population. Unfortunately, pregnant women continue to become seriously ill with influenza, and some of them die. Research is needed to further elucidate the reasons why some pregnant women are not vaccinated so that the problems can be addressed. In addition, by implementing the current antiviral treatment recommendations, clinicians can prevent complications in women with influenza. We need to ensure that the information about influenza and pregnancy that has been gained in the 5 years since the 2009 H1N1 pandemic is translated into reductions in the number of illnesses, hospitalizations, and deaths that occur in future influenza seasons.

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.

1. Uyeki TM. Preventing and controlling influenza with available interventions. N Engl J Med 2014;370:789-91.
2. Rasmussen SA, Jamieson DJ. Influenza and pregnancy in the United States: before, during, and after 2009 H1N1. Clin Obstet Gynecol 2012;55:487-97.
3. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2:395-404.
4. Wollenhaupt M, Chandrasekaran A, Tomianovic D. The safety of oseltamivir in pregnancy: an updated review of post-marketing data. Pharmacoepidemiol Drug Saf 2014.
5. Prevention of perinatal group B streptococcal disease — revised guidelines from CDC, 2010. MMWR Recomm Rep 2010;59:1-36.

DOI: 10.1056/NEJMp1403496

Copyright © 2014 Massachusetts Medical Society.

Ebola — A Growing Threat?

Heinz Feldmann, M.D.

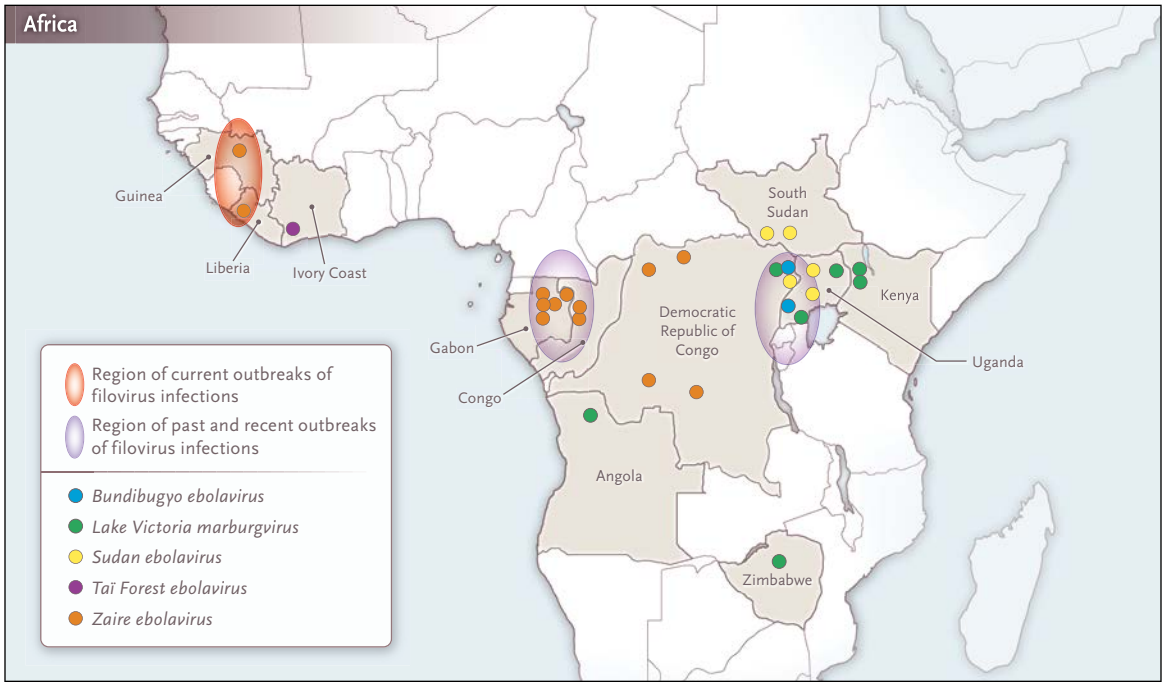
The recent emergence of *Zaire ebolavirus* in West Africa[1] has come as a surprise in a region more commonly known for its endemic Lassa fever, another viral hemorrhagic fever caused by an Old World arenavirus. Yet the region has seen previous ebolavirus activity (see map). In the mid-1990s, scientists discovered *Côte d'Ivoire ebolavirus* (now known as *Taï Forest ebolavirus*) as a cause of a single reported nonfatal case in a researcher who performed a necropsy on an infected chimpanzee. The episode initiated a major research investigation in and around the Taï Forest region — an effort that failed to identify the reservoir of this new Ebola species. Since that incident, West African countries have not reported any evidence of the presence of ebolavirus.

