# Ebola: Anatomy of an Epidemic

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## Keywords

Ebolavirus Zaire, West Africa, disease outbreaks, epidemiology, global health security

## Abstract

As of the end of March 2016, the West Africa epidemic of Ebola virus disease (Ebola) had resulted in a total of 28,646 cases, 11,323 of them fatal, reported to the World Health Organization. Guinea, Liberia, and Sierra Leone were most heavily affected, but Ebola cases were exported to several other African and European countries as well as the United States, with limited further transmission, including to healthcare workers. We review the descriptive epidemiology of the outbreak, novel aspects and insights concerning the unprecedented response, scientific observations, and public health implications. The large number of Ebola survivors has highlighted the frequency of persistent symptoms and the possibility of virus persistence in sanctuary sites, sometimes leading to delayed transmission. Although transmission appears to have ceased in 2016, the West Africa Ebola epidemic has profoundly influenced discussions and practice concerning global health security.

## INTRODUCTION

The West Africa epidemic of Ebola virus infection that started in Guinea in December 2013 and came to the world's attention three months later (1) has been a signature event in global health. Although transmission was interrupted in the three heavily affected West African countries—Guinea, Sierra Leone and Liberia—over the course of 2015 (2), further clusters of infection have occurred, initiated by survivors who may harbor the virus for many months after illness (3). In this article, we give an overview of the epidemic and discuss its scientific and public health implications. The West Africa epidemic of Ebola virus disease (Ebola) has not only changed the perception of what was once seen as an obscure tropical infection (4) but has also uniquely highlighted the challenges of global health security in the twenty-first century and influenced how we address them.

## DESCRIPTIVE EPIDEMIOLOGY

According to the World Health Organization (WHO), the West Africa epidemic resulted in a total of 28,646 cases of Ebola, 11,323 of them fatal, as of the end of March 2016 (5). In Africa, apart from in the three heavily affected countries, Ebola cases were recognized in Mali, Nigeria, and Senegal. Outside of Africa, Ebola was imported into several European countries and the United States by infected healthcare workers repatriated and by travelers incubating illness. Hospital transmission to staff caring for infected patients occurred in Spain and the United States.

The first reports of Ebola were in late March 2014, initially in Guinea and then in Liberia (**Figure 1**) (1, 6). Retrospective investigations suggested that the first case occurred in a two-year-old child in the Forest Region of Guinea in late December 2013. Within three weeks, three generations of cases had occurred and Ebola had reached Gueckedou, a local urban center, later spreading

