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Emerging and Reemerging Neurologic Infections

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Abstract

The list of emerging and reemerging pathogens that cause neurologic disease is expanding. Various factors, including population growth and a rise in international travel, have contributed to the spread of pathogens to previously nonendemic regions. Recent advances in diagnostic methods have led to the identification of novel pathogens responsible for infections of the central nervous system. Furthermore, new issues have arisen surrounding established infections, particularly in an increasingly immunocompromised population due to advances in the treatment of rheumatologic disease and in transplant medicine.

Keywords

neurologic infections, central nervous system infections, encephalitis, meningitis, infectious diseases, emerging pathogens

Emerging and Reemerging Neurologic Infections

The list of emerging and reemerging pathogens that cause neurologic syndromes is growing. Not only have advances in diagnostic methods led to the identification of novel pathogens but also several recognized pathogens have expanded their geographic distribution into previously nonendemic regions. Unprecedented spread of a number of arboviruses is attributable to human population growth, changes in agriculture practices (eg, rice farming and pig farming), and a dramatic rise in international travel. And finally, even for established pathogens, new issues have emerged in an increasingly immunocompromised population due to advances in the treatment of rheumatologic disease and transplant medicine.

In this article, we will review key emerging and reemerging pathogens that cause neurologic disease. We chose to focus on neurologic diseases that fall into 2 major categories of "emerging" infections. In the first category, we include newly discovered pathogens that typically cause acute neurologic syndromes and may be encountered in the inpatient setting, but of which neurohospitalists may be unaware. In the second category, we highlight novel issues that have recently emerged around established neurologic infections. Many of these pathogens result in nonspecific neurologic symptoms with tremendous overlap in clinical presentation. As a result, being familiar with their epidemiology is essential to diagnosis. For example, certain infections (eg, Nipah and Hendra) are exceedingly rare, but in the setting of travel to affected regions of the world (eg, Asia and Australia, respectively) and specific exposures, they should be seriously considered and tested.

Conversely, infections with free-living amoeba are similarly rare but can be acquired in one's own backyard and should be considered when the epidemiologic and clinical characteristics fit. Given the potential increasing clinical and public health relevance of these emerging and reemerging infections, neurohospitalists should be familiar with these pathogens to aid in prompt recognition and appropriate care.

Viral

Enterovirus 71

Enterovirus 71 (EV71), a member of the *Enterovirus* genus within the Picornaviridae family first isolated in California over 40 years ago,[1,2] has recently emerged as a cause of large outbreaks of infection, primarily in young children. The Asia Pacific has been hardest hit with hundreds of thousands of reported cases in epidemic years,[3,4] although countries worldwide, including the United States and Australia,[5-7] have seen clusters of infection.

Enterovirus 71, which peaks in summer and fall, is usually heralded by a prodromal illness of fever with or without other

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manifestations, including upper respiratory and gastrointestinal symptoms. The characteristic viral exanthem observed in EV71, which can be subtle,[8] is a maculopapulovesicular rash typically involving the hands, feet, and oral cavity, giving rise to the name "hand, foot, and mouth disease" (HFMD), of which EV71 is one potential etiologic agent. Enterovirus 71, unlike Coxsackie virus A16, the other common cause of HFMD, has a tendency to cause neurologic disease, which can occur in isolation without preceding HFMD.[9,10] An estimated 10% to 20% of patients with EV71 HFMD develop neurologic involvement.[3,9,11,12] A wide spectrum of neurologic disease can be seen, the onset of which occurs within days of the prodromal illness, including aseptic meningitis or meningoencephalitis,[13,14] a flaccid paralysis,[15] rhombencephalitis, often with myoclonus, tremor, or ataxia,[10,11] and rare manifestations such as opsoclonus-myoclonus or transverse myelitis.[16] Flaccid paralysis, which is clinically indistinguishable from poliomyelitis, is perhaps the most notable clinical syndrome associated with EV71.

Enterovirus 71 is most commonly isolated from stool and throat samples (Table 1). Unlike other enteroviral causes of meningitis in children, which can be detected by polymerase chain reaction (PCR) from cerebrospinal fluid (CSF), the utility of traditional PCR to detect EV71 from the CSF is limited, possibly due to low viral load.[7]

Parechoviruses

Reclassification of former enteroviruses, echovirus 21 and echovirus 22, resulted in the human parechovirus (HPeV) genus. Echoviruses 21 and 22 are currently classified as HPeV-1 and HPeV-2, respectively. At least 12 HPeV serotypes have been described to date; nearly all have been associated with encephalitis, typically in children less than 2 years of age.[17,18] Clusters of HpeV3 central nervous system (CNS) infections have been reported.[19] Young children and infants with HPeV encephalitis develop fever, seizures, irritability, feeding difficulties, and rash.[20] The relative frequency of HPeV encephalitis is unknown, particularly because HPeV testing has only recently become available (Table 1).

