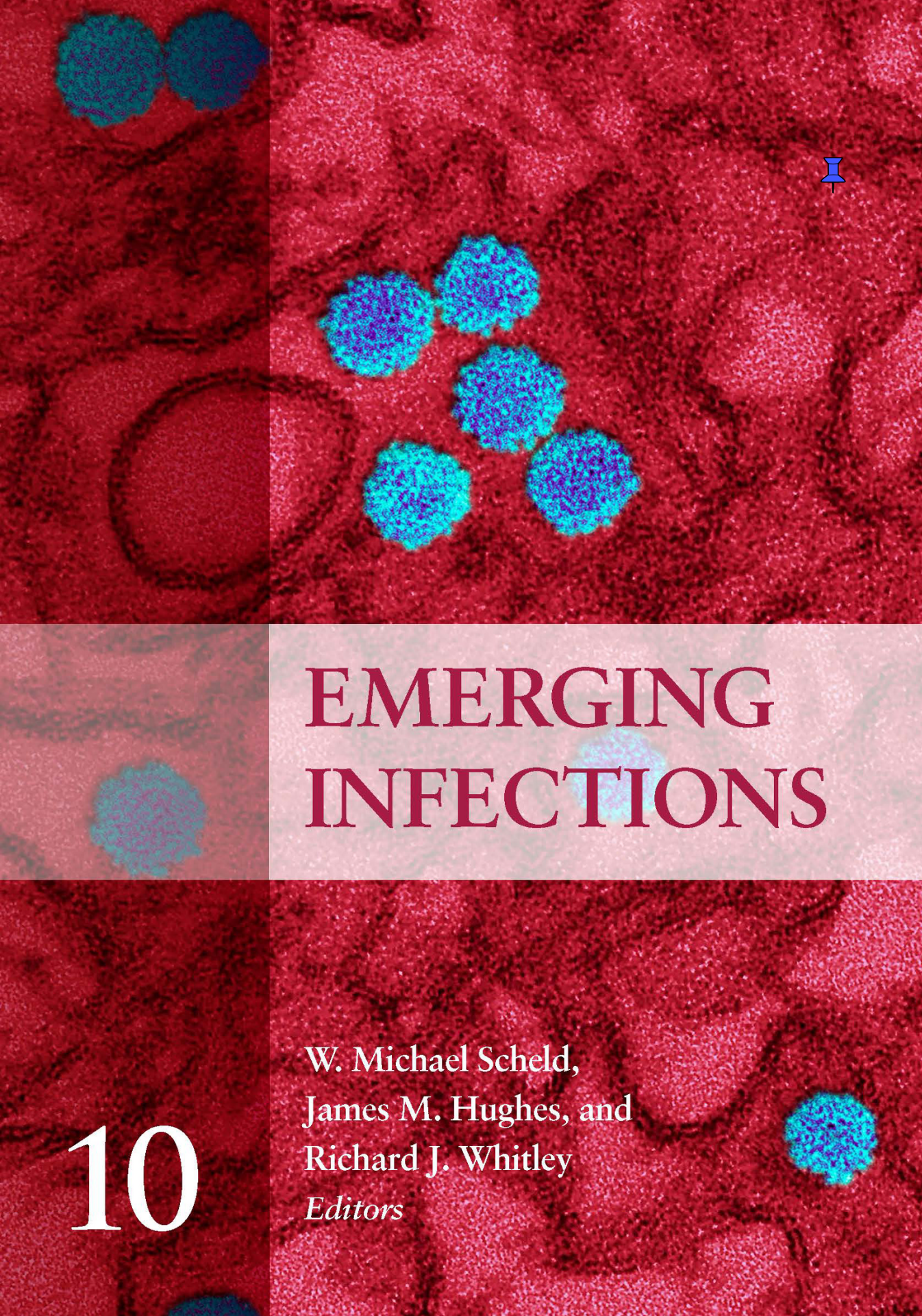

EMERGING INFECTIONS

10

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Editors

EMERGING INFECTIONS 10

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In memory of William A. Craig (1939-2015) and Robert C. Moellering, Jr. (1936-2014), two highly esteemed colleagues, clinicians, educators, investigators, and mentors. We thank them for their friendship, inspiration, and collective contributions to the development of nearly every new antibacterial agent in the last four decades.