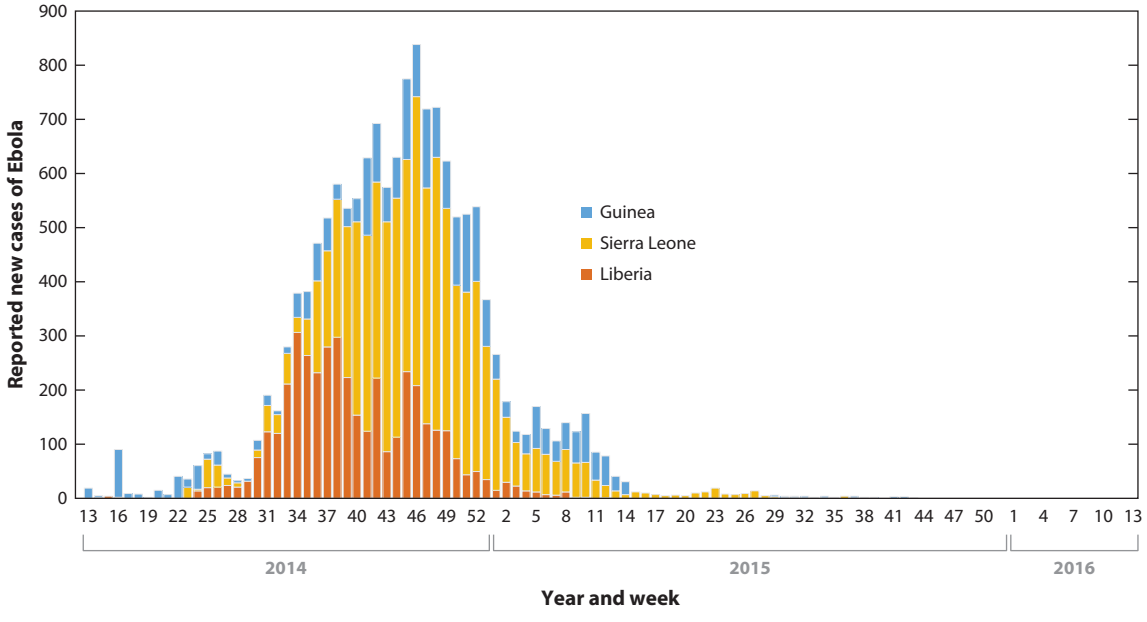


**Figure 1**

Reported new cases (probable and confirmed) of Ebola in Guinea, Sierra Leone, and Liberia, per week from March 2014 through March 2016. Data are from country situation reports.

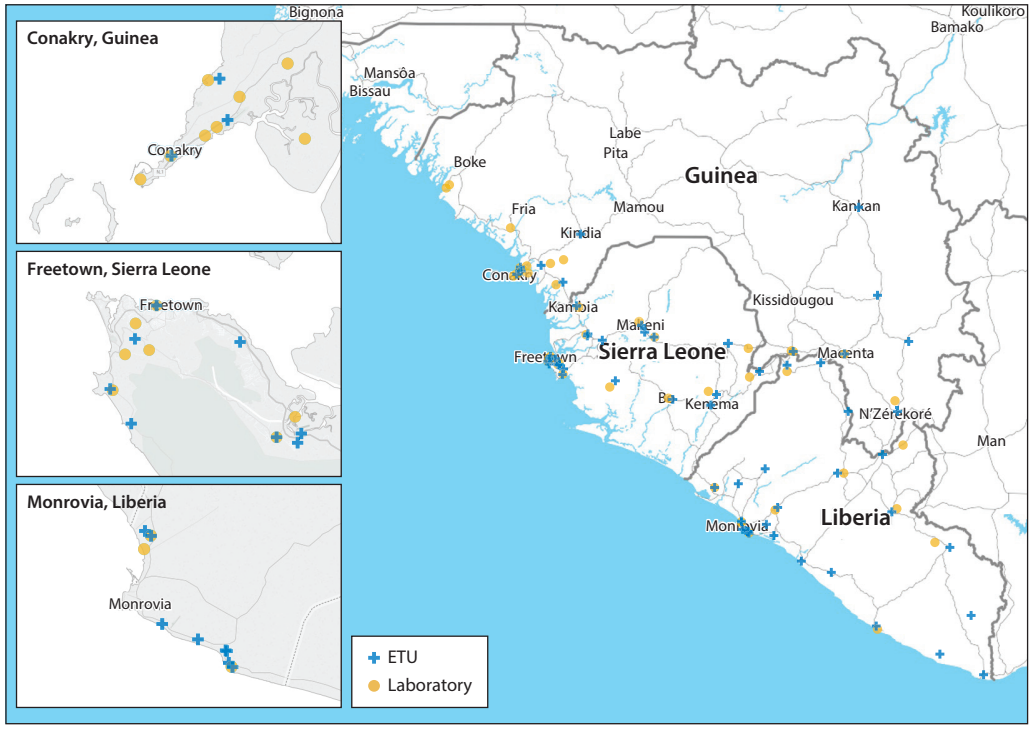


**Figure 2**

Ebola Treatment Units (ETUs) and laboratories testing for Ebola in Guinea, Sierra Leone, and Liberia, from March 2014 through March 2016.

to the national capital Conakry (7). Cases were first recognized in eastern Sierra Leone in May 2014 (8). These initial events determined subsequent epidemic spread from the original epicenter, located near where the borders of the three countries meet, to large areas across the subregion.