West Nile Virus

West Nile virus (WNV), a member of the *Flavivirus* genus, is the leading cause of neuroinvasive arboviral disease in the United States.[21] First isolated in the West Nile region of Uganda,[22] WNV is widely distributed throughout the world, including in Africa, Europe, the Middle East, and Western Asia. Since its Western hemisphere debut in New York City in 1999,[23] WNV has spread throughout the country and is now endemic in the continental United States.[24] In 2012, 5674 human cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), approximately half of which were neuroinvasive,[24] making it the second worst outbreak

of WNV after the 2003 epidemic which involved 9862 cases. The cause of the increase in cases in 2012 is unclear, although warmer temperatures, which result in increased viral replication and a shorter incubation period in mosquitoes, may have contributed.[25,26] An estimated 25% of individuals infected with WNV develop symptoms including fever, headache, generalized weakness, myalgias, and rash.[27] Severe neuroinvasive disease, which occurs in less than 1% of infected individuals, can manifest as meningitis, encephalitis, or flaccid paralysis.[28] Older age, history of alcohol abuse, cancer, chronic renal disease, diabetes mellitus, and hypertension have been identified as risk factors for neuroinvasive disease.[29]

Diagnostic testing for WNV is available in many laboratories. Immunoglobulin (Ig) M antibody seroconversion, which often coincides with the onset of symptoms, tends to occur 7 to 8 days after a mosquito bite, while IgG antibodies appear a median of only 3.4 days later.[30] Immunoglobulin M antibodies in the serum and CSF can remain positive for months to more than a year from the time of infection.[30-32] Patients with a positive IgM and negative IgG antibody test may be within the narrow window of hyperacute infection, whereas a negative IgM antibody test in conjunction with a positive IgG indicate prior infection.

Powassan Virus

Powassan virus (POWV), a tick-borne flavivirus, causes encephalitis in North America. About 50 cases of POWV have been reported to the CDC in the past 10 years.[33] Until recently, most cases have been reported from the northeastern United States. Since 2008, however, an increasing number of cases have been reported in Minnesota and Wisconsin.[34] Patients often experience a viral prodrome with fever and headache. When encephalitis occurs, mental status changes, seizures, cerebellar symptoms, and hemiplegia are described. Diagnostic testing is available at the CDC.

Japanese Encephalitis Virus

Japanese encephalitis virus (JEV) is the leading cause of encephalitis worldwide with an estimated 67 900 annual cases. The highest burden of disease occurs in Korea, China, India, and Indonesia.[35] Japanese encephalitis virus is considered an emerging pathogen due to significant geographic expansion in recent years. Despite a safe and effective vaccine, its use has been primarily in small and high-income Asian countries.[36] Like other arboviruses, many JEV infections are asymptomatic. Indeed, less than 1% of JEV infections leads to clinical disease. When symptoms occur, encephalitis is the most common presentation. Illness often begins with a febrile prodrome of headache and vomiting followed by mental status changes along with seizures, focal neurologic deficits, or movement disorders. Features of parkinsonism with mask-like facies, cogwheel rigidity, and choreoathetoid movements are particularly characteristic of JEV.[37] Similar to patients

Table 1. Available Diagnostic Studies for Emerging Neurologic Infections.

