

West Africa 2013: Re-examining Ebola

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INTRODUCTION

The outbreak of Ebola virus disease (EVD) that began in Guinea in 2013 and then rapidly spread through Liberia and Sierra Leone lasted over 2 years and resulted in over 28,500 cases and at least 11,000 deaths in West Africa, with 27 imported or medically evacuated cases and 5 deaths in the United States and Europe (Fig. 1) (1, 2). By comparison, fewer than 3,000 cases of EVD have been registered for *all* previous outbreaks combined (Table 1). The previous largest outbreak on record, which occurred in Gulu, Uganda, in 2000–2001, lasted only three and a half months and consisted of 425 cases with 224 deaths. But the impact of an outbreak of EVD or other emerging viruses cannot be measured simply by tallying cases and deaths. In 2015 the West Africa EVD outbreak resulted in \$2.2 billion in lost economic growth in the region, stalling fledgling economies that were struggling to recover from civil war. On a personal level, such sterile-sounding statistics translate to extreme personal suffering—upward of 3,000 orphaned children, children's education and development jeopardized as school is cancelled for a year, job loss, smaller harvests and hungry families, and deep but less easily measurable mental health and socio-cultural impacts. Furthermore, as the region's

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Emerging Infections 10

Edited by W. Michael Scheld, James M. Hughes and Richard J. Whitley

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doi:10.1128/microbiolspec.EI10-0022-2016

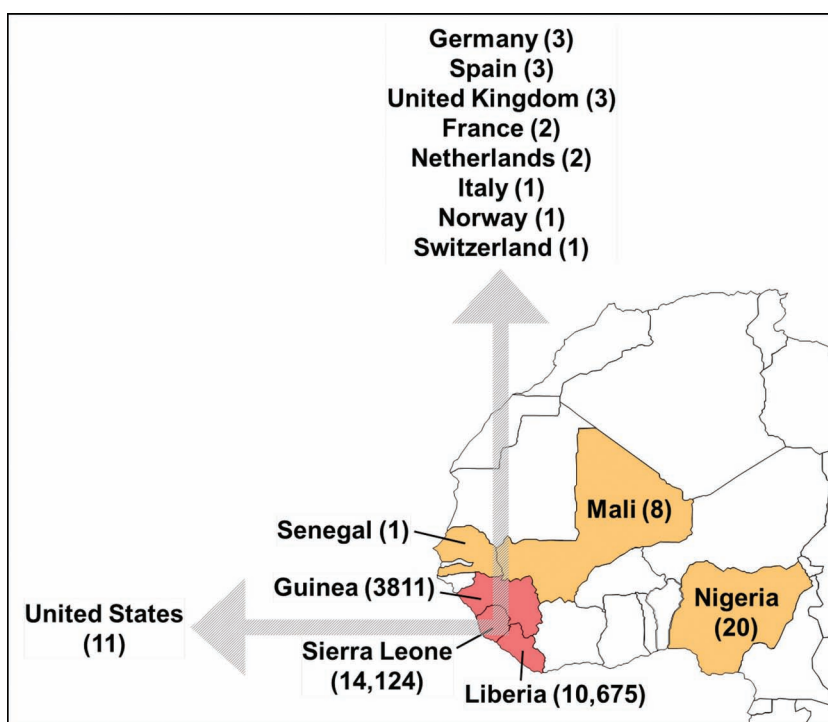


FIGURE 1 Map of West Africa showing the epicenter of the 2013–2016 outbreak of Ebola virus disease (red) and imported cases (orange and arrows). The total number of cases seen in each country is shown in parentheses.

resources were funneled to EVD, there were an estimated 10,000 excess deaths due to untreated malaria, HIV/AIDS, and tuberculosis. Reductions in vaccination coverage and a rise in teenage pregnancy were also noted (3).

The unprecedented scale of West Africa 2013 took the world by surprise and sadly added another tragic event to a region already struggling to escape decades of poverty and war. The outbreak also shook the international response community, laying bare deficiencies in our response capacity to complex humanitarian disasters of highly infectious and lethal pathogens. It also has taught the world many new things about EVD, previously considered so mysterious and usually seen only in small numbers and in remote and resource-poor locations that hindered systematic study. Here we re-examine EVD, reviewing the unique features of West Africa

2013, contrasting them with the prior assumptions and classical teachings, and identifying what they have taught us and what we still have to learn.

WHY WAS THE WEST AFRICA 2013 OUTBREAK SO BIG?

The reasons for the unprecedented size of West Africa 2013 are undoubtedly multifactorial. Many of the challenges had been encountered in previous EVD outbreaks but certainly not on the scale and with the intensity noted in West Africa. Whether the end result was just bad luck, or the perfect storm, is in the eye of the beholder. Although much will forever remain speculation, any attempt to understand the events requires a detailed look at a complex web of interrelated biological, economic, ecological, and social

determinants viewed in the context of the overall geopolitical history of the region.

Resource-Poor Countries with Fragile Health Care and Disease Surveillance and Response Systems

Much remains to be understood regarding the factors that dictate Ebola virus introduction into humans at a given time (4). However, once introduced, an almost invariable underlying determinant of large outbreaks is a backdrop of previous civil conflict or failed development resulting in fragile health care and disease surveillance and response systems (4, 5–9). Guinea, Liberia, and Sierra Leone sadly fit the bill, with all three countries working to recover from decades of civil war and unrest. All three rank near the bottom of the 187 nations on the United Nations Development Program Human Development Index, with a majority of their populations living below the national poverty lines. Thus, when Ebola virus was introduced, it unfortunately found not only an immunologically susceptible population, but also surveillance and health care systems that were unable to readily detect it or contain it.

The introduction of Ebola virus that initiated West Africa 2013 likely occurred in the town of Meliandou in a remote, largely deforested, and resource-poor region of Guinea in December 2013 (10, 11). However, with no organized surveillance or reporting system for hemorrhagic fever syndromes and no laboratory in all of West Africa with the standing capacity to diagnose EVD (Fig. 1), diagnostic confirmation and the first notification by Guinean health authorities to the World Health Organization (WHO) of a “rapidly evolving outbreak” did not occur until over three months later (11). By this time at least 49 cases with multiple but often poorly defined chains of transmission had occurred in Guinea, with the disease already slipping quietly across the border into Liberia (12, 13).

The West African countries also lacked the trained personnel (see below), disease

surveillance and response systems, and physical infrastructure and materials to contain the outbreak. Infection prevention and control (IPC) practices were undeveloped at best, with simple medical necessities such as soap, clean water, and sterile needles being far from given, much less the costly personal protective equipment (PPE) needed to safely care for EVD patients (14–18). Disease reporting and response systems for case identification, isolation, and treatment; contact tracing; and safe burials were close to nonexistent, as were ambulances to transport patients to health facilities.

Delayed Response by the International Community

Given the evident incapacity of the local response from West African countries, international assistance was clearly needed. The first order of business required recognition of the gravity of the situation by WHO and the international community. Much has been made of WHO’s slow response (19). Although they contributed personnel and resources from the onset, WHO did not formally declare the outbreak in West Africa to be a Public Health Emergency of International Concern (PHEIC), as outlined under the International Health Regulations, until 8 August 2015, 6 months after the first notice of EVD in the region. The reasons for the long delay are much debated but may include a true underestimate of the gravity of the situation (despite many organizations making vocal calls for an international response by this time), political pressures from the affected countries, and being “gun shy” in the wake of significant criticism that WHO overreacted in declaring the 2009 “swine flu” (H1N1 influenza virus) to be a public health emergency of international concern.

With case numbers rapidly mounting, including imported cases into the United States and Europe, and projections of millions of cases of EVD in West Africa if no aggressive response was taken (20), the international

TABLE 1 Laboratory-confirmed outbreaks of Ebola virus disease since discovery of the virus in 1976 through April 2016. Cases related to laboratory infections are not shown^a

Year of onset	Virus species	Country	Epicenter(s)	No. of cases (CFR [%])	Source of primary infection	Factors contributing to secondary spread	No. of cases in health care workers ^b	Reference
1976	Zaire	Zaire (present day DRC)	Yambuku	318 (88)	Unknown	Nosocomial transmission	≥13	141
1976	Sudan	Sudan	Maridi and Nzara	284 (53)	Unknown	Nosocomial transmission	70	23
1977	Zaire	Zaire	Tandala	1 (100)	Unknown	None	0	142
1979	Sudan	Sudan	Maridi and Nzara	34 (65)	Unknown	Nosocomial transmission	≥2	143
1994	Zaire	Gabon	Mékouka, Ogooué-Ivindo Province	52 (60)	Infection in gold mining camps	Traditional healing practices, nosocomial and community-based transmission	None reported	144
1994	Tai Forest	Côte d'Ivoire	Tai Forest	1 (0)	Scientist conducting autopsy on wild chimpanzee	None	0	145
1995	Zaire	DRC	Kikwit	315 (81)	Unknown	Nosocomial and community-based transmission	None reported	26
1996	Zaire	Gabon	Mayibout, Ogooué-Ivindo Province	21 (57)	Consumption of dead chimp	Community-based transmission	None reported	144
1996	Zaire	Gabon	Booué, Ogooué-Ivindo Province	45 (74)	Consumption of chimp?	Nosocomial and community-based transmission	None reported	144
1996	Zaire	South Africa	Johannesburg	2 (50)	Imported from Gabon by infected doctor	Nosocomial transmission	2	146
2000	Sudan	Uganda	Gulu	425 (53)	Unknown	Nosocomial and community-based transmission, traditional burial practices	≥3	146
2001	Zaire	Gabon and ROC	Ogooué-Ivindo Province (Gabon)	65 (82)	Hunting and consumption of NHPs	Nosocomial transmission and community-based transmission, traditional healing practices	2	148