Updates on the Ebola outbreak are available at NEJM.org

Ebolaviruses belong to the family Filoviridae, a taxonomic group of enveloped, nonsegmented, negative-strand RNA viruses that includes the genera marburgvirus and cuevavirus, with a single species each, and ebolavirus, with five distinct species (see figure). All known African ebolaviruses can infect humans and cause similar symptoms, but they vary in terms of disease progression and virulence, with case fatality rates ranging from less than 40% for *Bundibugyo ebolavirus* to approximately 50% for *Sudan ebolavirus* to 70 to 90% for *Zaire ebolavirus*.[2] The virulence of *Taï Forest ebolavirus* is difficult to assess because there has been only a single recorded case, and the only identified Asian species, *Reston ebolavirus*, seems to cause asymptomatic infection in humans.

Humans infected with ebolaviruses commonly present initially with nonspecific symptoms such as fever, vomiting, and severe diarrhea, with visible hemorrhage occurring in less than half the cases,[2] as in the current outbreak.[1] Owing to poor infrastructure, biosafety concerns associated with processes of patient care and autopsy, and the essential focus on disease containment during outbreaks, there has been little empirical study to elucidate the pathogenesis or pathology of human ebolavirus infection. The closest surrogate disease models are cynomolgus and rhesus macaques, which show clinical signs of viral hemorrhagic fever when infected with most ebolaviruses. *Zaire ebolavirus* is uniformly lethal in these macaques, and experts have assumed that its pathology and pathophysiology closely resemble those of ebolavirus infections in humans; immunosuppression, increased vascular permeability, and impaired coagulation have been identified as hallmarks of the disease.[2] Evidence of microscopic hemorrhage is usually found, but the degree of bleeding ranges from undetectable to acutely visible. The recently introduced term "Ebola virus disease" may not convey the seriousness of a viral hemorrhagic fever, a clinical syndrome that should trigger isolation guidelines that ensure appropriate case management and implementation of infection-control measures.

The New England Journal of Medicine
Downloaded from nejm.org on October 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.



Outbreaks or Episodes of Filovirus Infections.

The purple ovals indicate regions of past and recent filovirus activity (on the border between the Republic of the Congo and Gabon from 2000 to 2005 and on the border between the Democratic Republic of Congo and Uganda in more recent years), and the red oval indicates the current outbreak of *Zaire ebolavirus*.

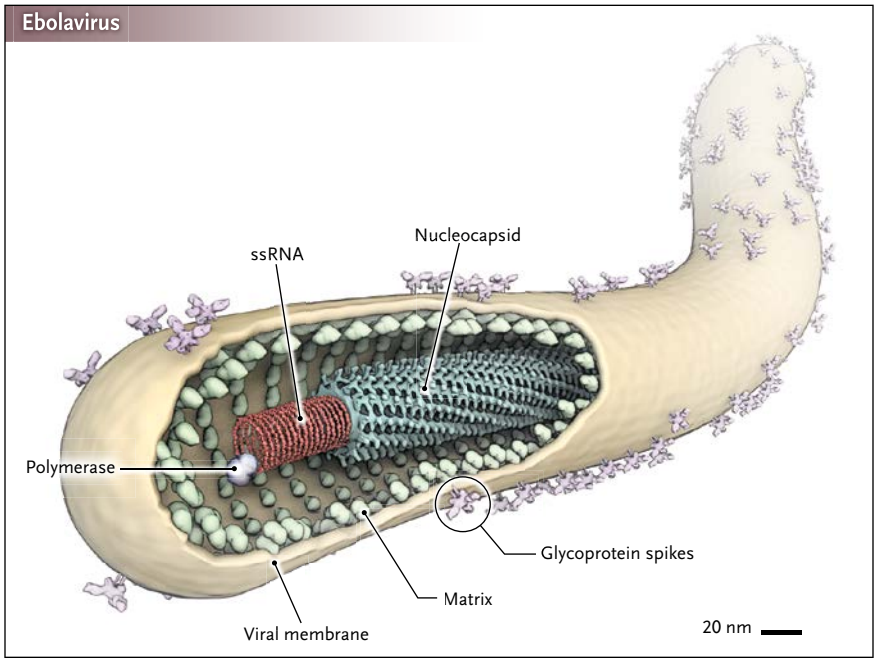
Ebolaviruses are zoonotic pathogens purportedly carried by various species of fruit bats that are present throughout central and sub-Saharan Africa. In contrast to marburgvirus, whose reservoir has been identified as *Rousettus aegyptiacus* fruit bats,[3] ebolaviruses have not yet been isolated from bats that have molecular and seroepidemiologic evidence of infection. Introduction into humans most likely occurs through direct contact with bats or their excretions or secretions or through contact with other end hosts, such as the great apes. Since *Reston ebolavirus* has been discovered in pigs on the Philippine islands, the possibility that there may be interim or amplifying hosts should not be dismissed, as we further elucidate ebolavirus ecology.