Agent	Diagnostic Studies	Limitations, Caveats, and Other Notes
Viruses		
Enterovirus (EV) 71	• CSF PCR • Respiratory PCR • Stool PCR or culture	• Testing of EV PCR on CSF alone may miss infection because EV present only transiently in CSF; test non-CNS site (respiratory sample PCR, viral stool culture) to increase yield. • High concentrations of serologies can be seen early in disease precluding the classic increase in titer between acute and convalescent samples.
Parechovirus	• CSF PCR • Respiratory PCR	• Enterovirus PCR does not detect Parechovirus. • Parechovirus PCR testing available in some commercial laboratories.
Arboviruses (general)		• Serology is often more sensitive than molecular assays for the diagnosis of arboviruses. • Important to note cross-reactions among closely related flaviviruses. • For most arboviral infections, serum collected within 8 days of illness onset may not have detectable IgM and testing should be repeated on a convalescent-phase sample to rule out arboviral infection. • Vaccination history, date of onset of symptoms, and information regarding cross-reactive arboviruses known to circulate in geographic area where patient was within 3 weeks of onset need to be considered when interpreting results. For fatal cases: • PCR, histopathology with immunohistochemistry, and virus culture of tissues. • Instructions for sending diagnostic specimens to CDC's Arbovirus Diagnostic Laboratory can be found at the following site: http://www.cdc.gov/ncezid/dvbd/specimensub/index.html (but need to always work with local and state health department before submitting samples)
West Nile virus	• CSF and/or serum IgM • Paired acute/convalescent serology-CSF or serum PCR (immunocompromised patients)	• Testing available at many commercial laboratories • IgM antibodies in the serum and CSF can remain positive for months to more than a year from the time of infection • Antibody testing may be less reliable in patients who are immunocompromised or early in course of disease.
Japanese encephalitis virus (JEV)	• CSF IgM • Serum IgM • Autopsy tissues	• JEV IgM usually detectable 3 to 8 days after onset of illness and antibodies often persist for 30 to 90 days, but longer persistence has been documented. • Vaccination with JEV vaccine can also cause a positive IgM test result. • For patients with JEV IgM antibodies, confirmatory neutralizing antibody testing should be performed. • Contact the CDC Arboviral Diseases Branch (phone: 970-221-6400) for assistance with diagnostic testing.
Tick-borne encephalitis virus	• CSF IgM • Serum IgM	• Early illness: TBEV or TBEV RNA can sometimes be detected in serum samples by virus isolation or RT-PCR. (however, typically, by the time of neurologic signs and symptoms, viral RNA is usually undetectable.) • Clinicians should contact their state or local health department. • Contact CDC's Viral Special Pathogens Branch (Phone: 404-639-1115) or CDC's Division of Vector-Borne Diseases (Phone: 970-221-6400) for assistance with diagnostic testing.
Toscana virus	• CSF culture • CSF PCR • Serology	• CSF should be obtained within 2-4 days of onset of disease for culture.
Chikungunya virus	• CSF IgM • CSF PCR • Paired acute/convalescent serologies	• Only a few state laboratories or other specialized laboratories, including those at CDC, are capable of doing this specialized testing.

Table 1. (continued)

Agent	Diagnostic Studies	Limitations, Caveats, and Other Notes
		• Contact the CDC Arboviral Diseases Branch (Phone: 970-221-6400) for assistance with diagnostic testing.
Nipah	• Blood/CSF/saliva/urine PCR, virus isolation, serology, and immunohistochemistry	• Notify Health Department Special Pathogens Branch at CDC for testing (Phone: 404-639-1115).
Hendra	• Blood/CSF/saliva/urine PCR, virus isolation, serology, and immunohistochemistry	• Notify Health Department Special Pathogens Branch at CDC for testing (Phone: 404-639-1115).
Cyclovirus	• Molecular assays	• Testing only available in research settings.
Bacteria		
Borrelia miyamotoi	• Serum and CSF PCR, antibody testing	• Current Borrelia testing may not distinguish between *B miyamotoi* and other *Borrelia* species. • Testing only available at specialized research labs and 1 commercial lab (L2 Diagnostics, 300 George Street, New Haven, CT 06530, USA; Phone: 203-737-1952)
Neisseria meningitidis	• Standard CSF bacterial culture	• CSF *Neisseria* PCR testing may be useful in some settings, particular if patient treated with antibiotics before CSF obtained for cultures.
Fungi		
Cryptococcus gattii	• CSF fungal culture • CSF and serum cryptococcal antigen	• Culture essential to differentiate between the different species of *Cryptococcus*. • *C gattii* cannot be distinguished from *C neoformans* without special laboratory testing available at CDC and at some state health department laboratories.
Parasites: free-living amoeba		
Naegleria fowleri	• Wet mount of warm CSF (to visualize amoeba) • CSF and/or brain PCR • Brain histopathology	• For diagnostic assistance, specimen collection guidance, specimen shipping instructions, and treatment recommendations for free-living amoeba infections, clinicians should contact the CDC Emergency Operations Center at 770-488-7100.
Balamuthia mandrillaris	• Serology • CSF and/or brain PCR • Brain histopathology (special stains)	
Acanthamoeba spp.	• CSF and/or brain PCR • Brain histopathology (special stains)	

Abbreviations: CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; IgM, immunoglobulin M; RT-PCR, reverse transcription polymerase chain reaction; EV, enterovirus; TBEV, tick-borne encephalitis virus.

with WNV, those affected by JEV can also develop acute flaccid paralysis.[38] The overall case fatality rate is 20% to 30% and neurologic sequelae occur in 30% to 50% of cases.[39,40]

While it is the leading cause of encephalitis worldwide, the overall risk of JEV is low for travelers to affected regions. Less than 1 case per 1 million travelers has been noted.[40,41] Only 19 cases have been reported in the United States since 1973; these include a very recent case series of 3 adults who contracted JEV while visiting Asia.[42] Nevertheless, JEV should be considered in travelers returning from affected countries, particularly if travel was in rural and agricultural areas, with compatible clinical features.[41] Diagnosis of JEV is generally by serologic methods, and testing is available at the CDC (Table 1).

