among all Ebola affected countries is the significant shortage of healthcare workers, with an estimated workforce density ranging from 1.5 to 3.7 per 10,000 people compared to countries like the United States who have an average of 117 healthcare workers per 10,000 people.[34,50] Not only did this limited workforce create significant delays in diagnosing and treating cases, but the lack of proper Ebola education and training resulted in poor infection control practices further contributing to the spread of Ebola. This lack of training often led to the misuse of PPE, such as the inconsistent use of gowns, masks, and gloves. Proper environmental cleaning protocols were also lacking to guide decontamination of rooms and equipment.

Population Perceptions

Addressing and containing Ebola outbreaks is heavily reliant on community participation and acceptance of recommended guidelines and procedures. While there have been limited studies conducted specifically aiming at the population's perception of various Ebola outbreak interventions, some common themes have been identified. One of the major barriers assessed in the literature is the population's distrust of local government and health authorities. Two studies conducted in the DRC highlighted the differences in public perceptions in rural versus urban areas of the country. Urban populations reported around 83% approval and trust of local authorities and 85% expressed interest in receiving the Ebola vaccine.[36] In rural populations, where the majority of Ebola cases are reported, only 40% of the population trusted the local authorities and even more concerning, over 25% of the population did not believe the Ebola outbreaks were a concern.[37] One hypothesized reason for this discrepancy is the need for increased military presence at health clinics in rural areas to help protect the facilities from militia attacks. This presence may deter the local community from utilizing these services due to the perception of coercive government control over the population.

Similarly, in Liberia and Sierra Leone, a major deterrent among the population was distrust of government authorities and their response during Ebola outbreaks.[38] This survey indicated that a major barrier among the community was low perceived risk of Ebola. Responses varied from disbelief in the existence of Ebola to believing that Ebola was not a direct risk to them because they did not know of anyone who had contracted the disease. A study in Guinea echoed these concerns: nearly 83% of survey respondents indicated their perceived risk of acquiring Ebola as low or none.[39] When responders started arriving at these local communities, it was perceived by the population that the government was trying to instill control over the area, further contributing to distrust of the government.

Across all of Central and Western Africa, the introduction of an Ebola vaccine has been received with mixed responses. While there are many that freely accept the vaccine as a useful and effective tool, others remain skeptical. Some of the major themes among vaccine hesitancy have been the acknowledgement of death of individuals from Ebola despite receiving the vaccination, risk of taking a newly developed vaccine, and worries the vaccine may be a tool used by the local governments to control and suppress the community.[40] These rumors could have detrimental effects on not only the effectiveness of the Ebola vaccine, but on all Ebola response measures. A study in Sierra Leone found that many refusing to receive the vaccine believe the Ebola crisis was made up by foreign governments to decrease the population of West Africa.[41] These concerns have decreased vaccine uptake, especially in more rural settings. Vaccine promotion has focused heavily on education to dispel rumors and on community engagement to encourage the population to receive the vaccine.[40]

Militia Violence

Militia violence, particularly in the North Kivu and Ituri regions of the DRC, has heavily impacted the Ebola response. These regions have over 75 known militia groups, with Ugandan Allied Democratic Forces (ADF), the Mai-Mai Kilalo, and the Islamic State militant group among the largest and most violent.[42] During the 2018-2020 outbreak in the DRC, 420 healthcare facilities and clinics were attacked resulting in the death and injury of not only those working in the facility, but also in people there to receive care.[43] One study assessed transmission could increase by as much as 60% when multiple violent events occur within a three-week span.[44] Further backing up this hypothesis was a study analyzing the average reproductive number of one case of Ebola, or how many people will become infected due to one infected person. The average reproductive number in nonviolent areas range from 0.81 to 1.08.