Human-to-human transmission leads to outbreaks, which are often started by a single introduction from the wildlife reservoir or another end host and involve virus variants with little genetic diversity, as in the current outbreak in West Africa.[1] Some recorded outbreaks, on the other hand, have stemmed from multiple introductions, which have resulted in greater genetic viral diversity among the subsequent distinct chains of human-to-human transmission. Within a given species, however, virus variants have been shown to have low genetic diversity, often less than a few percent, as illustrated by the new variant isolated from patients in Guinea.[1] Such limited diversity generally leads to neutralizing cross-reactivity within the species.

Biologic characterization of various *Zaire ebolaviruses*, their case fatality rates, and their virulence in animal models have so far failed to provide convincing evidence of obvious differences in pathogenicity. Thus, it should be assumed that the new West African variant is not more virulent than previous *Zaire ebolaviruses*; a case fatality rate of about 70%, if confirmed, might even indicate lower virulence. The finding that the Guinea variant resides at a more basal position within the clade than previously known *Zaire ebolaviruses*[1] argues against an introduction from Central Africa and instead supports the likelihood of distinct evolution in West Africa. These findings reinforce the hypothesis that ebolaviruses have a broader geographic distribution than previously thought.

There is currently no licensed prophylaxis or treatment for any ebolavirus or marburgvirus infection; therefore, treatment is mere-

The New England Journal of Medicine
Downloaded from nejm.org on October 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.



Structure of Ebolavirus.

Shown is an ebolavirus particle and its characteristic filamentous shape. The negative-strand RNA genome is found in the center of particles in an encapsidated form as the nucleocapsid, together with the polymerase complex. Embedded in the virus membrane are trimeric glycoprotein spikes. Beneath the membrane is the matrix protein, which facilitates morphogenesis and budding of virus particles. The image is based on Protein Data Bank identifiers 3CSY and 1ES6 (www.rcsb.org) and Electron Microscopy Data Bank identifier EMD-2043 (www.emdatabank.org). The abbreviation ssRNA denotes single-stranded RNA.

ly supportive.[2] Over the past decade, however, multiple countermeasure options have shown promising efficacy in macaque models of filoviruses, and some of the approaches have completed or are at least nearing phase 1 clinical trials in humans.[4]

The current front-runner for therapeutic intervention seems to be antibody treatment, which has been successful in macaques even when antibodies are administered more than 72 hours after infection. Treatment approaches involving modulatory RNA (i.e., small interfering RNAs or phosphorodiamidate morpholino oligomers) are following close behind, along with a promising synthetic drug-like small molecule, BCX4430.[5] The most promising vaccine approaches are based on recombinant technologies, such as viruslike particles produced through plasmid transfection and replication-incompetent and -competent viral vectors.[4] Among the latter, vesicular stomatitis virus vectors have shown efficacy within 24 to 48 hours after infection in rhesus macaques.

In the absence of effective intervention strategies, diagnosis becomes a key element in our response to ebolavirus infection.[2] Detection rests largely on molecular techniques utilizing multiple reverse-transcriptase–polymerase-chain-reaction assays that can be used at remote outbreak sites. Antigen detection may be performed in parallel or serve as a confirmatory test for immediate diagnosis, whereas assays for detection of antibodies (e.g., IgM and IgG) are secondary tests that are primarily important in surveillance. Molecular detection strongly depends on sequence conservation, and established assays may fail when applied to new variants, strains, or viruses. Therefore, real-time sharing of information, particularly sequence data, is absolutely critical for our response capacity, since any delay could have disastrous consequences for public health. In addition, diagnostics remain essential for the time-consuming process of tracing contacts during an outbreak and for overcoming the obstacles to reintroducing survivors into their community.

The latest outbreak of *Zaire ebolavirus* in West Africa again has shown the limited ability of our public health systems to respond to rare, highly virulent communicable diseases. The medical and public health sectors urgently need to improve education and vigilance. And rapid, reliable diagnostic procedures must be implemented in key regions within or closer to the areas where these viruses are endemic so that local public health systems do not have to rely on distant reference laboratories, which should play a more confirmatory role in the future. Moreover, to optimize diagnostic-response capabilities, it is essential that information be shared in real time, as it was during the pandemic of the severe acute respiratory syndrome and during recurrent outbreaks of influenza.

