way that leaves behind stronger systems to identify, stop, and prevent future health threats is a moral imperative.

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

From the Centers for Disease Control and Prevention, Atlanta.

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1. Outbreaks chronology: Ebola hemorrhagic fever. Atlanta: Centers for Disease Control and Prevention, 2014 (http://www.cdc.gov/vhf/ebola/resources/outbreak-table.html#eighteen).
2. Infection prevention and control recommendations for hospitalized patients with known or suspected Ebola hemorrhagic fever in U.S. hospitals. Atlanta: Centers for Disease Control and Prevention, 2014 (http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html).
3. Interim guidance about Ebola infection for airline crews, cleaning personnel, and cargo personnel. Atlanta: Centers for Disease Control and Prevention, 2014 (http://www.cdc.gov/quarantine/air/managing-sick-travelers/ebola-guidance-airlines.html).
4. Bausch DG, Feldmann H, Geisbert TW, et al. Outbreaks of filovirus hemorrhagic fever: time to refocus on the patient. J Infect Dis 2007;196:Suppl 2:S136-S141.
5. Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet 2011;377:849-62.

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The International Ebola Emergency

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On August 8, 33 weeks into the longest, largest, and most widespread Ebola outbreak on record, the World Health Organization (WHO) declared the epidemic to be a Public Health Emergency of International Concern (PHEIC). This declaration was not made lightly. A PHEIC is an instrument of the International Health Regulations (IHR) — a legally binding agreement made by 196 countries on containment of major international health threats.

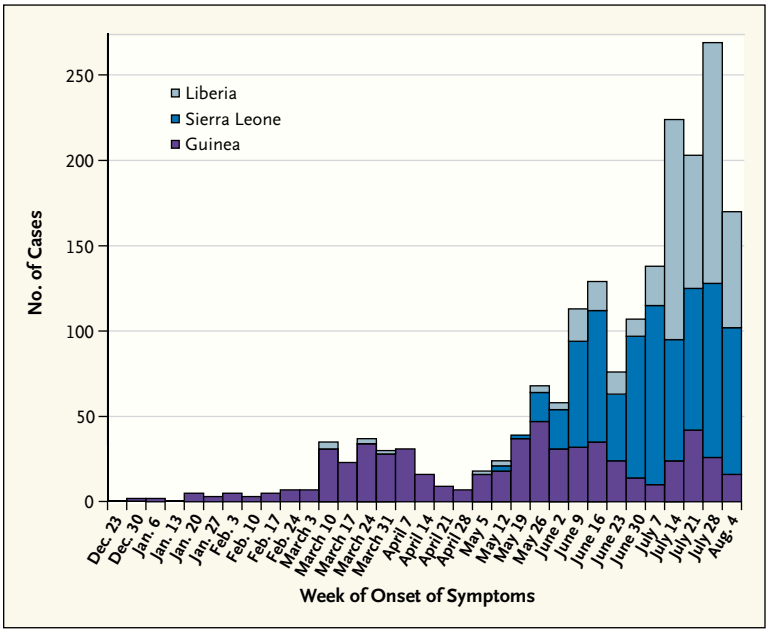
The August 8 statement made by WHO Director-General Margaret Chan followed advice from the independent IHR Emergency Committee. Reviewing all the available evidence, the committee concluded that further international spread of Ebola could have serious consequences. Their concern was based on the continuing transmission of Ebola in West African communities and health facilities, the high case fatality rate of Ebola virus disease (EVD), and the weak health services of Guinea, Liberia, Sierra Leone, Nigeria, and other neighboring countries at risk for infection.

An interactive map of the Ebola outbreak is available at NEJM.org

A Public Health Emergency carries immediate consequences for all IHR signatories (see Box 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). For the four currently affected countries, the Emergency Committee made several recommendations. Heads of state should declare a national emergency, activate national disaster-management mechanisms, and establish emergency operations centers. There should be no international travel of infected persons or their contacts. In areas of intense transmission — especially the border areas of Sierra Leone, Guinea, and Liberia — the provision of clinical care to affected populations could be used as a basis for reducing people's movement. Funerals and burials should be conducted in the presence of fully trained personnel so as to reduce the risk of spreading infection. And extraordinary supplementary measures, such as quarantine, may be implemented if necessary. These recommendations constitute a robust response to an extraordinary event but are not intended to be coercive. Rather, they should be introduced with the understanding and collaboration of affected communities.

