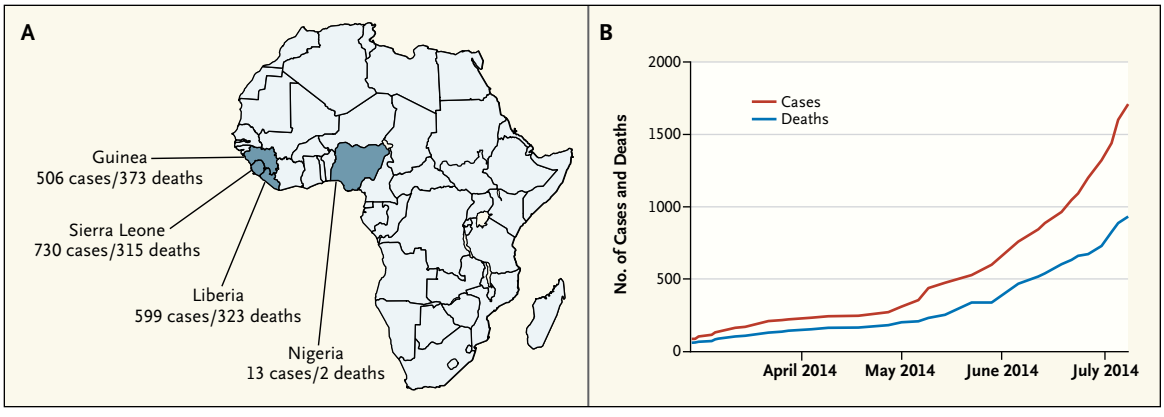
Ebola — Underscoring the Global Disparities in Health Care Resources

Anthony S. Fauci, M.D.

An outbreak of Ebola virus disease (EVD) has jolted West Africa, claiming more than 1000 lives since the virus emerged in Guinea in early 2014 (see figure). The rapidly increasing numbers of cases in the African countries of Guinea, Liberia, and Sierra Leone have had public health authorities on high alert throughout the spring and summer. More recent events including the spread of EVD to Nigeria (Africa's most populous country) and the recent evacuation to the United States of two American health care workers with EVD have captivated the world's attention and concern. Health professionals and the general public are struggling to comprehend these unfolding dynamics and to separate misinformation and speculation from truth.

EVD, originally identified in 1976 in Yambuku, Zaire (now the Democratic Republic of Congo), and Nzara, South Sudan, is caused by an RNA virus in the filovirus family. "Ebola" (named after a river in Zaire) encompasses five separate species — *Zaire ebolavirus*, *Bundibugyo ebolavirus*, *Taï Forest ebolavirus*, *Sudan ebolavirus*, and *Reston ebolavirus*. *Reston ebolavirus* is not known to cause disease in humans, but the fatality rates in outbreaks of the other four species have ranged from 25 to 90%.[1] The strain currently circulating in West Africa bears 97% homology to *Zaire ebolavirus* samples found in the Democratic Republic of Congo and Gabon.[2] This strain has historically resulted in the highest mortality (90%), although the estimated case fatality rate in the current outbreak is less than 60%.[3]

Outbreaks probably originate from an animal reservoir and possibly involve additional intermediary species. The most likely reservoir appears to be a fruit bat, although that linkage has not been confirmed.[1] Transmission to humans may have occurred through direct contact with tissue or bodily fluids from an infected animal. Notably, Ebola virus is a zoonotic pathogen, and its circulation among humans is uncommon, which explains the intermittent and unpredictable nature of outbreaks. In fact, although the virus has caused more than 20 outbreaks since its identification in 1976, it had caused fewer than 1600 deaths before 2014, with case counts ranging from a handful to 425 in the Ugandan outbreak of 2000 and 2001.[3] In most instances, the virus emerged in geographically restricted, rural regions, and outbreaks were contained through routine public health measures such as case identification, contact tracing, patient isolation, and quarantine to break the chain of virus transmission.



Ebola Virus Cases and Deaths in West Africa (Guinea, Liberia, Nigeria, and Sierra Leone), as of August 11, 2014 (Panel A), and Over Time (Panel B).

Data are from the World Health Organization (www.who.int/csr/don/archive/disease/ebola/en).

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Frequency of Symptoms Reported in 103 Cases of Ebola Virus Disease in Kikwit, Democratic Republic of Congo, in 1995.*

Symptom	Percent of Patients with Symptom
Fever	≥90
Weakness	80–90
Diarrhea	80–90
Nausea and vomiting	70–80
Abdominal pain	60–70
Headache	50–60
Sore throat, odynophagia, dysphagia	50–60
Arthralgia or myalgia	50–60
Anorexia	40–50
Rash	10–20
Bleeding	
Any type	40–50
Gingival	10–20
Hematemesis	10–20
Melena	0–10
From puncture sites	0–10
Hemoptysis	0–5

* The sample included 84 patients who died and 19 who survived, representing approximately one third of the total cases in the outbreak. Adapted from Bwaka et al.[4]

In early 2014, EVD emerged in a remote region of Guinea near its borders with Sierra Leone and Liberia. Since then, the epidemic has grown dramatically, fueled by several factors. First, Guinea, Sierra Leone, and Liberia are resource-poor countries already coping with major health challenges, such as malaria and other endemic diseases, some of which may be confused with EVD. Next, their borders are porous, and movement between countries is constant. Health care infrastructure is inadequate, and health workers and essential supplies including personal protective equipment are scarce. Traditional practices, such as bathing of corpses before burial, have facilitated transmission. The epidemic has spread to cities, which complicates tracing of contacts. Finally, decades of conflict have left the populations distrustful of governing officials and authority figures such as health professionals. Add to these problems a rapidly spreading virus with a high mortality rate, and the scope of the challenge becomes clear.

