

The Ebola Outbreak of 2014-2015: From Coordinated Multilateral Action to Effective Disease Containment, Vaccine Development, and Beyond

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ABSTRACT

The Ebola outbreak of 2014-2015 exacted a terrible toll on major countries of West Africa. Latest estimates from the World Health Organization indicate that over 11,000 lives were lost to the deadly virus since the first documented case was officially recorded. However, significant progress in the fight against Ebola was made thanks to a combination of globally-supported containment efforts, dissemination of key information to the public, the use of modern information technology resources to better track the spread of the outbreak, as well as more effective use of active surveillance, targeted travel restrictions, and quarantine procedures. This article will outline the progress made by the global public health community toward containing and eventually extinguishing this latest outbreak of Ebola. Economic consequences of the outbreak will be discussed. The authors will emphasize policies and procedures thought to be effective in containing the outbreak. In addition, we will outline selected episodes that threatened inter-continental spread of the disease. The emerging topic of post-Ebola syndrome will also be presented. Finally, we will touch on some of the diagnostic (e.g., point-of-care [POC] testing) and therapeutic (e.g., new vaccines and pharmaceuticals) developments in the fight against Ebola, and how these developments may help the global public health community fight future epidemics.

Key words: Diagnostic and therapeutic update, Ebola outbreak, epidemiology, socioeconomic developments, West Africa

INTRODUCTION

The current 2014-2015 Ebola virus (EBOV) outbreak is among the most significant global health threats in recent history. Despite a number of recorded EBOV transmission events dating back approximately four to five decades, the current outbreak is not only devastating locally and regionally but also presents a real possibility of the global spread of this highly lethal disease. The natural history and biology of the virus have previously been described in detail and are beyond the scope of the current review.^[1,2] Critically important to the evolving capability of the global community to effectively

respond to outbreaks and epidemics is the ever-growing armamentarium of our collective global knowledge and the ability to practically apply this knowledge. In September 2014, the United Nations (UN) Security Council passed Resolution 2177, which stated that the Ebola outbreak was a threat to world peace under article 39 of the UN Charter. This is the first time that

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the council determined a health issue to be a threat to world peace.^[3]

The purpose of this review is to summarize progress made during the globally supported fight against the current EBOV outbreak, and focus on a number of important new developments, including practical applications of modern information technology tools, coordinated deployment of public health and infrastructure resources, development of more effective and increasingly portable POC testing methods, as well as a general overview of the results of recent therapeutic trials of new vaccines and pharmaceutical agents.

OUTBREAK DYNAMICS: ACCURACY OF INITIAL OUTBREAK MAGNITUDE ESTIMATES

Since January 2015, significant progress has been made to contain the current Ebola outbreak. Multilateral efforts, supported by major global interests, are now producing results.^[1] Although some may attribute the magnitude of the much-needed Ebola coordinated global response to the early Centers for Disease Control (CDC) modeling team estimates of as many as 1,400,000 possible infections in West Africa, others point out that this number overestimated the actual magnitude of the outbreak by approximately 65 times.^[4] The CDC team responded that their estimates were made using a number of assumptions and represented the “worst case” scenario, which fortunately never materialized.^[4]

Latest estimates from the World Health Organization (WHO) indicate that over 11,000 lives were lost to the deadly virus since the first documented case was officially recorded [Figure 1]. While there are still a few new cases and deaths, the outbreak appears to be progressing toward eradication. Figure 2 represents declining monthly mortality since the initial case reports in March of 2014. This trend is likely a reflection of more aggressive disease surveillance, early identification and clinical intervention, as well as the increased level of resources available as a result of international relief efforts. Additional age-stratified epidemiologic data for the current outbreak, including incubation period, onset of hospitalization, and onset of death are summarized in Figure 3.^[5]

EXTINGUISHING THE OUTBREAK

As with many outbreaks in history, the declaration of victory may still be premature. In Liberia, for example, the country was declared “Ebola-free” on May 9, 2015.^[6] However, within two months of this date, at least 3 new

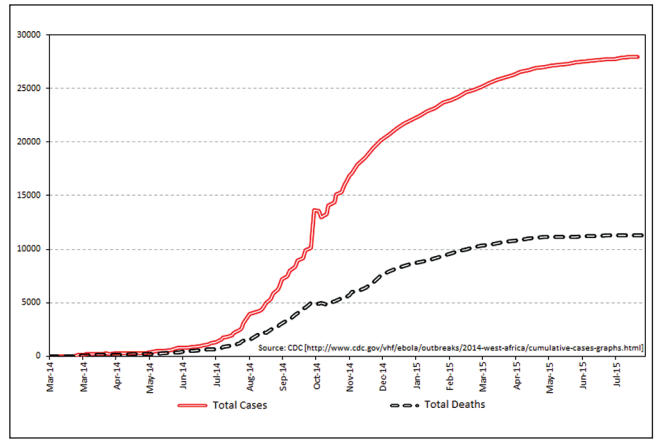


Figure 1: Total cases (red line) versus total deaths (black line) as reported by the World Health Organization between March 22, 2014 and August 19, 2015 (data reported for Guinea, Liberia, and Sierra Leone)