In areas that reported a violent event, the average reproduction increased to 1.12 to 1.23 in the three weeks following the event.[45]Deliberate attacks on healthcare workers and healthcare facilities have severely impacted disease surveillance and delayed case reporting. These attacks halted any immediate attempt in contact tracing for risk of further attacks. During the 2018-2020 outbreak, it was estimated that militia attacks resulted in case reporting delays from a high of 17.4 weeks to a low of 1.7 weeks.[46] Retrospective analysis estimates that the militia attacks in these regions severely hindered contact tracing attempts, with only an estimated 20% of contacts being traced and followed up.[42]

These militia attacks in the region have also created large population displacements of those fleeing these areas of conflict. These mass migrations could further spread Ebola to other regions of the DRC or even across national borders. Refugee camps that may be established may not have proper medical equipment to handle Ebola cases and may not have the capacity for vaccination due to the unstable safety in the region. During the 2018-2020 outbreak, Uganda and Rwanda experienced a high influx of refugees from the DRC due to the civil unrest and insecurity in the country. It is estimated that over 319,000 people were displaced because of local violence within the first month of the outbreak.[36] This migration highlighted the need for cooperation between the countries to strengthen border health infrastructure.

Impact of COVID-19 on Ebola Outbreaks

Since 2020, not only have Central and Western Africa battled multiple Ebola outbreaks, they have also had the added burden of the COVID-19 pandemic. Despite the differences in transmission of the two diseases, similarities in addressing the two highly infectious diseases lie in the need for rapid detection, treatment, and contact tracing. Many of the health policies and standard operating procedures (SOPs) in place due to Ebola outbreaks were adapted to address

COVID-19 cases, most notably the use of the 'ring vaccination' technique utilized in the Ebola response.[47] This technique helped prevent the spread of infection by identifying those at high risk and those in constant close contact with them and vaccinating them. Contact tracing procedures developed in the Ebola response were adapted for use in COVID-19 contact tracing. In areas affected actively by Ebola, COVID-19 contact tracing often took place at the same time.

Despite having some response measures already in place, addressing both the COVID-19 pandemic as well as five intermittent Ebola outbreaks have heavily impacted already burdened systems. Many of the Ebola affected countries that rely on external aid both financially and physically have had their resources reduced or completely cut off.[48] This abrupt decrease in support leaves already unstable health infrastructures vulnerable. At the time of writing, there are currently no published literature or studies on the specific effects the COVID-19 pandemic has had on Ebola response.

Discussion

The review of current literature highlights specific challenges that have hindered previous response efforts and threaten the future success of Central and Western Africa's Ebola response if they are not addressed. Many of the presented advancements lay the framework for a stronger and more efficient system, however further research and development are required to achieve this goal. These improvements include strengthening local and national health infrastructures, further development of treatment therapies, addressing the risk of sexual transmission of the disease, creating systems for efficient vaccine delivery, and addressing perceptions of mistrust

among the general population. Identifying the challenges in these sectors will guide recommendations for improving Central and Western Africa's Ebola response.

Further Development of Treatment Therapies

Recent research has demonstrated that MAb114 and REGN-EB3 yielded promising results in creating a standardized recommendation for treatment therapies. However, these treatments were only statistically effective in those with lower viral loads.[24,26] Additionally, both of these therapies are currently offered only through intravenous injection which often require multiple supplies and specialized storage options. This means administration can only take place at medical facilities with those capabilities. Further research is needed to find even more effective therapies that can be administered outside of medical facilities such as community clinics.

In recent years, sexual transmission of Ebola through semen months after treatment has been the cause of numerous Ebola cases.[1,18] This potential route of transmission requires multiple interventions to decrease the risk of subsequent infection. Currently, research has demonstrated Remdesivir may have the ability to lower Ebola RNA over time.[18] Currently only a five-day course of Remdesivir has been studied, but further research is needed to determine a potential standard for treatment. Education needs to inform the population of this risk and provide recommendations to decrease risk of transmission. These recommendations may include abstaining from all types of sex or the use of a condom when engaging in sexual activities with a person who has recovered from Ebola within the last year.

Improving Vaccination Strategy

The recent introduction of two viable vaccines, the single dose rVSV-ZEBOV and the two dose Ad26.ZEBOV/MVA-BN-Filo gives Ebola response more tools for interrupting the

transmission of Ebola. Ebola vaccines are only approved for use during outbreak situations and not approved for routine immunization due to lack of supplies.[32] However, research has shown that immunity from the vaccine wanes after two years and individuals may require additional doses to remain protected.