Although WHO announced on January 14, 2016, that Ebola transmission in the three countries had ceased (2), two further clusters have occurred subsequently, one each in Sierra Leone and Guinea, the latter resulting in spread to Liberia (9). The total numbers of Ebola cases and deaths reported by the end of March from Guinea, Liberia, and Sierra Leone were 28,616 and 11,310, respectively (5), with a then-ongoing cluster subsequently contributing additional cases.

The epidemic affected males and females in approximately equal proportions and all age groups. Healthcare workers, especially early on, had an incidence of infection at least 100 times that of the general population and accounted for up to 12% of all cases (10). Most healthcare workers were likely infected outside of Ebola Treatment Units (ETUs) (**Figure 2**), either in general health facilities or in private, informal settings (10, 11). Members of the general population were most commonly infected in their homes, when exposed to persons suffering from Ebola; while participating in traditional funerals, which frequently included touching cadavers; or in healthcare settings.

It is difficult to accord proportions to these different modes of exposure and transmission, but data from Liberia and Guinea suggest that death at home was associated with a greatly increased risk of infection among contacts, whereas early isolation of ill persons in ETUs protected against community transmission (12, 13). In the study concerned, mode of burial ("safe," by trained staff with personal protective equipment, versus burial by untrained persons) was not associated

with transmission risk, likely because precautions were incomplete or exposure occurred before they were implemented (13). Patients with "wet" symptoms (diarrhea, vomiting) and bleeding, features occurring later in illness, are generally considered more infectious than those in the "dry" stage of illness; this conclusion was supported by viral load estimation using polymerase chain reaction (PCR) cycle threshold, with lower cycle thresholds indicating a higher viral burden. Certain individuals seem to have been disproportionately efficient transmitters of Ebola, for which biological factors, such as viral load, and social factors, such as occupation and frequency of physical interactions with others, were likely relevant factors.

## WHAT WAS NEW ABOUT THE WEST AFRICA EPIDEMIC?

Prior to 2014, the furthest west in Africa that Ebola had been recognized was in the Tai Forest of Côte d'Ivoire, where in 1994 a Swiss veterinarian became infected after performing an autopsy on a chimpanzee (14). There have been serologic surveys in humans in Liberia and Sierra Leone showing widespread serologic reactivity to Ebola (15), but the specificity of the assays used has been questioned. Spengler and colleagues (16) discuss the potential zoonotic origin of the West Africa epidemic, including spillover of Ebola from bats to humans; fruit bats are the known reservoir for Marburg virus, and although they are suspected to be the natural reservoir for Ebola, this has not been proven. Whether environmental change in West Africa such as deforestation from extensive logging is relevant, potentially bringing human populations closer to putative nonhuman reservoirs or affected species, is speculative. No clear answers exist as to why and how Ebola broke out at this time in West Africa so far west of the endemic Congo River Basin.

Once initiated, the West Africa outbreak extended more broadly and for longer than any previous Ebola epidemic, for the first time simultaneously affecting several countries, rural and urban areas, and capital cities. Liberia's Lofa County borders the Forest Region of Guinea, as does Sierra Leone's Kailahun District. The people of this region share a common culture and engage in commerce and travel that largely ignore national boundaries. Extensive movement of infected persons from this area carried infection throughout the three countries and to their crowded capitals. Guinea, the largest and most populous of the three countries, had the longest period of Ebola transmission but did not experience the very high rates of infection in its capital (Conakry) that occurred in the capitals of Liberia and Sierra Leone (Monrovia and Freetown, respectively); furthermore, unlike in the other two countries, a substantial number of Guinean *préfectures* saw no cases. Spread to Nigeria occurred in late July 2014, when a visibly ill traveler from Liberia collapsed upon arrival in Lagos, was hospitalized,and initiated a secondary cluster before containment (17). Infections were also imported into Senegal and Mali but were rapidly contained. Further spread of Ebola to other parts of Africa was feared but fortunately was not realized.