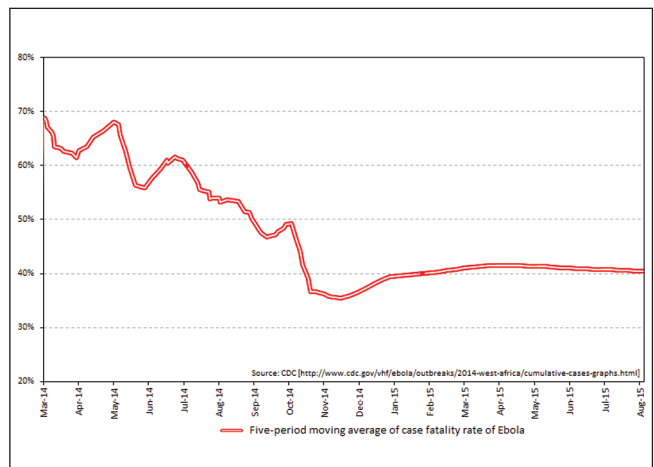


Figure 2: Five-period moving average of case fatality rate of Ebola (red line) as derived from the World Health Organization data between March 22, 2014 and August 19, 2015 (data from Guinea, Liberia, and Sierra Leone)

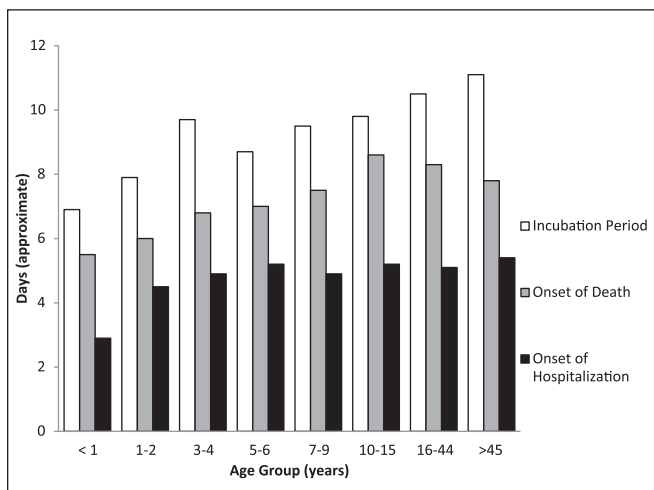


Figure 3: Age-stratified comparison of incubation periods, onset of death, and onset of hospitalization (expressed in days) for the current Ebola epidemic^[5]

cases of Ebola surfaced, all allegedly linked to consumption of dog meat.^[6] An estimated 175 people were reportedly linked to cases under surveillance in this latest episode.^[6] Fortunately, the situation appears to have improved again as the country was declared free of the EBOV transmission for the second time on September 3, 2015.^[7] Then, there were 2 confirmed cases of Ebola in the week leading up to September 6, 2015 (1 in Guinea and 1 in Sierra Leone).^[7] Overall, the incidence has remained stable at two or three cases per week for the six consecutive weeks leading up to September 6, 2015.^[7,8] Around that time, there were three active chains of transmission, two in Guinea and one in Sierra Leone.^[8] In addition, the WHO has announced that it is monitoring 2000 contacts in Guinea and Sierra Leone.^[9] Moreover, the WHO also warned that the arrival of the rainy season may significantly complicate the logistics of Ebola outbreak containment, specifically listing the three countries hit hardest by the disease — Sierra Leone, Liberia, and Guinea.^[9] While the recent incidence of Ebola has been very low and the outbreak relatively well contained, the optimism must be tempered with continued vigilance.^[7,8,10-12] Recently, Sierra Leone's President Ernest Bai Koroma prematurely announced the end of the country's Ebola quarantine after a 2-week "Ebola-free" status.^[10] A country meets "Ebola-free" status once 42 days have passed since the last confirmed case has tested negative for the virus on two separate samples. The WHO recommends an additional 90-day surveillance period after the 42 days have elapsed.^[13]

GLOBAL EVENTS: CLOSE CALLS AND FALSE ALARMS

Although the actual number of suspected Ebola cases globally is impossible to accurately estimate, certain high profile events must be discussed in order to enhance our understanding of the dynamics of the outbreak and the potential for its spread beyond West Africa. Occurrences associated with potential or actual appearance of Ebola outside of the primary outbreak geographic territories can be classified as either "close calls" (e.g., cases of Ebola that were treated in secondary locations and posed risk for potential viral transmission) or "false alarms" (e.g., instances where the risk of transmission was high, but individuals affected did not actually contract the virus).