2001	Zaire	Gabon and ROC	Cuvette Ouest Region (ROC)	57 (75)	Unknown	Community-based transmission	0	148
2002	Zaire	ROC	Mbomo and Kéllé, Cuvette Ouest Region	143 (89)	Hunting and consumption of NHPs	Nosocomial and community-based transmission, traditional healing practices	None reported	28
2003	Zaire	ROC	Mbomo and Mbandza, Cuvette Ouest Region	35 (83)	Hunting and consumption of NHPs	Traditional healing practices	None reported	149
2004	Sudan	South Sudan	Yambio	17 (41)	Exposure to baboon meat?	Nosocomial transmission and community-based transmission	None reported	150
2007	Zaire	DRC	Kasai Occidental Province	264 (71)	Exposure to local wildlife, including bats	Nosocomial and community-based transmission	None reported	28
2007	Bundibugyo	Uganda	Bundibugyo	149 (25)	Unknown	Nosocomial transmission and community-based transmission	None reported	29
2008	Zaire	DRC	Mweka and Luebo	32 (47)	Exposure to fruit bats through hunting?	Unknown	None reported	151
2011	Sudan	Uganda	Luwero	1 (100)	Unknown	None	0	152
2012	Sudan	Uganda	Kibaale	11 (36)	Unknown	Community-based transmission	None reported	153
2012	Bundibugyo	DRC	Province Orientale	36 (36)	Hunted bushmeat?	Community-based transmission	≥13	141
2012	Sudan	Uganda	Luwero	6 (50)	Unknown	Unknown	None reported	154
2013	Zaire	Multiple, mostly Republic of Guinea, Liberia, and Sierra Leone	Southeast forest region of Guinea	Ongoing, ≥28,646 cases at this writing (31–76)	Unknown, suspected exposure to bats	Nosocomial and community-based transmission, unsafe burial practices	≥874	155
2014	Zaire	DRC	Province Equateur	66 (74)	Hunted bushmeat?	Community-based transmission	≥8	141

^aAbbreviations: CFR, case fatality rate; DRC, Democratic Republic of the Congo; ROC, Republic of the Congo; NHP, nonhuman primate.

^bMay include cleaners and other ancillary staff working in Ebola treatment units.

community finally stirred to action. Responses generally aligned with historical connections between the United States and European countries and their colonial-era African counterparts. In September 2014 U.S. President Obama committed to the construction of 17 100-bed Ebola treatment units (ETUs) in Liberia, deployment of up to 3,000 medical military and support personnel, and support to train 500 health care workers (HCWs) a week. The United Kingdom and France soon followed with commitments to combat EVD in their ex-colonies of Sierra Leone and Guinea, respectively. Ultimately, a vast array of government and nongovernmental organizations contributed. However, the response remained agonizingly slow, hampered by the logistical challenges of operationalizing work in the poorest countries in the world with fledgling governments and poor infrastructure. Even after laboratories began being rapidly established, the steep increase in the number of samples exceeded local diagnostic capacities in many areas until well into the outbreak. In addition, the response operations were initially poorly coordinated, with each organization acting independently or in bilateral concert with the government. In August 2014 the United Nations appointed a special envoy on Ebola, followed by the creation in September 2014 of a coordination body, the United Nations Mission for Ebola Emergency, headquartered in Ghana (Fig. 2). Opinions vary on the efficacy of these measures. Without doubt, the enormous scale and complexity of the outbreak and the sheer number of organizations involved (far more than had ever been involved in an EVD outbreak before and at times compounded by historical frictions between them) made seamless coordination a substantial challenge.

The Labor Problem

Certainly the greatest single impediment to controlling the West Africa EVD outbreak was the lack of skilled labor in the health

sciences. Caring for patients with EVD and controlling transmission require experience and resources that most health care systems and HCWs do not possess. Furthermore, as discussed above, EVD outbreaks almost invariably occur in areas with inadequate human resources in general. Before the outbreak, Guinea, Liberia, and Sierra Leone had less than 1 doctor per 1,000 population, among the lowest HCW coverages in the world (21). The ranks were then further thinned by the estimated 500 HCW deaths due to EVD (14) (see below).

International support for EVD outbreaks is almost invariably needed and has traditionally come from a relatively small group of organizations with the necessary expertise, including WHO, the U.S. Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), the International Federation of the Red Cross, and Public Health Agency of Canada. However, the number of people in each of these organizations with experience responding to EVD outbreaks was small and was further complicated in some cases by significant turnover of personnel between outbreaks, with consequent loss of institutional memory. With the exception of MSF, none of the traditionally responding organizations had ever focused on providing clinical care (in fact, most made a specific decision against it). Nevertheless, these organizations had a collective successful history of supporting national governments to contain EVD outbreaks to usually at most a few hundred cases and a few months duration (Table 1). And they responded in a typical manner in West Africa, no doubt expecting the same outcome. But as the case counts skyrocketed, it became clear that a much greater investment of personnel, time, and funds would be needed.

Recognizing the shortage of personnel, many governments and international organizations implemented training programs (22). But who was there to be trained? The West African HCWs were already maximally deployed, and then their numbers were

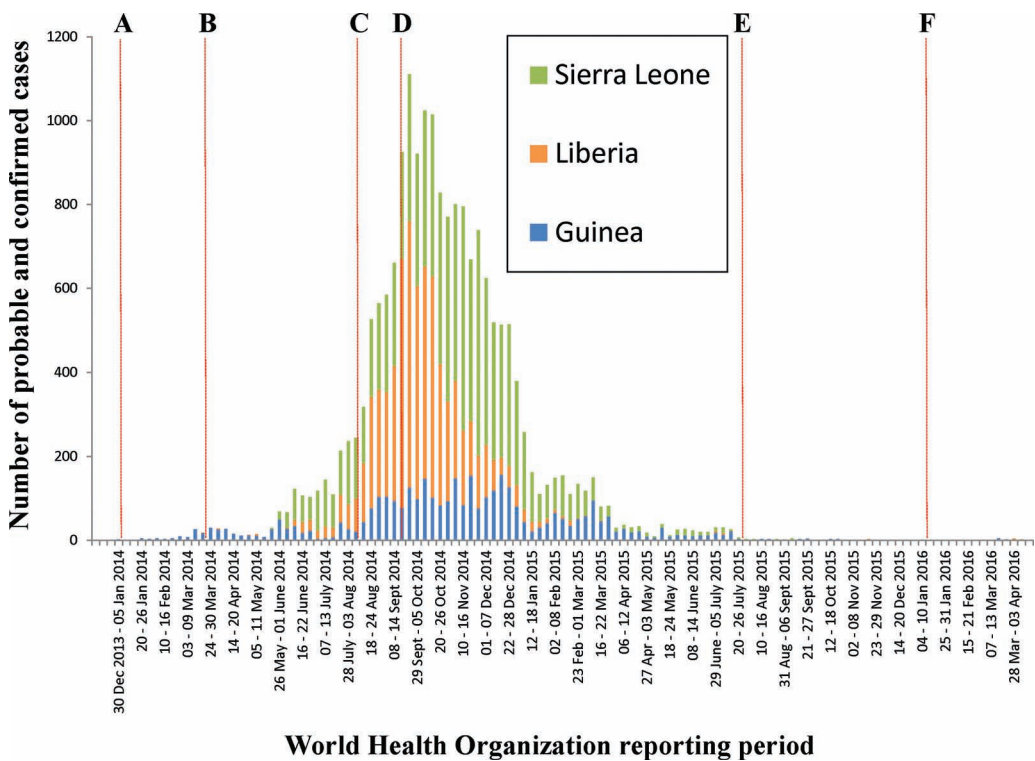


FIGURE 2 Epidemiologic curve of the West Africa 2013 Ebola virus disease (EVD) outbreak. The dashed vertical lines indicate key events during the outbreak: (A) First suspected case in Meliandou, Guinea. (B) Laboratory confirmation of EVD and disease reported by Guinean Health Authorities. (C) WHO declares public health emergency of international concern. (D) U.S. President Obama announces major initiative to help control EVD in Liberia; creation of the United Nations Mission for Ebola Emergency. (E) Publication of preliminary results from first EVD phase III vaccine efficacy study (rVSV-EBOV). (F) Publication of preliminary results of first EVD phase III therapeutic efficacy trial (convalescent plasma). Adapted from WHO Ebola Response Roadmap Situation Reports with publicly available data. World Health Organization: <http://apps.who.int/gho/data/node.ebola-sitrep.main-countries?lang=en>.

further thinned by EVD. In addition, pulling the few remaining local HCWs into EVD care threatened to further degrade the already very significant loss of general health services for so many other important conditions. The handful of international experts on EVD had already been deployed for months and were exhausted, with few qualified and trained replacements waiting in the wings. Military personnel were deployed, but very few had clinical experience with EVD. Certainly, a theoretical international pool of new HCWs was there, but who would be interested and able to leave their families,

jobs, and patients for months to manage patients with EVD in West Africa? The situation was further complicated by questions of legal and financial liability if an international HCW became infected.

The potential labor pool from the United States was thinned even more by draconian, largely politically motivated quarantine policies in some states that mandated 3 weeks of strict isolation (the maximum incubation period of EVD), and thus another 3 weeks away from work, of all people returning from West Africa, regardless of possible exposures or symptoms. This was despite the lack of

evidence of risk of virus transmission from asymptomatic people or even during the first few days of disease. The phrase “out of an abundance of caution” became a well-worn preface to the subsequent expression of a strict policy or decision without scientific evidence to support it. The contradictory messages (e.g., “Ebola virus cannot be transmitted from an asymptomatic person but, out of an abundance of caution, we will require strict quarantine of all asymptomatic persons.”) ultimately gave the impression that we were operating in a complete scientific vacuum, despite 40 years’ experience with the disease—fomenting, rather than quelling panic.

