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Editorial overview: Lassa virus

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Lassa fever (LF) is endemic in West Africa, with cases occurring annually in Sierra Leone, Liberia, Guinea and Nigeria. It is likely that Lassa virus (LASV) is also present in surrounding countries, as the virus is carried primarily by *Mastomys* rodents, which have an extensive range over sub-Saharan Africa. Other rodent species have also been found to have evidence of LASV infection when molecular techniques were used for virus-testing and species-identification [1,2]. Although the yearly LF disease burden has been estimated to be as high as 300 000 cases and 5000 deaths, the true incidence of LF is not known as epidemiological studies are incomplete. Human infections usually occur through contact with LASV-infected rodents, but person-to person transmission is also possible and hospital acquired LF has been frequently documented [3]. LASV is listed as a Category A priority pathogen both by the US Centers for Disease Control (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID). These pathogens pose the highest risk to public health in part because they can be easily disseminated or transmitted and result in high mortality.

Although LF has long been an underappreciated disease, public awareness was heightened over the past three years due to an unprecedented number of severe cases in Nigeria [4]. In addition, in 2018 the World Health Organization (WHO) designated LF as one of eight Blueprint priority diseases. These diseases have been determined to pose a public health risk because of their epidemic potential and due to the absence of effective medical countermeasures [5].

This issue of *Current Opinion in Virology* includes nine excellent reviews from experts in this field that aim to summarize the current understanding of all aspects of LASV from discovery and characterization through medical countermeasures to prevent and treat human disease. This compendium is especially timely, in that it is now 50 years since LASV was first described in Nigeria. The paper by Monath details his personal involvement in that discovery and pays tribute to key individuals who participated in these early studies, to include Jordi Casals-Ariet, Graham Kemp, and Joseph McCormick, as well as the first known survivor of LF, Penny Pinneo. Further, he describes subsequent outbreaks of LASV in the 1970s, the hiatus in work due to political constraints in Africa in the 1990s, and the reintroduction of modern research programs in the past 20 years.

The recent identification of genetically diverse LASV strains has prompted the development of new laboratory techniques to safely and rapidly diagnose and then characterize new lineages as they are discovered. In the paper by Happi, Happi, and Schoepp, both standard and contemporary methods of diagnosis are described. Modern field-friendly diagnostic methods are now

being implemented in even the most resource poor countries to supplement, enhance, or replace older methods. Especially promising are multiplexed magnetic bead-based (Magpix) assays, which can quickly differentiate hemorrhagic fever-causing viruses such as Ebola virus and LASV. These assays can detect antigen or antibodies and have been consistently more sensitive than the currently used assays such as immunofluorescent antibody staining or ELISA.

Next generation sequencing has contributed greatly to our understanding of the breadth of LASV strains causing disease in various regions. In this issue, Beitzel *et al.* describe the currently known LASV genetic lineages and how these lineages might impact disease. They further describe how current gene sequencing techniques have already been used to identify new LASV strains and are expected to uncover even more genetically diverse strains without the need for virus isolation from natural samples. Finally, these authors describe the use of reverse genetics methods to safely recover novel viral strains in a controlled laboratory environment. Such isolates will provide investigators much needed access to LASV for use in animal modeling, vaccine, and therapeutic studies.

Animal modeling is a critical component for developing effective medical countermeasures. The review by Tang-Huau, Feldmann, and Rosenke provides a comparative evaluation of laboratory animals that have been used for LASV research to date. They further correlate the acute disease characteristics and pathological findings of each model to those seen in humans. They conclude that although nonhuman primates remain the most relevant model for human disease, small animal models can provide valuable information as well.

In addition to modeling acute disease, mice [6], guinea pigs [7] and nonhuman primates [8] have been used to study a serious sequelae to LASV infection in humans; that is, sensorineural hearing loss [9]. Sattler *et al.* review studies using STAT1$^{-/-}$ knockout mice as a small animal model of LASV-associated hearing loss. Although the reasons for deafness caused by LASV infection of humans is still poorly understood, animal modeling has provided new information that might lead to improved treatment or even prevention of hearing loss in LF survivors. The authors also present information on small animal models of cytomegalovirus-associated deafness and how this might correlate with and inform LASV animal studies on hearing loss.

Garnett and Strong provide a detailed overview of LF in humans, to include clinical presentation, pathophysiology and organ involvement during acute disease. They also describe risk factors associated with contracting LASV from natural reservoirs or by person-to-person transmission. They point out that these risks are increased for pregnant women who suffer both a higher mortality rate themselves and have a fetal loss rate approaching 100% [10]. The authors also discuss how there are still no completely effective treatments for LF. Although treatment with ribavirin has been considered the standard of care for many years, the authors point out the need for additional efficacy studies, especially in light of the side-effects that the drug can cause.

Warner, Siragam, and Stein also describe studies with ribavirin in animal models, and suggest that additional treatment options are critically needed. They provide an overview of animal model studies with newer antiviral drugs, such as favipiravir and ST-193, as well as studies using immunoglobulin therapies. The authors contend that much more work needs to be conducted to evaluate the efficacy of these treatments both in animal models and humans.

Cross *et al.* further detail current work on antibody therapy as a treatment for LF. Early work indicating that passive transfer of convalescent patient sera from LF survivors was not particularly useful in treating disease stymied research in this area. Only recently have efforts been renewed to evaluate immunotherapy treatment of LF through the use of human monoclonal antibodies derived from survivors of LF. The authors describe how the use of modern imaging methods have provided clues as to the types of antibodies that are effective in neutralizing LASV, and also indicate that cocktails of such antibodies are protective in animal models. In addition, they suggest that non-neutralizing antibodies might also be playing a key role in clearing the infections and that further studies should help to elucidate the best immunotherapy approaches.

Prevention of LF is clearly preferable to treatment of the disease. Approved vaccines for LF do not currently exist. With the designation of LF as a priority disease by the WHO along with the engagement of the Coalition for Epidemic Preparedness Innovations (CEPI) in funding vaccine studies, this will hopefully change soon. In their review, Salami *et al.* introduce the need for effective vaccines for LF and summarize vaccine development efforts to date. Several vaccine platforms have been tested in animals and CEPI has supported development through human testing of at least three of these platforms. The authors summarize desirable attributes of vaccine candidates for LF to include stability without extensive cold chain requirements, durability and safety in immunocompromised individuals, pregnant women and children. They further evaluate how each of the current candidates meet these objectives.

Clearly, LF research has made progress over the past 50 years; however, much more remains to be accomplished. There is still no clear understanding of what

constitutes a protective immune response against disease or how to treat patients with mild or severe disease to prevent not only death but the neurological consequences and sensorineural hearing loss that frequently follow infections. Although vaccine development efforts are underway, it is not clear who should be vaccinated. A strong case could be made for widespread vaccination due to the endemic nature of and high number of cases of disease. Alternatively, or in conjunction with general vaccination, a strategy for interrupting an apparent epidemic could also be argued.

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