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Foreword

The field of emerging and re-emerging infectious diseases has traveled from A (anthrax) to Z (Zika) in less than 15 years. Fortuitously, over that same interval, the insights, tools, and investments needed to address these challenges to medicine and public health have kept pace. The One Health Initiative has its roots in antiquity but only began to gather momentum with the appearance of West Nile virus in the Americas in 1999. Investigators now prospect wildlife and domesticated animals worldwide looking for novel agents and hints for origins of the next pandemic.

Molecular strategies for microbial surveillance, diagnosis and discovery have largely supplanted more laborious and expensive classical methods, resulting in an explosive expansion of genetic data that require increasingly complex and powerful resources for bioinformatic and biostatistical analysis. Discovery, an activity once focused in the West, is becoming decentralized as costs and expertise required for sequencing decrease. Governments and foundations invest in support of the United Nations International Health Regulations of 2005—a document signed by all member states "designed to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." The importance of this document and of the commitment of the scientific and communities to transparency has been underscored by the emergence of pandemic strains of influenza, antibiotic-resistant bacteria, Nipah, SARS, chikungunya, MERS, Ebola, and most recently Zika, which threaten regional and global public health as well as economic security.

The U.S. Supreme Court decision in the *Association for Molecular Pathology v. Myriad Genetics* that challenged the patentability of sequences existing in nature had ramifications far beyond the field of diagnostic oncology that prompted the initial litigation. It effectively ended the race to simply recover, claim and license microbial sequences of emerging pathogens. The result has been to encourage more mechanistic science. The number of laboratories focused on work in high-level biocontainment has dramatically increased. This has enabled more investigators to contribute to research into the biology, pathogenesis, diagnosis, prevention and treatment of emerging infectious diseases. It has also driven concerns about gain-of-function and dual use research as well as inadvertent release of high threat agents. An appropriate balance will be essential if the needs of all stakeholders are to be met.

Emerging Infections 10 is the latest in an American Society for Microbiology series initiated in 1998. My dear friend and mentor, the late Josh Lederberg, who

wrote the foreword to *Emerging Infections* 1, would be pleased to see that the series is alive and well and that the authors include an international cast of veterinarians, physicians, basic scientists, and public health practitioners. He would have anticipated the emergence of novel agents and the re-emergence of old foes like measles. In channeling Josh and his propensity for driving the field with predictions, I expect that volume 11 will feature chapters on modeling and the role of social media in biosecurity.

W. Ian Lipkin
New York, NY
2016

Preface

Despite progress in the prevention and control of infectious diseases during the past several decades, the first 15 years of the 21st century continue to provide evidence of the persistence and tenacity of emerging microbial threats. The interplay of rapid globalization, demographic shifts, ecological changes, environmental degradation, climate change, and unprecedented movement of people, animals, and commodities yield unexpected risks to health, often with attendant social, economic, and political repercussions. The emergence and rapid global spread of diseases such as MERS, Ebola virus disease, chikungunya, and Zika virus disease provide dramatic evidence of the continued ability of microbes to emerge, spread, adapt, and challenge the global infectious diseases, microbiology, and public health communities. In addition, the resurgence of long recognized diseases such as measles and pertussis and the spread of diseases such as coccidioidomycosis beyond endemic areas pose additional challenges.

Since 1995, annual infectious diseases meetings including those organized by the Infectious Diseases Society of America and the American Society for Microbiology have included updates on emerging infectious diseases. The 22 chapters in *Emerging Infections 10* provide important updates on a broad range of emerging and re-emerging bacterial, viral, parasitic, and fungal infectious diseases in the United States and globally. Highlights include timely chapters on MERS, Ebola virus disease, chikungunya, and Zika virus disease which have recently been the focus of clinicians, researchers, and public health officials around the world and have received extensive media attention. The global threat of antimicrobial resistance is addressed in chapters on carbapenem-resistant *Enterobacteriaceae,* multiply-resistant gonococcal infections, non-typhoidal *Salmonella* infections in sub-Saharan Africa, and artemisinin-resistant *Plasmodium falciparum* malaria. Topics range from recently recognized diseases to long-recognized diseases posing current challenges to the clinical, laboratory, research, public health, and animal health communities.