Although the international community committed to and ultimately did provide the necessary infrastructure and labor to help combat EVD in West Africa, the process was too slow. At the height of the epidemic, the beds for patients with EVD, the HCWs to care for them, and the field workers to trace their contacts simply were not there (Table 2). Thus, highly infectious patients remained untreated in the community, and patients who were admitted to the drastically understaffed ETUs could expect little more than palliative care. Furthermore, with cases of EVD in HCWs mounting, some ETUs opted to enhance safety by proscribing close contact with patients, including the controversial measure of not placing IVs for fluid repletion. This move likely further under-

mined the local population’s already shaky faith in the response operation.

High Population Density and Frequent Travel, Including Across Borders and to Large Urban Areas

EVD outbreaks have usually occurred in remote and sparsely populated areas of Central Africa (23–29). While the remoteness may add logistical complexity to mounting the outbreak response, the large distance between the epicenter and other populations also presents a barrier to virus transmission. In contrast, Guinea, Liberia, and Sierra Leone are generally very densely populated countries, with a surface area much smaller and more navigable than the vast expanses of Central Africa (Fig. 3). Furthermore, the Guinean Prefecture of Guéckédou where the outbreak began is a point where borders of the three countries converge (Fig. 1).

The geopolitical historical context is again important here; in reality, borders in this area of the world exist more on maps, originally drawn by former colonial powers, than as a barrier on the ground. The region is highly polyglot, dotted with small towns, dispersed on all sides of the “border,” comprised of populations who often self-identify just as readily by ethnic group as by nationality. While there may be a degree of passport control at the few major roads (or, just as often, rivers) that traverse borders, in most places the borders are crossed at will. And crossed they are, quite readily—for weekly market days, to see friends and family, even for the daily walk to school. However, while individuals readily cross back and forth, the governmental jurisdictions and corresponding operational capacity for outbreak response are fixed along the national boundaries. Surprisingly, especially considering the very frequent influx of refugees into Guinea from both Liberia and Sierra Leone in recent decades, prior to the outbreak there was very little communication or coordination between local government authorities on different

TABLE 2 Bed capacity and bed requirements for patients with Ebola virus disease in West Africa in October, 2014^a

Country	Current number of beds	Estimated number of beds required	Current capacity/estimated demand (%)
Guinea	160	210	76%
Liberia	620	2,930	21%
Sierra Leone	304	1,148	26%

^aBed capacity in each district was planned on the basis of a needs assessment carried out by the relevant Ministry of Health. Source: WHO: Ebola Response Roadmap Situation Report, October 8, 2014, World Health Organization: http://apps.who.int/iris/bitstream/10665/136020/1/roadmapsitrep_8Oct2014_eng.pdf?ua=1.

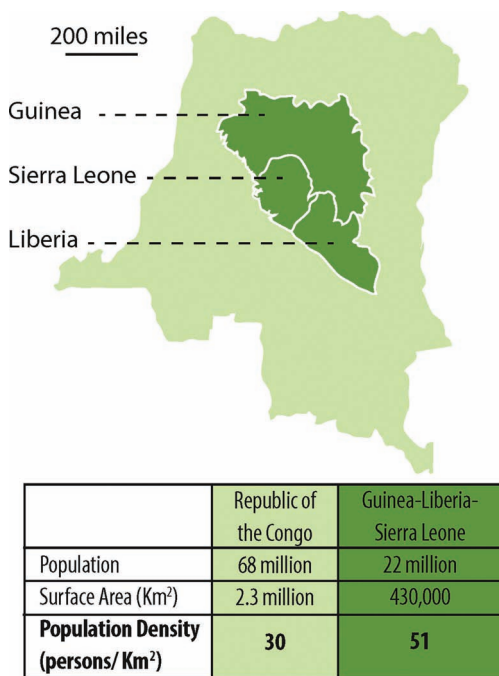


FIGURE 3 Sizes and population densities of Guinea, Liberia, and Sierra Leone combined compared with the Democratic Republic of the Congo. To illustrate the difference in size, the three West African countries are shown superimposed on the Democratic Republic of the Congo.

sides of the borders. The challenge to communication was exacerbated by the fact that government functionaries were often assigned to regions distant from their places of upbringing, making communication difficult since they spoke the national language (French in Guinea and English in Liberia and Sierra Leone) but little of the local dialects or the national language of the country on the other side of the border. Consequently, in the early stages of the outbreak, cases or contacts of EVD patients who crossed the border were effectively lost to follow-up. Cross-border meetings and communication were eventually established, but not until the virus was already widely disseminated on all sides of the borders.

In addition to the porous borders and frequent local crossings, the relatively short distances and low cost of travel between even

the farthest reaches of Guinea, Liberia, and Sierra Leone and their major urban centers was a major factor. Go to any bus or taxi station in any village early any morning in Guinea, Liberia, and Sierra Leone and you will see vehicles being overloaded with people and goods destined to arrive late that night at densely populated capital cities of millions of people (Fig. 4). The constant back-and-forth travel, be it for commerce or social visits, ultimately resulted in the introduction of Ebola virus into the capital cities and posed a major impediment to case finding and contact tracing. From there, it was just a matter of time until international air travelers carried the virus to neighboring, and occasionally more distant, countries (30–38) (Fig. 1).

Cultural Clashes and Community Resistance to Control Measures

In the absence of effective therapeutics and vaccines (a work in progress; see below), control of EVD is almost completely based on the classic control measures of thorough case identification, isolation, and contact tracing. Since the early symptoms of EVD (fever, headache, myalgia) are undetectable from casual observation, this approach is completely dependent on individual cooperation both to agree to follow-up and to report symptoms should they occur. Crucial to this cooperation is a common understanding of the nature of the disease threat and the appropriateness of the measures advocated to mitigate it—an understanding unfortunately lacking throughout much of West Africa 2013.

Community resistance to biomedical explanations for EVD outbreaks and proposed control measures is not unique to West Africa 2013, but the scale and tenacity of the distrust and resistance were more than had ever been met before. Again, an understanding of the geopolitical history of the region is essential; after four centuries of colonialism, much of it involving the slave trade, Guinea and Sierra



FIGURE 4 “Bush taxis” in Guinea traveling back and forth between remote areas and major cities. Photos by Frederique Jacquerioz.

Leone were granted independence from France (1958) and the United Kingdom (1961), respectively. Liberia was founded as an independent nation in 1847 after originating as a haven for resettled slaves from the United States. Unfortunately, colonial rule was generally replaced by weak and often corrupt governments. The situation ultimately deteriorated to civil war in Liberia (1989–1996) and Sierra Leone (1991–2002), fueled largely not by a desire for good governance by rebels or government soldiers (who were often thought to change sides at night), but rather by the desire to control the region’s rich mineral wealth, especially diamonds. The civilian population was caught in the middle. While never formally embroiled in civil war, Guinea’s governance was also suspect, a situation that culminated in widespread violence after the death of strong-man leader Lansana Conteh in 2008. In the past few decades, all three countries were struggling to overcome the decades of war and government neglect, with some significant progress until they were hit by EVD in 2013. Given this history, it is hardly surprising or illogical (in fact, the opposite) that a deep distrust of authority was pervasive, creating from the beginning an exceptionally challenging sociocultural backdrop in which outbreak control must take place.

In more concrete terms on the ground, this distrust fueled misconceptions, denial, and fear surrounding EVD, occasionally culminating in violence. The practice of isolating patients with EVD who, due to the high case fatality rates (CFRs), often die, frequently translates to the perception of causality to the local population; that is, “If you go into the ETU, they will kill you and you will die.” Other often invoked and arguably effective control measures such as roadblocks for health and temperature checks and quarantine of individuals, households, or whole villages reinforced the impression of a desire for control and the nefarious intentions of the health authorities, especially when the measures exacerbated the developing problem of food insecurity as a result of the outbreak. With the outbreak control teams viewed as a threat and the ETU as a mortuary, not surprisingly, sick people and their contacts frequently opted to hide or abscond.

Another challenging and delicate issue was that of burials of EVD victims, which proved to be a major source of transmission during the outbreak (39–41). The importance of respecting traditional burial ceremonies, which in many African cultures often involve touching the corpse, can hardly be overstated. On the surface, slight changes to

ceremony to avoid such contact and virus transmission would seem to be a simple matter. But while Western cultures tend to draw a very distinct line between life and death, this is not always so in West Africa, where varying from proper burial practices may be believed to have very real consequences on the living, including bringing future bad luck, disease, and crop failures. Faced with such consequences, is it any wonder that advice from distrusted authorities to change centuries-old customs (including Liberia's well-intended but ultimately disastrous policy of cremation of the corpses of EVD victims) to avoid transmission of an invisible and previously unheard of viral threat often went unheeded?

The perhaps inevitable cultural clashes inherent in response to an EVD outbreak have been increasingly recognized by the international community over the past few decades, prompting routine inclusion of anthropologists and social scientists to lead community engagement, education, and social mobilization efforts. These efforts typically include working with village chiefs, religious leaders, traditional healers, and other prominent leaders in the community to come to common ground on the approach to the outbreak. But changing beliefs and mindsets rapidly, especially those cultivated across centuries, is never easy, and it becomes harder as distress and fear grow in a community. The task is often oversimplified by outbreak response teams that sometimes have a mindset more oriented toward dictating steps that communities must follow rather than working with communities to develop solutions. Clearly, there is still much more to be learned and work to be done to put local populations and outbreak response teams in reasonable concert in the control of EVD.

