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IMPACT OF CLIMATE CHANGE ON OUTBREAKS OF ARENAVIRAL INFECTIONS

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25.1 INTRODUCTION

The *Arenaviridae* (Salvato et al., 2012) are a family of 23 enveloped viruses with bisegmented RNA genomes of around 10 kb in total length. Each of these RNA segments encodes two viral proteins in an ambisense arrangement. Their principal hosts are members of the mammalian order *Rodentia*. In terms of human health, they constitute an important family because six of these viruses infect humans and can cause serious and frequently fatal hemorrhagic fevers. With the exception of the type species *Lymphocytic choriomeningitis virus* (LCMV), which is widely distributed in Europe, Asia, and the Americas, each individual arenavirus species is found in a relatively localized area in Africa or in North or South America. The purposes of this review are to outline the general features of arenavirus diseases and to consider how currently predicted global climate changes might change the geographic distribution and human impact of these dangerous viral pathogens during the twenty-first century.

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25.2 NATURAL HISTORY OF ARENAVIRUSES

The arenaviruses are principally viruses of rodents of the family *Muridae*. Each virus is associated primarily with a single rodent species (the reservoir species), although in several cases infected animals of another species have been detected from time to time. Viruses are spread among populations through excretion in body fluids, and vertical transmission from mother to offspring also contributes to maintaining infection. Although we have insufficient knowledge of the details of the dynamics of virus–host interactions, the infected rodents show little or no overt disease, and their fitness appears not to be impaired to any significant extent. It is currently thought that the arenavirus–rodent host associations observed today are the results of coevolution of parasites and hosts. It has been a long-standing observation that the geographic range of a host rodent is usually more extensive than that of its associated arenavirus. However, it is likely that such apparent discrepancies may be clarified by recent molecular approaches to host rodent taxonomy (Coulibaly-N'Golo et al., 2011; Lecompte et al., 2006; Salazar-Bravo et al., 2002).

Some members of the arenavirus family are important causes of viral hemorrhagic fevers when humans become infected. These include *Lassa*, *Junín*, *Guanarito*, and *Machupo viruses*, which have caused quite large outbreaks, and *Sabiá* and *Chapare viruses*, which are known to have caused disease in a few cases (including laboratory workers). The geographic locations where these viruses have been found are indicated in Figure 25.1.