Regarding "false alarms," several high-profile instances have been publicized since the summer of 2014. Such cases usually involve individuals considered to be at high risk because of recent contact with Ebola-affected persons or travel to Ebola-affected regions.^[14-18] In one instance,

88 Indian nationals evacuated from Liberia were screened for the virus, and one patient was quarantined for fever and "sore throat." Active surveillance was instituted for those at greatest risk of contracting Ebola and phone helpline numbers provided to those deemed at low risk of developing the disease.^[19] In another case, healthcare volunteers were transferred to the United Kingdom after potential Ebola exposure in Sierra Leone.^[20] In a most recent scare, a patient with Ebola-like symptoms in Birmingham, Alabama, as well as several other people who were in close contact with that individual, were quarantined because of concerns over recent travel history to high-risk areas.^[21] Following negative confirmatory tests, all individuals were released from quarantine.^[21]

CONTAINING EBOLA: COORDINATION OF GLOBAL EFFORTS

The WHO is the lead agency in developing strategies to control the current outbreak, including case management, case finding, laboratory services, and contact tracing.^[1,22-24] WHO has been working in conjunction with the CDC, UN, United Nations International Children's Emergency Fund, National Institutes of Health (NIH), various countries, and other public health coalitions to create strategies to combat the outbreak.^[1,25-27] The goals outlined by WHO involve extinguishing the outbreak in affected countries, preventing the development of new Ebola outbreaks, providing essential services to affected communities, accelerating and advancing Ebola-related research and development, as well as coordinating national and international Ebola response efforts.^[23,24]

Initially, efforts to combat the epidemic were hampered due to insufficient surveillance and laboratory services. WHO developed the Ebola Response Roadmap (ERR) that requested an estimated \$490 million in order to create 160 isolation centers containing 1500 beds, to increase the diagnostic capacity to an estimated 600 samples monthly, and to assist approximately 13,000 health care workers in offering critical services and assistance, conducting active and passive surveillance, as well as establishing safe burial practice protocols.^[28] For numerous reasons, WHO reduced the 2014-2015 ERR's budget by an estimated 51%.^[28] At approximately the same time, the UN Mission for Ebola Emergency Response formulated a coordinated and unified operational framework to approach donors for funding.^[29] In light of the reduced budget and associated constraints in available resources, major countries and public health coalitions donated and deployed much-needed resources and health care workers to supplement the overall effort.

The outbreak in West Africa spread quickly among local rural communities and villages. To help prevent disease transmission and more effectively control infection, WHO and its partners published emergency guidelines which were distributed to local and global public health agencies. In addition, support was offered to healthcare workers in the areas of clinical management of Ebola patients, personal protective equipment (PPE), contact tracing, laboratory testing, waste management, and safe burial protocols.^[30] WHO, CDC, and other coalition partners developed a Community Care Campaign, which initially aimed to cover an estimated 400,000 vulnerable households.^[28] This campaign created local community care centers (CCCs). The CCCs were intended to supplement the work of the Ebola Treatment Units (ETU) and thus aided in contacting potential cases that were not in close proximity to an ETU.^[31] The CCCs were able to provide a package of services based on the four pillars of the Ebola response strategy.^[31] These centers were managed by nongovernmental organizations, local healthcare workers, and family members of those affected by Ebola. Table 1 has been compiled from materials published by WHO, USAID, and CDC data and outlines key differences and similarities between ETUs and CCCs.

SOCIOECONOMIC IMPACT OF EBOLA

In Sierra Leone, Guinea, and Liberia the Ebola outbreak has affected a broad range of socioeconomic parameters. The virus to date has caused 28,256 confirmed cases and 11,306 deaths (of which 513 were healthcare workers).^[33] Age groups most impacted were those under the age of six and older than 16 years of age.^[5,33] Table 2 compares general population health characteristics of the countries hardest hit by the 2014-2015 Ebola outbreak to the population

characteristics of the United States. Figure 4 demonstrates that children between the ages of 10 and 15 years appear to have the lowest case fatality rate.^[5] Figure 4 also shows that highest fatality rates were seen among patients <5 years of age and those >45 years of age.^[5]

Observed gross domestic product (GDP) growth rates from 2013 to 2014 drastically declined in each West African nation affected by the outbreak [Figure 5].^[34-36] The

