THERAPEUTIC ADVANCES in
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Review

Public health trends in neurologically relevant infections: a global perspective

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***Abstract*:** Neuroinfectious diseases represent a growing threat to public health globally. Infections of the central nervous system remain challenging to diagnose and treat, partially driven by the fact that a high proportion of emerging pathogens are capable of causing neurological disease. Many of the trends driving the emergence of novel pathogens, including climate change, ecological degradation, urbanization, and global travel, have accelerated in recent years. These circumstances raise concern for the potential emergence of additional pathogens of pandemic potential in the coming years, necessitating a stronger understanding of the forces that give rise to the emergence and spread of neuroinvasive pathogens and a commitment to public health infrastructure to identify and treat these diseases. In this review, we discuss the clinical and epidemiological features of three types of emerging neuroinvasive pathogens of significant public health consequences that are emblematic of key ongoing trends in global health. We first discuss dengue viruses in the context of climate change, considering the environmental factors that allow for the expansion of the geographic range and seasonal population of the viruses' vector. We then review the rising prevalence of fungal meningitis secondary to medical tourism, a trend representative of the highly globalized nature of modern healthcare. Lastly, we discuss the increasing prevalence of antibiotic-resistant neurological infections driven by the intersection of antibiotic overuse in medical and agricultural settings. Taken together, the rising prevalence of these conditions necessitates a recommitment to investment in public health infrastructure focused on local and global infectious disease surveillance coupled with ongoing development of novel therapeutics and vaccines for emerging pathogens. Such emerging threats also obviate the need to address the root causes driving the emergence of novel infectious diseases, including a sustained effort to address anthropogenic climate change and environmental degradation.

Plain language summary

Public health trends in neurologically-relevant infections: a global perspective

Globally, infections that impact the central nervous system, referring to the brain and spinal cord, are of significant public health concern. In the medical setting, these infections are challenging to diagnose both because of the overall difficulty of diagnosing any neurological infection but also because many infections of the nervous system are caused by newly emerging pathogens that lack reliable tests for diagnosis. Some of the trends contributing to emergence of new pathogens are the result of increasing globalization combined with climate change, destruction of the natural environment, increased growth of cities, and global travel. In our review, we discuss three types of infections that can affect the nervous system in the context of these trends. We discuss dengue viruses, which are spread by mosquitoes, in the context of climate change that increases the range at which dengue-carrying mosquitoes can

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live. We also discuss fungal meningitis, referring to fungal infections of the lining of the brain, resulting from patients traveling globally for surgical procedures. We lastly discuss the increase in neurological infections resistant to antibiotic treatment, which has resulted from overuse of antibiotics in medical and agricultural settings. As a whole, these trends show the need to invest further in public health systems at monitor for newly emerging diseases, as well as a commitment to developing vaccines and treatments for these diseases. The threats of these pathogens also make clear the need to address the underlying causes leading to their emergence and spread, including climate change and environmental degradation.

Keywords: dengue, drug resistance, meningitis, neuroinfectious disease, public health

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Introduction

The recent COVID-19 pandemic and other regional infectious disease epidemics have contributed to a growing recognition of the threat that novel emerging pathogens pose to the global population. Broadly defined, emerging infections are diseases found to be newly infecting humans, spreading into a wider geographic range, displaying new pathogenic characteristics, or only recently having been identified as pathologic agents.[1,2] Such infections represent a significant challenge even to well-established health systems, both due to limited therapeutic options for emerging infectious diseases and the increased volume of patients that may occur. In recent decades, the forces that drive the emergence of novel pathogens, namely climate change, disruption of established ecosystems, global travel, and urbanization, have accelerated and been coupled with a degree of globalization allowing for rapid international dissemination of such pathogens. As a result, much recent focus has been placed on Pathogen X, a representation of the knowledge that an infectious pathogen currently unknown to cause human disease could cause a future international pandemic.[3,4] Indeed, the World Health Organization (WHO) considers Pathogen X alongside such known epidemic pathogens as Ebola, Zika, and Sars-Cov-2 viruses in terms of priority for research and development. Many suspect that Pathogen X will be a zoonosis, emerging as a result of spillover from an animal reservoir into humans.[3]

Globally, the pathogenic etiology of most neurological infections remains undiagnosed. This is at least partially driven by the fact that some may be from emerging and re-emerging pathogens without available diagnostic testing, in addition to the difficulty of pathogen identification in the central nervous system (CNS) in general. Focusing on emerging viruses, one study estimated that 39% of emerging viral infections may cause severe neurological illness, while another 10% do so on a more infrequent basis.[5] These diseases inflict a significant burden on the communities they affect, both in terms of acute mortality but also with respect to the long-term, disabling sequelae neuroinvasive and neurotropic infections cause.[6] Though viruses represent the most likely neuroinvasive pathogenic class with pandemic potential, bacterial and fungal infections of the CNS also pose a significant threat to global health. Like viruses, opportunistic fungal pathogens have similarly expanded in terms of geographic range but are also notable for their impact on the growing population of immunocompromised and post-surgical patients.[7] Although significant advances have been made in the diagnosis and treatment of CNS bacterial infections, emerging antibiotic resistance to widely available therapeutics may pose a substantial threat to health security.[8]

In this review, we focus on relevant trends contributing to the emergence and re-emergence of neuroinvasive pathogens in recent decades. Understanding relevant public health trends that drive emergence of such pathogens is essential for neurologists, infectious disease specialists, and general clinicians, both in terms of utilizing epidemiology to determine patient risk of disease and recognizing how health systems contribute to

these trends. To this end, we provide a selected review of public health issues impacting the present and future epidemiology of neuroinvasive infections: climate change, medical tourism, and antimicrobial resistance (Box 1).