Tick-Borne Encephalitis

Tick-borne encephalitis virus (TBEV), closely related to POWV, is one of the most common causes of arboviral encephalitis in Europe and Russia.[43] Its geographic range has expanded to include China and Japan. Due to better diagnostic assays, improved case reporting, and increased recreational activities in tick-infested areas, the number of recognized cases has risen dramatically. In Europe and Russia, an average of 2755 cases per year occurred from 1976 to 1989 compared with 8755 cases per year from 1990 to 2007.[44] Tick-borne encephalitis virus is characterized by 3 different subtypes: European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-Fe). The TBEV-Eu subtype circulates predominantly in Western, Central, Northern, and Eastern Europe, while the TBEV-Sib circulates predominantly in Asian parts of Russia and TBEV-Fe circulates predominantly in China, Japan, and Eastern Russia. The clinical manifestations range from mild meningitis to severe meningoencephalitis with or without myelitis and paralysis.[45] Analogous to WNV, neuroinvasive disease is more common in older populations. In individuals affected with the TBEV-Eu subtype, the illness is often

described as biphasic with the first stage characterized by fever, fatigue, general malaise, headache, and body pain. Neurologic manifestations occur in the second phase of the illness. The TBEV-Fe subtype is the most severe and has a case fatality rate of 20% to 40% and higher rates of neurologic sequelae. Between 2000 and 2009, only 5 cases have been diagnosed in the United States. Of the 4 patients who traveled to Europe or Russia, all had a history of tick bite and biphasic illness. Two had encephalitis and 2 had meningitis. The fifth case, who traveled to China, had a monophasic illness and presented with severe encephalitis.[46] Diagnosis is generally made by serologic methods and, like other imported arboviruses, testing is available at the CDC (Table 1).

Toscana Virus

Toscana virus (TV), a member of the *Phlebovirus* genus within the Bunyaviridae family transmitted by the sandfly, is one of the most common causes of meningoencephalitis in the summer months in the Mediterranean.[47] In 1 study in Tuscany, Italy, more than half of the cases of aseptic meningoencephalitis over a 7-year period were attributed to TV.[48] Seroprevalence rates of anti-TV IgG antibodies may be as high as 26%.[49-51] Few cases of Toscana infections in the United States in returning travelers have been reported.[52,53] Overall, the natural history of TV meningoencephalitis is considered to be relatively benign with a self-limited course.

A review of all cases of TV meningoencephalitis reported in the English literature between 1971 and 2012 revealed 42 patients, 3 of whom were diagnosed in the United States. Compared to other common causes of meningoencephalitis in the United States (EV, herpes simplex virus [HSV], and WNV), patients with TV were more likely to present with classic symptoms and signs associated with meningitis, including fever in 97% (compared with HSV and WNV), headache in 100% (compared with EV and WNV), stiff neck in 87% (compared with all 3 other viruses), photophobia in 86% (compared with EV and WNV), and nuchal rigidity in 89% (compared with all 3 viruses). Interestingly, 44% of patients with TV also presented with signs/symptoms consistent with encephalitis, comparable to the proportion of patients with HSV and WNV infections. Cerebrospinal fluid profile demonstrated a moderate pleocytosis (median white blood cell count 208 cells/mm^3), mildly elevated protein (median protein 88 mg/dL), and normal glucose. Brain imaging is typically normal, although hydrocephalus was present in 15% of cases who underwent magnetic resonance imaging. A poor neurologic outcome, defined as a Glasgow outcome score ranging from 1 (death) to 4 (moderate disability), occurred in 2 (8%) of the 25 patients with TV compared with 15 (50%) of the 30 for WNV. Detection of IgM antibodies, isolation of virus from CSF, and reverse transcription PCR are the most common laboratory techniques for confirming the diagnosis of TV (Table 1).[47]