Table 1: Comparison between ETU and CCC^[28,31,32]

| Characteristics | CCCs | ETUs |
|-----------------------------------|--|---|
| Size | Up to 15 beds | >100 beds |
| Ebola diagnostic capability | Variable upon facility | Yes |
| Oversight of Ebola treatment | Conducted off-site | Conducted on-site |
| Healthcare services provided | Open 24/7; Oral rehydration/clean water; Medications: Antipyretics, analgesics, antimalarials, antibiotics | IV therapy: Transfusions, hydration fluids; Maintenance of BP and oxygenation; Treatment of other possible infections |
| Professionals offering Ebola care | NGOs, community health workers, family members of afflicted Ebola patients | Trained healthcare professionals |

ETUs: Ebola treatment units, CCCs: Community care centers, NGOs: Nongovernmental organizations, IV: Intravenous, BP: Blood pressure

Table 2: Country comparison of population health characteristics in 2014^[34-36]

| Parameter | Sierra Leone | Guinea | Liberia | USA |
|--|--------------|--------|---------|------|
| Live birth rate (per 1000 of population) | 37.0 | 37.7 | 34.4 | 12.5 |
| Death rate (per 1000 of population) | 10.8 | 9.46 | 9.69 | 8.15 |
| Infant mortality rate (per 1000 live births) | 71.7 | 53.4 | 67.5 | 5.87 |
| Life expectancy (years) | 57.8 | 60.1 | 58.6 | 79.7 |
| Under-5 years malnourished (%) | 18.1 | 18.7 | 15.3 | 0.5 |

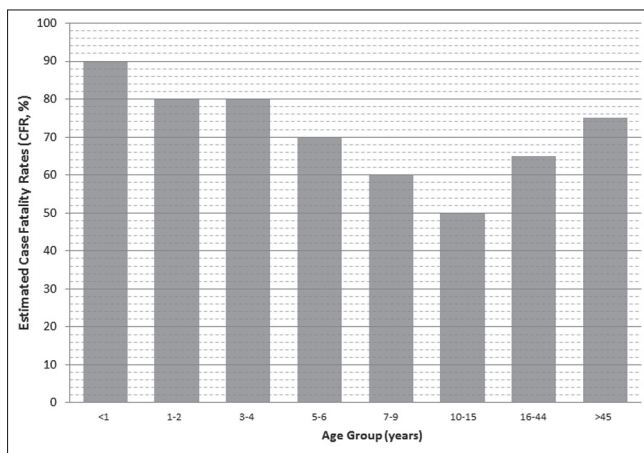


Figure 4: Comparison of case fatality rates of Ebola virus across various ages groups^[5]

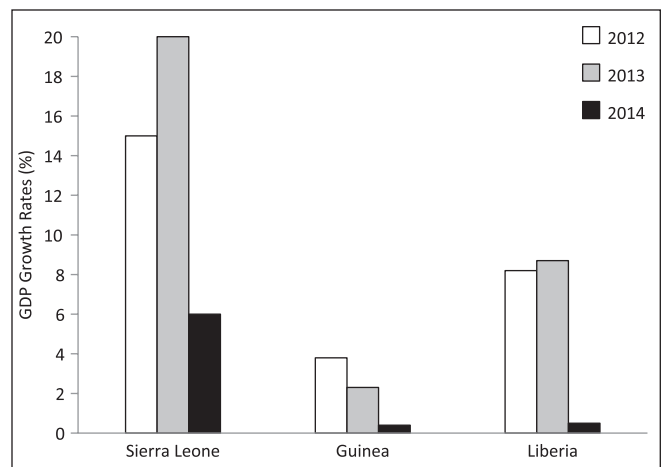


Figure 5: Gross domestic product growth rate percentages from 2012 to 2014 for Sierra Leone, Guinea, and Liberia^[34-36]

corresponding decline in current account balance can be attributed to the combination of slowing economic growth and significant costs associated with providing medical care to acutely ill patients and containing the spread of Ebola. Healthcare expenditures of the three most affected nations rose substantially throughout the course of the outbreak, noting that the “baseline” percentage of GDP spent on healthcare was 11.8%, 4.7%, and 10% in Sierra Leone, Guinea, and Liberia, respectively.^[34-36] The percentage of the population living below poverty level in 2014 was 70.2%, 47.0%, and 68.8% in Sierra Leone, Guinea, and Liberia, respectively [Figure 6].^[34-36]

In order to assist the public health sector in the most affected areas of West Africa, the World Bank developed the Ebola Recovery Response Plan with the objective to “...eradicate Ebola, restore basic socioeconomic services across countries, and lift economic growth rate.”^[37] The plan centered around two pillars:

- Immediate recovery strategies and
- Building national systems for resilience and sustainable development.^[37]

The World Bank estimates that this plan will require approximately \$219 million US dollars to ensure sustained control of the outbreak.^[37] Preliminary cost for immediate recovery programs is estimated at around \$625 million. Therefore, the total costs for the recovery plan will be approximately \$844 million.^[37] The World Bank has developed specific response teams for each of the West African nations affected by the Ebola outbreak.^[37-39] The overall framework will also involve the WHO, the United States government, various public health coalitions, as well as other third party organizations to secure the funds needed for the development, initiation, and successful execution of this plan.