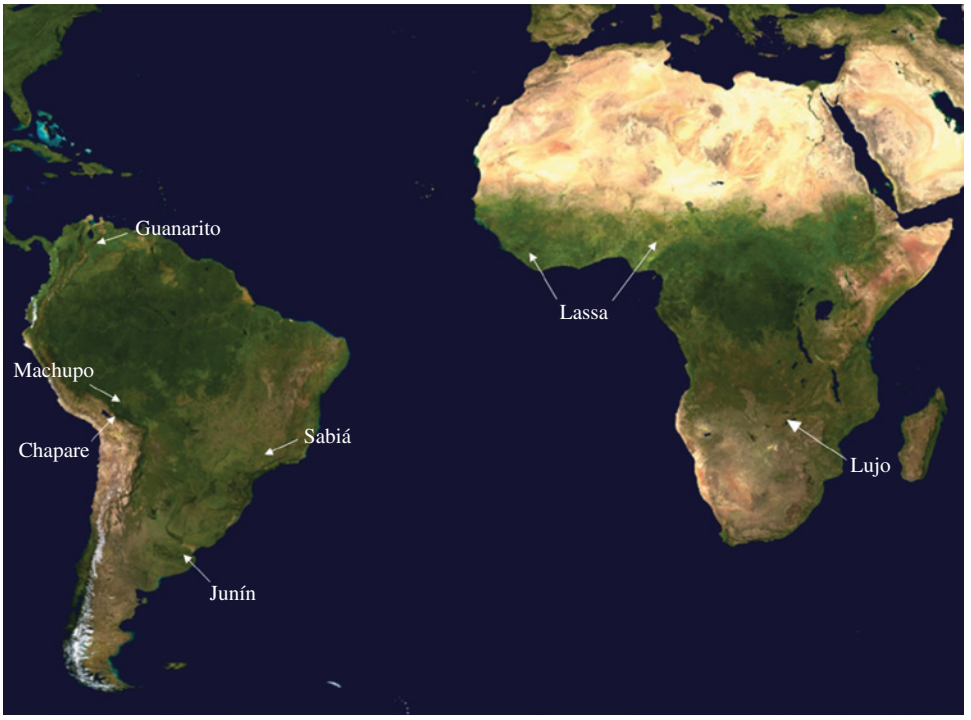

Figure 25.1. Geographic locations of arenaviruses associated with human hemorrhagic fevers. Map provided by NASA Visible Earth. Available at http://visibleearth.nasa.gov/. For color detail, please see color plate section.

The hemorrhagic fevers caused by these viruses are similar to each other, usually presenting as a nonspecific illness with symptoms including fever, headache, dizziness, asthenia, sore throat, pharyngitis, cough, retrosternal and abdominal pain, and vomiting. In severe cases, facial edema, hemorrhagic conjunctivitis, moderate bleeding (from nose, gums, vagina, etc.), and exanthema frequently occur. Neurological signs may develop and progress to confusion, convulsion, coma, and death. Case fatality rates range from 5% to 20% for hospitalized cases. In contrast, the type species LCMV causes aseptic meningitis or meningoencephalitis with an overall case fatality of less than 1%, but it has also been associated with hemorrhagic fever-like infections in organ transplant recipients (Fischer et al., 2006).

Lassa fever was first recognized in the 1960s and the causative arenavirus was isolated in 1969. It is now known to be present in large areas of both savannah and forest zones of sub-Saharan west Africa. The principal foci are in the west in the border regions of Guinea, Sierra Leone, and Liberia and in the east in Nigeria. The rodent host of Lassa virus is the multimammate rat *Mastomys natalensis*. This often-quoted relationship has recently been elegantly confirmed, by simultaneous sequence analysis of both infecting virus and infected rodent, in Guinea (Lecompte et al., 2006). Lassa virus was found only in *M. natalensis*, and not in another *Mastomys* species nor in 12 other rodent genera. *M. natalensis* is a peridomestic rodent that infests houses and food stores. Infection of humans can occur in the process of catching and preparing the animals for food, as well as by contact with animal excreta or contaminated materials. Lujo virus, an arenavirus recognized recently in a Zambian patient, is only distantly related to Lassa virus or to other African arenaviruses. It has caused a cluster of fatal human infections in South Africa (Briese et al., 2009).

The arenavirus Junín is the causative agent of Argentine hemorrhagic fever, first described in 1955. When first encountered, human cases were limited to an area of 16 000 km^2 in the humid pampas in the north of Buenos Aires province. However, the endemoepidemic area now extends to over 150 000 km^2, reaching north of Buenos Aires, south of Santa Fe, southeast of Cordoba, and northeast of La Pampa provinces. The human population at risk is estimated to be around five million. The virus is carried mainly by the vesper mouse *Calomys musculinus*, but other rodents (*Calomys laucha* and *Akodon azarae*) have also been implicated. These rodents mainly infest maize crops, and most human infections are seen in agricultural workers.

Venezuelan hemorrhagic fever is caused by Guanarito virus, which is carried by the cane mouse *Zygodontomys brevicauda*. Persons most affected are male agricultural workers around the town of Guanarito in Portuguesa State and adjacent parts of Barinas State in Venezuela. The virus was discovered in 1989 and the disease incidence has exhibited cyclical behavior with a period of 4–5 years.

Machupo virus is the cause of Bolivian hemorrhagic fever, which was first recognized in 1959 in the remote, sparsely populated savannah of Beni State, Bolivia. Ecological studies indicate that the rodent *Calomys callosus* is the principal animal reservoir. Agricultural workers are those most at risk, in the fields and in houses to which rodents have easy access. There were several local outbreaks of the disease in the 1960s, but the incidence fell markedly in the following decade following the institution of rodent control measures.