Funding for Global Health Preparedness and Response

While not absolving the international community and WHO from responsibility, it must

be noted that funding for general global health preparedness and response has not kept pace over the past decade of global economic downturn. Global health funding increased significantly from 2000 to 2009, but growth has been minimal since that time (42). The majority of funding since 2000 has been focused on specific Millennium Development Goal areas (HIV/AIDS, malaria, and tuberculosis) and has not passed through WHO. Funding for WHO specifically has plateaued or decreased since 2010 (43), challenging the organization to maintain capacity for response to disease outbreaks while simultaneously addressing the ever increasing burden of noncommunicable disease in low- and middle-income countries (LMICs). This prompted Dr. Oyewale Tomori, an international expert on emerging viruses and long-time WHO collaborator, to declare, "They killed WHO and then blamed it for being dead" (44). In addition, over 70% of WHO's annual budget typically comes from voluntary contributions from donor countries. This money is generally earmarked for specific projects. Whether the new Global Health Security Agenda led by the United States can rejuvenate investment in broader global health preparedness and response remains to be seen.

Too Many Fronts

In the fight to control EVD, it is difficult to resist war analogies; it is a war against a dangerous and stealthy enemy. Victory requires manpower and material resources strategically organized for efficiency and speed. In the Ebola war, each battle front requires an ETU and appropriately trained and equipped HCWs to isolate and treat patients; field teams for case identification, contact tracing, social mobilization, and safe burials; laboratory diagnostics; and logistical and financial support for communications and travel to coordinate the operation. The international community has successfully fought this battle and won Ebola wars before,

but only on a few fronts at a time. West Africa 2013 ultimately presented too many fronts, quickly outstripping both local and international capacity. We eventually caught up, but only after heavy losses, too late to prevent an international humanitarian disaster.

CLINICAL PRESENTATION

The enormous size of West Africa 2013 has provided the opportunity for much more detailed clinical observation (45–48). Perhaps the most definitive conclusion in this regard is confirming observations from recent outbreaks that hemorrhage occurs in a minority (less than 20%) of patients, prompting the renaming of the disease from “Ebola hemorrhagic fever” to “Ebola virus disease.” The contribution of volume loss from diarrhea to the pathogenesis of EVD, with the potential for almost cholera-type fluid losses of up to 10 liters per day, has also become clear. Debate persists over whether this is something specific to the Makona variant of Ebola virus that is the etiology of West Africa 2013 or is common to EVD from all virus species and variants but was previously poorly documented and underappreciated. Enteropathy may extend beyond severe diarrhea, based on the frequency of abdominal pain and peritoneal signs as well as ultrasound evidence of paralytic ileus (49–51). Hiccups, previously considered an end-stage manifestation, have also often been recognized in early disease, the pathogenesis of which remains unclear.

Relatively newly described, or at least described in significantly greater detail, severe complications of acute EVD include meningoencephalitis (with evidence of microvascular occlusion and ischemia on magnetic resonance imaging), renal and respiratory failure, and rhabdomyolysis (48, 52–54; M. Lado, personal communication). Cardiac arrhythmias have been reported in high-income settings (50) and inferred as the cause of sudden death in some patients in

West Africa (48), but it is not clear whether this reflects direct myocardial pathology or is secondary to electrolyte disturbances or systemic inflammatory response syndrome. Another possible cause of sudden death may be thrombotic cardiac or cerebrovascular accidents related to thrombocytosis and a hypercoagulable state that have been documented in early EVD recovery (55). Some of the more severe complications have been described primarily in medically evacuated cases, raising questions as to whether they are truly common manifestations in all infected people, but perhaps go undetected or unreported in West Africa, or are rather a consequence of the intensive care and/or investigational drugs received by patients treated in resource-rich areas of the world.

While the expanded clinical observations from West Africa 2013 help refine our understanding of EVD, the noted variation in clinical presentation also poses challenges to surveillance and case identification. Given the public health implications of missed cases, case definitions for suspected EVD have always been designed to maximize sensitivity at the expense of specificity. Fever has always been a central feature, augmented through the addition of various equally non-specific symptoms and a history of contact with another person with EVD (56). However, during West Africa 2013, patients with confirmed EVD were frequently noted who did not meet this broad case definition; in one study, 9% of confirmed cases reported neither a history of fever nor a risk factor for Ebola virus exposure (57, 58). The sensitivity and specificity of the standard WHO case definition for EVD were only 79.7% and 31.5%, respectively. Given the frequent reluctance of local populations in West Africa to be identified as possibly having EVD, inaccurate histories could perhaps underlie these findings. Nevertheless, since such reluctance, and perhaps inaccurate reporting, are unfortunately likely to be encountered in future outbreaks, these results are very concerning and create operational challenges to field surveil-

lance and clinical triage alike. Whether the enormous amount of clinical data gathered during West Africa 2013 can be harmonized and analyzed to further refine and improve sensitivity and specificity of the EVD case definition remains to be seen. The task can be facilitated by standardized minimum data collection protocols and forms for EVD generated by the International Severe Acute Respiratory and Emerging Infection Consortium with support from WHO (59). Such data standardization and coordination should be an early consideration in all outbreaks of EVD and other emerging infections to facilitate real-time improvement of case definitions and analysis of clinical signs and symptoms.

One specific area where an expanded spectrum of clinical presentations has been noted is in pregnant women with EVD. While most present with typical EVD symptoms and signs, more atypical presentations have recently been documented. In Liberia a pregnant woman near term presented with ruptured membranes accompanied by mild lower abdominal pain and sparse contractions but was afebrile (60). Routine testing performed at the time revealed her to be PCR-positive for Ebola virus RNA, with a high viral load. Three days after admission she developed symptoms of EVD and ultimately succumbed to disease with the baby *in utero*. It is hypothesized that in this case the immune tolerance of pregnancy dampened the initial inflammatory clinical manifestations. How frequently this occurs is unknown, although anecdotal reports exist of similar atypical presentations, with obvious challenging implications for case identification and implementation of proper IPC procedures, especially when emergency invasive obstetric procedures are indicated during an outbreak.

CLINICAL MANAGEMENT

Once thought futile or too dangerous to implement, efforts to provide and enhance the

quality of clinical care for patients with EVD have gradually increased over the years (61). Treatment guidelines for EVD have been developed by WHO (62) and interim guidelines by MSF. The level of care provided during West Africa 2013 varied widely by the phase of the outbreak and ETU. After being overrun in the early phases, and consequently offering essentially no or minimal care (often only oral rehydration and oral acetaminophen), most ETUs gradually scaled up to at least standard practices of intravenous fluid and electrolyte management. A few in West Africa and virtually all in the United States and Europe provided full-service intensive care, including mechanical ventilation and renal replacement when indicated.

CFRs were consistently higher for patients at the extremes of age (45, 46), but it unfortunately remains difficult to assess the impact of level of care on patient outcome. Reported CFRs from West Africa 2013 vary widely (31 to 76%) by phase of the outbreak and ETU (63, 64), without obvious associations between level of care provided and CFR. This likely reflects patient selection and survival bias from the extremely varied levels of case finding across time and place. In some areas the sickest patients presented to ETUs, while in other areas they hid or absconded. Although caution is in order, since the findings are anecdotal and uncontrolled, it is perhaps illustrative to note that the CFR of the 27 cases who received care in the United States and Europe was only 18.5% (65). It is unknown whether this outcome relates to better fluid and electrolyte monitoring, organ support (including mechanical ventilation and renal replacement therapy), the use of experimental therapies, genetic predisposition, and/or diminished comorbidities relative to the West African population.

After the major struggle to implement the quantity of medical care necessary in West Africa 2013, the outbreak rightly brought up the issue of quality of care. Implicit in this is a just rejection of a perhaps long-held but

implicit acceptance of disparate qualities of care between patients in LMICs and resource-rich countries, an archaic notion whose time must now be passed. Regardless of country of origin or personal wealth, patients should have the right to HCWs with the right training for their condition and who implement evidence-based standards of care. Of course, this gap between rich and poor cannot be closed overnight. There is much work to be done with regard to both scientific research to generate the best evidence and advocacy and organization to ensure thorough and equitable implementation.

SEQUELAE, VIRUS PERSISTENCE, AND RECRUDESCENCE

Although a host of both short- and long-term sequelae after EVD have been noted dating back to the first recognized outbreak in the Democratic Republic of the Congo in 1976, little attention was typically afforded to survivors, in part due to the limited infrastructure for study in the outbreak areas (66). Only two controlled studies have been reported (67–69), neither incorporating the detailed microbiological and physical examination (especially ocular, audiometric, and mental health exams) required for a thorough understanding of the sequelae and associated pathogenesis. However, the estimated over 10,000 EVD survivors in West Africa have created both a moral imperative to provide clinical care and an opportunity for greater scientific understanding. In addition, survivors among the 20 medically evacuated cases to the United States and Europe have generally been seen in advanced medical settings that allow more detailed clinical observation and laboratory analysis than is typically possible in West Africa (70–73). WHO has developed clinical care guidelines for EVD survivors (74), and various studies on EVD sequelae are underway. In particular, PREVAIL III, a large multiyear controlled cohort study of EVD sequelae and

virus persistence being undertaken in Liberia promises to eventually yield a wealth of information (75).

As preliminary data begin to roll in, it is clear that the full scope of the medical and psychosocial challenges faced by EVD survivors has been underappreciated. Persistent arthralgia, ocular complications (including potentially sight-threatening uveitis that may result in early cataract formation), abdominal pain, extreme fatigue, and anorexia are very frequent, as are mental health sequelae, including sleep and memory disturbances, anxiety disorders, depression, posttraumatic stress disorder, and survivors' guilt in not only survivors, but also other family and community members (53, 66–68, 71, 72, 76–92).