Our experiences in responding to recent outbreaks, many of which are of vectorborne or zoonotic origin, provide important lessons for the future and highlight the relevance and importance of the One Health concept which emphasizes the importance of closer collaboration among the human, animal (both domestic and wildlife), and environmental and ecosystem health sectors. Recent experience emphasizes the importance of preparedness to respond to domestic and global threats with a co-ordinated, evidence-based, interdisciplinary response guided by strong, effective leadership at the national and global levels and accelerated implementation of a research agenda to provide tools to support diagnostic, therapeutic, and prevention strategies.

Because weak health systems in many areas of the world pose threats to all, investments in health system strengthening, national public health institutions, response capacity, and workforce development can yield substantial returns for the health and security of the global community. Recent experiences with and lessons learned from MERS, Ebola virus disease, chikungunya, and Zika virus disease have highlighted the importance of strengthening national capacities in support of the International Health Regulations and the Global Health Security Agenda. Fortunately, important scientific and prevention opportunities in the future are likely to result from advances in molecular diagnostics, next generation sequencing, utilization of big data, microbiome research, pathogen discovery, and epidemic modeling.

Future infectious disease challenges are difficult to predict but certainly include antimicrobial-resistant infections in healthcare and community settings, foodborne and waterborne diseases, influenza and other respiratory diseases, and vectorborne and zoonotic diseases, as well as new threats for immunocompromised and disadvantaged populations. Additional links between chronic diseases and infectious agents and between the microbiome and human health and disease will certainly be identified, providing new prevention and treatment opportunities. We hope the tenth volume in the *Emerging Infections* series will serve as a valuable resource for those currently working to address emerging infectious disease threats to national and global health and security as well as for the next generation of talented, committed professionals needed to confront these threats in the future.

W. Michael Scheld
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We thank all of our colleagues who have helped us in preparing this volume. Most importantly, we thank all of the authors for their outstanding contributions. As editors, we are particularly grateful to the members of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) Program Committees who assisted us in coordinating topic and speaker selection for and/or moderating the joint symposia on emerging infections during previous ICAAC and IDSA meetings. As past presidents of IDSA, we would especially like to thank Mark Leasure, the soon to retire CEO of IDSA, for nearly 20 years of outstanding service to the Society and the infectious diseases profession. Numerous other colleagues provided helpful discussion, advice, and criticisms. We are also grateful to our assistants, Lisa Cook, Dianne Miller, and Dunia Ritchey. We also want to thank Lauren Luethy, Megan Angelini, and their colleagues at ASM Press for their superb work in coordinating production of the book. And finally, we thank our families for their understanding and support during this undertaking.

1

West Africa 2013: Re-examining Ebola

DANIEL G. BAUSCH[1] and AMANDA ROJEK[2]

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 fledging 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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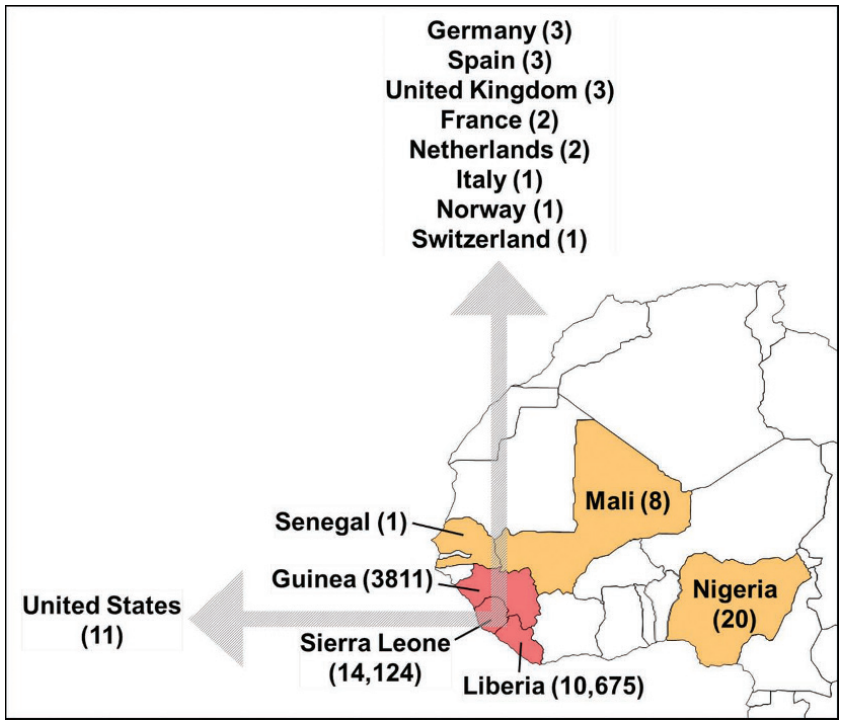

