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Ebola virus in West Africa: new conquered territories and new risks—or how I learned to stop worrying and (not) love Ebola virus

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After being restricted to Central Africa for 35 years, the Ebola virus has suddenly emerged in Guinea in early 2014. The virus rapidly spread to Liberia and Sierra Leone and was imported to Nigeria, Senegal, Mali and even USA. The main features of this outbreak are a relentless dissemination among several countries, a dramatic number of cases including health-care workers and an inability to control the outbreak which grows exponentially. This conquest of new territories by Ebola virus implies that new risks have now to be taken into account. Filoviruses have been promoted from the status of neglected diseases to that of international public health and security concerns and we now have to live with that threat. A vaccine is probably the only efficient approach to avoid future re-emergence.

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Current Opinion in Virology 2015, 10:70–76

This review comes from a themed issue on **Emerging viruses: interspecies transmission**

Edited by **Antoine Gessain** and **Fernando Garcia-Arenal**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 6th February 2015

<http://dx.doi.org/10.1016/j.coviro.2015.01.008>

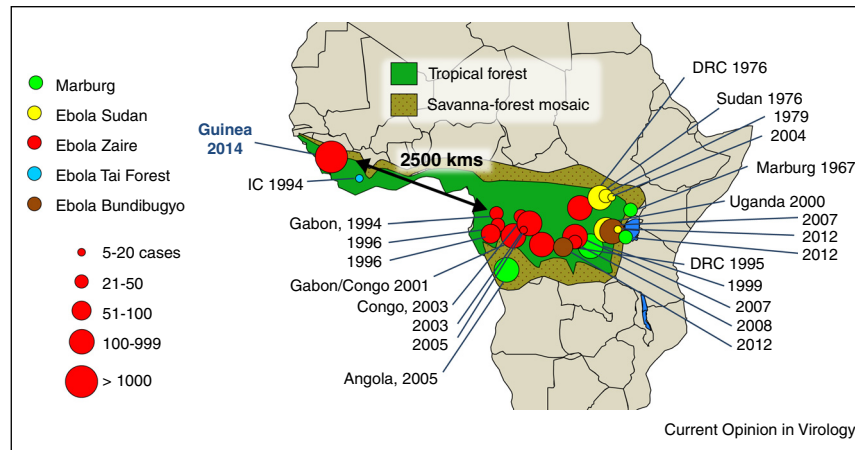
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Filoviruses are enveloped, single-stranded negative RNA viruses belonging to the *Filoviridae* family. They cause severe hemorrhagic fevers in humans. There is currently no vaccine or treatment to combat these viruses, and the only means of controlling outbreaks is to stop human-to-human transmission by isolating patients, protecting healthcare workers (HCW) and monitoring subjects that have come into contact with patients. Indeed, filoviruses are transmitted through contact with the biological fluids of symptomatic patients. The filovirus species known to cause disease in humans — Ebola virus (Zaire Ebola-virus), Sudan virus (Sudan Ebolavirus), Tai Forest virus

(Tai Forest Ebolavirus), Bundibugyo virus (Bundibugyo Ebolavirus), and Marburg virus — circulate in Africa. By contrast, the only species that appears to be nonpathogenic to humans, Reston virus (Reston Ebolavirus), is present in the Philippines [1,2]. The African filoviruses seem to use bats as a reservoir. In the case of Marburg-virus, cave bats (*Rousettus aegyptiacus*) act as the reservoir, and the virus has been isolated from animals [3,4]. Some fruit bats appear to act as a reservoir for Ebolavirus (EBOV). Indeed, Zaire EBOV-specific antibodies and viral genetic material have been found in several bats of the species *Hypsignathus monstrosus*, *Myonictes torquata* and *Epomops franqueti* [5]. However, infectious EBOV has never been isolated from these animals, in which viral replication probably occurs without clinical signs. Persistent infection and horizontal transmission between colonies has been suggested. This balanced adaptation of a filovirus to its reservoir has allowed the virus to persist in tropical forests over thousands of years [6]. The transmission of filoviruses to humans is a relatively rare event resulting from direct contact with the raw tissues or blood of infected wildlife, bats or accidental hosts, such as great apes. Such events are frequent during hunting activities, but, until 2013, were restricted to several Central African countries: Democratic Republic of Congo (DRC), Gabon, Republic of Congo, Uganda and Angola (Figure 1). Frequent introductions into human populations have occurred since 1994 in these countries and have often been attributed, at least for Zaire EBOV, to contacts between humans and great apes (chimpanzees and gorillas), which, like humans, are highly sensitive to the disease and act as accidental hosts. Indeed, a large epizootic principally affecting chimpanzees and gorillas occurred in Central Africa in the 1990s. In addition to favoring contact between humans and EBOV, this epizootic caused a major decline in animal populations [7–9], with an estimated 5000 deaths among gorillas [10]. Other outbreaks have resulted from direct introduction into the human population from bats [11].