Chikungunya Virus

Chikungunya virus (CHIKV) is an emerging and reemerging mosquito-born alphavirus associated with high attack rates and potential for rapid, exponential, and sustained transmission during outbreaks. First described in the Makonde Plateau in Eastern Africa in the mid 20th century,[54] the virus has since caused sporadic and epidemic cases throughout Africa and Asia.[55] A massive outbreak of CHIKV infection that began in Kenya in 2004 and spread over 4 years to the Indian Ocean islands, India, and Southeast Asia[55,56] redefined the virus' public health relevance and potential to cause widespread infection, including in more temperate regions. Between 1995 and 2009, 109 laboratory-confirmed cases of CHIKV were diagnosed in adult travelers in the United States returning from India and other endemic countries, the majority (97%) of which occurred after 2006.[57] The principal *Aedes* mosquito vector for CHIKV is found across the United States and Europe, underscoring the potential for the virus to spread to nonendemic regions of the Western hemisphere. An autochthonous outbreak (from human to mosquito to human) of CHIKV occurred in Italy in 2007 after a viremic traveler returned from India.[58] Similar to outbreaks of dengue in southern regions of the United States, an autochthonous CHIKV outbreak, heralded by infection in nontravelers, is certainly plausible.[57] In December 2013, the first cases of CHIKV in nontravelers in the Western hemisphere were reported in St Martin in the Caribbean.[59]

Chikungunya virus causes an acute febrile illness characterized by severe arthralgia, typically of the distal joints, with or without rash.[56] Gait disturbance may result from involvement of the joints of the lower extremities, resulting in a broad-based, halting gait.[56] In returning travelers, CHIKV can be difficult to distinguish clinically from dengue fever and malaria, although arthralgias, particularly severe and more prolonged joint involvement, is more characteristic of CHIKV. In a large outbreak on the Indian Ocean island of La Reunion that began in March 2005, during which more than 47 000 cases per week occurred at its peak, the ability of the virus to cause neurologic disease became manifest.[60] In a retrospective, single-institution study in La Reunion, 19 (12%) of the 157 laboratory-confirmed cases of CHIKV had evidence of neurologic involvement, the majority of which were an acute confusional state.[61] Other neurologic manifestations include meningoencephalitis, acute flaccid paralysis, and Guillain-Barre syndrome.[60,62-64] Although the case fatality rate is low, the infection is associated with significant morbidity and can lead to a debilitating, chronic syndrome of fatigue and joint pain.[65,66]

Nipah Virus

Nipah virus, a paramyxovirus, was first identified in 1991 in a large encephalitis outbreak among pig farmers in Sungai Nipah, a village in the Malaysian peninsula in 1991. The

wildlife reservoir of Nipah virus is bats of the genus *Pteropus*, which infect pigs. The virus is effectively transmitted from pig to pig and then can infect humans. This virus has caused outbreaks in Singapore, Australia, India, and Bangladesh.[67-69] Human disease can range from asymptomatic infection to fatal encephalitis. When neurologic illness occurs, individuals often experience an influenza-like illness followed by dizziness, excessive drowsiness, and altered conscious. Of particular concern is the discovery that Nipah can be transmitted from person-to-person, and nosocomial transmission has been described.[70]

Although no cases have been identified in the United States, Nipah should be considered in individuals with recent travel to affected areas of the world. Both serologic and molecular methods are used for diagnosis and available through the CDC (Table 1).

Hendra Virus

Hendra virus is a paramyxovirus first recognized in Hendra, Australia, where it was associated with an outbreak of respiratory and neurologic disease in horses and humans in 1994. The natural reservoir of the virus is thought to be flying foxes (bats of the genus *Pteropus*). The virus is transmitted from bats to horses to humans via direct contact with infected horses. More than 60 equine and 4 human fatalities have been reported.[71] Human illness due to Hendra virus is characterized by influenza-like symptoms often followed by acute encephalitis. A relapsing neurologic syndrome has also been described in a few individuals.[71] Diagnostic methods are similar to Nipah virus and are available through the CDC (Table 1).

Cycloviruses

Recently, a novel virus genus, *Cyclovirus* of the *Circovirdiae* family, has been implicated as a new human pathogen using virus discovery techniques, including amplified fragment length polymorphism and next generation sequencing methods. Until the discovery of cycloviruses, there were only 2 known genera in the *Circoviridae* family: *Circovirus* type species and *Gyrovirus* type species. These viruses have been associated primarily with disease in animals, including birds and pigs and less commonly in dogs. Two patients in Vietnam were found to have a novel cyclovirus by pathogen discovery methodology.[72] After the identification of the new cyclovirus, CSF from additional patients with noninfectious and presumed infectious disorders was tested. None of the samples from patients with noninfectious disorders were found to have cyclovirus present, whereas cyclovirus was identified in 4% of 642 CSF samples from the presumed infectious group. However, several of these cases had an alternative diagnosis. In 2010 to 2011, cyclovirus was identified in a subset of 58 adult patients with paraplegia in Malawi.[73] Of the 54 patients, 8 (15%) and 5 of the 40 (1%) serum and CSF samples, respectively, were found to have cyclovirus by PCR methodology.