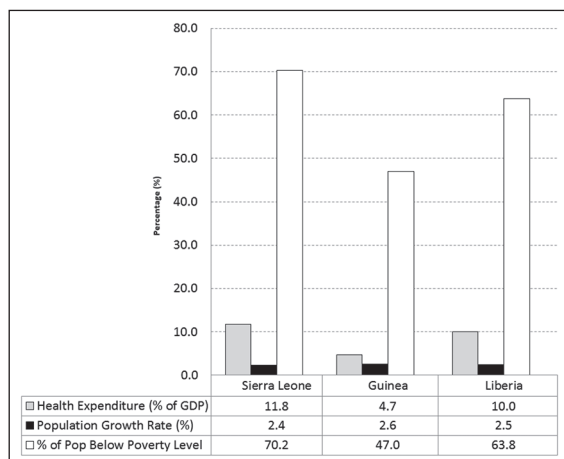


Figure 6: Recent data reflecting key socioeconomic parameters for the countries most affected by the 2014-2015 Ebola outbreak^[34-36]

RESOURCES TO FIGHT THE OUTBREAK, INCLUDING SUPPORT FOR REGIONAL RECOVERY

Since our last update in late 2014, nearly \$2.0 billion were spent on building infrastructure and providing much needed resources to the affected regions of Africa. In effect, each of the involved countries received a substantial amount of public health funding that was dedicated to furnishing essential supplies and medications, PPE, infection prevention and control materials, health worker education, hazard pay and death benefits for health workers and volunteers, contact tracing and data management, transportation, as well as door-to-door public health outreach.^[40]

The funding from key global institutions and networks has been instrumental in actively supporting the presence of health workers and other experts in the affected region, with over 1300 foreign medical workers deployed.^[40] This large healthcare contingent included over 830 personnel working for the African Union Support to the Ebola Outbreak in West Africa task force as well as 230 medical personnel from Cuba.^[40]

In all, the World Bank has reported that at least \$1.62 billion was devoted to fighting the current Ebola outbreak.^[40] Of those funds, \$260 million were assigned to Guinea, \$385 million to Liberia, and \$318 million to Sierra Leone, among other designated causes.^[40] Substantial financial resources were dedicated to providing social safety net programs, reviving agriculture and addressing hunger-related issues in Ebola-affected locales.^[40] In addition, \$450 million was designated to providing financing for trade, investment, and employment in the outbreak-affected regions, with additional \$250 million dedicated to a rapid response program that helps businesses in affected areas to continue their operations.^[40] Finally, \$200 million is earmarked for an Ebola recovery program that finances long- and medium-term projects during the post-outbreak period.^[40]

ETHICAL CONSIDERATIONS: QUARANTINE AND RELATED TOPICS

Many opinions emerged over the past year in response to mandatory and voluntary quarantine efforts. Given the fact that those with suspected exposure are not contagious until symptoms develop, some have called into question mandatory, time-defined quarantine systems.^[17] Others have pointed out that mandatory quarantine of foreign healthcare volunteers on return to their home countries acts as an active deterrent for those who are willing to commit

their time and effort to helping fight the outbreak.^[41] For some, the possibility of a 3-week quarantine made the option to volunteer prohibitive.^[42] For those in the military, the mandatory quarantine orders come from the highest echelon of military leadership, affecting those who helped build the health infrastructure needed to respond to the outbreak, but not coming into direct contact with affected patients.^[43] The US military decided to institute more stringent initial steps in order to avoid viral transmission events within its ranks, with indications provided that this policy will be reviewed and potentially revised based upon the initial experiences.^[43]

In one highly publicized case, an Ebola survivor who was originally treated and recovered from the infection in Liberia was quarantined on return to his native India after his semen sample tested positive for Ebola.^[18] Of interest, the CDC has listed one possible case of Ebola acquisition by sexual contact,^[7] adding some credence to the concerns of the Indian government in the above case. In another instance, five passengers returning from Nigeria to India were quarantined in Delhi for observation and released only after definitive testing at the National Centre for Disease Control demonstrated that they were not infected.^[19]