Current vaccine strategies rely on the ring vaccination technique. This method faces many logistical challenges as it relies on accurate case contact tracing, something that is not always feasible in certain settings, in particular areas prone to civil unrest and violence such as the DRC. This instability leads to attacks on healthcare workers attempting to contact trace or vaccinate. This can lead to numerous missed vaccinations. High distrust of healthcare workers and contact tracers may leave individuals wary of identifying potential contacts and highly mobile populations create challenges in tracking down and vaccinating an identified contact. Additional concerns raise the ethical implications of vaccinating only certain people. Many may feel ostracized by the selectivity of vaccination and lead to further distrust among the population.[52]

While it is currently not feasible to vaccinate all at-risk populations, a hot-spot strategy may help decrease potential transmission. This method utilizes geospatial and epidemiological data to predict potential outbreak regions to initiate vaccination programs before an outbreak has a chance to occur.[32] This strategy decreases the need for intensive contact tracing and creates an equal opportunity approach for vaccines. This may also help decrease costs by limiting the resources needed to contact trace across the region. This strategy also ensures that everyone in the at-risk regions becomes immunized.

Outside of outbreak situations, routine vaccinations against Ebola should be considered for certain at-risk persons. These can include healthcare workers, transportation services, and

traditional healers. These persons come in contact with multiple people from all over the region and can serve as a potential conduit of transmission. Vaccination of this population may significantly decrease the spread of Ebola to different villages or regions.

Improving Health Infrastructure

Strengthening health infrastructure should be of great importance to not only create or upgrade medical facilities but also to increase the number of healthcare workers to adequately staff these facilities. Ebola requires special treatment rooms to prevent further transmission to other patients. These rooms should be private and have a way to close them off to other areas of the facility. Healthcare workers also need improved access to personal protective equipment to prevent rationing of supplies. Improvements to these medical facilities will not only improve treatment capabilities but also help reduce potential nosocomial infections of other patients due to poor infection control practices.

The Alliance for International Medical Action (ALIMA) first helped address these needs by creating what they called the "CUBE".[49] The "CUBE" is an easily deployable plastic structure that can house individual Ebola patients. These structures have one wall with arm slots that allow the healthcare worker to interact with the patient without entering the space, decreasing risk of transmission. While these structures present a possible solution for improving Ebola medical facility capacity, they remain extremely limited in quantity with currently only 16 cubes deployed to the DRC.[49]

In addition to the improvements of the medical facilities, there needs to be a substantial increase in properly trained healthcare workforce. Currently, outside organizations make up most of the current workforce but are typically only deployed once an outbreak has been detected.[34] An increase in buy-in and training of local healthcare workers is needed to not only help treat

Ebola patients, but also to help with contact tracing, case identification, and vaccination programs. Training related to proper infection control practices and case detection protocols need to be created and disseminated often to ensure these healthcare workers have the most up to date recommendations and guidelines.

Addressing Population Perceptions and Mistrust

Many of the Ebola-affected countries have high levels of mistrust of the government and healthcare workers in the region. This high level of mistrust has hindered vaccination uptake, contact tracing, and case identification. Government mistrust has led to numerous civil wars and the formation of militia groups. This fear and mistrust have played a large role in prolonged transmission of Ebola. In order to improve this trust, community leaders need to work with government officials and aid organizations to formulate the best way to approach different regions. In the DRC in the early stages of the COVID-19 pandemic, social scientists and local community leaders were enlisted to understand local context, create appropriate target measures for the population, and encourage transparency of government policies.[54]

The employment of Ebola survivors is also imperative for trust building. Ebola survivors can help educate local populations about the risks and dangers of contracting the disease. This can give others, including Ebola skeptics, a chance to speak first hand to someone in their community who had been infected to combat the notion of the government lying to them or hiding information. UNICEF has been the leader in employee Ebola survivors to help spread their story to their local community. This approach has already proved successful and should be

broadened to a wider scale to reach more individuals, especially in regions where healthcare workers and aid organizations face scrutiny.[53]

Vaccine hesitancy needs to be addressed to ensure these vaccines make it to the population. Curbing vaccine hesitancy begins with providing education and quickly dispelling rumors. Engagement of trusted community or political leaders are needed to ensure correct information is disseminated appropriately. These leaders can make sure the information is culturally sensitive and delivered in a way that will be more acceptable to the population. Those from external aid organizations should communicate with the leaders to formulate a communication and vaccination strategy that will be most effective for the region they are in.

