EBOLA

Hidden reservoirs

West Africa's Ebola epidemic continues to reveal surprises. Although the animal species that originally passed the virus to people remains a mystery, a virus reservoir and persistent disease have been identified in some human survivors.

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Animals are reservoirs for many pathogens that occasionally jump species and infect humans. In December 2013 in the forests of Guinea, a two-year-old boy became infected with the Zaire strain of Ebola virus from an unidentified animal source[1]. This event triggered the largest and longest human epidemic of Ebola viral infection in recorded history. Across several countries in West Africa, over 28,000 people were infected and more than 11,000 died. This fatality rate of less than 50% was lower than in most previous outbreaks, and it left more than 16,000 survivors[2]. Studies of these survivors are changing our understanding of Ebola virus infection and raising concern for the long-term well-being of these individuals and their communities. Writing in the *New England Journal of Medicine*, Deen *et al.*[3] reveal that Ebola virus RNA can persist in the semen of men for months

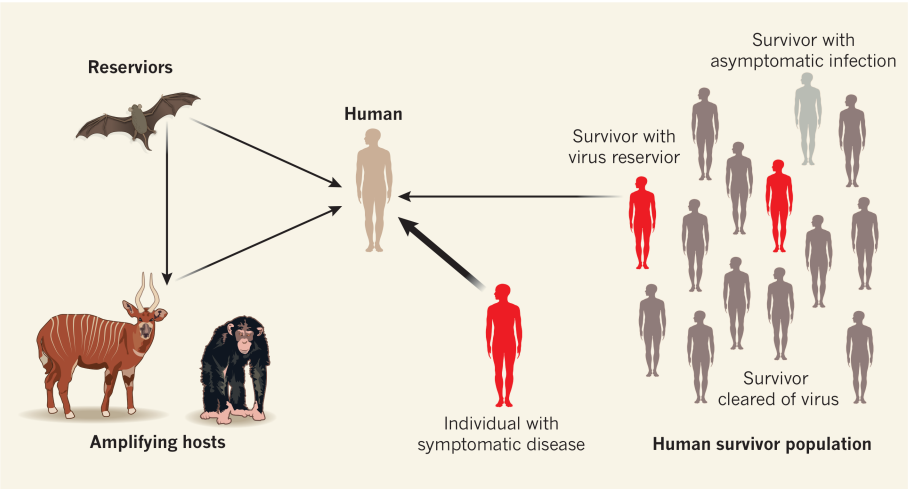

Figure 1 | Ebola infection dynamics in animals and humans. Ebola virus has been identified in several animal species, including bats, chimpanzees and forest antelopes. Transmission to humans can occur directly from reservoir species, in which the virus may persist without causing active infection, or from amplifying host species, in which the virus replicates to high levels, often causing illness and death. Most infected people develop acute Ebola virus disease and are highly infectious, although some individuals survive exposure and infection without developing symptoms. There is also growing evidence[3,4] that the virus can persist in the central nervous system and reproductive organs of some survivors of the disease, with the possibility that these survivors could infect others months after resolution of their acute symptoms[4].

after their recovery from the disease, and Mate *et al.*[4] demonstrate that such persistence can be the source of new infections through sexual transmission.

Deen and colleagues obtained semen samples from 93 Sierra Leonian men who had survived Ebola virus disease (EVD) at various intervals after the onset of their disease. Although the authors find that the proportion of men whose semen contained Ebola virus RNA waned with time, the viral genomes persisted for as long as 7–9 months after recovery. Mate and colleagues provide convincing evidence that a female patient in Liberia, who subsequently died, had contracted Ebola virus through unprotected vaginal intercourse with her male partner, who had survived EVD.

These observations support similar findings in previous epidemics of filoviruses, the virus family to which Ebola belongs. There have been reports[5,6] of the persistence of Marburg virus in the anterior chamber of the eye and semen of human survivors, and of the persistence of Ebola virus in the semen of men who survived the 1995 outbreak in the Democratic Republic of the Congo[7]. This has obvious implications for sexual partners.

The fact that Ebola virus is found at high levels in placental tissues also suggests that transmission could occur from pregnant women who survive EVD to their baby, although pregnant women who become infected usually abort the fetus before term[8]. Mother-to-child transmission by breastfeeding in survivors of Marburg virus has been reported[9], and the potential for transmission through breast milk has also been suggested for Ebola[10].

Although the relative risk of virus transmission from survivors is low compared with transmission from patients with acute EVD, a single case of new infection is sufficient to trigger an epidemic (Fig. 1). Thus, there is a strong need for rigorous assessment of the tissue reservoirs of Ebola in human survivors and the associated public-health risks. Follow-up health care should be combined with compassionate education of survivors and their communities by qualified and knowledgeable personnel, including advice on condom use.

Another lesson to emerge from this epidemic is that some survivors experience symptoms after their recovery from the main disease episode, suggesting that viral persistence in certain compartments of the body is more serious in some survivors than previously recognized. Reported symptoms include blurred vision, pain behind the eyes, hearing deficits, painful swallowing, joint pain, fever, memory loss and difficulty in sleeping[11,12]. The rehospitalization of a British nurse who developed neurological complications more than 9 months after surviving acute EVD[13] is a chilling indication that the virus can persist in the central nervous system and be triggered to reactivate or escape immune surveillance, or both. Fortunately, diagnosis and successful clinical intervention were possible for the nurse in Britain, but this situation is unlikely in most communities in West Africa.

The existence of a reservoir state in human Ebola survivors is now beyond debate. But we do not know how long viable virus can persist in these tissue reservoirs, nor whether the virus replicates there at low levels or is dormant and then triggered to replicate. Better definition and understanding of the reservoirs and the underlying mechanisms of post-EVD symptoms are needed to inform clinical management and treatment.

For example, studies of survivors may identify features of their immune responses (such as neutralizing-antibody determinants) that correlate with either full viral clearance or the persistence of viral reservoirs. Such correlates may enable survivors to be classified into 'carrier' or 'cleared' subtypes. Potential factors that could predispose survivors to viral re-emergence also need to be taken into account, including genetics, compromised immunity owing to poor health, concurrent infections such as HIV, or use of immunosuppressive drugs. However, Ebola, like other RNA viruses, may be prone to mutational changes, and virus escape from the host's immune response may eventually occur even without predisposing factors.

It is also not clear how, or whether, post-EVD immunity is affected by the stage of treatment or type of therapy given, such as monoclonal antibodies or the antibodies in convalescent plasma. As well as helping to classify survivors, enhanced understanding of viral persistence will help to guide therapeutic choices — treatment with small antiviral molecules, for example, may facilitate full clearance of the virus.

Although we are learning much about Ebola from this epidemic, we have yet to identify the events that caused the virus to jump to the Guinean boy almost two years ago. The consumption of bushmeat has been associated with previous epidemics, and some bushmeat species, such as great apes and forest antelopes, are susceptible to high levels of Ebola-virus replication and die from the infection. They are thus best considered as amplifying hosts, rather than the initial reservoir species (Fig. 1). Prime suspects for the reservoir include several species of bat, although a bat source has not been confirmed for this latest epidemic[14]. Indeed, the animal reservoirs of Ebola may be cloaked by sequestration of the virus in much the same way as its persistence in human survivors, waiting for physiological triggers for transmission to unexposed animals of the same species or to amplifying hosts.

Understanding the triggers of Ebola emergence, the persistence of the virus in humans and the infection dynamics in its animal reservoirs is vital not only for the long-term care of survivors of this epidemic, but also for preventing the next one. ■

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