THE 2014-2015 EBOLA OUTBREAK: BROADER ECONOMIC CONSIDERATIONS

Although the true extent of economic damage is difficult to measure, the World Bank Group has estimated the GDP losses for the three countries to be approximately \$2.2 billion (\$240 million for Liberia, \$535 for Guinea, and \$1.4 billion for Sierra Leone).^[44,45] The amounts given above are related to specific interventions, but the total economic Ebola impact (not simply money spent, but all opportunities lost) will likely range from \$3.8 billion to \$32.6 billion, including factors such as investor aversion and interruptions to mining operations.^[46,47]

One way to mitigate the economic consequences of future Ebola epidemics (or other similar public health emergencies of international concern) may be to proactively address the potential for zoonotic spillovers in conjunction with enhanced recognition of regional disease patterns.^[48] Castillo-Chavez *et al.* comment that changes in land use, crop selection, migration and travel patterns, livestock use, and transportation all need to be carefully studied and considered.^[49] For instance, the incidence of zoonotic spillovers may be reduced by educating farmers on how to expand the production of conventional livestock.

According to a computational model developed by Bartsch *et al.*,^[50] the cost of a single Ebola case through December 2014 ranged from \$480 to \$912 if the patient recovered, and for patients that did not survive the range was from \$5929 to \$18,929. These results varied by locale. The total costs to society in Guinea, Liberia, and Sierra Leone are estimated to have been \$82,000,000 to \$356,000,000 related to patient care alone, excluding nonmedical impact. As indicated earlier in this review, total losses (economic/investment) will be much higher.

Although the current outbreak continues to primarily affect the three West African countries and their economies, there are significant differences in regard to the local impact across the Ebola-ravaged region.^[45] Liberia has experienced resurgence in mining and agriculture with 2015 GDP growth projected at 3% - an increase from the 1% GDP growth of 2014, but well below the pre-Ebola estimate of 6.8% growth. Guinea has rebounded with mining, but agriculture still struggles. The GDP is projected to continue to stall, compared to pre-Ebola projected growth of 4.3%. In Sierra Leone, the mining sector has essentially shut down and some estimates place the short-term economic contraction of GDP at a devastating 23.5%.^[45]

Inflation has moderated below 10% in the three countries, helped by lower international food and fuel prices, but food security remains a major concern.^[1,51] The simultaneous decline in government revenues and unplanned increases in health expenditures have led to widening fiscal deficits in the primarily affected countries.^[45] Economic losses continued to accrue from various sources, including agriculture, decreased cross-border trading, lower store sales, decline in construction and transportation activity, and significant reductions in the hospitality industry.^[1,45,52] Airlines canceled or restricted flights to Ebola-affected countries, and foreign companies slowed activities as expatriates (temporarily) exited the affected region.^[53] All of the above forces contributed to rise in local unemployment.^[52]

Substantial financial resources were dedicated to maintaining social safety net programs, reviving agriculture, and actively addressing hunger-related issues in Ebola-affected locales.^[40,44,45] As previously outlined, a total of nearly \$700 million in aid was designated to providing financing for trade, investment, “economic continuity,” and employment in the outbreak-affected regions.^[40,44,45] Additional \$200 million was earmarked for an Ebola recovery program that finances medium- and long-term projects in the post-outbreak period.^[40,44,45] It is critical to acknowledge that the pace of overall post-Ebola economic recovery will depend

on adequate financial support and effective recovery plans. Eradication of Ebola and enhancement of regional health care systems predominate the “top priority” list. Ongoing support from the international community continues to be crucial.

PHARMACEUTICAL AND THERAPEUTIC DEVELOPMENTS

The research focused on the pharmaceutical treatment of Ebola infection has produced somewhat disappointing results. One candidate drug, TKM-Ebola, after showing promise in primates, has subsequently been demonstrated to be ineffective in treating human Ebola infection.^[54] Although the other experimental IgG-based monoclonal antibody-based drug ZMapp has shown good efficacy in primates,^[55] there is no compelling evidence that it is effective in humans.^[56] In addition, despite a poorly defined safety profile, the drug recently received fast track approval by the Food and Drug Administration (FDA).^[57]

A number of so-called “small-molecule” agents have been tried during the 2014-2015 Ebola outbreak, including Lamivudine (a nucleoside analog of cytidine by GlaxoSmithKline, UK); Favipiravir (a pyrazinecarboxamide derivative by Toyama Chemical, Japan); and Brincidofovir (a lipid-conjugated analog of cidofovir by Chimerix, USA).^[56] Following review by the WHO, lamivudine was not recommended in the management of EBOV disease.^[58] The clinical trial of brincidofovir by Chimerix was canceled due to lack of participation in Liberia.^[56] There is ongoing clinical trials work (phase II) on favipiravir.^[59]