FIGURE 1 Map of West Africa showing the epicenter of the 2013–2016 outbreak of Ebola virus disease (red) and imported cases (orange and arrows). The total number of cases seen in each country is shown in parentheses.

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	Taï Forest	Côte d'Ivoire	Taï 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

[a]Abbreviations: CFR, case fatality rate; DRC, Democratic Republic of the Congo; ROC, Republic of the Congo; NHP, nonhuman primate.
[b]May 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

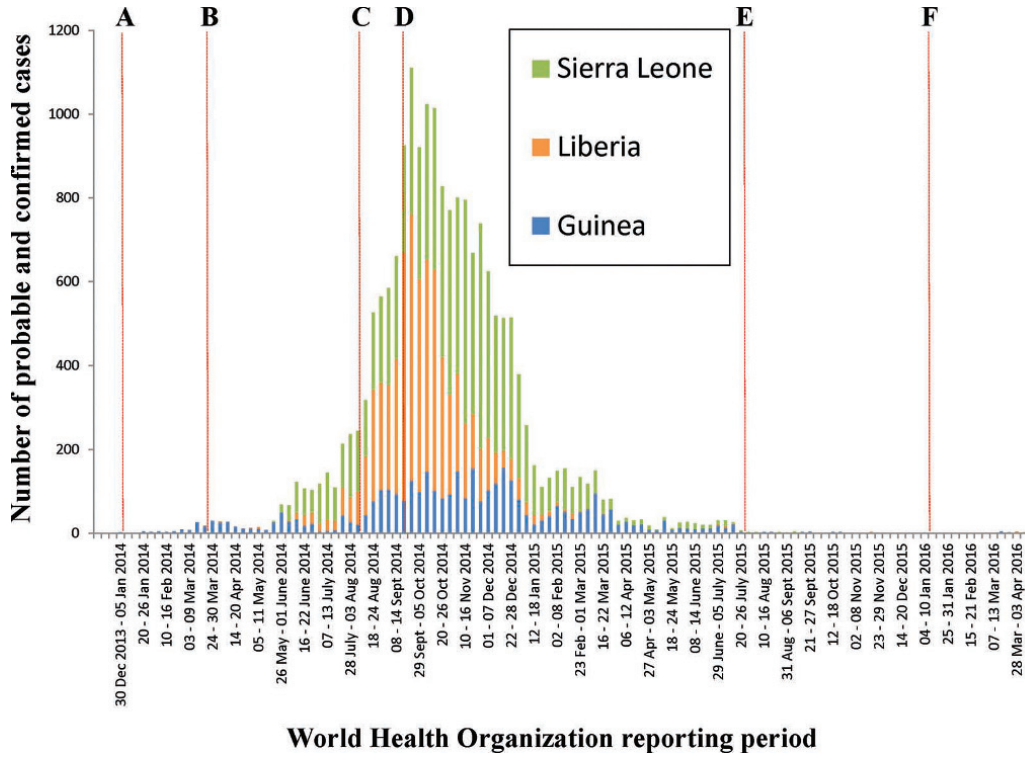

FIGURE 2 Epidemiologic curve of the West Africa 2013 Ebola virus disease (EVD) outbreak. The dashed vertical lines indicate key events during the outbreak: (A) First suspected case in Meliandou, Guinea. (B) Laboratory confirmation of EVD and disease reported by Guinean Health Authorities. (C) WHO declares 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 undermined the local population's already shaky faith in the response operation.

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%

[a]Bed 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.

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

	Republic of the Congo	Guinea-Liberia-Sierra Leone
Population	68 million	22 million
Surface Area (Km²)	2.3 million	430,000
Population Density (persons/ Km²)	**30**	**51**

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