A small outbreak of viral hemorrhagic disease was caused in 2003–2004 in Cochabamba, Bolivia, by an arenavirus distinct from Machupo virus, the causative agent of the previously recognized Bolivian hemorrhagic fever (Delgado et al., 2008). It has been named Chapare virus. There is as yet no information about the extent of the public health threat from this virus, nor the identity of its normal rodent host species.

A single case of hemorrhagic fever caused naturally by the arenavirus Sabiá has been described. It occurred in Sabiá village, near São Paulo, Brazil. No natural rodent host has been identified. Two laboratory infections by the virus have also occurred.

It seems that arenavirus-caused disease in humans is an accidental product of their encounters with infected rodents and their excreta and body fluids. Infection of humans can occur through contact with rodent excreta or materials contaminated with them or ingestion of contaminated food. Direct contact of broken or abraded skin with rodent excreta is likely to be an important route, and inhalation of small droplets or particles containing rodent urine or saliva is also thought to be a significant source of infection. The nature of these incidental contacts evidently depends on the details of the living patterns and habits of both the rodent carriers and the human population. Where infected rodents prefer a field habitat, infection is primarily associated with agricultural workers. Where the rodents infest dwellings and other buildings, infection occurs in a domestic setting.

25.3 PREDICTED CLIMATE CHANGES

This discussion is mainly based on the findings of the Fourth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC). This is the most recent published report, which appeared in 2007. The overwhelming scientific consensus is that anthropogenic greenhouse gas (GHG) emission is causing global warming at a rate quite without precedent in the Earth's climate history (Meehl et al., 2007). The current rate of increase in global mean surface temperature of about 0.2 °C per decade is projected to continue until around 2030, irrespective of whether GHG emissions continue at present rates or whether reductions can be achieved. This implies mean surface temperatures in the period 2011–2030 about 0.66 °C warmer than in the period 1980–1999. Further into the future, there is greater uncertainty because of increasing differences among the various scenarios modeled. These scenarios cover a range of possibilities for the mitigation (or lack of it) of GHG emissions. For a number of plausible scenarios, the best estimates of the IPCC for the increase in global mean surface temperature for the period 2090–2099 relative to 1980–1999 range from 1.8 to 4.0 °C. Surface temperature increases on land are predicted to be roughly twice this global mean, that is, in the range 3.6–8 °C by the end of this century. On the global scale, it is predicted that there will be more frequent and more extreme heat waves, fewer cold periods, and increased and more intense rainfall in regional tropical precipitation maxima. In subtropical and mid-latitudes, precipitation will decrease, but intense rainfall events interspersed with long periods of drought will become more common. Sea levels are expected to rise globally on the order of 0.5 m by the end of the century, but there is a great deal of uncertainty in making these estimates and in assessing their possible impact in particular geographic regions.

Disturbingly, more recent scientific and economic reviews of present GHG emission rates and their likely future trends and the lack of significant political progress in moving towards their reduction indicate that it is increasingly unlikely that any prospective global agreement can stabilize atmospheric GHGs at 450 ppm or even at 650 ppm CO_2 equivalent (Anderson and Bows, 2008; Anderson et al., 2008; Clark et al., 2008; Garnaut et al., 2008; Hansen et al., 2008). Hence, the IPCC scenarios are very likely to significantly underestimate the degree of climate change in the future.

For the purpose of this review, two specific geographic regions are of particular importance. These are the locations where Lassa fever is currently endemic (sub-Saharan west Africa) and the broader region where South American hemorrhagic fevers are found (South America). The East African Lujo virus will not be considered further, since very little is presently known about its natural history. It is worth pointing out though that the example of Lujo virus suggests that other pathogenic arenaviruses may well remain as yet