Cyclovirus has been detected in the blood of patients with febrile illnesses and acute flaccid paralysis.[74] Because cyclovirus has been isolated from the feces of healthy children, pigs, and chickens, a fecal–oral route of transmission has been proposed. Current information is insufficient to understand the role of cycloviruses in neurologic illness, and further study is needed.

Bacterial

Borrelia miyamotoi

Recent reports of human disease attributed to infection with *Borrelia miyamotoi*, a spirochete classified in the relapsing-fever family, have raised the possibility that it may be an underrecognized cause of subacute to chronic meningoencephalitis in regions where Lyme is endemic. Gugliotta et al described a case of an elderly woman from rural New Jersey with non-Hodgkin lymphoma treated with chemotherapy, including rituximab in the months prior.[75] She had also previously been treated on 2 occasions for Lyme disease, the most recent of which was with doxycycline 5 years previously. Over a 4-month period, she developed progressive confusion, withdrawn personality, gait difficulty, hearing impairment, and weight loss. Neuroimaging was unremarkable while CSF analysis revealed a mild lymphocyte-predominant pleocytosis with significantly increased protein and a potentially borderline low glucose. Spirochetes were identified in the CSF on both Giemsa and Gram stains. Microscopic, immunofluorescence, and serological results were inconsistent with expected findings for *Borrelia burgdorferi*, *Babesia microti*, or *Anaplasma phagocytophilum*. The diagnosis was eventually made on the basis of a PCR assay on a CSF specimen that amplified 2 gene targets for *B miyamotoi*, confirmed by sequencing and phylogenetic analysis of the 16s ribosomal RNA and flagellin genes. After a 30-day course of intravenous penicillin G, the patient's mental status returned to her baseline and a posttreatment CSF sample was PCR negative.

Borrelia miyamotoi, a bacterium originally identified in Japan in 1995,[76] is genetically more closely related to the *Borrelia* species that cause relapsing fever than those that cause Lyme disease. However, unlike relapsing fever spirochetes that are transmitted by soft ticks, *B miyamotoi* is associated with hard-bodied ixodid ticks and has been shown to infect or coinfect a proportion of vector ticks that harbor *Borrelia* species associated with Lyme disease,[77,78] although the clinical relevance of this is unclear. In Lyme endemic areas in the United States, the seroprevalence of *B miyamotoi*, detected with surveillance methods using a *B miyamotoi*-specific G1pQ protein, was 1% and up to 3.2% among patients with suspected Lyme disease.[79] The first case series of human disease associated with *B miyamotoi* was described in Russia,[80] and other nonimmunocompromised patients have also been described.[79] Not surprisingly given its genetic similarity with relapsing fever spirochetes, patients tended to present with a

systemic febrile viral-like illness. Erythema migrans, the characteristic rash associated with Lyme disease, was infrequently present.[80] While nonspecific headache is a common feature,[80] the prevalence of neurologic involvement with *B miyamotoi* infection, as described by Gugliotta et al, is unknown. Two other recently reported cases in the United States have described associated leukopenia, thrombocytopenia, and elevated liver enzymes.[79] Primers used to detect *Borrelia* species that are responsible for Lyme disease may not amplify *B miyamotoi* given its closer genetic resemblance to relapsing fever spirochetes. Likewise, the accuracy of standard serological testing in discriminating between *B miyamotoi* and species that cause Lyme disease is unknown (Table 1).[75,79] A specific protein enzyme immunoassay (eg, using G1pQ antigen specific to *B miyamotoi*) may be needed to distinguish Lyme disease from this potentially emerging infection.