The current outbreak has caused more cases and deaths than any previous EVD epidemic (see graph in the Supplementary Appendix). It appears to have started in the Guéckédou district of Guinea. The first case was recorded in December 2013, but that case was probably not the first in this outbreak.[1,2] Until the end of April 2014, most cases were reported from Guinea, with a small number in bordering parts of Liberia and Sierra Leone (see graph). In late April, a dip in reported cases in Guinea gave hope that the epidemic was beginning to subside and could be confined largely to one country. That hope was abandoned as the number of confirmed cases in Liberia and Sierra Leone rose sharply during May. By August 16, the cumulative number of confirmed, probable, and suspected cases of EVD in the three worst-affected countries plus Nigeria was 2240, with 1229 deaths. The ratio of deaths to cases implies a case fatality rate of 55%. However, this estimate is approximate, since some

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Numbers of Confirmed and Probable Ebola Cases Reported Weekly from Guinea, Sierra Leone, and Liberia from December 23, 2013, to August 11, 2014.
Data are from the WHO.

cases and deaths (perhaps many) have been missed; in particular, contact tracing in Guinea during the initial period was far from adequate, allowing further opportunities for transmission. Moreover, the fatality rate varies markedly among geographic sites, ranging from 30 to 90% in this epidemic.

Although the largest number of cases was reported in the week starting July 28, the data compiled from Guinea, Liberia, and Sierra Leone give little indication that incidence has begun systematically to decline (see graph). As yet, there is no persuasive evidence that the epidemic is under control. And the recent discovery of cases in Nigeria, which shares no border with Guinea, Liberia, or Sierra Leone, highlights the risk of wider spread across Africa and to other continents. Beyond the immediate health concerns, Ebola is also becoming a humanitarian and economic emergency: schools are being closed, agriculture and mining are under threat as workers leave the affected areas, and cross-border commerce has slowed.

We do not yet have an Ebola vaccine or specific antiviral treatments (see Box 2 in the Supplementary Appendix), but evidence from the current and previous epidemics indicates that transmission can be interrupted by infection-control measures. The mode of transmission is well known: the chance of infection is high if there is direct contact with blood, secretions, organs, or other body fluids of infected persons. Patients become infectious once they are symptomatic (2 to 21 days after infection; see box), and may remain infectious even after symptoms subside (virus persists in body fluids). The primary animal reservoirs of Ebola are probably fruit bats, and human infection can be acquired from intermediate mammalian hosts, including domestic pigs and primates. But this epidemic is almost certainly being sustained by person-to-person transmission through physical contact. Although contact with infected body fluids carries great risk, Ebola virus does not usually spread rapidly through large populations. From previous epidemics it has been calculated that 1 primary human case generates only 1 to 3 secondary cases on average,[3] as compared with 14 to 17 for measles in West Africa.[4]

These observations point to immediate priorities for control: early diagnosis with patient isolation, contact tracing, strict adherence to biosafety guidelines in laboratories, barrier nursing procedures and use of personal pro-

Health services are understaffed. Essential personal protective equipment is in short supply. Capacities for laboratory diagnosis, clinical management, and surveillance are limited, and delays in diagnosis impede contact tracing. On top of these problems, health services are operating in a climate of fear and discrimination.

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Management of Suspected Cases of Ebola Virus Disease (EVD).*

Clinical presentation and course of illness

- Usually abrupt onset 3–12 days after exposure
- Nonspecific initial signs and symptoms: fever and malaise followed by anorexia, headache, myalgia, arthralgia, sore throat, chest or retrosternal pain, conjunctival infection, lumbosacral pain, maculopapular rash
- Gastrointestinal signs and symptoms follow in first few days: nausea, vomiting, epigastric and abdominal pain, diarrhea
- Early-stage EVD may be confused with other infectious diseases (e.g., malaria, typhoid fever, septicemia including meningococcemia, and pneumonia)
- Hemorrhage seen in about 50% of patients, mostly in later stages, usually leading to death within days
- Patients with fatal disease tend to have more severe clinical signs early and to die from complications (e.g., multiorgan failure, septic shock) between days 6 and 16
- Nonfatal cases may improve around day 6–11

Initial evaluation

- Clinical criteria: fever >38.6°C (>101.5°F) with additional symptoms listed above
- Epidemiologic risk factors:
  - Contact within previous 3 weeks with blood or other body fluids of patient with known or suspected EVD
  - Residence in or travel to area with active EVD transmission
  - Participation in funeral and burial rituals in disease-endemic areas
  - Direct handling of bats, rodents, or primates from disease-endemic areas
- Use personal protective equipment to examine persons with suspected infection
- Isolate patients immediately to prevent transmission

Diagnosis

- Laboratory testing of blood samples should be performed at highest biosafety level (BSL-4).
- For definitive diagnosis:
  - Within a few days after symptoms begin: antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM ELISA, polymerase-chain-reaction assay
  - Later in course of illness or after recovery: virus isolation, IgM and IgG antibody testing

Treatment

- There are no approved, specific treatments or vaccines
- Provide supportive care for complications, such as hypovolemia, electrolyte abnormalities, refractory shock, hypoxemia, hemorrhage, septic shock, multiorgan failure, and disseminated intravascular coagulation
- Recommended care: volume repletion, maintenance of blood pressure (with vasopressors if needed), maintenance of oxygenation, pain control, nutritional support, treatment of secondary bacterial infections and preexisting conditions
- Implement infection prevention and control measures; consider all bodily fluids and clinical specimens potentially infectious

* Information is from the WHO and the Centers for Disease Control and Prevention.

tective equipment by all health care workers, disinfection of contaminated objects and areas, and safe burials. Patients with Ebola require symptomatic treatment and intensive care, and clinical reports suggest that better supportive care improves patients' chances of survival. The establishment of emergency operations centers is critical, as are communication and social mobilization programs, both to help affected populations understand and comply with control measures and to help health authorities understand how these measures can be introduced in a culturally sensitive way.