undiscovered and that climate change-driven population movements or other factors may lead to human infections. Unfortunately, there are major difficulties in moving from global-scale climate change predictions towards more detailed descriptions of future outcomes at a regional level. These are particularly acute in west Africa, because of the relatively sparse data on past and current weather conditions, the complex nature of the terrain, and the influence of ocean basins. It is predicted (Christensen et al., 2007; Conway 2009) that Africa as a whole will warm more than the global annual mean throughout the year. Drier regions will warm more than the moister tropics. Changes in rainfall in the Sahel, the Guinean coast, and the southern Sahara in this century remain very difficult to predict because of shortcomings in the current models, which result in systematic errors, disagreements among different climate models, and inability to simulate correctly twentieth-century conditions. Key features such as the frequency and spatial distribution of tropical cyclones affecting Africa cannot be reliably assessed. Nonetheless, the frequency of extremely wet seasons is likely to rise markedly, as is also the case in East Africa. The west African coast and the Gulf of Guinea are thought to be at high risk of flooding due to sea-level rise (Boko et al., 2007).

In South America, the annual surface temperature increase is predicted to be similar to the global mean (Christensen et al., 2007). This represents an increase in the range of 3°–4 °C by the end of the century. Systematic differences among different models, together with large variations in predictions of changes in El Niño amplitude, and the height and sharpness of the Andes mountains make assessments at regional scale over much of Central and South America very unreliable. Rainfall changes show that regional differences are likely to occur; most models suggest a wetter climate around the Rio de la Plata but reduced precipitation in parts of northern South America. Extremes of weather and climate are likely to occur more frequently. Water stress will increase as a result of glacier retreat or disappearance in the Andes, leading to highly adverse effects on agriculture.

25.4 ARENAVIRAL DISEASES AND CLIMATE CHANGE

A well-recognized example of a change in the incidence of an infectious viral disease already exists. The spread of bluetongue virus disease in cattle from the Middle East and north Africa first to southern and then to northern Europe has been attributed to ongoing climate changes in these regions (Purse et al., 2008; Weaver and Reisen, 2009). The main factors that can affect the burden of infectious diseases in humans are (i) changes in abundance, virulence, or transmissibility of infectious agents; (ii) an increase in probability of exposure of humans; and (iii) an increase in the susceptibility of humans to infection and to the consequences of infection. A wide range of biological, physicochemical, behavioral, and social drivers can influence one or more of these factors (Wilson, 1995). In particular, alterations in the environment, brought about by currently predicted climate changes, clearly have the potential to affect, to a greater or lesser extent, all three of these factors. We need to consider the possible effects of climate changes within the currently known endemic areas of each arenavirus disease and also the extent to which such changes may influence transfer and persistence of arenavirus diseases to hitherto unaffected regions. However, it must be appreciated that the reliability of any such predictions remains very low, not only because of the relatively coarse scale of available climate change predictions but also because of our lack of reliable data on the current incidence of these diseases. This applies particularly to the prevalence of Lassa fever and other possible arenavirus diseases in Africa.

When we examine how these factors could affect arenavirus-caused disease, all three are likely to exert significant influence. In the first category, there are likely to be changes in the abundance of arenaviruses, in the sense that the reservoir host rodent populations are likely to be affected one way or another by changes in climate. Thus prolonged drought in a particular region may lead to reduction in population size, while increased seasonal rain may lead to a population explosion. Such events have been observed for other rodent-borne zoonoses, as documented in the IPCC Report (Confalonieri et al., 2007). In the case of another rodent-borne virus disease, hantavirus pulmonary syndrome (HPS), there is evidence that El Niño Southern Oscillation-induced increases in rainfall in the Four Corners region of the southwestern United States led to increases in the population of the rodent reservoir *Peromyscus maniculatus* and subsequent emergence of the disease in the human population (Glass et al., 2002). There may be a similar explanation for the emergence of HPS in Panama in 2000, following increases in the peri-domestic rodent population following heavy rainfall and flooding in the surrounding areas (Bayard et al., 2004). Further discussion of the influence of climatic factors on mammalian vector ecology and impact on the burden of zoonotic disease can be found in Mills et al. (2010). In Guinea, there is significant risk of infection by Lassa fever throughout the year, but there is an increased rate of infection during the dry season as a result of the greater number of rodents, some carrying the virus, infesting dwellings (Fichet-Calvet et al., 2007). In an analogous manner, the greater expected frequency of extreme weather events may lead to scenarios with increased rodent–human contact following heavy rain and subsequent flooding and consequent increases in the incidence of arenaviral diseases. More recently, analysis of geographic location of Lassa fever outbreaks in humans and incidence of infected rodents in relation to environmental variables across sub-Saharan west Africa has emphasized the important role of rainfall as a predictor of disease incidence (Fichet-Calvet and Rogers, 2009). Lassa fever outbreaks occurred in areas with annual precipitation in the range 1500–3000 mm. Areas with either less rainfall or more rainfall were not subject to Lassa fever outbreaks. It is thus very likely that changes in climate leading to altered rainfall intensity and/or distribution very likely alter the geographic and temporal distribution of Lassa fever disease outbreaks. However, detailed predictions must await the development of accurate local climate models.