Although the regional threat of Ebola in West Africa looms large, the chance that the virus will establish a foothold in the United States or another high-resource country remains extremely small. Although global air transit could, and most likely will, allow an infected, asymptomatic person to board a plane and unknowingly carry Ebola virus to a higher-income country, containment should be readily achievable. Hospitals in such countries generally have excellent capacity to isolate persons with suspected cases and to care for them safely should they become ill. Public health authorities have the resources and training necessary to trace and monitor contacts. Protocols exist for the appropriate handling of corpses and disposal of biohazardous materials. In addition, characteristics of the virus itself limit its spread. Numerous studies indicate that direct contact with infected bodily fluids — usually feces, vomit, or blood — is necessary for transmission and that the virus is not transmitted from person to person through the air or by casual contact. Isolation procedures have been clearly outlined by the Centers for Disease Control and Prevention (CDC). A high index of suspicion, proper infection-control practices, and epidemiologic investigations should quickly limit the spread of the virus.

Recognizing the signs of EVD can be challenging, however, since early symptoms are nonspecific (see box). It is essential to obtain a careful and prompt travel history. The incubation period typically lasts 5 to 7 days, although it can be as short as 2 days and as long as 21 days. Blood specimens usually begin to test positive on polymerase-chain-reaction–based diagnostics 1 day before symptoms appear. Typical symptoms include fever, profound weakness, and diarrhea. A maculopapular rash has been described, as have laboratory abnormalities including elevated aminotransferase levels, marked lymphocytopenia, and thrombocytopenia. Hemorrhagic complications occur in fewer than half of infected persons, and gross bleeding is relatively rare.[1,4]

Once Ebola virus is suspected, the CDC can confirm diagnoses with the use of a diagnostic test approved under an Emergency Use Authorization. Public health measures such as early isolation and infection control are critical. In addition, aggressive supportive care should be administered. Advanced hemodynamic monitoring and interventions that are available in hospitals throughout the United States could result in much higher survival rates than those currently seen in West Africa. With regard to the international transport of patients, the benefits of advanced life-support capabilities that are available in resource-rich countries must be weighed against

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the risks of air transport, given the hemodynamic instability associated with EVD.

Recently, substantial attention has been paid to unlicensed therapies and vaccines. Among the therapies in development is a "cocktail" of humanized-mouse antibodies ("ZMapp"), which has shown promise in nonhuman primates. ZMapp was administered to two U.S. citizens who were recently evacuated from Liberia to Atlanta, and both patients have had clinical improvement. However, it is not clear whether ZMapp led to the recovery, and with only two cases, conclusions regarding its efficacy should be withheld. Moreover, the supply of ZMapp remains limited to a handful of doses, and production scale-up, though under way, will take time. Other candidate therapeutics include RNA-polymerase inhibitors and small interfering RNA nanoparticles that inhibit protein production.[5]

An audio interview with Dr. Fauci is available at NEJM.org

Preclinical evaluation of several vaccine candidates is also under way, and it is anticipated that a candidate developed at the National Institutes of Health will enter a phase 1 trial this fall, pending a decision from the Food and Drug Administration. This vaccine, a chimpanzee adenovirus-vector vaccine, includes two inserted Ebola genes encoding glycoproteins. Two other vaccine candidates involve vesicular stomatitis virus pseudotypes. Human clinical testing of one of these vaccines is expected to begin in early 2015.

While these interventions remain on accelerated development paths, public health measures are available today that have a proven record of controlling EVD outbreaks. Moreover, premature deployment of unproven interventions could cause inadvertent harm, compromising an already strained relationship between health care professionals and patients in West Africa. Rapid but proper evaluation of candidate therapies and vaccines is needed. Should exemptions be offered for compassionate or emergency use, distribution of scarce interventions must be conducted with careful ethical guidance and regulatory review. It is unlikely that any miracle cure will end the current epidemic. Rather, sound public health practices, engagement with affected communities, and considerable international assistance and global solidarity will be needed to defeat Ebola in West Africa.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.

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Studying "Secret Serums" — Toward Safe, Effective Ebola Treatments

Jesse L. Goodman, M.D., M.P.H.

Ebola virus (EV), the cause of an ongoing deadly epidemic in West Africa, has been one of the world's most feared pathogens, causing catastrophic clinical disease and high mortality. Although the highest priority must be given to public health and infection-control measures that have contained past outbreaks, the current outbreak — the largest ever recorded — also highlights the need for effective treatment.

The report that two seriously ill American volunteers, Kent Brantly and Nancy Writebol, received an experimental cocktail of three monoclonal antibodies, never before administered to humans, has raised questions around the globe. Dubbed "secret serum" by the media, the treatment has generated hope, suspicion, accusations of inequity, and requests for additional product, of which, since the manufacturers provided

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