Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Major advances in neuroinfectious diseases in the past two decades

The past two decades have seen an increasing number of outbreaks of public health importance, of which the most recent and devastating is COVID-19, with a death toll of more than 5 million people and around 30% of survivors reporting long-term neurological symptoms. Other recent outbreaks include Zika virus infection, mainly affecting populations in South America and Central America, Ebola virus in west Africa, dengue virus in Asia, West Nile virus in the Americas, and enterovirus associated acute flaccid paralysis in North America. Hundreds of other endemic pathogens can also affect the nervous system. Conditions such as community-acquired bacterial meningitis and tropical neurological infections remain major drivers of death and disability-adjusted life-years (DALYs) worldwide. Infections like neurocysticercosis, HIV, and Zika virus not only cause neurological injury in the acute setting, but also contribute substantially to long-term sequelae, such as neurodevelopmental disorders, cerebrovascular disease, epilepsy, or cognitive impairment.

Neurological infections encompass pathogens that can damage the nervous system directly and those that have indirect effects on the nervous system. Emerging and re-emerging neuroinfectious diseases, including arthropod-borne infections, are of growing concern to the global-health community, given the multiple drivers for disease propagation that include climate change, expanding host susceptibility, and pathogen-related factors. The current COVID-19 pandemic is a reminder that pathogens are a global threat to humanity. Although SARS-CoV-2 is identified as a primary respiratory pathogen, many neurological complications (i.e., encephalopathy, stroke, and neuromuscular disorders) manifest during the acute phase of COVID-19. Furthermore, impaired concentration, headache, and sensory disturbances can persist for months after infection, as part of a constellation of symptoms termed long-COVID-19 or post-acute sequelae of COVID-19. The effects of such outbreaks are enormous, not only for individual patients, but also because of their large-scale socioeconomic consequences. These global threats have highlighted our need to invest in lasting research projects into the pathogenesis, enhanced diagnostics, and treatments of neurological infections.

Some of the greatest achievements in this field during the past two decades have been in molecular diagnostic assays. There is a dire need to advance diagnostics for CNS infections, because many remain undiagnosed. One such technique concerns the ability to combine several targets in a single PCR reaction, known as multiplex PCR. One such panel test is now routinely used in clinical practice in resource-rich settings to diagnose acute CNS infections. Hypothesis-free diagnostic testing using sequencing methods is also increasingly used for pathogen identification of CNS infections that remain undiagnosed by traditional methods. This approach is unbiased as it does not rely on the clinician’s differential diagnosis but on a shotgun approach of investigating all non-human DNA in a sample. Specific diagnostic assays have improved our ability to detect pathogens that were previously identified only on brain biopsy or autopsy samples. The availability of the RT-QuIC test has greatly improved the specificity of CSF testing for prion-related diseases. But probably no single instrument has improved our diagnostic capabilities in neurological infections during the past 20 years more than MRI. The improvements in resolution and the increased availability of MRI in many locations have allowed the quick identification of infectious lesions in resource-rich settings.
Major treatment trials in neuroinfectious diseases during the past two decades have defined the use of adjunctive steroids in community-acquired bacterial meningitis and treatment regimens for cryptococcal meningitis and tuberculous meningitis in high-burden settings. However, optimising regimens to identify those antimicrobials that have better CNS penetration and indications for adjunctive treatment are just two of many continuing efforts that are urgently needed. The repurposing of antiviral medications, use of monoclonal antibodies, and targeting of immunological pathways are novel approaches to treat both systemic (including SARS-CoV-2) and neuroinvasive infections. An example is the evaluation of pembrolizumab in the treatment of progressive multifocal leukoencephalopathy. This antibody can inhibit programmed cell death receptors in lymphocytes, an approach that could target neurological infections without relying on antigen-specific antimicrobials.

Preventive strategies are the cornerstone of public health, and major achievements in neurological infectious diseases have taken place in the past two decades. With widespread availability of antiretroviral therapy, incidence rates of CNS opportunistic infections for patients with HIV have dropped considerably, by more than 75% of cases in many countries. In patients with multiple sclerosis, appropriate risk stratification has led to notable preventive measures for progressive multifocal leukoencephalopathy. But perhaps the best example of a prevention and surveillance system for a neuroinfectious disease is the Global Polio Eradication Initiative (GPEI), launched in 1988, which has reduced paralytic poliomyelitis cases by more than 99%. High-quality surveillance of acute flaccid paralysis is crucial to detect poliovirus transmission, although complete global eradication has been hampered by several factors in endemic regions, including warfare, terrorism, and inadequate laboratory and environmental surveillance infrastructure. The GPEI is a key example of global surveillance to detect, monitor, and treat neurological infections—a model that is especially salient now, as all countries struggle to see an end to the current pandemic.