By late summer 2014, the magnitude, geographic extent, and impact of the outbreak—including reports of associated horrors such as corpses abandoned in houses or in city streets, particularly in Liberia—attracted the world's attention. Around the same time that Ebola was introduced into Nigeria, two American missionary healthcare workers in Monrovia became infected, the first expatriate healthcare workers in Africa to acquire Ebola (11). Their subsequent medical evacuation for treatment in the United States stimulated formulation of policy and guidance on evacuation of international staff, and raised questions about access to medicines not yet licensed. The epidemic also drew attention early on to the widespread inadequacy of infection prevention and control in healthcare settings in West Africa and throughout much of the continent (4). The inadequacy of infection control procedures increased the risk to healthcare workers; early in the outbreak, these insufficiencies led to the closure of key health facilities in the three heavily affected countries. Evaluations documented frequent lack of basic essentials such as soap and water, shortages of

protective equipment, absence of triage procedures, and incomplete understanding of infection control principles and procedures.

In late September 2014, a person infected with Ebola presented to Dallas Presbyterian Hospital in Texas, having traveled to the United States from Liberia during the incubation period of his illness. He transmitted Ebola to two nurses before he died (18). Some weeks before, nosocomial transmission of Ebola in a modern medical facility had also occurred: A nurse in Spain was infected by a missionary evacuated from Liberia.

Following these events, Ebola suddenly seemed potentially dangerous far beyond West Africa, and the epidemic was discussed at the highest political levels internationally. Ebola was debated on the floor of the United Nations (UN), and the Security Council described it as a threat to peace and security. In September 2014, the UN Secretary General established the United Nations Mission for Ebola Emergency Response (UNMEER) to scale up the response on the ground in the heavily affected countries, coordinating the delivery of logistic, technical, and financial support. This gesture not only conveyed the perceived gravity of the situation but also lack of confidence in WHO's organizational capacity for emergency response to the crisis (19). Hitherto, the only disease to have received such high-level attention internationally was AIDS, which had a specific United Nations structure (UNAIDS) established for its response. UNMEER was disbanded at the end of July 2015 (**http://ebolaresponse.un.org/un-mission-ebola-emergency-response-unmeer**).

WHO was criticized for its delay in declaring the epidemic a public health emergency of international concern, a decision reached on August 8, 2014 (20). As a further indication of the global concern with the epidemic, several countries took the unusual step of involving their military in their response. In mid-September 2014, during a visit to the US Centers for Disease Control and Prevention (CDC) headquarters, US President Barack Obama committed to send 3,000 troops to Liberia to strengthen the response, and the United Kingdom's military played a prominent role in Sierra Leone. The response was characterized by unusual alliances between multilateral, governmental, and civil society groups of very different technical, social, and political persuasions.

As the gravity of the epidemic became increasingly recognized, particularly from July 2014 onward, the response accelerated to unprecedented levels. In late 2014, the US Congress allocated emergency funding of $5.4 billion for Ebola, more than allocated previously for any other emerging infection (21). Substantial funding was also provided by other bilateral and multilateral donors such as the World Bank. Following historical ties, assistance from the United States and United Kingdom was most prominent in Liberia and Sierra Leone, respectively. Francophone Guinea may have received less international assistance than the other two countries, not receiving, for example, large-scale military deployment from outside.

Thousands of health professionals traveled to West Africa from numerous countries and organizations to assist in the Ebola response, many through WHO's Global Outbreak Alert and Response Network, helping to establish dozens of Ebola diagnostic laboratories and ETUs across the three countries. CDC's Ebola response, involving activation of its Emergency Operations Center (EOC) for more than 18 months and deployment of >2,200 staff to the affected countries during 2014–2015, was the largest in its history; for comparison, CDC deployed four times as many staff during the Ebola response as during the campaign to eradicate smallpox (16, 22). Although somewhat late, extensive south-to-south collaboration occurred. The African Union recruited and sent hundreds of staff to West Africa from different African countries. China, demonstrating its increased commitment to global health, set up an ETU in Liberia and provided laboratory support in Sierra Leone. Numerous nongovernmental organizations were engaged in the response, particularly Médecins Sans Frontières (MSF), which was, as in previous outbreaks of Ebola elsewhere in Africa, heavily involved in the direct medical care of Ebola-infected patients

in ETUs. Despite the contributions by these and other groups, responding to the West Africa Ebola epidemic stretched the world's response capacity and highlighted the need for reserves of deployable staff with appropriate technical and language skills. *Time* magazine, in its traditional end-of-year issue reviewing major events of 2014, named the "Ebola fighters" as Person of the Year (23).

