Emerging viral infections

Michael R. Wilson

Purpose of review
This review highlights research and development in the field of emerging viral causes of encephalitis over the past year.

Recent findings
There is new evidence for the presence of henipaviruses in African bats. There have also been promising advances in vaccine and neutralizing antibody research against Hendra and Nipah viruses. West Nile virus continues to cause large outbreaks in the United States, and long-term sequelae of the virus are increasingly appreciated. There is exciting new research regarding the variable susceptibility of different brain regions to neurotropic virus infection. Another cluster of solid organ transplant recipients developed encephalitis from organ donor-acquired lymphocytic choriomeningitis virus. The global epidemiology of Japanese encephalitis virus has been further clarified. Evidence continues to accumulate for the central nervous system involvement of dengue virus, and the recent deadly outbreak of enterovirus 71 in Cambodian children is discussed.

Summary
In response to complex ecological and societal dynamics, the worldwide epidemiology of viral encephalitis continues to evolve in surprising ways. The articles highlighted here include new research on virus epidemiology and spread, new outbreaks as well as progress in the development of vaccines and therapeutics.

Keywords
aseptic meningitis, emerging viral infections, poliomyelitis, viral encephalitis, zoonosis

INTRODUCTION

In response to complex ecological and societal dynamics, the worldwide epidemiology of viral encephalitis continues to evolve in surprising ways. These forces operate in a context in which we are increasingly able to identify novel pathogens because of improved diagnostic techniques and enhanced surveillance regimes [1▪▪,2]. This review summarizes a number of articles over the past 12 months that highlight developments in the field of emerging and re-emerging viral infections of the central nervous system (CNS).

Emergence of an infectious disease can be defined in a number of ways. One definition states that an infectious disease emerges when its incidence increases following its introduction into a new host population. Prominent emerging neurotropic pathogens include Nipah and Hendra viruses, Japanese encephalitis virus (JEV) and West Nile virus (WNV). A re-emerging infectious disease can be defined as one whose incidence increases in an existing host population as a result of changes in the pathogen, the host population or the environment. Re-emerging CNS pathogens include measles virus, mumps virus, lymphocytic choriomeningitis virus (LCMV), poliovirus and dengue virus.

EMERGING DISEASE VS. EMERGING DIAGNOSIS?

Outside the world of infectious disease, neurologists are increasingly familiar with the dramatic encephalitis syndrome associated with autoantibodies to the *N*-methyl-D-aspartate (NMDA) receptor. This condition was defined after the identification of the NMDA receptor autoantibody by Dalmau *et al.* in 2007 [3]. Although this disease is newly recognized, no one argues that the disease

Departments of Neurology and Medicine, Boston University School of Medicine, National Emerging Infectious Diseases Laboratories, Boston, Massachusetts, USA

Correspondence to Michael R. Wilson, MD, Boston University School of Medicine, Departments of Neurology and Medicine, National Emerging Infectious Diseases Laboratories, Boston, MA, USA. Tel: +1 617 414 4290; e-mail: michaelneuro@gmail.com

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KEY POINTS

- Neurotropic viruses that cause significant morbidity and mortality continue to emerge and re-emerge as a result of globalization, climate change, political instability and other social and cultural factors.
- As a result of enhanced surveillance networks and new diagnostic techniques, our understanding of zoonotic infections continues to grow.
- The recent research on the viruses discussed in this review reflects the increasing sophistication of our surveillance programs, diagnostics and even therapeutics but also highlights the significant gaps in our understanding of these pathogens that future research needs to urgently address.

itself is new. As recent work by the California Encephalitis Project and other investigators demonstrates, for years these cases had been labeled 'viral encephalitis of unknown etiology' [4–6].

Recent work is also challenging whether seemingly isolated spillover events of viruses from animals to humans are really just the tip of the iceberg under which there are many more undiagnosed endemic human cases. Rabies virus and the hemorrhagic fever viruses (e.g., Ebola, Marburg and Lyssa viruses) are infamous zoonotic viruses that periodically spillover from animals to humans. Since these viruses are highly lethal in humans, it has been thought that there is little to no asymptomatic human exposure.