The underlying pathogenesis of EVD sequelae is not well understood, but anecdotal observations increasingly suggest that at least some relate to persistent virus in selected immunologically protected tissue compartments and fluids, including the testes/semen, chambers of the eye, central nervous system, and the fetus, placenta, and amniotic sac/fluid of women infected during pregnancy (53, 67, 71, 86, 87, 93–95). Anecdotal evidence from previous outbreaks of virus in the semen detected by PCR up to 101 days after disease onset and by cell culture up to 82 days (94) are now being complemented by much larger and more systematic investigations in West Africa. Albeit in low copy numbers and in a small minority of EVD survivors, viral RNA has been detected in the semen up to a year or more after acute disease (95). In most cases cell culture data are not yet available, but virus has been cultured from the semen of an EVD survivor in the United States 70 days after disease onset (96). Tests of semen years after recovery from acute EVD have consistently been negative, indicating that the virus is eventually cleared (94).

Although sexual transmission still appears to be rare (97), male-to-female sexual transmission in Liberia 6 months after resolution

of acute EVD was well-documented with both classic epidemiologic evidence and a molecular sequence match between the virus found in the man's semen and woman's blood) (86, 87). Interestingly, although PCR-positive for RNA, virus could not be isolated on cell culture from the semen sample, which was taken 20 days after the suspected transmission event. Sexual transmission is also suspected to be behind a flare of EVD in Guinea in an area where the disease had not been seen for over a year. These cases illustrate the need for continued surveillance even after the immediate threat of EVD from more common modes of transmission has been extinguished, and also call into question the norm of calling an EVD outbreak "over" once 42 days (twice the longest incubation period) have passed.

Two recent cases of prolonged virus persistence associated with recrudescence have been noted. In a medically evacuated U.S. HCW with uveitis, Ebola virus was detected by PCR and cell culture from the aqueous humor 14 weeks after disease onset and 9 weeks after clearance from the blood, which remained negative during the episode of uveitis (71). Sequence data from the aqueous humor isolate revealed five point mutations compared to the virus obtained from the blood months earlier during the initial acute EVD, suggesting persistent viral replication in the eye during convalescence. In the United Kingdom, Ebola virus was noted by reverse-transcription PCR in both the cerebrospinal fluid (CSF) and blood in a medically evacuated HCW who developed severe meningitis with seizures nine months after resolution of acute disease (M. Jacobs, personal communication). The RNA copy number was lower in the blood than in the CSF, and virus could be isolated in cell culture only from the CSF, leading to the conclusion that the viremia was due to reseeded of the blood from the central nervous system. Sequencing of viruses obtained from the blood during the initial bout of EVD and the blood and CSF 9 months later showed

greater than 99% homogeneity, again suggesting persistence of virus since initial infection. No obvious underlying immunosuppressive condition or trigger for virus reactivation could be identified in these cases.

A low index of suspicion, and limited diagnostic capacity, may have allowed similar recrudescence EVD with fever, systemic symptoms, and viremia to go undetected or misattributed to malaria and other typical causes in prior outbreaks. An alternative explanation is that these recrudescence cases follow severe initial EVD that previously would have been fatal without intensive medical care and are the consequence of high viremia (true for both cases) that seeds the immune-privileged sites. Nevertheless, recent anecdotal reports of recrudescence disease and viremia exist in West Africa, in some cases thought to be related to underlying HIV infection, although this association remains to be validated (53).

CFRs for pregnant women with EVD and their offspring are extremely high, with fetal loss approaching 100% due to spontaneous abortion, stillbirth, and neonatal death in the first three weeks of life (60, 98–102). However, in West Africa 2013 a few cases have been noted in which women infected with Ebola virus during pregnancy, possibly with no or atypically mild disease, have recovered and remained pregnant, only to spontaneously abort a macerated and nonviable fetus in subsequent weeks or months (101, 107). Although the mothers' blood remained free of virus at the time of delivery, swabs of the fetus, placenta, and amniotic fluid in some cases have tested positive for Ebola virus RNA by reverse-transcription PCR, although cell culture results are not yet available (98, 100, 101, 103). The underlying pathogenesis is yet to be determined but is presumed to be due to delayed virus clearance from the immunologically protected gravid uterus.

In addition to the semen, CSF, and products of conception, Ebola virus RNA has been found in various other body fluids

and compartments, including urine (49), skin swabs/sweat (49), vaginal secretions (93), rectal swabs/stool (94), saliva (90), and breast milk (104), for weeks or even months after disease onset and after virus has been cleared from the blood (Fig. 5). However, the significance of these findings is unknown; in most cases infectious virus could not be isolated by cell culture a few weeks after disease onset. With the exception of sexual transmission, no cases of secondary transmission resulting from EVD survivors have been suspected. Nevertheless, nonstigmatizing but heightened surveillance and research are warranted to document the duration of virus persistence in EVD survivors, the implicated cellular reservoirs, and the nature and frequency of recrudescence disease and risk of secondary transmission. Full genome sequencing of Ebola viruses identified during acute infection and recrudescence may help shed light on the mechanisms of these events, especially the possibility of escape mutants.

HCW INFECTIONS AND IPC

IPC for EVD entails diverse measures, including adequate numbers of trained staff with supervision, clear operational protocols (especially for triage), appropriate design for safe workspace flow of patient and staff, water-sanitation measures, disinfection procedures, and the availability and appropriate use and removal of PPE. Unfortunately, many of the measures were lacking during the early chaos of the outbreak in West Africa, during which almost 900 HCWs contracted EVD, with over 500 deaths (14). In addition, three HCWs contracted EVD in the United States and Spain while caring for patients there. Although the high number of HCW infections has engendered speculation that the Makona virus variant of Ebola virus is more transmissible than other variants, no data are available. Most of the focus has turned instead to the issue of appropriate IPC, especially PPE. Although PPE is but one component of IPC, it tends to garner the

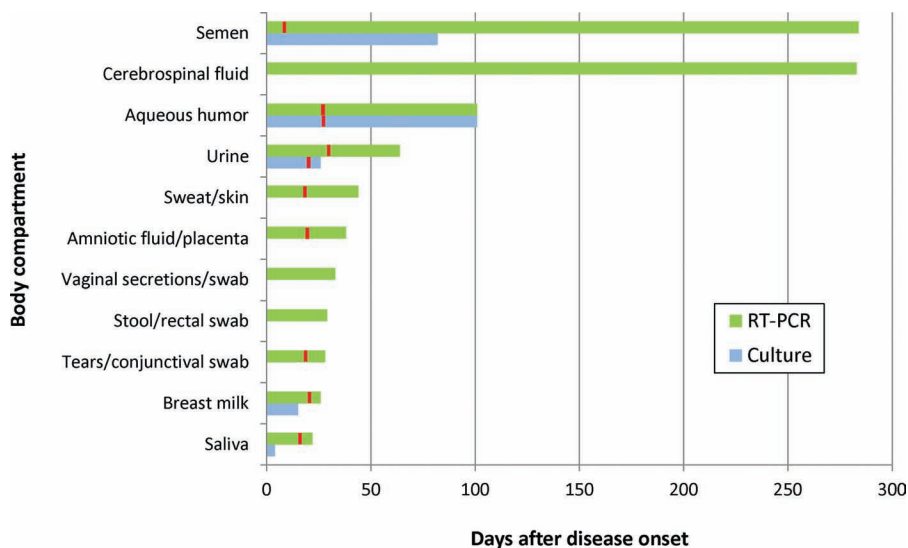


FIGURE 5 Virus persistence after the day of disease onset in various body compartments in survivors of Ebola virus disease as detected by reverse-transcription polymerase chain reaction (RT-PCR, green) and cell culture (blue). Red bars represent the day of the first negative RT-PCR detection in the patient's blood, when available. Reprinted with permission from reference 66.

most attention due to its visibility and the general tendency to focus on commodities rather than HCW competencies and the organization of health care facilities.

Although HCW infections have occurred in virtually every EVD outbreak to date (Table 1), prior to West Africa 2013, they were relatively uncommon once international support and resources arrived to assist with establishing ETUs with appropriate IPC measures. Indeed, implementation of IPC measures was attributed to the abrupt halt of HCW infections in the EVD outbreak in Kikwit, Democratic Republic of the Congo, in 1995 (25). Specific IPC and PPE guidelines were subsequently laid out in a manual coproduced by WHO and the CDC in 1998 (105). These guidelines were employed during the Gulu 2000 outbreak, in which, similar to the Kikwit experience, very few HCW infections occurred once the ETUs and accompanying IPC measures were implemented. However, the death due to EVD of Matthew Lukwiya, the hospital superintendent managing the ETU at St. Mary's Hospital Lacor in Gulu and the person who first recognized that Ebola virus could be circulating in the region, was one very high-profile exception and a tragic reminder that the IPC measures were not foolproof.

After Gulu 2000, different points of view evolved among the principal international organizations involved in EVD outbreaks regarding what constitutes appropriate PPE; MSF took a more conservative approach, requiring all skin to be covered and the use of impermeable but heavy suits originally designed for protection against chemical hazards (Tychem by DuPont Co., USA). In contrast, WHO and the CDC, until recently, emphasized only the use of gloves, an impermeable gown, a waterproof apron, and facial protection (either face shield or mask with goggles) (106) (Fig. 6). The difference in these approaches is very significant with regard to comfort, potentially dangerous heat stress (and thus the duration

that an HCW can work in an ETU), cost, and most importantly, ability to deliver quality clinical care. In April 2014, MSF, WHO, and other key stakeholders agreed to address these issues in a systematic way through a WHO-established process of evidence-based interim guideline development. However, a rapid systematic review concluded that there was insufficient comparative evidence regarding the effectiveness or harm of PPE (107). Although guidelines were nevertheless produced, which for the first time included technical specifications for PPE, the lack of evidence precluded a consensus on the most effective PPE to be used (107). The lack of consensus often generated confusion and posed a significant challenge in training HCWs, with different organizations simultaneously providing training that was not standardized or uniform with regard to PPE (108). The unlikely specter of Ebola virus mutation to enable airborne spread further obfuscated the picture. The CDC chose to offer training on the use of the PPE advocated by both MSF and WHO.