BLOOD OR PLASMA TRANSFUSION FROM SURVIVORS

Another promising treatment option reviewed in this group’s previous article was a transfusion of blood or plasma from convalescent Ebola survivors.^[1] It is noteworthy to mention that whole-blood or plasma transfusion therapy was determined to be ethically acceptable by the WHO during the 2014-2015 outbreak, provided that certain risk-benefit elements are taken into consideration by the treating healthcare team.^[60] Specific safety and ethical considerations include donor testing for EBOV RNA (must be negative on two independent blood draws conducted at least 48 h apart) and testing of the donated blood for donor-recipient compatibility and blood-borne infections. This general consideration also implies a requirement for facilities that are able to properly handle and process blood and blood products.^[56] Donated blood may vary in

protective efficacy because neutralizing antibodies may take several weeks to months to appear at sufficient levels.^[56] Clinical research is underway to determine if there are benefits associated with such transfusion therapy in the setting of EBOV disease.^[58]

VACCINE DEVELOPMENT

Very recently, trials of new Ebola vaccine vesicular stomatitis virus (VSV)-EBOV (an attenuated livestock vaccine developed by the Public Health Agency of Canada and licensed to NewLink Genetics and Merck) have been shown to carry sufficient promise that WHO felt it was indicated to immediately vaccinate all individuals at risk of being in close contact with an infected person.^[61] Henao-Restrepo *et al.* recently completed an open-label, cluster-randomized ring phase III vaccination trial in Guinea.^[62] This trial was called “Ebola, çasuffit” (in French, “Ebola, that’s enough”), and was designed based on the 1970s smallpox elimination programs. When a case was identified, all known close contacts were vaccinated (e.g., the “ring” of contacts). The authors reported an interim analysis of a recombinant, replication-competent VSV-based vaccine expressing the surface glycoprotein of Zaire Ebolavirus. The vaccine was tested on 90 clusters of 7651 people between April 1, 2015 and July 20, 2015. Two distinct sub-groups were studied:

- (a) An immediate vaccination “ring” group of 48 clusters of 4123 individuals; and
- (b) A delayed vaccine “ring” group (vaccinated 21 days later) of 42 clusters of 3528 individuals.

The presence of EBOV disease was sought during the first 10 days after vaccination. There were no cases of Ebola in the immediate vaccine group, and in the delayed group there were 16 cases from seven clusters. In brief, the vaccine demonstrated excellent overall efficacy.^[62] However, there were few cases in the immediate vaccine group beyond the 10-day window and because the groups were small, the true efficacy will likely be somewhere between 75% and 100%.^[63] Regardless, these results are exceptionally promising. Of note, it has been proposed that the development of vaccine should focus on more than one route of delivery, highlighting the possibility of creating and implementing nasal immunization that would provide a number of distinct benefits, including ease of delivery, improved patient compliance, and application of such methodology to other emerging infectious diseases.^[64]

Due to a large number of potential therapeutic agents being evaluated and utilized in the setting of the current

Ebola outbreak, the topic exceeds the scope of the current review. However, for all those who wish to obtain more information on specific agent's mechanism of action, use in prophylaxis, current and completed clinical trials, and other key information, we provide key references to the most important high-level review sources.^[54-59, 65-67]

POINT-OF-CARE TESTING

Significant progress has been made in the area of POC diagnostic testing for the EBOV. The ability to rapidly and accurately determine the presence or absence of an infection in individuals who are at high risk of contracting the virus provides an especially appealing method in the setting of an active Ebola outbreak because infected individuals do not become infectious until the onset of clinical symptoms.^[1,68-70] Consequently, the ability to identify those who are infected, but not yet acutely ill or actively infectious, provides two potentially unique benefits—early detection of those patients who require isolation, and the potential for instituting early antiviral therapy well before clinical symptoms appear. In a recently published report, the fingerstick ReEBOV rapid diagnostic test achieved 92% specificity and 100% sensitivity in both POC and reference laboratory testing in 28 reverse transcription polymerase chain reaction (RT-PCR) Ebola-positive patients and 77 RT-PCR Ebola-negative individuals; ReEBOV is the only rapid diagnostic test approved for use through an Emergency Use Authorization from the WHO and FDA.^[71,72]