Neisseria meningitidis Outbreaks in the United States

Rates of bacterial meningitis in the United States have declined in the last decade due in large part to the introduction of highly effective vaccination programs. The incidence of meningitis caused by *Neisseria meningitidis*, which remains one of the most common causes of bacterial meningitis in older children and young adults, fell from 0.44 cases per 100 000 population between 1998 and 1999 to 0.19 cases between 2006 and 2007.[81] Because the quadrivalent meningococcal conjugate vaccine (MCV4) covers serogroups A, C, Y, and W-135 but not serogroup B, the relatively similar decline in rates across serogroups, including B, suggests that, in contrast to other causes of meningitis, the effect is unlikely to be attributable to the MCV4 vaccination program in the United States,[82] which was implemented in 2005 and recommended routine use of the vaccine in adolescents aged 11 to 18 years and anyone between 2 and 55 years at increased risk.[83]

Despite the all-time low incidence of invasive meningococcal disease,[82] recent outbreaks have garnered particular attention in the United States and highlighted emerging issues surrounding the infection. Between August 2010 and February 2013, 22 cases of serogroup C invasive meningococcal disease among men who have sex with men (MSM) were identified and reported to the Department of Health and Mental Hygiene in New York City. One novel risk factor in the outbreak was meeting sexual partners through online social networking sites. The incidence of invasive disease in MSM between the age of 18 and 64 years in 2012 was 12.6 cases per 100 000 population versus 0.16 cases per 100 000 population in a comparable non-MSM age group.[84] Of the 22 cases, 12 were HIV infected but with relatively intact immune function overall.[85] Case fatality rates in outbreaks are often higher than with sporadic cases.[86] In New York, 7 men died, underscoring the importance of timely recognition of an outbreak and implementation of control measures.

Population-based surveillance data demonstrated a vaccine coverage rate of 74.0% among adolescents in the United States in 2012.[87] As uptake increases, a corresponding decline in the rates of meningitis due to serogroups A, C, Y, and W-135 covered by MCV4 may result. Two outbreaks, however, on university campuses in the United States in 2013, have highlighted the gap in coverage of the currently recommended vaccine for adolescents, with a huge proportion of meningococcal disease in the United States caused by group B strains. Beginning in March 2013, 8 cases of serogroup B meningococcal disease have been identified at Princeton University.[88] Several of the cases had evidence of meningitis. Similarly, at University of California Santa Barbara, 4 cases of serogroup B disease have been identified within a 3-week period in November 2013.[89] Although available in Europe, Canada, and Australia, a vaccine against serogroup B is not currently licensed in the United States. Several factors have hampered the development of a serogroup B vaccine, including homology between serogroup B and human polysaccharide glycoprotein epitopes, which results in poor immunogenicity and autoantigenicity.[90] However, an innovative new approach to vaccine development termed "reverse vaccinology" led to formulation of a vaccine with activity against serogroup B, although its widespread use in certain countries has been hindered by the economics of health care.[91] In the United States, Novartis has advanced a vaccine that covers serogroups A, B, C, Y, and W into the late stages of development.

Fungal

Cryptococcus gattii

An outbreak of 3 clonal subtypes (VGIIa, VGIIb, or VGIIc) of *Cryptococcus gattii*, a fungus found in soil and select trees, has been ongoing in British Columbia, Canada and the US Pacific Northwest since 2004.[92,93] More recently, 25 cases of *C gattii* infection outside of the Pacific Northwest (Alabama, California, Florida, Georgia, Hawaii, Michigan, Montana, and New Mexico) have been reported, many of which have occurred in young, previously healthy men without any travel history to recognized areas of endemicity.[94] Thirteen of the reported cases were from California, where *C gattii* is now also considered to be endemic. The incidence of outbreak-associated and sporadic *C gattii* cases in the United States, however, is unknown, in part due to limitations in recognition and diagnosis to the species level of the infection.[95] Unlike the related and better-known species, *Cryptococcus neoformans*, which is a common cause of opportunistic infection in HIV-positive patients, *C gattii* rarely occurs in HIV-infected individuals.[96,97] Additionally, the distribution of *C gattii*, which was previously thought to be found solely in tropical and subtropical climates (eg, Australia, New Zealand, Brazil, and Southeast Asia), is less widespread than *C neoformans*.[98]

Infection with outbreak strains in the Pacific Northwest predominantly causes pulmonary disease in individuals with

comorbid medical illnesses or underlying immune compromise,[92] while sporadic cases tend to involve the CNS, with or without concomitant pulmonary disease.[92,94,97] Headache, visual disturbance, nausea, cranial nerve palsies, and hydrocephalus are frequent presenting signs and symptoms.[94] The case fatality rate in the 25 sporadic cases was 24%. Female sex and cryptococcemia were associated with a greater risk of death.[94]

Parasitic

Free-Living Amoeba

Balamuthia mandrillis, *Naegleria fowleri*, and several species of *Acanthamoeba* have been known to cause encephalitis for a few decades.[99] Recently, a number of issues related to neurologic infections and free-living amoeba (FLA) have emerged: newly discovered types of FLA causing human illness, new routes of transmission, geographic expansion, and novel treatment options.

