Philippines, which saw an outbreak involving more than 47,000 cases and was the source of an estimated 22 importations to the United States. The NVAC advocates that the United States support efforts to eliminate measles in each of the World Health Organization's six geographic regions. In fact, although we have not yet set a global goal of measles eradication, all six regions have their own such goal.

Measles meets the biologic criteria for eradication. Humans are necessary to maintain the virus in nature, since there is no nonhuman reservoir. There is an effective intervention measure — measles vaccines. Diagnostic tests can confirm whether someone has measles. And proof of principle has been demonstrated by prolonged elimination of indigenous circulation of the virus in the Western Hemisphere.

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

It may be premature to embark on another global eradication effort until polio eradication is achieved; however, much more can be done to reduce measles transmission in its current reservoirs. We can increase support for improving global routine-immunization programs so that they include two doses of measles vaccine in their schedules and for ensuring that there is adequate vaccine and infrastructure to conduct special mass-vaccination campaigns against measles. Support is also needed for strengthening the global laboratory network to permit detection and analysis of which measles strains are persisting and which have been eliminated.[5]

We must also overcome vaccine hesitancy. Despite the overwhelming evidence that vaccines — including the measles, mumps, and rubella vaccine — are safe, too many people still believe that greater risk is posed by vaccinating than by not vaccinating. Research is needed on how best to address public concerns about vaccine safety. The lack of apparent measles disease in the United States — which is attributable to the enormous success of the U.S. immunization program — gives a false sense that there is little or no threat. Efforts are also needed to educate the public that measles is a serious disease, which no one need suffer from, and that vaccines are highly effective in preventing it.

In the end, we can best protect our population against measles by ensuring that people eligible for vaccination are vaccinated and by supporting global efforts to go on the offensive against this major cause of the global disease burden.

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

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Ebola Then and Now

Joel G. Breman, M.D., D.T.P.H., and Karl M. Johnson, M.D.

In October 1976, the government of Zaire (now the Democratic Republic of Congo [DRC]) asked what was then the U.S. Center for Disease Control, where we worked, to join an international group of scientists in elucidating and controlling an outbreak of an unusually lethal hemorrhagic fever. Just before we arrived in Zaire, our laboratory had used virologic and immunologic tests to identify the cause as a new filovirus, and we brought electron micrographs of the agent.[1] In Zaire, we became, respectively, the chief of surveillance, epidemiology, and control and the scientific director of the International Commission for the Investigation and Control of Ebola Hemorrhagic Fever in Zaire.

The 2013–2014 outbreak of Ebola virus disease (EVD) has much in common with the 1976 outbreak. Both were caused by *Zaire ebolavirus*[2] and began in rural forest communities, where wild game is hunted for food (though no animal has been implicated as the trigger of these outbreaks). Severely ill patients came to provincial hospitals with systemic ill-

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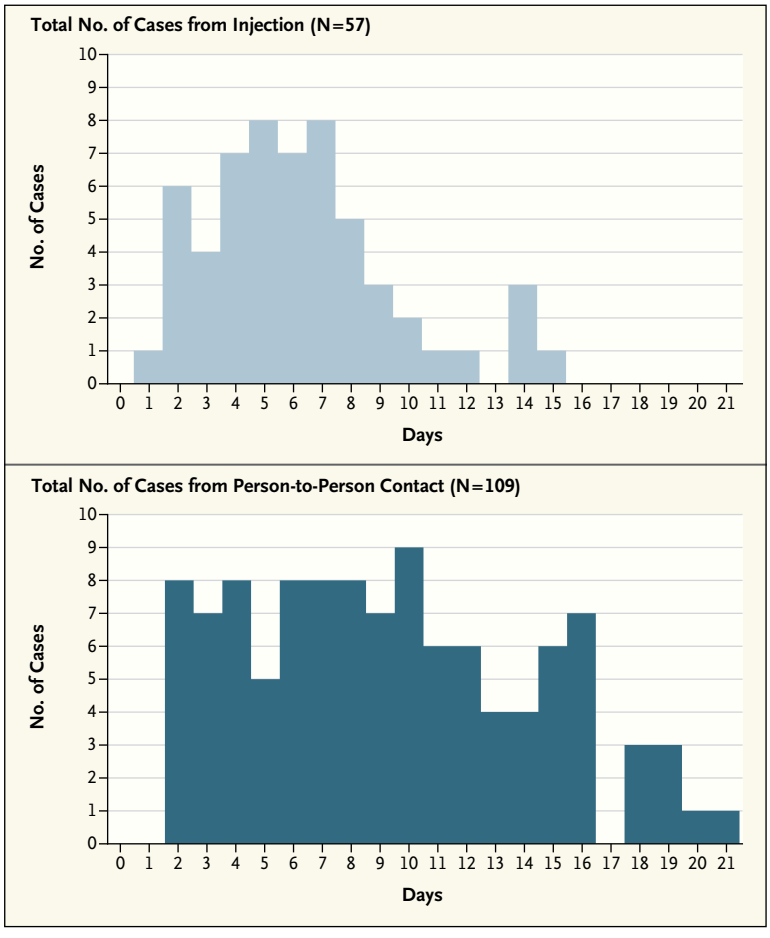