Despite years of research on ebolaviruses and marburgviruses, it is still not possible to administer vaccines or treatments to the at-risk population or medical aid teams. If we are to practice cutting-edge medicine, rather than simply outbreak control, we need to advance leading approaches to-

The New England Journal of Medicine
Downloaded from nejm.org on October 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

ward approval and licensing. This gap should close over the next several years — if we can continue making progress before Ebola (or a related virus) strikes again.

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

From the Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratories, Hamilton, MT.

This article was published on May 7, 2014, and updated on May 22, 2014, at NEJM.org.

1. Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa1404505.
2. Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet 2011;377:849-62.
3. Towner JS, Amman BR, Sealy TK, et al. Isolation of genetically diverse Marburg viruses from Egyptian fruit bats. PLoS Pathog 2009;5(7):e1000536.
4. Friedrich BM, Trefry JC, Biggins JE, et al. Potential vaccines and post-exposure treatments for filovirus infections. Viruses 2012; 4:1619-50.
5. Falzarano D, Feldmann H. Possible leap ahead in filovirus therapeutics. Cell Res 2014 April 15 (Epub ahead of print).

DOI: 10.1056/NEJMp1405314
Copyright © 2014 Massachusetts Medical Society.

The Little Things

Danielle Ofri, M.D., Ph.D.

It was the second time during this frigid December that the elderly Mr. Cheng was found lethargic by his son. Last week, he had injected too much insulin for his diabetes. This week, he'd omitted a dose of his lactulose for the cirrhosis from his advanced liver cancer.

Each time, the EMTs treated Mr. Cheng in the ambulance, so by the time we saw him in the ER, he was already awake and cantankerous, itching to be discharged. He was fretfully anxious to leave immediately so he wouldn't miss his afternoon dialysis appointment in Chinatown. And he needed his morning dose of Nepro — the nutritional milkshake for dialysis patients.

"He's totally independent," the son told me. "He takes his meds, gets to his appointments, never misses dialysis. The home attendant does cooking and cleaning in the mornings."

But two admissions in 2 weeks for medication errors was a blazing red flag. A frail, elderly man with complicated illnesses, taking high-risk medications, living alone — it was a recipe for disaster.

"Trust me," the son said with a tired smile, "he does not want to be in a nursing home."

Mr. Cheng broke in, shaking his rail-thin arms vehemently. "No nursing home," he said, in his smattering of English. "I go home!"

The social worker applied for increased home-attendant hours. Although the attendant couldn't administer meds, she could remind him to take them. It wasn't ideal, but at least Mr. Cheng was amenable. The catch was that it would take several days for the paperwork to go through, and Mr. Cheng would have to stay in the hospital until then.

"As long as he gets his Nepro," the son said wearily. "He swears by that stuff."

"Nepro," Mr. Cheng echoed, nodding heartily. "Nepro."

And so Mr. Cheng settled into our ward, even though he wasn't acutely ill. He was charming, if a bit ornery, shuffling along the halls to the vending machine. He spoke enough English to greet everyone — and to request his daily Nepro shake. For some reason, although the ward always had a sufficient supply of other nutritional supplements, there never seemed to be much of the kidney version. Our constant requests for stat doses of Nepro on 17-West became a running joke.

Unfortunately for Mr. Cheng, his hospital stay included Christmas, which slowed the already glacial pace of his paperwork. Every time I had a new patient waiting hours in the ER for a bed, I felt guilty that Mr. Cheng was still in the hospital despite being medically stable. But we were told, "That's the way the system works."

Hospitals are, of course, the worst places for elderly patients, and Mr. Cheng duly illustrated that maxim. Three days into his stay, he spiked a fever, raising concern about peritonitis. We stuck a needle in his swollen belly to check the ascites fluid for infection, but that dropped his hematocrit, so we had to get a CT scan to evaluate the bleed. Mr. Cheng, annoyed by all the procedures, refused his lactulose. That caused him to become lethargic, nearly unresponsive, which, in turn, triggered a "rapid response" of the resuscitation team. His cirrhosis caused his blood pressure to fall, which meant he couldn't get dialysis. Lack of dialysis caused electrolyte chaos.

We finally called a family meeting that Friday morning. Mr. Cheng already knew that his advanced liver cancer gave him a life expectancy in the range of months. But if he couldn't get dialysis, he wouldn't survive more than a week. He signed a DNR form and told us he wanted to go home. Right now.

The New England Journal of Medicine
Downloaded from nejm.org on October 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.