These recommended control methods are, of course, more easily recited than implemented. Extraordinary resources are required by any health service confronted by Ebola; those in Guinea, Liberia, and Sierra Leone are severely stretched. Health services are understaffed. Essential personal protective equipment is in short supply. Capacities for laboratory diagnosis, clinical management, and surveillance are limited, and delays in diagnosis impede contact tracing.

On top of these problems, health services are operating in a climate of fear and discrimination. Some contacts of patients with confirmed cases have evaded follow-up by medical teams (which ideally covers the full incubation period of 3 weeks). Some patients and their contacts have been ostracized in areas where Ebola is thought to be a product of witchcraft. Health care workers are aware of the risks they face: more than 150 health care workers have already been infected, and at least 80 have died. Fear has also turned to hostility against national and international response teams and has compromised care delivery and transport of essential equipment and samples to laboratories.

This epidemic's unprecedented scale has been a surprise, but the response is now firmly under way. The August 8 declaration kick-started a plan to stop the epidemic that will cost at least $100 million to enact in Guinea, Liberia, Sierra Leone, and Nigeria between now and the end of 2014.[5] Key elements of the plan are to strengthen the field response through surveillance, case investigation, patient care, and

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contact tracing; activate and test preparedness plans in countries at risk; and coordinate the response internationally (see Box 1 in the Supplementary Appendix). Supporting national governments, the World Bank has pledged to help fill the funding gap.

At the national level, Liberia and Nigeria have declared national emergencies and are screening people arriving at and departing from airports and seaports. Guinea has closed its borders with Liberia and Sierra Leone. Members of Liberia's National Traditional Council have addressed their communities throughout the country. The engagement of local communities is vital. We have already seen how, in Télimélé, site of a cluster of cases in Guinea, transmission was rapidly curtailed with the support of community leaders.

Monitoring of funds raised and disbursed, and of control measures implemented, is now intense. Above all, we are looking for a sustained decrease in incidence, from week to week and district by district, with no sign of further geographic spread. In the coming days and weeks, that will be our primary measure of success in preventing infections and saving lives.

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

From the World Health Organization, Geneva.

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1. Ebola virus disease (EVD). Geneva: World Health Organization, 2014 (http://www.who.int/csr/don/archive/disease/ebola/en).
2. Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea — preliminary report. N Engl J Med. DOI: 10.1065/NEJMoa1404505.
3. Chowell G, Hengartner NW, Castillo-Chavez C, Fenimore PW, Hyman JM. The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. J Theor Biol 2004;229:119-26.
4. Legrand J, Grais RF, Boelle PY, Valleron AJ, Flahault A. Understanding the dynamics of Ebola epidemics. Epidemiol Infect 2007;135:610-21.
5. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford, England: Oxford University Press, 1991.

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Ebola Virus Disease in West Africa — No Early End to the Outbreak

Margaret Chan, M.D.

Many people have asked me why the outbreak of Ebola virus disease in West Africa is so large, so severe, and so difficult to contain. These questions can be answered with a single word: poverty.

The hardest-hit countries, Guinea, Liberia, and Sierra Leone, are among the poorest in the world. They have only recently emerged from years of conflict and civil war that have left their health systems largely destroyed or severely disabled and, in some areas, left a generation of children without education. In these countries, only one or two doctors are available for every 100,000 people, and these doctors are heavily concentrated in urban areas. Isolation wards and even hospital capacity for infection control are virtually nonexistent. Contacts of infected persons are being traced but not consistently isolated for monitoring.

Large numbers of people in these countries do not have steady, salaried employment. Their quest to find work contributes to fluid population movements across porous borders. The area where the borders of the three countries intersect is now the designated hot zone, where transmission is intense and people in the three countries continue to reinfect each other. Recent decisions to quarantine this area have brought extreme hardship to more than a million people — but are essential for containment.

These are only some of the many challenges to be overcome in the worst Ebola outbreak in the nearly four-decade history of this disease. The needs are enormous; the prospects for rapid containment are slim. The outbreak, in all its unprecedented dimensions, is an emergency of international concern and a medical and public health crisis, but it is also a social problem.

Now, 6 months into the response to the outbreak, fear remains the most difficult barrier to overcome. Fear causes people who have had contact with infected persons to escape from the surveillance system, relatives to hide symptomatic family members or take them to traditional healers, and patients to flee treatment centers. Fear and the hostility that can result from it have threatened the security of national and international response teams.

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