Conclusion and Public Health Implications

Examining literature about current challenges faced in Central and Western Africa is crucial in identifying future Ebola response plans. In recent years there have been numerous medical advancements in the form of two viable vaccines and two therapeutic treatments, however current challenges have hindered their potential. Future investment should be made in improving healthcare infrastructure to support the capacity for Ebola treatment, the continual development of effective medications, developing a more comprehensive vaccination strategy, and addressing and building trust among the population. In Liberia, after the 2014-2016 outbreak, the development of a community health program aimed to recruit and train healthcare workers to substantially increase their work force. This program also focused on developing a centralized national monitoring and evaluation system while also improving community-based surveillance for infectious diseases. These implementations greatly improved Liberia's overall health infrastructure by creating a stronger workforce.[55]

Investment in improving health infrastructure will not only improve Ebola response, but also strengthen Central and Western Africa's health systems as a whole. Identifying and securing stable supply chains will ensure that adequate resources such as PPE or vaccines are always available. Building health facilities in more remote regions can help improve access to necessary medical care. Standardizing educational protocols will improve healthcare workers knowledge and preparedness. All of these implementations will not only help in outbreak response, but also in providing routine medical care, treatment for HIV and AIDS, and maternal and child care. It is important to note that each country faces different challenges, and it is not feasible to have a "one plan fits all" strategy but many of the Ebola-affected countries do endure similar challenges paving the way forward for solutions to be shared to help decrease the burden Ebola has on Central and Western Africa.