Time of Onset of Ebola Virus Disease, According to Transmission Route, Zaire, 1976.

ness resembling malaria, typhoid, Lassa fever, yellow fever, or influenza. Unsuspecting hospital staff had contact with patients' blood and body fluids, which amplified the outbreaks. Cases were exported to cities, and chains of transmission were established.

In 1976, in the 120-bed Yambuku Mission Hospital (YMH) in Zaire, the virus initially spread through use of unsterilized syringes and needles. Of the hospital's 17 staff members, 13 became sick, and 11 died.[3] The hospital was closed when the medical director and three Belgian missionaries died from Ebola. Many infected people and their contacts fled to their home villages out of fear and suspicion of the nonfunctioning Western medical system, seeking treatment from traditional healers.

Several factors contributed to stopping Ebola's spread and facilitated investigations, beginning with careful attention to our commission's leadership, organization, coordination, administration, logistics, and communications and a series of rapid actions. The minister of health, the overall authority for commission activities who reported directly to the Council of Ministers and President Mobutu Sese Seko, convened daily meetings for sharing information and defining action steps. We had more than 70 people working in the field, with backup in Kinshasa, Antwerp, and Atlanta.

Five commission members went to the village of Yambuku almost immediately to define the geographic extent of the outbreak, find active cases, find possible survivors for a plasmapheresis program, and assess needs for clinical care and laboratory facilities. Other members remained in Kinshasa to care for hospitalized patients, enforce surveillance and isolation of contacts, marshal resources, and assess options.

The government had quarantined the 275,000 people in Bumba Zone — no commercial planes or boats could land there, and citizens were told not to leave their villages or allow strangers to enter. People lacked basic commodities and were fearful and agitated. We explained to them that we knew what caused the outbreak and showed authorities the electron micrograph. People along the road from the town of Bumba to Yambuku were relieved when we said we'd come to stop the disease's spread, treat patients, and meet their families.

Some patients had been placed in huts outside their villages — a common practice for isolating patients with smallpox. We encouraged this practice and the designation of one family member — preferably someone who had recovered from the illness — to bring each patient food and medicines until we established a clinical care unit at the mission hospital. When patients died, traditional rites were abbreviated, a practice we encouraged. We advised that bodies be covered with hypochlorite disinfectant (bleach), wrapped in shrouds, and buried without the usual washing and

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prolonged contact with relatives and friends. Isolation huts and patients' garments were burned in many villages.

Although YMH had been closed, villagers trusted the hospital and the mission staff, and trained personnel were needed for acute health problems. A Zairean doctor was therefore assigned to the hospital, and credibility was gradually restored, especially when we began visiting villages accompanied by the three remaining nuns.

In November, our clinical and laboratory teams moved to Yambuku, since transmission had stopped in Kinshasa. We shipped a generator, a refrigerated centrifuge, a plastic glove box equipped for negative pressure (see slide show, available with the full text of this article at NEJM.org), an immunofluorescent microscope and immunofluorescence-assay (IFA) slides, plasmapheresis equipment, liquid nitrogen tanks, personal protective materials, and assorted supplies — and a single-sideband radio for improved communication with Kinshasa.

A slide show is available at NEJM.org

But our most important tool was house-by-house visits. It was difficult to get medical staff to participate in field activities, so the national vaccination program, sleeping-sickness program, and smallpox–monkeypox surveillance program assigned us mobile teams, and the health minister ordered clinicians from the university hospital and public health services to join us. We assured all team members that they would be treated equally if they became ill. We advised them to take antimalarial medications, record their temperatures daily, and report elevated temperatures or other signs or symptoms of EVD to their team leader or us. When a Peace Corps volunteer working with blood specimens became ill with fever, headache, malaise, and rash, he was evacuated to a South African hospital — where he was discovered not to have EVD (and recovered).