Free-living amoeba are ubiquitous in the environment, and many human cases result from exposure to either soil or water. The FLA that cause encephalitis classically are divided into 2 clinical entities: (1) primary amebic meningoencephalitis (PAM) due to *N. fowleri* (also known as "the brain-eating amoeba") and the newly recognized *Paravahlkampfia francinae* and (2) granulomatous amebic encephalitis.[100]

Primary amebic meningoencephalitis, first described in Australia in 1965, is a fulminant, often fatal disease occurring in children and young adults. Since then, PAM has been detected in Europe, Asia, Africa, and North America. In the United States, most cases occur in the southern tier of the country due to warm water conditions. More recently, Minnesota (2010 and 2012), Kansas (2011), Indiana (2012), and Virginia[101-103] have reported human cases. Most reports of PAM occur after swimming, diving, or washing in warm, fresh water, leading to entry of contaminated water into the nose and migration to the brain. In 2011, 2 cases of PAM were identified in Louisiana in patients without a history of recreational water exposure. They had, however, used "neti" pots for nasal and sinus irritation; *N fowleri*-contaminated tap water was implicated as the source of infection.[102]

The onset of PAM is usually within 2 to 7 days after exposure. Signs and symptoms are similar to bacterial meningitis, including severe headache, fever, stiff neck, nausea, vomiting, diplopia, seizures, behavioral changes, and coma. Distortion of taste or smell, often present in patients with PAM, may be helpful in distinguishing from bacterial meningitis.[99] The case fatality rate is extremely high; of the 111 reported cases in the United States between 1962 and 2008, only 1 individual survived.[102] In 2009, a new species of FLA was isolated from an 18-year-old man with onset of PAM after a swimming pool exposure.[100] Unlike cases due to *N fowleri*, this individual made a full recovery after only a few days of hospitalization. The authors suggest that previously reported PAM "survivor" cases may have been due to *P francinae* rather than *N fowleri*.[100,104,105]

Like PAM, granulomatous amebic encephalitis (GAE) also has a poor prognosis but typically has a more subacute to chronic presentation. To date, 3 closely related amoeba genuses have been associated with granulomatous encephalitis: *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Sappinia* spp. Acanthamoeba granulomatous encephalitis is generally an opportunistic, chronic disease that may have a prodromal period of weeks to months. Historically, acanthamebiasis has been associated with autoimmune conditions, organ transplantation, chemotherapy, radiation therapy, alcoholism, pregnancy, and long-term corticosteriod use. Recently, increasing numbers of Acanthamoeba cases have been described in immunocompetent children and adults.[106-108] Clinical features of CNS Acanthamoeba infections are variable and may include fever, vomiting, headache, neck stiffness, seizures, ataxia, personality change or abnormal behavior, lethargy, and/or confusion. Cranial nerve palsies, meningeal signs, or hemiparesis may be seen on physical examination.

Balamuthia mandrillis was first reported as a cause of encephaliits in humans in 1980 and over 200 cases have been reported worldwide. Symptoms of Balamuthia GAE are similar to Acanthamoeba infection. Otitis media has preceded the onset of Balamuthia granulomatous encephalitis in several pediatric cases, and hydrocephalus is a common occurrence.[109] Of the cases recognized to date, most were initially thought to be due to other entities such as acute disseminated encephalomyelitis, stroke, progressive multifocal leukoencephalopathy, neurocysticercosis, and tuberculosis.[110]

A new development in this field has been the recognition that Balamuthia can be transmitted via organs. Recent clusters of transplant-associated Balamuthia GAE have been recognized.[111,112] Not only do these cases demonstrate the varied presentations of CNS Balamuthia, but they also illustrate the diagnostic challenge associated with the infection. The diagnosis was only realized after a few individuals developed neurologic illness and extensive studies were performed.

Treatment options for FLA are limited, and survival rates are poor. Of patients who have survived, treatment has generally included a combination of several drugs including antifungals, antiparasitics, and antibiotics, making it unclear which, if any, were effective. Miltefosine is an antileishmania drug and has shown some promise when used in combination with other drugs in the treatment of patients with FLA.[113] The CDC has recently expanded its investigational new drug protocol to provide miltefosine directly to clinicians to treat FLA infections of the CNS.[114]

Conclusion

In this article, we reviewed a group of emerging and reemerging pathogens that are either newly discovered or for which there is a specific novel issue. These infections are an important reminder of why the quote from decades ago stating it is "time to close the book on infectious diseases, and declare the

war against pestilence won" was premature. Indeed, with novel pathogen discovery methods, changes in agricultural techniques, widespread international travel, and an increasingly immunocompromised patient population, the "war against pestilence" wages on.

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