

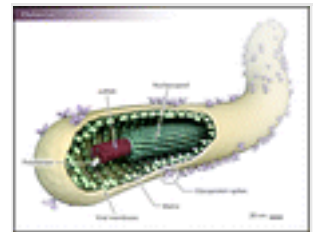
Ebola — A Growing Threat?

The recent emergence of *Zaire ebolavirus* in West Africa 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 *Tai 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 Tai 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.



Outbreaks or Episodes of Filovirus Infections.

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*. The virulence of *Tai 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.



Structure of Ebolavirus.

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, as in the current outbreak. 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. 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.

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, 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. 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. 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* 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 merely supportive. 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.

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. The most promising vaccine approaches are based on recombinant technologies, such as virus-like particles produced through plasmid transfection and replication-incompetent and -competent viral vectors. 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. 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 toward 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.