The many HCW infections that occurred during West Africa 2013 have unfortunately shed little light on the common modes of HCW infection and therefore the best IPC practices or most efficacious PPE. First, it is not clear that the attack rate for HCWs living and working in ETUs is consistently higher than that of the general population. Local HCWs are members of the communities where Ebola virus is circulating and thus may share many of the same risks. There are also many anecdotal reports of HCWs seeing patients in their homes, where the use of full PPE and other IPC measures are unlikely to be adequate (109, 110). One might expect the source of exposure for the expatriates infected during West Africa 2013 to be clearer, since this group generally lodged in hotels or the dedicated residence of the sponsoring organization, with less contact in the community at large, and was less likely to engage in informal medical consultation outside the ETU. Nevertheless, for national and expatri-



FIGURE 6 Examples of various types of personal protective equipment used during the care of patients with Ebola virus disease during the 2013–2016 outbreak in West Africa. The equipment shown is for demonstration only and should not be construed as advocating or confirming the efficacy of any specific equipment. Photos by Thomas Fletcher and Frederique Jacqueroiz.

ate HCWs alike, and regardless of type of PPE worn, the specific route of infection remains unknown in the vast majority of HCW infections during any EVD outbreak, including West Africa 2013. Discrete recognizable exposures, such as needle sticks and blood splashes to mucous membranes, are rare. The procedure for doffing contaminated PPE, often considered confusing and a vulnerable point for infection, is logically a focus of attention, but again, no data are available.

More in-depth investigations are needed, and indeed are ongoing, to reveal vulnerable points for HCW infection in the care of EVD patients. Meanwhile, various initiatives have been taken to encourage innovative approaches to enhance HCW safety while optimizing patient care in ETUs, including various types of redesigned suits that simplify doffing and disinfection and minimize heat stress, aided by the addition of cooling vests and temperature monitors, decontamination chambers and other chemical approaches to inactivation of virus on physical surfaces,

rapidly deployable portable ETUs, and infusion monitors and vital sign sensors to minimize the need for close contact between HCWs and infected body fluids from patients. Although promising, most of these innovative products are still in the pilot phases and have generally come too late to be applied during West Africa 2013. It remains to be seen whether both political will and commercial viability will endure to make them widely available in the future.

EXPERIMENTAL THERAPEUTICS

Before West Africa 2013, the funding for development of EVD therapeutics and vaccines was largely driven by governmental defense departments, which were concerned about the potential use of Ebola virus as a bioweapon. While this development pipeline was far from robust, it is reasonable to suggest that, compared to other emerging infectious diseases with analogous case numbers, the scientific agenda for EVD was not

languishing. Numerous therapeutic candidates were under development in cell culture and animal models. As the gravity of the situation in West Africa rose, the global community felt increasingly compelled to consider the use of various experimental therapeutics and vaccines being developed. In August 2014, WHO convened a meeting in Geneva, Switzerland, of the diverse stakeholders, including representatives from ministries of health, pharmaceutical companies, drug regulatory agencies, nongovernmental organizations providing clinical care, and experts in virology and medical ethics. Indeed, one of the first questions to be addressed was whether the use of these experimental compounds, which had varied safety and efficacy profiles, was ethical given the extreme suffering in West Africa, to which the committee unanimously replied in the affirmative. WHO created a scientific and technical advisory committee for Ebola experimental interventions to guide the process. One of their first objectives was to identify the most promising therapeutics among a long list of proposed candidates, including many of dubious quality. This process required consideration not only of the evidence for safety and efficacy, but the anticipated feasibility and utility of conducting a clinical trial in a setting of limited production capacities or intermittent drug availability.

The first therapeutic approach that received priority classification from WHO was convalescent whole blood and plasma (Table 3). This approach has been successful for a number of severe viral infections and was considered feasible in the most affected countries, especially in the context of a growing number of survivors who could serve as donors. Convalescent whole blood was used with apparent success (CFR 12.5%) in eight patients with EVD during the 1995 outbreak in Kikwit (111). However, interpretation of the outcome is confounded by the improved level of general supportive care provided to the patients relative to those seen

earlier in the outbreak (associated with a much higher CFR) and the fact that the transfusions often took place after the mean time to death for EVD during the outbreak and after many of the patients had already produced IgG antibody, suggesting that the recipients may have been likely to survive regardless. Studies of convalescent plasma have met with mixed results in nonhuman primate (NHP) models of EVD (112).

A clinical trial was conducted in Guinea in which two transfusions of convalescent plasma were administered to 84 patients with EVD in a single-arm design (113). No significant survival benefit was noted compared with historical controls. However, due to the lack of a biosafety level 4 (BSL-4) laboratory in Guinea, which is necessary to assess the neutralizing antibody titers in the transfused plasma, this crucial information has not yet been available. Interpretation of the results will therefore be somewhat clouded until these tests can be performed at an overseas BSL-4 laboratory. While convalescent plasma was well tolerated in the trial, a suspected transfusion-related case of acute lung injury was reported in a medically evacuated patient who received convalescent plasma on a compassionate use basis (90).

Monoclonal antibody therapies were considered among the most promising approaches prior to West Africa 2013 and then received significant attention from both the scientific community and the public following compassionate use in medically evacuated HCWs early during the outbreak. Enthusiasm for ZMapp, a cocktail of three monoclonal antibodies, was perhaps highest, based on *in vitro* and NHP data. It provided 100% protection in NHPs when given up to 5 days following a lethal Ebola virus challenge, at which time animals are routinely viremic and symptomatic (114). However, the drug was initially in short supply due to a time-consuming production method reliant on growth in genetically modified tobacco plants. Production was eventually scaled up to allow a multicenter randomized controlled

TABLE 3 Registered clinical trials of experimental therapeutics for Ebola virus disease during the West Africa 2013 outbreak^a

Agent under investigation	Trial sponsor	Trial objective	Trial design	Registered status (as of April 2016)	Outcome
ZMapp	National Institute of Allergy and Infectious Diseases, USA	Evaluate efficacy on survival at day 28 post-EVD onset (with potential inclusion of other experimental agents)	Open label RCT with adaptive design, with comparison to optimized care alone (including favipiravir in Guinea)	Ongoing analysis but not recruiting	Interim report showed no definitive conclusion but targeted statistical endpoints not yet met 115
TKM 130803	University of Oxford, UK	Evaluate efficacy on survival at day 14 post-EVD onset	Open label, single arm with historical controls, as part of a multistage approach	Completed	No overall survival benefit 119
Favipiravir	Institut National de la Sante et de la Recherche Medicale, France	Evaluate efficacy on survival at day 14 post-EVD onset	Open label, single arm with historical controls	Completed	No overall survival benefit 156
Convalescent plasma	Institute of Tropical Medicine, Belgium	Evaluate efficacy on survival at day 14 post-EVD onset	Open label, single arm with historical controls	Completed	No overall survival benefit 113
Convalescent plasma	Clinical Research Management, Inc., USA	Evaluate efficacy on reducing viral load	Open label, single arm	Recruiting	None reported
Convalescent plasma	Cerus Corporation, USA	Evaluate safety and efficacy on survival at 1 year post-EVD onset	Open label, single arm	Recruiting	None reported
Brincidofovir	University of Oxford, UK	Evaluate efficacy on reducing viral load at day 14 post-EVD onset	Open label, single arm with historical controls, as part of a multistage approach	Recruitment suspended	None reported
Azithromycin, sunitinib, erlotinib, atorvastatin, and irbesartan	Clinical Research Management, Inc., USA	Evaluate efficacy of multiple therapeutic agents on reducing viral load at day 14 post-EVD onset	Multiarm RCT with adaptive design. Initial comparison arms are azithromycin versus sunitinib and erlotinib versus atorvastatin and irbesartan versus intravenous fluids and laboratory testing alone	Not yet open for recruitment	None reported
Amiodarone	Emergency, Italy	Evaluate efficacy on reducing viral load at day 10 post-EVD onset	Open label RCT with comparison to best supportive care	Withdrawn	None reported

^aAbbreviations: EVD, Ebola virus disease; RCT, randomized controlled trial.

trial in West Africa and the United States. Although patient recruitment to the trial was insufficient to reach targeted statistical endpoints indicating conclusive benefit, preliminary analysis of existing efficacy data look promising (115). Efforts to produce an agent equivalent to ZMapp with a more scalable production method led to the development of the monoclonal antibody formulation MIL-77. Unpublished data suggest efficacy of MIL-77 in NHPs, and the drug has also been given to HCWs with EVD on a compassionate use basis, for which no firm conclusions of efficacy can be drawn. One concern with monoclonal antibody therapies is the development of drug resistance through rapid virus mutation resulting in escape mutants, which have been noted in NHPs treated with a related antibody cocktail, MB-003 (116).

Of the various antiviral drugs proposed, TKM130803, a small interfering RNA compound encapsulated in a lipid nanoparticle formulation, was arguably the front-running candidate. TKM130803 had demonstrated efficacy in NHPs (117), but phase I trials were on partial hold due to concerns of induction of a cytokine release syndrome. These were eventually addressed and, in addition, the drug composition was adjusted to improve specificity to the Makona variant of Ebola virus. Although a small study ($n = 3$) demonstrated 100% efficacy in NHPs (118), a phase II single-arm study completed in June 2015 in Sierra Leone concluded that TKM130803 did not improve survival in patients with severe EVD when compared with historical controls (119).