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Tables and Figures

Figure 1. Timeline of Major Ebola Events

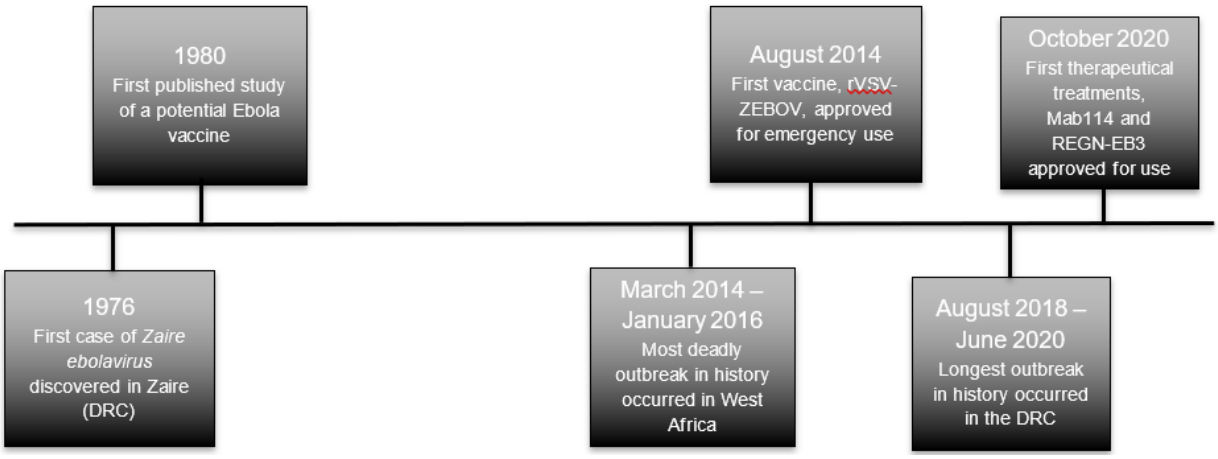
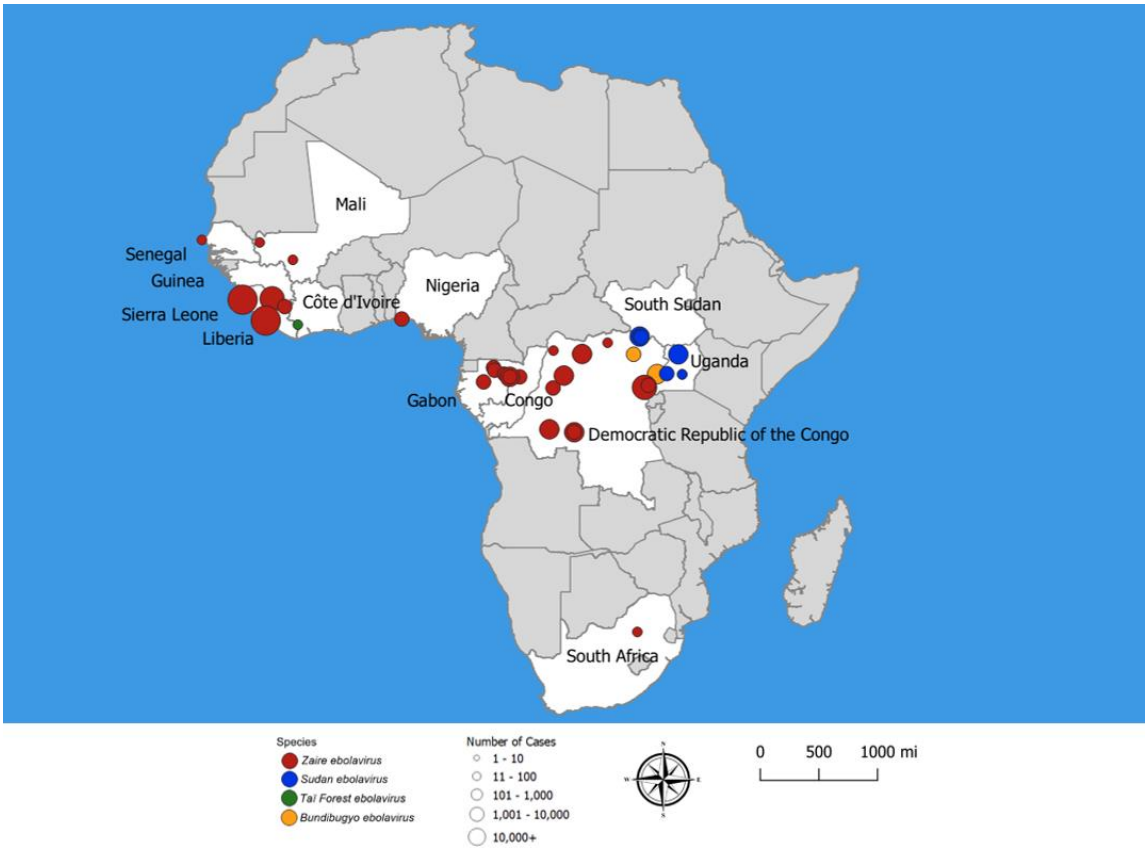


Figure 2. Map of Ebola Outbreaks



(CDC, 2021)

Table 1. List of all Ebola Outbreaks With Total Case and Death Totals

Dates	Location	Total Cases	Total Deaths
September - October 1976	DRC (Zaire)	318	280
December 1994 - February 1995	Gabon	51	31
December 1994 - March 1995	Gabon	60	45
May - July 1995	DRC (Zaire)	315	254
January 1996 - April 1996	Gabon	31	21
July 1996 - March 1997	Gabon	60	45
October 2001 - July 2002	Gabon	65	53
October 2001 - July 2002	Republic of the Congo	59	44
December 2002 - April 2003	Republic of the Congo	143	128
November - December 2003	Republic of the Congo	35	29
April - May 2005	Republic of the Congo	12	10
August - November 2007	DRC	264	187
December 2008 - February 2009	DRC	32	15
March 2014 - January 2016	Liberia, Sierra Leone, and Guinea	28,616	11,308
August - November 2014	DRC	69	49
May - July 2017	DRC	8	4
May - July 2018	DRC	54	33
August 2018 - June 2020	DRC	3,470	2,287
June - November 2020	DRC	130	55
February - May 2021	DRC	12	6
February - June 2021	Guinea	23	12
October - December 2021	DRC	11	6

Adapted from WHO, 2022