## PUBLIC HEALTH AND SCIENTIFIC INSIGHTS

The urgency of the situation on the ground meant that the public health response was prioritized over research, and organized studies of novel therapeutics and vaccines were generally implemented only when the number of new cases had dwindled. Nonetheless, important findings were documented concerning prevention of Ebola transmission and care of Ebola-infected patients, and the unprecedented field experience confirmed basic principles and gave new insights into operational effectiveness.

Isolating the sick as quickly as possible; providing the best and safest care possible, whatever the local conditions; and safely burying the dead were the essentials of an effective response. Tracing persons who had been in contact with Ebola-infected persons and placing those exposed under active surveillance (contact tracing), though not comprehensively possible at the height of the epidemic because of overwhelming numbers, facilitated rapid identification and isolation of new cases and disrupted chains of transmission. A mathematical model usefully drew attention to the severity of the epidemic and the need for increased control efforts at a time when the number of cases was increasing exponentially (24). The model was also helpful in illustrating how essential rapid isolation of Ebola-infected patients and safe burials were for Ebola control. In the field, this was demonstrated in Monrovia, Liberia, where precipitous decline in Ebola incidence occurred following more rapid isolation of Ebola-infected patients after expansion of ETU beds in the fall of 2014 (25; F. Mahoney, personal communication). In contrast, in Freetown, Sierra Leone, the number of new cases continued to increase in early December 2014 when immediate isolation of patients, whatever the facilities available, was delayed by efforts to perfect ETUs under construction (K.M. De Cock, unpublished observations).

Innovative field approaches were used to implement basic strategies. In Liberia, the so-called Rapid Isolation and Treatment of Ebola (RITE) strategy was applied in remote areas. This utilized community engagement to optimize case finding, rapid isolation of cases, contact tracing, voluntary quarantine of high-risk contacts, movement of contacts closer to ETUs in case of illness, and social support including provision of essential sustenance (26). With time, the RITE approach resulted in shorter outbreaks with fewer secondary cases. Deeper analyses illustrated that duration of a sick person's presence in the community was a critical factor for determining secondary spread (12, 13) and demonstrated the importance of community engagement and education. Elsewhere during the epidemic, failure to secure the confidence of the community delayed control efforts. In Monrovia, for example, sociocultural traditions and beliefs hampered implementation of safe burials and of the order for cremation of all cadavers that was in force for several months. Tragically, community resistance resulted in death or injury for some responders in Guinea (27).

Limited clinical research was conducted on case management in West Africa during the current outbreak. Although summarizing clinical descriptions is difficult due to variable case definitions and their inherent bias from predefined criteria, incubation periods in a case series in Sierra Leone ranged from 6 to 12 days and the case fatality proportion was 74%. The most common symptoms among Ebola cases were fever (89%), headache (80%), weakness (66%), dizziness (60%), diarrhea (51%), abdominal pain (40%), and vomiting (34%). An increase in case fatality was associated with higher viral load, older age, and severe illness, including indicators of renal failure (28). In

Guinea, the risk of death in patients aged 40 years or above was three and a half times higher than in younger people (29). A clinical observation in the West Africa outbreak was the rarity of hemorrhagic symptoms; consequently, nomenclature now refers to Ebola virus disease rather than Ebola hemorrhagic fever (28, 29).

Uyeki and colleagues reviewed the clinical course of 27 Ebola-infected patients treated in Europe and the United States (30). The clinical course for these patients included diarrhea, sometimes as voluminous as 10 L daily, and electrolyte disturbances including hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia. Approximately one-third of patients received mechanical ventilation and one-fifth renal support. The overall mortality was 18.5%, lower than the 37–74% mortality reported from West Africa. Ability to monitor and correct fluid and electrolyte balance and availability of intensive care for respiratory and renal support were deemed critical to the more favorable outcomes documented in Europe and the United States.