Several existing broad-spectrum antivirals were also investigated. Of particular interest was favipiravir (T-705), an RNA polymerase inhibitor that showed efficacy against Ebola virus in small animal models (120) and was already licensed in Japan for emergency use in pandemic influenza. A clinical trial conducted in Guinea reported no efficacy in patients with a high viral load (cycle threshold [Ct] < 20), with some suggestion of an

effect in patients with less severe disease (Ct ≥ 20), although this remains to be substantiated (121). A clinical trial of brincidofovir, an initially promising broad-spectrum antiviral drug, was abruptly stopped when the drug company withdrew support for use in EVD. No specific reason was given and results have not yet been published. A clinical trial of interferon in Guinea was similarly halted, with no further information available to date.

Alongside these clinical trials, many of the short-listed compounds were used under compassionate use settings, particularly for patients seen in the United States and Europe, of whom 85% received one or more experimental therapies (65). Because of the uncontrolled nature of their use in these settings and variable composition of supportive care received, no conclusions on efficacy can be made. Nevertheless, some intriguing and perhaps promising observations are worthy of mention: the only known neonate with EVD born to a mother who was viremic at birth received the broad-spectrum antiviral GS-5734, as well as ZMapp (66). Lastly, when MSF's supply of the routine antimalarial artemether-lumefantrine given empirically to all patients admitted to the ETU ran out, they replaced it with artesunate-amodiaquine and subsequently noted improved survival (122). More formal clinical trials are necessary to assess efficacy, although it is reasonable to make artesunate-amodiaquine the drug of choice for empiric treatment of malaria coinfection in EVD.

While there is disappointment that clinical trials during West Africa 2013 have not produced definitive evidence of an efficacious drug for EVD, the experience cannot be considered futile. There is no doubt that the many complex scientific, logistical, and sociocultural challenges ultimately could not be met quickly enough to take full advantage of the large case numbers potentially affording statistical power early in the outbreak. There was also an opportunity missed to enroll more patients in clinical trials in resource-

rich settings. Many difficult lessons were learned regarding the challenges of inconsistent reproducibility of *in vitro* experiments, poorly predictive animal models, and the operational demands of conducting trials overseas in an ETU during an outbreak without any pre-existing research infrastructure. Rigorous debate continues regarding the scientific and ethical merit of the various clinical trial designs used in this outbreak. Nevertheless, numerous drug candidates progressed through phase I, II, and III clinical trials at an unprecedented pace, and the recognition that some agents are ineffective, along with promising interim results for others, provides a starting point for prioritization in future outbreaks. However, much work remains to be done to capitalize on the lessons learned from West Africa 2013 and make the accelerated pace of clinical trials during outbreaks the norm, including prioritizing drug candidates, working out trial designs, prepositioning protocols and ethics committee reviews, and setting logistical frameworks for rapid operationalization. In addition, we must not forget the importance of the upstream pipeline, recognizing that the potential for clinical trials during West Africa 2013 was heavily bolstered by decades of basic science and preclinical research to provide at least some viable candidates to test in the field. Lastly, it would be naive to think that profit-driven market forces will not retain a major influence on what drugs are developed, or not, for EVD and other emerging infectious diseases.

EXPERIMENTAL VACCINES

As with therapeutics, the urgency of West Africa 2013 thrust vaccines for EVD from a conventional protracted research and development timeline into high gear, with an unprecedented rapid mobilization of researchers, vaccine manufacturers, and coordinating agencies to expedite clinical trials and vaccine deployment. Since the start of

West Africa 2013, at least 40 clinical trials are underway with more than eight filovirus vaccine candidates. Resource-rich countries' concerns over Ebola virus as a bio-weapon again resulted in having numerous candidates, with at least 15 vaccines under development in North America, Europe, Russia, and China (123). The candidates in the most advanced stages were a replication-competent recombinant vesicular stomatitis virus-vectored vaccine (rVSV-ZEBOV) (124–126) and a replication-incompetent recombinant chimpanzee adenovirus-3-vectored vaccine (ChAd3-EBO-Z) (127), both expressing the Zaire Ebola virus surface glycoprotein.

rVSV-ZEBOV is the only vaccine for which efficacy data exist. Preclinical data had been available for some years showing impressive preventive and postexposure prophylactic efficacy in NHPs, but the vaccine awaited an interested pharmaceutical partner to take it forward into clinical trials. West Africa 2013 finally provided such an initiative. Rapid phase I and II clinical trials were undertaken at various sites in the United States, Europe, and Africa (outside the EVD epidemic zone) with generally favorable results. A large phase III trial was then implemented in Guinea with a ring vaccination approach in which close contacts of newly diagnosed EVD cases were randomized to receive either immediate or 21-day delayed vaccination (124). The trial design is indicative of the unique circumstances and sensitivities of West Africa 2013, in which inclusion of a placebo group was considered to be unacceptable. Preliminary results show 100% efficacy (no infections in those immediately vaccinated, compared with 16 who received delayed vaccination). Given the favorable results, the vaccine was employed in the later stages of the outbreak to help stem the spread from reintroduced virus from sexual transmission. However, the clinical trials also engendered considerable safety concerns, with vaccine-induced arthritis, dermatitis, and vasculitis (124, 130). Further investigation is necessary to deter-

mine the cause of these adverse events and the optimal dose to achieve maximal immunogenicity with minimal toxicity.

ChAd3-EBOZ also had undergone promising preclinical testing prior to West Africa 2013. Phase I and II trials were again expedited, with overall favorable safety results, as one might expect from a nonreplicating vaccine (128). However, preliminary data suggest that while a single dose of ChAd3-EBOZ may be sufficient for short-term protection, boosting with a modified vaccinia virus Ankara vaccine (MVA-BN-Filo) is necessary to achieve long-lasting immunity (127, 129), a requirement that would add complexity and expense. The optimal dose of ChAd3-EBOZ may also be quite high—up to 10^{11} particle units. Lastly, the immune response to primary adenovirus vaccination appears to reduce uptake of subsequent vaccinations with the same virus, meaning that subsequent vaccines would be required to use a heterologous adenovirus vector. Thus, although overall ChAd3-EBOZ appears to be a safe and efficacious vaccine, the various logistical complications threaten to reduce its utility during outbreaks. However, it may have a favorable profile for more stable settings, such as vaccination of HCWs or members of the military, or even inclusion in routine Expanded Program on Immunization (EPI) vaccination schedules.

As with the therapeutics, West Africa 2013 prompted significant but incomplete advances in vaccines for EVD, with many lessons on how to conduct vaccine research during complex humanitarian disasters. But many scientific, economic, and logistical questions remain: How do the safety and efficacy profiles of rVSV-ZEBOV and ChAd3-EBOZ compare? The ongoing PREVAIL I trial in Liberia should provide answers by directly comparing the two vaccines. Although designed as a safety and immunogenicity study, it is designed to upgrade to an efficacy trial if EVD were to reemerge in the area. What are the ideal doses of these vaccines that provide the best balance of

long-term immunity and minimal toxicity? Are the existing data on rVSV-ZEBOV sufficient to allow full licensure? If so, will rVSV-ZEBOV or any vaccine for EVD be considered sufficiently economically viable to the pharmaceutical industry to ensure production and availability? And if available, how would an EVD vaccine be used—incorporated into the routine vaccine schedule in sub-Saharan Africa, given to all HCWs, or reserved for ring vaccination or mass vaccination campaigns once an outbreak of EVD is confirmed?

NEW DIAGNOSTIC METHODS

The nonspecific clinical presentation of EVD has always posed a challenge for both early detection of outbreaks and identification of individual cases. Furthermore, since most cases that initially appear to be EVD turn out to be other diseases, laboratory diagnosis is imperative. It is a required first step in initiating the international response that has almost always been necessary to control outbreaks and for case identification in the subsequent outbreak response. Unfortunately, very few established laboratories in sub-Saharan Africa had diagnostic capacity for EVD, usually necessitating diagnostic samples to be sent to one of the very few BSL-4 laboratories that specialize in viral hemorrhagic fevers. This has usually resulted in delays of weeks to months between virus introduction and the first cases and laboratory confirmation (6, 18). The first laboratory confirmation of EVD in West Africa in early 2014 was performed by the Institut Pasteur at the Jean Mérieux-INSERM Laboratory in Lyon, France, over 3 months after the retrospectively identified first case in Guinea.

Since the first recognized EVD outbreak in 1976, the capacity for diagnostic laboratory support during outbreaks has gradually increased. For many years, laboratory diagnosis was only available retrospectively. Samples were taken from people who met the EVD

case definition and were eventually sent to one of the few overseas laboratories that could perform the diagnostic testing. Enzyme-linked immunosorbent assay with back-up cell culture were the predominant diagnostic modalities (130, 131). In the Gulu 2000 outbreak, for the first time, a laboratory was established on site by the CDC to provide near real-time diagnostics by both PCR and enzyme-linked immunosorbent assay (132). This then became the norm, with one or two diagnostic laboratories on site for virtually all EVD outbreaks since then.

In recent years, PCR has become the platform of choice due to the increasing availability of reagents and thermocyclers and streamlined methods for their use at ever diminishing cost. The incredible number and widespread distribution of cases in West Africa 2013 necessitated a vast laboratory network, a challenge to which the international community responded by establishing over 50 EVD diagnostic laboratories, most providing reliable diagnostic results within 24 hours after receipt of a specimen. This could be considered one of the success stories of the outbreak response. However, a major question now is how much of this capacity will be retained once the outbreak in West Africa has been extinguished. Indeed, most of these laboratories closed, and the staying power of those that remain is yet to be determined. It is imperative that the efforts to establish EVD laboratory diagnostics during the outbreak transition to long-term capacity—perhaps a reference laboratory in each country or, at a minimum, a central laboratory for the region.

