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Editorial overview: Emerging viruses

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Recent years have seen the identification of a number of emerging and reemerging viruses infecting humans. The recognition of these pathogens likely stems from an increased awareness of the problem of emerging viruses, increased surveillance for such pathogens and the availability of new technologies for virus detection. The emerging virus umbrella includes new viruses not previously described, viruses which had been previously described but not known as human pathogens and viruses known as human pathogens but which are now recognized as having an increasing impact on human health. In this issue, recent examples from each category are reviewed. Among the novel human viruses are the novel Middle East Respiratory Syndrome coronavirus (MERS-CoV) and newly emerged phleboviruses. As an example of a previously recognized virus that has only recently been recognized as a serious human pathogen, we include H7N9 influenza A viruses. Among the previously described human pathogens exhibiting an increased impact of human health, we describe hepatitis E virus (HEV), human enterovirus 71 (EV71) and the New World arenavirus Machupo virus.

Almost 10 years after the SARS epidemic, which infected more than 8000 patients and has caused more than 750 deaths, the emergence of MERS-CoV in the Middle East in 2012 has already affected countries in Asia, Europe and Africa and has infected more than 180 patients and led to more than 70 deaths [1,2]. MERS-CoV is a novel betacoronavirus closely related to previously reported *Tylonycteris* bat coronavirus HKU4 and *Pipistrellus* bat coronavirus HKU5 discovered in lesser bamboo bats and Japanese pipistrelles respectively [3,4]. In addition to severe respiratory tract infections, many patients infected with MERS-CoV also suffered from renal failure. Recently, neutralizing antibodies against MERS-CoV were detected in serum samples and MERS-CoV RNA was detected in nasal swabs in dromedaries in the Middle East [5,6]. Fortunately, human-to-human transmission of MERS-CoV is still uncommon. In this issue, [Raj et al.](#) reviewed the virology, genomics and epidemiology of MERS-CoV infections.

The bunyaviruses are enveloped, three segmented negative-sense RNA viruses [7]. The family contains more members than any other RNA virus family and includes viruses that infect vertebrates, invertebrates and plants. Within the bunyavirus family is the genus *Phlebovirus*. Among the 70 phleboviruses are important pathogens of agricultural and human pathogens [8]. Of these arthropod-transmitted viruses, Rift Valley fever virus is the best known because of its ability to cause disease in ruminants and to cause sometimes fatal infection in humans [9]. In recent years, novel phleboviruses have been recognized. Among these are two tick-transmitted viruses, severe fever with thrombocytopenia syndrome virus and Heartland virus, that cause severe hemorrhagic illness in humans [10,11]. The potential for severe infections and their emerging nature makes these viruses significant

new pathogens. In their review, [Elliott and Brennan](#) provide an overview of these viruses, describing their identification, the manifestations of human infections and their molecular biology. The information summarized will provide the basis upon which effective control measures can be based.

Globally, HEV is the most common cause of acute viral hepatitis in humans. The disease is generally self-limiting but high mortality rates are observed in pregnant women and young infants. Chronic HEV infection is also a problem in immunocompromised patients, such as solid organ transplant recipients and HIV patients [12,13]. Traditionally, HEV infection has been transmitted mainly through fecally contaminated water, with most large outbreaks occurring in developing countries such as China and India [14]. Among the four known HEV genotypes, genotypes 1 and 2 are restricted to humans, whereas genotypes 3 and 4 are able to infect humans, pigs and other mammals. Recently, a large community-based surveillance for disease burden due to HEV was performed in a rural community in eastern China where the zoonotic genotype 4 HEV predominated. This was followed by two parallel studies that analyzed the efficacy of vaccine against HEV infection. In this issue, [Huang et al.](#) reviewed the data from this effort as they pertain to natural history of HEV and highlighted features.

EV71, which belongs to the family *Picornaviridae*, is a non-enveloped, positive-sense RNA virus that causes hand-foot-and-mouth disease (HFMD). In addition, EV71 infections can lead to severe neurological disease and death in infants and young children. EV71 outbreaks have been recognized at many sites across the globe. The emerging nature of EV71 has been highlighted by extensive epidemiological studies in China which highlight EV71 as a substantial cause of disease and death in young children [15]. Significant recent progress has been made on EV71 biology and vaccine development. The crystal structure of EV71 has been solved as has the structure of EV71 in complex with a capsid binding inhibitor [16,17]. The structure has also been used to develop more potent capsid-binding inhibitors [18]. The mechanistic basis by which EV71 neutralization occurs has also been recently described [19], and vaccines have been shown to be effective in clinical trials [20,21]. In their review, [Huang and Shih](#) highlight progress made toward the identification of EV71 entry receptors, discuss new understanding of host factors that influence viral translation and virus-encoded determinants of replication efficiency. Because evaluating pathogenesis as well as drug and vaccine efficacy requires *in vivo* testing, the authors then discuss animal models of EV71 infection and developments in antiviral and vaccine approaches.

Machupo virus is the causative agent of Bolivian hemorrhagic fever [22,23]. The arenavirus family, of which

Machupo virus is a member, is comprised of enveloped viruses with two-segmented RNA genomes and is divided into Old World and New World viruses [24]. Zoonotic pathogens, most arenaviruses infect rodent hosts. Their geographic distribution is therefore determined, in part, by the distribution of their host species [25]. Infections of humans likely occur via the respiratory route or through direct contact with infectious material [24]. First identified in 1959, no cases of BHF were reported from 1976 to 1993. However, recent years have seen a re-emergence of Machupo virus-related infections and illness [26]. [Paessler and colleagues](#) review the history of Machupo virus, its reservoir host *Calomys callosus*, the manifestations of infection and the limited treatment options available for infected individuals. Given the limited understanding of Machupo virus pathogenesis and the need to test vaccine and antivirals, the authors discuss in depth the status of animal models.

In February 2013 an H7N9 subtype avian influenza virus emerged as a pathogen causing severe infections and deaths in people in China [27]. While a variety of avian influenza viruses have been documented to infect humans, most such infections have been relatively mild [28]. Severe, life-threatening human infections seemed to be restricted to those caused by H5N1 viruses and, in one case an H7N7 virus, that were highly pathogenic in poultry [29–31]. Distinguishing the recent H7N9 viruses was the fact that these viruses exhibit low pathogenicity in poultry but still cause severe human disease. That H7N9 infections continue to occur in humans poses an obvious and immediate public health issue. These infections also raise concerns that H7N9 avian viruses could reassort their gene segments with circulating human strains and become more transmissible between humans, or that these viruses could acquire enhanced human-to-human transmission without reassortment. Either scenario raises concerns that new pandemic strains, for which there is little to no pre-existing immunity in the human population, could arise. In their review, Dr. [George Gao and colleagues](#) discuss the epidemiology, clinical presentation, immunology and molecular biology of these viruses, and they summarize the status of antivirals and vaccine development for these worrisome pathogens.

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