Two articles published in 2012 complicate this picture. A provocative editorial by Gire *et al.* [7▪] cites a number of recent studies that have found high antibody seroprevalence to Ebola, Marburg and Lyssa viruses in multiple African countries. This has led to estimates that tens of thousands of hemorrhagic fever cases go unrecognized every year, far outstripping the well recognized virus outbreaks associated with very high mortality rates. Similarly, a recent article found high neutralizing antibody titers to rabies virus in 11% of a small cohort of asymptomatic Peruvians living in the Amazon [8▪]. Prior exposure to bats was noted in all cases, and only one person had received postexposure prophylaxis. Although this small number of cases certainly does not suggest that rabies virus is endemic, it does raise the possibility that in some populations the disease may be more common (and have a lower fatality rate) than previously recognized. It should be stressed that this research is still preliminary as antibody seroprevalence studies can overestimate exposure to a particular pathogen if people develop cross-reactive antibodies to closely related, and potentially still unknown, viruses. However, these studies at least highlight the need to constantly reevaluate how we define the emergence of infectious diseases in the face of ever improving surveillance and diagnostic techniques.

NIPAH AND HENDRA VIRUSES

Nipah virus and Hendra virus are two closely related paramyxoviruses in the *Henipavirus* genus that emerged separately in the 1990s, each causing encephalitis outbreaks with mortality rates ranging from 40 to 75% [9]. Hendra virus encephalitis cases have only occurred thus far in Australia. The virus spreads from its fruit bat host reservoir to horses via a route of transmission that is assumed to involve exposure to bat urine and feces. Horses develop pneumonia and encephalitis and serve as an amplifying host able to transmit the virus to humans who work closely with infected animals [10]. Nipah virus was first identified in 1998 when a respiratory illness spread rapidly through domesticated pigs living in close proximity to fruit bat colonies in Malaysia. The outbreak ultimately reached Singapore necessitating the slaughter of over one million pigs. Two hundred seventy-six people, mostly pig handlers, were infected and 106 people died. Since 2001, Nipah virus outbreaks have occurred at least annually throughout Southeast Asia. More recent outbreaks in Bangladesh demonstrated the ability of Nipah virus to transmit from human to human presumably via respiratory droplets [11,12]. Both viruses preferentially infect endothelial cells, causing a systemic vasculitis that is most pronounced in the small arteries and capillaries in the brain. Neurons also express the target receptor for both viruses (i.e., ephrinB2), and extensive neuronal infection has been demonstrated in cases of relapsed encephalitis up to 24 months after the acute infection. The pathology in these cases is reminiscent of subacute sclerosing panencephalitis, a disease caused by persistent infection by another human paramyxovirus, measles virus [13,14]. For additional information, a 2012 issue of *Current Topics in Microbiology and Immunology* exhaustively reviews the epidemiology, pathogenesis and molecular biology of henipaviruses [15▪].

Although human cases of *Henipavirus* infection have been restricted to Southeast Asia and Australia, the geographic range of fruit bats extends into Africa. Three articles in 2012 suggest there is a risk of zoonotic *Henipavirus* infection in Africa. The most comprehensive article by Drexler *et al.* [16▪▪] identified more than 60 new paramyxovirus sequences in bats and rodents around the world including virus sequences strikingly similar to mumps virus,

respiratory syncytial virus and canine distemper virus. In addition, these investigators also greatly expanded the number of known *Henipavirus* sequences by detecting *Henipavirus* RNA in six different bat species across five African countries. Phylogenetic analysis suggests that some of these sequences represent the precursors to Hendra and Nipah viruses. Two additional articles found *Henipavirus*-related sequences (and antibodies) in straw-colored fruit bats (*Eidolon helvum*) in Ghana and Congo [17,18]. *E. helvum* is commonly hunted and sold as bushmeat. In fact, the article by Weiss and colleagues tested bats that were originally intended for sale in markets in Brazzaville, Republic of Congo. The authors noted that the lack of resources for extensive diagnostic testing in many parts of Africa raises the possibility that human infections have thus far gone undetected. It should be stressed that these articles report many new virus sequences obtained through powerful polymerase chain reaction (PCR) techniques, but they have been unable to isolate and culture live viruses from sampled bats.