Despite its utility, the widespread availability of PCR for EVD has also created some challenges; the laboratories established in the West Africa outbreak did not constitute a coordinated network. Rather, each operated independently with varied PCR platforms and protocols, including criteria for calling a sample positive. Informal quality control efforts performed in Sierra Leone through

analysis of a common serum panel did fortunately indicate that most laboratories were rendering comparable results (Gary Kobinger, personal communication). Nevertheless, significant discrepancies have been occasionally noted, especially for samples near the margins of the threshold for being considered positive.

A major challenge throughout the outbreak has been that of interpreting PCR results. The relative availability and ease of the PCR platform has resulted in the technique largely replacing cell culture—a technique that requires not only a BSL-4 laboratory but also overcoming the ever-increasing regulatory hurdles for shipment of biological samples. While cell culture directly demonstrates the presence of infectious virus, interpretation of PCR relies mainly on the Ct, a parameter that varies inversely to viral load (i.e., a low Ct represents a high viral load). Because of the extreme amplification capacity of PCR, very small quantities of viral RNA may result in a positive test, often with a high Ct near the limits of the threshold for a positive test. In these cases, there is considerable confusion about whether the result represents the presence of infectious virus or simply residual RNA in recovering patients. Furthermore, the interpretation of the result has come to have major significance for both individual patients and the overall outbreak response. Despite the lack of evidence-based algorithms for their use, PCR results have been widely incorporated into patient discharge criteria, at times resulting in the perhaps unnecessary retention of patients who have clinically recovered but have persistence “positive PCRs,” usually with high Cts. This has even at times resulted in blocking beds in ETUs that are desperately needed for newly diagnosed and highly infectious cases with patients who have largely clinically recovered and likely pose minimal risk of infection (133).

The difficulty in interpreting PCR results is also a reminder of the trade-off of the

United States and other resource-rich countries' research priorities over the past few decades, which have relatively narrowly targeted the development of specific countermeasure products—i.e., diagnostic assays, therapeutics, and vaccines. The program can be considered a success in that regard, having produced numerous products sufficiently advanced in their preclinical development to enable clinical trials when EVD hit West Africa. However, the down side of this approach is that few funds were available for studies oriented toward a deeper understanding of the basic modes of virus transmission or EVD pathogenesis—knowledge gaps that have posed significant challenges both in mounting outbreak response operations in the field and setting public policy. More research regarding the natural history of EVD and virus shedding and the relationship of Ct to the presence of infectious virus as well as standardized PCR reagents and platforms is needed to produce evidence-based patient management and discharge algorithms. Optimal utility will likely only be achieved by incorporating both laboratory and clinical data.

While the widespread availability of PCR diagnostics generally represents a great step forward, the limitations of any technique requiring a fixed laboratory (need for sophisticated equipment and trained laboratory staff, requirements for safe phlebotomy and specimen delivery to the laboratory, and 24-hour turn-around time for results) have brought about great interest in point-of-care rapid tests for EVD. Such tests have a particular attraction given the remote terrain often involved. Suspected cases requiring a rapid decision on the need for isolation and treatment might be seen at sites at a day's drive over rugged terrain from the diagnostic laboratory. In response to this need, numerous rapid diagnostic tests for EVD have been developed and received emergency use approval from WHO (134). However, concerns over moderate sensitivity and specificity, with potentially grave consequences of both

false-positive and -negative results, have brought about considerable hesitation to field implementation, resulting in very limited use to date. Enhancing and validating the sensitivity and specificity of these tests, perhaps in diagnostic algorithms combining clinical and epidemiologic data, could perhaps render a tool that could drastically change the landscape with regard to both initial detection of EVD outbreaks as well as patient management and outbreak control across sub-Saharan Africa.

Lastly, genetic sequencing technology was increasingly employed during West Africa 2013 to give a better understanding of the molecular epidemiology. Whole-genome sequencing was performed on hundreds of samples, a far larger number than had been sequenced before, to give a rapid understanding of the virus evolution and geographic provenance during the outbreak (135, 136). The bulk of this work was done through shipment of samples to overseas laboratories. However, by the end of the outbreak sequencing capability was also being built in West Africa (137). In the future, if real-time sequencing technology can be routinely folded into the repertoire of existing laboratories in sub-Saharan Africa and/or mobile laboratories established during EVD outbreaks, we can envision sequence data becoming an integral and invaluable part of field operations, with real-time transmission of sequence and epidemiological data linked to surveillance teams to provide leads in contact tracing. Sequence data are especially valuable toward the tail end of outbreaks or when cases pop up in new areas with no clear epidemiological link. Indeed, sequence data have been key in helping to pinpoint the probable origins of late EVD flares in Liberia and Guinea (87, 137). In addition to its utility in field surveillance, mutations identified by sequence monitoring could provide early warning of developing drug resistance (especially with monoclonal antibody and sequence-based therapies, such as small interfering RNAs) (138) and primer mis-

matches that could inhibit sensitivity of sequence-based assays, including PCR.

INFORMATION TECHNOLOGY TO IMPROVE FIELD SURVEILLANCE AND CASE MANAGEMENT

Increasing convergence of the fields of medicine, epidemiology, and information technology holds enormous potential to enhance field surveillance and case management. The incredible dissemination of cell phone technology even to the farthest reaches of sub-Saharan Africa in the past few decades holds the potential for real-time digital sharing that could never have been imagined 20 years ago. Myriad uses can be envisioned.

Digital data sharing and tracking technology through cell phones and simple SMS text messaging could be used to streamline and largely replace the logistically cumbersome, expensive, and slow processes of physical contact tracing, especially for contacts living in remote locations. Instead of relying on physical meetings of surveillance teams, the day could start with cell phone teleconferences to receive the key information from the night before and lay out the day's surveillance priorities, perhaps with set check-ins twice daily to provide and receive updates from the field and relevant laboratory data. The movement of field teams could be monitored with the GPS systems routinely incorporated into smart phones. Daily physical visits to contacts could be replaced by daily time-stamped SMS texts, reserving in-person visits for those who report symptoms. Digital photos could also be taken and sent for verification purposes or for inquiries to expert clinicians. Although somewhat more complex, systems for on-site data entry and immediate download to a central server could provide real-time actionable information to surveillance coordinators as well as improve the quality of data, since such systems have controls to ensure that key

variables are not skipped and are answered within allowed parameters. These data could be augmented by scanning reports of social media programs, such as the popular WhatsApp, to glean informal surveillance chatter, providing early leads to areas of possible new transmission.

Digital technology could also be used to streamline and enhance the quality of case management, enabling patients and their data to be tracked throughout the process. For example, a bar-coded scannable and washable plastic wrist-band could be placed on the patient upon presentation to the ETU or pick-up in their village by the field team. Daily scanning with a simple bar-code reader would allow tracking of the patient from ambulance pick up through admission, stay, and discharge from the ETU. Inside the ETUs, digital data transfer can (and already has been in some ETUs) used to transfer clinical data from the "red zone" to the outside for real-time analysis.

Although the aforementioned applications of information technology, and undoubtedly many more, are certainly possible, most of them remained at the "idea stage" during West Africa 2013. There are also logistical issues about power and connectivity to be considered, although as mentioned above, simple SMS messaging is now possible, and indeed already used, in nearly every community in Africa. Perhaps more challenging as information technology is increasingly relied upon to collect and share data, are ethical issues regarding patient confidentiality and data ownership. Advanced planning to work out these nontrivial issues and allow rapid implementation of these new and powerful tools in future outbreaks will be the challenge now.

CONCLUSIONS AND FUTURE CHALLENGES

Albeit unwelcome, the magnitude of West Africa 2013 provided a unique opportunity

and obligation to better understand the biology and epidemiology of EVD and, equally as important, the many scientific, economic, social, political, ethical, and logistical challenges in confronting emerging diseases in the modern era. As the global population surges and becomes more interconnected, the risk of such outbreaks is destined to increase. In the absence of redoubled efforts to build capacity for surveillance and response, outbreaks such as West Africa 2013 threaten to become the “new norm.” One need not look much further for the proof than to the Zika virus outbreak that, at this writing, is riffling through the Caribbean and Latin America.

But despite the tragedy of West Africa 2013, the outbreak also provided us with a notion of how we can and must respond better. The pressure is, rightly, on to capitalize on these glimpses of innovation and research progress to create a new norm of comprehensive surveillance and organized response. Much of the pressure rightly falls on WHO to revamp and restructure its operations, but WHO cannot do it alone or in the absence of sufficient funding. Lastly, let us remember that, while important, scientific and technological advancement alone will never be sufficient; poverty and a lack of the fundamental human right to health consistently underlie outbreaks of emerging pathogens (139). EVD is but the proverbial “canary in the coal mine,” indicative of the world’s most vulnerable populations. We must advocate for and work toward restitution of the right to health in LMICs. This will entail much more than simply building a laboratory or conducting a research project. Local educational institutions must be strengthened and career opportunities created to stop the “brain drain” of HCWs to high-income countries and produce future “home-grown” leaders in the health sciences. Novel and technology-appropriate approaches to local problems must be sought, as well as the funding mechanisms that enable their execution. Responsibility

falls also on LMICs to create strong and transparent governmental and public health administrative frameworks that are capable of capitalizing on international collaboration and support. Long after West Africa 2013 is over, these will be our true measures of success.

ACKNOWLEDGMENTS

The authors thank Ian Crozier, Frederique Jacquerioz, Lina Moses, Mikiko Senga, Nahoko Shindo, Armand Sprecher, and Constanza Vallenias for input on the manuscript’s content and Lara Schwarz for assistance with its preparation.

DEDICATION

This article is dedicated to the many health care workers who sacrificed their time, energy, and all too often, their lives to combat the Ebola virus disease outbreak in West Africa (140).

CITATION

Bausch DG, Rojek A. 2016. West Africa 2013: Re-examining Ebola. *Microbiol Spectrum* 4(3):EI10-0022-2016.

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