One of the novel aspects of this epidemic was the establishment of sophisticated medical care units for responders in West Africa. In Liberia, the US Public Health Service established the Monrovia Medical Unit, a 25-bed facility intended to care for foreign medical teams and local healthcare providers. Similar units were established in Kerrytown, Sierra Leone, and in Conakry, Guinea, by the United Kingdom and French military, respectively.

Although individual patients received experimental medications on a compassionate basis, few systematic and adequately powered studies of novel therapeutics were conducted. A nonrandomized study in Guinea using historical controls showed no benefit from the use of convalescent plasma from Ebola survivors (31). A trial of brincidofovir was abandoned, and a study of favipiravir was unpersuasive about any clinical benefit (32). Throughout the epidemic, ZMapp—humanized monoclonal antibodies to the Ebola glycoprotein prepared in tobacco plants—was considered the most promising drug on the basis of its performance in nonhuman primate experiments. A trial of ZMapp versus standard of care was unable to reach the planned sample size, studying only 72 patients instead of the planned 200. There was a trend toward better survival, the mortality proportion in the control group being 37% versus 22% in the group receiving ZMapp, but the difference was not statistically significant (33). Currently, enthusiasm is high regarding the investigational compound GS-5734, a small-molecule prodrug of an adenosine analogue with demonstrated high efficacy against Ebola in macaques and penetration into potential sanctuary sites such as testes, eyes, and brain (34). The drug has been used on a compassionate basis in two patients.

Development of vaccines and therapeutics generally occurs on a timeline measured in years or decades; the evaluation of medical countermeasures in the midst of the epidemic required a balance between adherence to regulatory requirements and rapidly implementing public health research activities. Sometimes conflict arose between research priorities and broader public health requirements, and some valid research questions, such as whether asymptomatic Ebola infections occur, could not be addressed.

An ambitious study was planned in Liberia to compare two Ebola vaccines: a product based on live attenuated vesicular stomatitis-virus (VSV), which incorporated the Ebola glycoprotein, and a nonreplicating chimpanzee adenovirus preparation. By the time the study began, there were no active cases, and the study was converted into one assessing immunogenicity (35). Similarly, a vaccine trial in Sierra Leone will also generate substantial safety and immunogenicity data but will not generate efficacy data because of an absence of cases by the time the trial was launched. A study of the VSV product was successfully conducted in Guinea using a ring vaccination approach, and showed a high level of efficacy (36). Despite lack of formal regulatory approval, the VSV product was used in the public health response late in the outbreak.

A new population of interest is Ebola survivors, who may number close to 17,000 across the three countries and who face considerable medical and social challenges. Half or more had

persistent symptoms, predominantly ocular, musculoskeletal, and neuropsychiatric (37, 38). In Liberia, one-quarter had signs of ocular abnormality, 8% musculoskeletal findings, and 5% neuropsychiatric signs, all significantly more frequent than in controls. Ten percent had uveitis. Survivors have faced stigma and discrimination, such as rejection by family and social contacts, ejection from housing, and dismissal from work.

New insights have been gained into viral persistence in survivors. Several patients have been described in whom Ebola persisted in sanctuary sites such as the eye and the brain several months after initial recovery, with the possibility of viral and clinical reactivation (39, 40). In March 2015, Liberia seemed on the way to being declared Ebola-free when a woman presented with, and then died from, Ebola with no obvious source for her infection. A sex partner with whom she had intercourse one week before her illness onset was an Ebola survivor whose semen was subsequently shown to be PCR positive, 199 days after his onset of illness (41, 42). Sequencing of genetic viral material from both partners showed common mutations suggesting these infections were linked. A study from Sierra Leone examining semen specimens from 93 survivors showed approximately half of them tested positive for Ebola on PCR, the relative proportions declining from 100% at 2–3 months to 65% at 4–6 months and 26% at 7–9 months (43). Cycle threshold values suggested declining viral load over time. Workers in Liberia reported that semen positivity could be intermittent and found one survivor positive at 18 months after illness onset (37). Each of the three countries has seen clusters of Ebola after being declared Ebola-free, likely initiated by survivors (44).