The past year also saw two exciting articles in the area of prevention and treatment for these two devastating infections. The first was a report of a recombinant fully humanized monoclonal antibody that potently neutralizes both Nipah and Hendra viruses. The antibody completely protected African green monkeys from Hendra virus challenge and even prevented significant disease when peripherally administered up to 72 h after a virus challenge that would otherwise be 100% fatal [19▪▪,20]. Although still in preclinical testing, this antibody has already been administered to two people infected with Hendra virus on a compassionate use basis. The same research group also reported the development of a vaccine based on a recombinant, soluble form of the Hendra virus attachment glycoprotein [21▪▪]. This immunogen elicits a robust antibody response that completely protects African green monkeys from Nipah and Hendra virus challenge and has recently received regulatory approval for use in horses in Australia.

WEST NILE VIRUS

WNV is a mosquito-borne flavivirus in the JEV serocomplex that continues to circulate in the United States after its introduction in New York in 1999. Surveillance studies showed a large spike in cases of WNV infections in 2012 to levels not seen since 2002 and 2003 when the virus caused more than 3000 cases of neuroinvasive disease per annum. As of December 11, 2012, 5387 human cases including 243 deaths had been reported to the Centers for Disease Control and Prevention [22]. Of these cases, 2734 (51%) were classified as neuroinvasive. The southwestern United States was hit particularly hard with one third of all cases occurring in Texas. It is not yet clear what led to the spike of infections in 2012, but people have noted that the environmental conditions (i.e., drought with mosquitoes breeding in shallow creek beds) in the summer of 2012 were the same as those during the initial US WNV outbreak.

A retrospective study by Lindsey *et al.* [23▪] has also put the spotlight on the long-term consequences of WNV infection. In a group of 201 patients in northern Colorado admitted for acute WNV infection in 2003, they found a two-fold increase in mortality that persisted up to three years after infection. Leading causes of death were cardiovascular and pulmonary complications. Risk factors for increased mortality included a history of neuroinvasive WNV disease, intubation during the acute hospitalization, a history of tobacco use, autoimmune disease and increasing age. This extends earlier work on the long-term consequences of acute WNV infection and argues for close and sustained surveillance of survivors.

It has long been recognized that encephalitic arboviruses like WNV, JEV and eastern equine encephalitis virus have a characteristic pattern of neuronal involvement (i.e., basal ganglia, midbrain and thalamus) that differs dramatically from other encephalitis-causing viruses like the herpes simplex viruses, which typically damage the temporal lobes. A new article by Cho *et al.* [24▪▪] makes a major advance in our understanding of why different neuronal subpopulations are more or less susceptible to virus infection. They demonstrate that neurons from evolutionarily distinct brain regions exhibit differential innate immune responses when exposed to a variety of positive-stranded RNA viruses including WNV, St. Louis encephalitis virus, mouse hepatitis virus and Venezuelan equine encephalitis virus.

JAPANESE ENCEPHALITIS VIRUS

JEV represents the most important cause of viral encephalitis worldwide with a 20–25% case fatality rate occurring primarily in children and a 50% rate of severe disability amongst survivors [25]. Like its cousin WNV, JEV circulates amongst birds and mosquitoes and is transmitted to humans via a mosquito bite. Over the past few decades, it has continued to expand its geographic range throughout Southeast Asia and even into the northern tip of Australia and Papua New Guinea [26]. A meta-analysis by Campbell *et al.* [27] provides updated epidemiologic data on JEV that will be useful for

surveillance and vaccination programs. They compiled epidemiologic studies from 24 JEV-endemic countries, and revised upward the annual number of encephalitis cases caused by JEV to nearly 70 000 from a previous estimate of 30 000–50 000. About half the cases occur in China, and it is frustrating that 81% of cases occur in countries with established or developing vaccination programs. The authors felt this latter finding reflects the fact that vaccination programs have yet to reach enough of the at-risk population in JEV-endemic areas. They advocate for continued and strengthened vaccination programs throughout endemic areas.