Climate change in Venezuela, Bolivia, and Argentina may lead to changes in agricultural land use, with relocalization of crop-growing areas that are becoming unsuitable for agricultural use to others with more favorable climates. Where arenaviral diseases are carried by rodents infesting crops, as is the case with Venezuelan, Bolivian, and Argentine hemorrhagic fevers, there will be corresponding changes in the geographic location of rodents and thus disease.

It is unlikely that changes in virus virulence will result directly from climatic changes, but it is conceivable that virus transmissibility could be influenced. Arenaviruses are enveloped viruses that are not particularly robust when exposed to high temperatures or low humidity. Thus some climatic factors may be expected to influence the survival of the viruses in the environment either negatively or positively. However, it is difficult to estimate the importance of these effects compared with other climatic impacts on disease incidence.

It is very likely that in some environments, climate change will increase the probability of human exposure to arenavirus infections, whereas in others it will decrease the probability. Such effects are likely to be mediated through changes in the probability of encounters with reservoir rodents and contact with their excreta or contaminated materials. We can envisage direct effects of climate on the size and behavior of virus-carrying rodent

populations, as discussed earlier, as well as on the human populations themselves, through changing land use (for instance, irrigation) triggered by increasing temperatures, fluctuating weather conditions, and the resultant disturbance of local landscapes. Climate change is likely to lead to mass migration and movement of populations, with consequent stresses associated with inadequate shelter and overcrowding. Such considerations are likely to be more significant in respect of Lassa fever compared with the South American arenaviral hemorrhagic fevers, because of the much larger human populations in the endemic areas. As well as possible changes in areas favorable for food production, flooding along the west African coast as a result of storm surges and sea-level rise could drive large-scale population movements in the area. It has been projected that the 500 km of this coast between Accra and the Niger delta will be a continuous urban megalopolis of some 50 million people by 2020 (Boko et al., 2007; Hewawasam, 2002). It has already been shown that Lassa fever can be a significant risk in refugee camps in Guinea (Bonner et al., 2007; Fair et al., 2007). There is increased risk in areas where there are higher numbers of infected rodents (Fair et al., 2007) and in poor quality housing and households with reduced levels of hygiene (Bonner et al., 2007). Thus populations driven onto higher ground by coastal flooding may be at increased risk from Lassa fever (among other diseases) unless sufficiently adequate housing and rodent control measures can be provided. It should be noted that rodent control is the key measure in any program to mitigate arenavirus disease in humans. However, authorities in the Lassa fever endemic regions, which include some of the most underdeveloped countries in the world, do not currently have the necessary resources and infrastructure to mount effective healthcare or disease prevention programs.

Finally, it is possible that predicted climate change may lead to more frequent transfer of arenavirus-infected patients to regions of the world without experience of these diseases. Although natural rodent vectors will be almost certainly absent, it is important that infected persons be swiftly recognized and diagnosed so that further transmission during patient care can be avoided. This can readily be achieved through careful barrier nursing techniques, but the fear engendered by viral hemorrhagic fevers, including those caused by arenaviruses, can place a heavy burden on hospital systems. It would be prudent if such considerations were included in healthcare planning to meet the challenges of global climate change.

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