Despite the unprecedented field laboratory network established during the West Africa epidemic, PCR methodology was not standardized. A diagnostic advance late in the epidemic was the introduction of rapid tests for Ebola, and WHO has issued guidance on their use (45). Sequencing of viral material was conducted in real time, giving insight into transmission patterns and sources of infection (42, 44). Despite suspicions that bats played a role in the initiation of the epidemic in West Africa, limited progress was made toward determining Ebola's natural reservoir (16). In retrospect, more investment early on in all aspects of data management would have given more reliable data on epidemic trends (4, 46).

## PUBLIC HEALTH IMPLICATIONS

The Ebola epidemic raised profound questions about global health architecture and responsiveness, and it uniquely illustrated systemic weaknesses that allowed this local outbreak to develop into a global threat. "How did this happen?" was the dominant question that numerous bodies and commentators addressed. An independent report from the Harvard Global Health Institute and the London School of Hygiene and Tropical Medicine offered ten recommendations concerning prevention and response to major outbreaks, research and sharing of data and technology, and governance of the global system (47). A report from MSF criticized the slow response from the global community and especially WHO (48), and the Ebola experience has been one of the drivers of calls for WHO reform.

An overriding conclusion is that weaknesses in public health systems, especially inadequate surveillance and response capacity, were important factors in the development and expansion of the epidemic (4, 46, 49). It has been suggested that such health systems capacity had been strengthened in other African countries that received substantial funding for HIV/AIDS, whereas the three Ebola-affected countries generally have low HIV prevalence and have not seen large inflows of assistance for HIV/AIDS (49). In the wake of the Ebola epidemic, there has been great emphasis on strengthening capacity in health security (50), as well as on availability of internationally deployable rapid public health responders. For optimal global health security,

however, adequate public health systems for epidemiology and surveillance, laboratory diagnosis, and responsiveness to emergencies are essential in all countries.

There was a substantial but hard-to-quantify impact on basic health care and services during the West Africa Ebola epidemic, due in large part to poor infection prevention and control. Healthcare-associated transmission of Ebola resulted in tremendous fear and insecurity throughout the healthcare system, and healthcare workers and patients often refused to enter facilities or abandoned them. Childhood immunizations were often interrupted, and post-Ebola measles outbreaks have occurred; models have estimated 2,000 to 16,000 additional measles deaths (51, 52). Admissions for maternal health services fell by up to 87% during the height of the epidemic, with similar declines in deliveries at health facilities (53–56). Treatment for malaria, which has initial symptoms similar to Ebola's, dropped by up to 69% in areas affected by Ebola (57, 58). Collectively, these interruptions of essential services may have caused more deaths than Ebola itself.

## CONCLUSIONS

There has been much attention to the epidemiologic transition under way in global health, with better child survival, an increasing burden of noncommunicable diseases, and progress against major infectious diseases such as HIV/AIDS, tuberculosis, and malaria (59). The West Africa Ebola epidemic has been a stark reminder of global interconnectedness and persistent and collective vulnerability to infectious diseases. Following the severe acute respiratory syndrome (SARS) epidemic in 2003, WHO revised the International Health Regulations, but global compliance with the core capacities remains low (60). New infections, such as Middle East respiratory syndrome (MERS), have presented themselves, and in recent years large outbreaks have occurred of different virus infections including influenza H1N1, dengue, Chikungunya, yellow fever, and most recently Zika. Antimicrobial resistance, including to bacterial, parasitic and viral infections, is an increasing concern.

To help countries strengthen their public health systems and achieve compliance with the International Health Regulations, the United States and other countries have launched the Global Health Security Agenda (**https://ghsagenda.org**). This initiative defines 11 different priority areas for strengthening, including surveillance, laboratory capacity, workforce development, emergency operations centers, and immunization. Countries prioritized for this initiative include the Ebola-affected countries in West Africa. It is hoped that the investments in health security in response to the West Africa Ebola epidemic will result in broad and geographically widespread systems strengthening, so that inevitable future infectious disease challenges, wherever they occur, do not result in such uncontrolled epidemic spread.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. The findings and conclusions in this review are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

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