On March 21st 2014, we demonstrated that Zaire EBOV was the etiologic agent of an outbreak of hemorrhagic fever that had been underway for three months in a forest area of Guinea [12]. This was surprising, but not because of the detection of EBOV, as the Tai Forest species of EBOV had been known to be circulating since the isolation of the virus during an epizootic in Tai forest chimpanzees in Ivory Coast in 1994 [13]. Only one human case was associated with this event and the Tai Forest

Figure 1



Historical and geographical distribution of filovirus outbreaks. The different outbreaks of filovirus hemorrhagic fever described from the discovery of the viruses are plotted on the map of Africa. The name of the countries where the outbreaks have occurred is figured, as well as the year. The filovirus species involved is represented by the different colors and the number of cases by the size of the circles.

virus had not since re-emerged [14]. What was surprising in this new outbreak was the identification of the Zaire species of EBOV as the causal agent. Indeed, the emergence of EBOV some 2500 km away from its current circulation area was unexpected and particularly worrying. Given the remoteness of the village in which the index case was discovered and its location close to the forest, it seemed very likely that this epidemic resulted from the introduction of the virus from local wildlife, rather than importation due to the travel of an infected patient. This hypothesis was confirmed by the whole-genome sequencing of the virus, which demonstrated that the Guinean strain and the Central African strains belonged to different clusters (Figure 2) [12^{**}]. This study, and a more recent description of the viruses currently circulating in Sierra Leone, indicated that the virus has diverged from Central African strains since 2004 [12^{**}, 15^{**}]. The circulation of EBOV in the West African tropical forest can be accounted for by the distribution area of the fruit bat species thought to act as the reservoir host, which covers the whole African tropical forest, from Tanzania to Casamance (Senegal) [16]. It remains unclear how the virus traveled from Central to West Africa, but this movement does not seem to have been mediated by great apes. Indeed, as rivers constitute impassable barriers to great apes, they cannot have transported the virus over such a large distance. It seems more likely that fruit bats were involved in the release of the virus in a distant area, through migration or neighboring colony-to-colony contamination over a large distance. Contacts between bats and humans are not rare, as these animals are frequently eaten in this area. The origin of the outbreak remains unclear. The suspected first case was a 2-year-old child who died in Guéckédou prefecture on December 6, 2013 [12^{**}]. This was followed by the death

of other members of his family. The cross-species transmission of the virus could have been due to contacts between the index case and Ebola virus-infected bats, but it will probably remain a hypothesis, as there is no means to further investigate this event. Nevertheless, it will be crucial to perform field studies to evaluate the viral burden among bats in the West African forest and the risk of further transmission to humans. The long time interval between the index case and the identification of the etiologic agent, about three months, was due to the remoteness of the first villages affected, which have limited access to healthcare, and the absence of previous EBOV outbreaks. As a result, by the time of EBOV identification, the virus was already spreading into Conakry and several highly active foci of the virus were found in the forest region. This situation rendered control of this outbreak intrinsically complex, particularly as the epicenter of the epidemic was located in a region of intense human circulation, very close to the borders of Liberia and Sierra Leone. The further massive spread of the virus through these three countries and the exponential increase in the number of cases was unprecedented and bore no resemblance to the pattern of previous outbreaks in Central Africa. Indeed, the re-emergence of filoviruses in human populations is a frequent, almost annual, event in this region, but is generally brought under control fairly rapidly. This also appears to be the case in the current outbreak in DRC which was due to butchering of a monkey found dead by a pregnant woman [17]. In DRC, the virus also emerges in remote locations close to the equatorial forest, but the dilapidated state of roads and the structure transport networks, which differs considerably from that in West Africa, together with the experience of health authorities in coping with these viruses often makes it possible to limit the number of

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