POST-EBOLA SYNDROME

Few scientific investigations have looked at the continuing health-related sequelae among Ebola survivors. Experiences from prior outbreaks identified a set of potential complication “themes” that were seen among survivors, resulting in a loosely coined term, “post-Ebola syndrome.”^[73,74] A small, retrospective study of Ebola survivors in the Democratic Republic of Congo in 1995 found that survivors had significant joint pain, muscle aches, and lethargy up to 2 years after the acute viral illness.^[75] In the 2007 Uganda outbreak, Ebola survivors suffered from retro-orbital pain, blurred vision, hearing loss, neurological abnormalities, sleep disturbance, arthralgia, memory loss, confusion, trouble swallowing, and other enduring health complications, the residual effects of which persisted beyond 2 years in some cases.^[76] In West Africa approximately 50% of survivors endured these symptoms in addition to fatigue, increased ocular pressure, uveitis, blindness, hair loss, myalgia, menstrual problems, rashes,

and various pain syndromes.^[77] Furthermore, detailed evaluations of post-Ebola symptomatology should be performed for different outbreaks and strains of EBOV, which may aid in determining potential differences in post-Ebola syndromes between various viral strains.

A more recent study of 81 patients who were disease free for 4 months in Sierra Leone found that more than half of survivors experienced joint/muscle pain or headaches. Furthermore, 40% of survivors reported insomnia and vision disturbances.^[78] Cumulatively, these conditions have the potential to cause a multitude of social, economic, and cultural problems. Consequently, more insight is needed into various post-Ebola physical ailments, the direct impact on survivors, as well as the indirect impact on the society and the economy. Among the countries of Guinea, Sierra Leone, and Liberia alone, the WHO estimates there are at least 13,000 survivors.^[79] Of special concern is the recently publicized case of potential post-Ebola relapse in a Scottish survivor who initially contracted Ebola 9 months previously.^[80] This case also raised concerns regarding disease “reactivation” and possible risk of viral transmission associated with such occurrences.^[81]

Despite greater awareness of post-Ebola sequelae, it is still extremely difficult to analyze the pathological mechanisms of post-Ebola syndrome. However, there has been recent progress made with an ocular fluid examination in cases of post-Ebola uveitis.^[82] Understandably, human studies will continue to be limited because of biosafety concerns, the remote location of outbreaks, inadequate infrastructure in certain areas, and poor surveillance. Currently, the NIH in the United States has initiated the Partnership for Research on Ebola Virus in Liberia III study in partnership with Liberia's Ministry of Health in order to understand the long-term health implications of Ebola, with other similar research efforts in the region being considered.^[83-85]

PREPARING FOR FUTURE OUTBREAKS

While the current outbreak seems to have been quelled and the vaccine trials look hopeful, it would be in the best interest of the international medical and public health community to consider the handling of future outbreaks in regard to the one that Africa has just experienced.^[86-89] What the global community has learned about ethics and culture,^[90-92] and obligations for care,^[93] let alone the controversies over vaccine trials,^[94] are of primary importance. The enormity of the 2014-2015 Ebola outbreak presented the international community with important questions regarding global

health governance and had reopened the discussion of political reform that is badly needed in order to achieve better health equity.^[95,96]

While countries make plans for responding to epidemics, they must ensure that their provinces, states, and other administrative locales have guidance in making important ethical decisions on significant clinical issues because focusing solely on ensuring drugs and equipment supplies is clearly not sufficient.^[97] Resource-rich states outside of the affected area must not hesitate to become involved, quarantine and its ramifications must be discussed, as should crisis communication, selectively caring for or “air-lifting” certain populations, the use of untested medical treatments, and the determination of who will care for the sick.^[93,97-101] Furthermore, our collective experience with the controversies surrounding vaccine trials in under-resourced areas of the world and the culture of trust among host nations must always be in the foreground of any coordinated global plans and actions.^[87,94,102-104]

CONCLUSIONS

Since the first identification of the EBOV in the mid-1970's, each Ebola outbreak has sparked a public health campaign to improve awareness and disease containment. Due to multiple factors including rapid spread and invasion into city centers, large numbers of secondary cases due to insufficient personnel availability and training, inadequate use and limited quantities of PPE, and initial public health failures, the latest and worst EBOV outbreak became an international public health emergency.^[105,106] With advances in rapid diagnostics never before used in prior Ebola outbreaks, effective POC testing should prove useful for improving active public health surveillance.

Ebola outbreaks have been documented for over 40 years, and likely will occur in the future. Technology has made world-wide communication instantaneous, and these outbreaks will quickly become known to the international community and hopefully, prompt immediate, coordinated response efforts. Such efforts should build upon lessons learned during the 2014-2015 outbreak, with emphasis on successful techniques of control and containment, but this alone is not sufficient. The global community should strive to achieve better means of prevention, which in turn depends on continued interest in, and active support of, vaccine efforts as previously discussed.^[63,107,108] Now is the time for the international community and specifically those most capable of vaccine research and development to focus on this effort. Sustained

containment will depend on coordinated multi-national and multi-disciplinary efforts, community involvement and trust, as well as continued commitment from local, regional, and global leadership.

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