DENGUE VIRUS

A worldwide scourge with 70–500 million human cases annually, dengue virus is not typically thought to be neuroinvasive. Rather, encephalopathy in dengue virus-infected patients has been attributed to cerebral edema resulting from complications of multiorgan failure. However, increasing evidence points to possible direct CNS involvement of dengue virus [28–31]. A Brazilian research group further buttressed this argument by examining the cerebrospinal fluid (CSF) and blood and tissue specimens from 150 patients who likely died of an infectious disease in a dengue virus-endemic area of Brazil [32▪,33]. The CSF from the 84 patients found to have evidence of systemic dengue virus infection was evaluated for evidence of dengue virus using virus isolation, RNA extraction, reverse transcription PCR, as well as antigen and antibody detection. Nearly half of the dengue virus-positive individuals had evidence of dengue virus in the CSF but no evidence for other bacterial or fungal pathogens. All these patients had clinical evidence of encephalitis, meningitis or both.

LYMPHOCYTIC CHORIOMENINGITIS VIRUS

LCMV is an Old World arenavirus long recognized as a cause of aseptic meningitis in humans. Its reservoir host is the house mouse (*Mus musculus*). Human infection occurs sporadically but typically does not result in significant morbidity except via vertical transmission in neonates and in a number of solid organ transplant recipients [34–36]. Worldwide there were four such organ transplant recipient clusters before 2012, which resulted in the deaths of 12 of the 13 infected patients. In 2012, there was a fifth cluster of solid organ recipients who developed LCMV infection resulting in multiorgan failure and neurologic sequelae [37▪]. In this cluster, all four people who received solid organs from a single donor became infected. As in previous clusters, the recipient of the corneal transplant did not get ill. Two of the four patients survived without receiving any LCMV-specific therapy. Three of the patients and the donor had clinical signs and symptoms consistent with meningoencephalitis including one patient with a compatible CSF profile. Notably, many of these donors were asymptomatic and had little to no known rodent exposure. Ribavarin has proven efficacy in the treatment of another Old World arenavirus, Lassa virus. Early recognition of possible LCMV infection in transplant recipients allows for the option to treat empirically with ribavarin.

ENTEROVIRUS 71

First identified in 1969, enterovirus 71 (EV71) has continued to expand its geographic range and has caused numerous outbreaks in Southeast Asia since 1997. Typically associated with hand-foot-and-mouth disease, up to 30% of patients also demonstrate neurologic complications ranging from meningitis, encephalitis to a poliomyelitis syndrome [38]. In 2012, an outbreak of a deadly form of encephalitis was first noticed by personnel at Kantha Bopha Hospital, a children's hospital in Siem Riep, Cambodia run by a Swedish non-governmental organization. Ultimately 54 of the 78 children died. Most were three years old or younger. Although diagnostic samples were not available for the majority of the children, most of the 31 available samples tested positive for EV71 genotype C4 according to the World Health Organization and the Institute Pasteur in Phnom Penh [39–41]. This genotype is widespread in China and Vietnam. The true number of cases as well as the actual case fatality rate will never be known because of the limited healthcare resources in Cambodia, but the large number of detected fatalities is suggestive of a particularly neurovirulent outbreak.

CONCLUSION

This review highlights developments over the past year in the field of emerging neurotropic viral infections. The review is not exhaustive and does not discuss a number of important emerging neurotropic pathogens such as chikungunya virus, Toscana virus and tick-borne encephalitis virus. Nor does it discuss the 25-year global campaign to eradicate poliovirus that has seen spectacular successes including the announcement in 2012 that India has now been free of polio for nearly 2 years [42]. Successes like this have been tempered by the persistent difficulty controlling polio in the three

remaining endemic countries: Nigeria, Pakistan and Afghanistan [43,44]. Vaccination campaigns in these countries continue to be hampered by social unrest and conflict, exemplified by the tragic murders of vaccination workers by local Taliban insurgents in northwest Pakistan.

The high mortality and morbidity inflicted by the large number of emerging neurotropic viruses poses a real and evolving threat to human health. We have significant shortcomings with regard to the development of sensitive viral diagnostic tests, and we lack effective therapies and vaccines for many of these highly morbid and often fatal infections. A pathogen like Nipah virus poses a special threat given its high mortality rate, wide host range and ability to spread from human to human. The ease with which it can be grown in the laboratory also raises concerns about its potential use as a bioweapon. Tackling the problem of emerging neuroinvasive infections requires the concerted effort of scientists and physicians. However, the expertise of public health experts, ecologists, economists and politicians will also be necessary to confront the wider systemic issues that fundamentally drive the emergence and re-emergence of infectious diseases in our increasingly interconnected world.

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Conflicts of interest

There are no conflicts of interest.

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