Ten four-person surveillance teams — led by a physician or nurse and trained in recognizing the features of EVD and other common diseases, interview techniques, patient isolation, and personal protection — visited 550 villages at least twice over a 2-month period; the 55 villages where Ebola was found were visited a third time. Patient identification was facilitated by the local tradition of shaving one's head when in mourning for a relative (see slide show). The teams had personal protective gear consisting of surgical scrubs, gloves, goggles, paper gowns, masks, caps, and booties. They brought standardized clinical and epidemiologic forms, first-aid kits, thermometers, antimalarials, antibiotics, and antipyretics. Any febrile person with suspected EVD was given medicines, advised to stay home with limited contacts, and visited again shortly thereafter. The teams were supervised by an epidemiologist or microbiologist who assessed possible active or recovered cases. Special teams went to selected communities for in-depth studies and to collect blood for IFA testing.

The epidemic had peaked before we arrived; there were a total of 318 cases and 280 deaths, but we saw few active cases. The virus spread only through injection with an unsterilized needle or very close and repeated patient contact (see graphs).[4] The median incubation period was 6 days among people infected through the common outpatient practice of intramuscular injection and 8 days among those infected through person-to-person contact (range, 1 to 21 days).[4] The secondary attack rate was low — 5.6% among all family contacts; in only one instance did we find five chains of transmission. It was decided that quarantine of an area could end after 42 days (double the maximum incubation period) without a new case. Cohorts of contacts were isolated together for 21 days in two instances: first a group of Yambuku students and then Kinshasa hospital staff.[5]

Overall, we found that coordination of partners, transparency, and clear designation of authority and responsibilities were essential. We assuaged fear by working closely with national and local leaders, explaining what we knew and didn't know, and promising to remain in the area, treat patients, visit villages, and give evidence-based guidance. Reopening YMH addressed the community's daily needs, and our field IFA system permitted rapid diagnosis. Assuring international and Zairean health and support workers that they would be treated equally if they became ill helped us keep dedicated workers in the field. One dilemma was whether to care for sick team members locally or to evacuate them, which could delay treatment and expose many other people to the disease. The recent cases of two U.S. aid workers who were treated with an experimental therapy and then flown to Atlanta underscore such ethical questions.

In the current Ebola epidemic, we believe that the main priorities should be adequate staff for rigorous identification, surveillance, and care of patients and primary contacts; strict isolation

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of patients; good clinical care; and rapid, culturally sensitive disposal of infectious cadavers. Timely control will require convincing community leaders and health staff that isolation and rapid burial practices are mandatory; that patients can be cared for safely in improved local conditions; and that only trained, qualified, and properly equipped health staff should have patient contact.

These steps from the first Ebola outbreak may help bring the current epidemic under control. We also await key virologic, clinical, epidemiologic, and anthropologic descriptions of the epidemic — which will permit comparison with the other Ebola outbreaks that have occurred since 1976 and help us prepare for future outbreaks.

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

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Antidepressants' Black-Box Warning — 10 Years Later

Richard A. Friedman, M.D.

In 2004, the Food and Drug Administration (FDA) issued a black-box warning on antidepressants indicating that they were associated with an increased risk of suicidal thinking, feeling, and behavior in young people. The agency's decision was immediately controversial: many members of the medical community worried that this warning would do more harm than good because it would discourage depressed patients from seeking help and discourage doctors from prescribing antidepressants when they were clinically indicated. Now, 10 years later, there are substantial epidemiologic data to address these important concerns. What effect has the FDA warning had on the rates of detection and treatment of depression? And is there any evidence that rates of suicide or suicide attempts have changed?

In retrospect, it seems that the FDA had little choice but to issue its black-box warning. The agency had conducted a series of meta-analyses of 372 randomized clinical trials of antidepressants involving nearly 100,000 participants, which showed that the rate of suicidal thinking or suicidal behavior was 4% among patients assigned to receive an antidepressant, as compared with 2% among those assigned to receive placebo,[1] although none of the suicide attempts documented in the trials were fatal. Subsequent age-stratified analyses showed that this increased risk was significant only among children and adolescents under the age of 18 years; there was no evidence of increased risk among adults older than 24 years, and among adults 65 years of age or older, antidepressants had a clear protective effect against the development of suicidal ideation and behavior.

The meta-analyses provoked considerable debate about various methodologic issues. In particular, some experts questioned the validity of the assessment of suicidality in the trials that were included, which were generally not designed to prospectively assess suicidality.

The FDA was obviously mindful of the need to balance the small risk associated with antidepressant treatment against its proven benefits: an expanded black-box warning issued in 2007 stated that depression itself was associated with an increased risk of suicide. Has this well-intended warning accomplished its task — to educate clinicians about risk without discouraging appropriate treatment of depression?

Some worrisome trends in the rates of treatment of depression, diagnoses of new cases of depression, and suicide attempts since the black-box warning was issued suggest that the answer may be no. In a very large cohort study — including 1.1 million adolescents, 1.4 million young adults,

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