The possibility of infections as key pathogenic agents in neurodegenerative diseases and neuroimmunological conditions has gained renewed interest and includes the association of herpes viruses with Alzheimer’s disease, and of human endogenous retrovirus (HERV)-K, an endogenous retrovirus, with amyotrophic lateral sclerosis. Epstein-Barr virus and HERV-W (another endogenous retrovirus) have both been implicated in multiple sclerosis. These new lines of investigation open up the exciting possibility for new diagnostic and therapeutic targets for neurodegenerative diseases.

Despite breakthroughs in diagnostics, our therapeutic options for most viral infections are few. The COVID-19 pandemic has shown that vaccines and antivirals can be developed in record time. Similar efforts are necessary for the other infections discussed previously. Globally, we are ill prepared to manage major pandemics and our health-care systems are fragile. Since the long-term complications of these infections are largely neurological, policy makers need to take a leadership role in curtailing infections and developing a pandemic preparedness for any future ones. Priorities include a better understanding of the natural course of neurological infections and their epidemiological landscape, preventive measures, efficient and reliable point-of-care diagnostic assays, and treatment interventions. These research efforts are of the utmost importance, given the global burden and substantial morbidity and mortality that are associated with neuroinfectious diseases.

AN received grant funding from the US National Institutes of Health (NIH; grant number NS003130) and is a board member for the American Neurology Society and the International Society of Neurovirology. KTT received research funding from NIH Center for Disease Control and Prevention and Biomereux/Filmarray. BRS declares no competing interests.

*Avindra Nath, Bryan R Smith, Kiran T Thakur
avindra.nath@nih.gov

Section of Infections of the Nervous System, US National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA (AN, BRS); Department of Neurology, Columbia University Irving Medical Center—New York Presbyterian Hospital, New York, NY, USA (KTT)

1. Feigin VL, Vos T, Nichols E, et al. The global burden of neurological disorders: translating evidence into policy. Lancet Neurol 2020; 19: 255–65.
2. Rocklov J, Dubrow R. Climate change: an enduring challenge for vector-borne disease prevention and control. Nat Immunol 2020; 21: 679–83.
3. Morens DM, Fauci AS. Emerging pandemic diseases: how we got to COVID-19. Cell 2020; 182: 1077–92.
4. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021; 38: 101019.
5. da Silva IFR, Frontera JA, Bispo de Filippis AM, Nascimento QJM. Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol 2017; 74: 1190–98.
6. UNDP and the International Federation of Red Cross and Red Crescent Societies. A socio-economic impact assessment of the Zika virus in Latin America and the Caribbean: with a focus on Brazil, Colombia and Suriname. April 2017. https://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP-Zika-04-03-2017-English-WER.pdf (accessed Feb 25, 2022).
1. McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis* 2018; 18: 992–1001.

2. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; 10: 835–44.

3. Rhein J, Bahr NC, Hemmert AC, et al. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. *Diagn Microbiol Infect Dis* 2016; 84: 268–73.

4. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med* 2019; 380: 2327–40.

5. Schmitz M, Cramm M, Llorens F, et al. The real-time quaking-induced conversion assay for detection of human prion disease and study of other protein misfolding diseases. *Nat Protoc* 2016; 11: 2233–42.

6. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med* 2018; 378: 1004–17.

7. Gans J, van de Beek D. Desamethasone in adults with bacterial meningitis. *N Engl J Med* 2003; 347: 1549–56.

8. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med* 2016; 374: 124–34.

9. Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med* 2019; 380: 1597–605.

10. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000–2010. *J Infect Dis* 2016; 214: 862–72.

11. Ho P-R, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; 16: 925–33.

12. Greene SA, Ahmed J, Datta SD, et al. Progress toward polio eradication—worldwide. January 2017–March 2019. *MMWR Morb Mortal Wkly Rep* 2019; 68: 458–62.

13. Garcia-Montojo M, Doucet-O’Hare T, Henderson L, Nath A. Human endogenous retrovirus-K (HML-2): a comprehensive review. *Crit Rev Microbiol* 2018; 44: 15–38.

14. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* 2022; 375: 296–301.