To discuss climate change, we focus on the dengue viruses (DENV), arboviruses that have long circulated globally but have rapidly expanded into new geographic zones with outbreaks of increasing magnitude in recent decades as a result of rising global temperatures. As the most common and most rapidly spreading vector-borne disease worldwide,[9] DENV infections are becoming increasingly relevant and offer insight into the factors driving emergence of other neuroinvasive vector-borne pathogens. In addition to climate change, rapid increases in medical tourism are altering the epidemiology of neuroinfectious diseases. Recently, cosmetic medical tourism to Mexico directly contributed to the development of highly virulent fungal meningitides that pose a significant challenge for physicians treating returning travelers.[10] Lastly, across pathogenic classes of neuroinvasive diseases, antimicrobial resistance significantly threatens the efficacy of existing therapeutics for neurological diseases that are already challenging to manage. We discuss antimicrobial resistance in the setting of bacterial meningitis, herpes simplex virus 1 (HSV-1) encephalitis, and tuberculosis meningitis (TBM) as a subset of the most epidemiologically significant neuroinfectious diseases for which therapeutic resistance is emerging rapidly.

Box 1. Key considerations of public health trends contributing to emergence of neuroinfectious diseases.

A. Anthropogenic climate change

- Pathogen/disease implicated: arboviruses (i.e., dengue viruses)
- Mechanisms of effect:
  - Increases the suitable host range geographically, allowing the vector to expand into new populations
  - Amplification of the disease vector population within existing vulnerable regions
  - Possible increase in incubation rates and feeding of disease-transmitting mosquitoes at higher temperatures

B. Medical tourism

- Pathogen/disease implicated: neuroinvasive fungi (i.e., fungal meningitis)
- Mechanisms of effect:
  - Increasing global travel for treatment exposes patients to health risks otherwise not encountered locally
  - Variable norms and regulations globally increase risk of exposure to contaminated medications or surgical supplies
  - Otherwise rare fungal pathogens are directly introduced into the CNS and perpetrate severe disease

C. Antibiotic resistance:

- Pathogen/disease implicated: acute bacterial meningitis, HSV-1 encephalitis, tuberculous meningitis
- Mechanisms of effect:
  - Antimicrobial overuse in clinical and agricultural settings selects for resistance genes
  - Contamination of soil, water, and food supplies results in spread of resistant pathogens into human populations
  - Difficult-to-manage CNS conditions require higher levels of systemically toxic medications or less efficacious alternatives

Dengue viruses

Clinical features and neuroinvasive potential

DENV, of which there are four recognized distinct serotypes (DENV1-4), belong to the family *Flaviviridae* and are positive single-stranded ribonucleic acid (RNA) viruses primarily spread by *Aedes aegypti* and *A. albopictus* mosquitoes found ubiquitously in tropical and subtropical climates.[11–13] Transmission of DENV is maintained via a human-mosquito-human cycle, as well as a distinct sylvatic monkey-mosquito-monkey cycle with periodic human spillover.[14,15] While the majority of DENV infections are mild, the disease has acquired the moniker "break-bone fever" due to its presentation with severe retro-orbital pain in half of patients and myalgias or arthralgias in more than 75%.[16–18] Notably, while infection with one serotype conveys immunity to that serotype for several years, secondary infection with a distinct serotype increases risk for severe dengue characterized by plasma leakage leading to shock, organ impairment, and bleeding.[19,20]

Approximately 1% of patients develop neurological manifestations, most often secondary to infection with DENV-2 and DENV-3 serotypes.[21] The specific pathophysiology of DENV neuroinvasive disease remains unclear, but it is likely that DENV directly invade the CNS given the detection of viral RNA in cerebrospinal fluid (CSF) and autopsied brain tissue. This may occur in the absence of blood-brain barrier (BBB) dysfunction, as CSF viremia has been detected in the presence of negative serum reverse transcriptase polymerase chain reaction (RT-PCR) testing.[21] DENV have been shown to infect and replicate within BBB endothelial cells, which may facilitate entry into the CNS.[22] In addition to the BBB,

DENV may also enter the CNS via the blood-CSF barrier at the choroid plexus, as has been suggested for other flaviviruses.[23] Multiple lines of evidence also suggest the neurotropic potential of DENV, including *in vitro* ability to bind CNS cell receptors and actively replicate within neurons.[24] Animal models have additionally displayed an increase in dengue virions in the rough endoplasmic reticulum and Golgi body of infected neurons during disease progression.[25] DENV-3 antigens have been demonstrated in human brain tissue at autopsy by immunohistochemistry, and DENV replication in human neurons, microglia, and endothelial cells has been identified in autopsy tissue.[26]

Encephalopathy is the most common neurological presentation of DENV, resulting from the systemic complications that accompany severe infection, including shock, metabolic disturbances, cerebral edema, and hepatic or renal failure.[27] Encephalopathy occurs in approximately 5–6% of individuals hospitalized with dengue hemorrhagic fever.[28,29] Encephalitis, most readily distinguished from encephalopathy by the presence of CSF pleocytosis or viremia, occurs in an estimated 1% of patients hospitalized with DENV. DENV encephalitis is commonly complicated by seizures, in addition to presentation with altered mental status, headache, behavioral changes, and other focal neurologic deficits.[30,31] Neuroimaging in encephalitis patients demonstrates T2-weighted and fluid-attenuated inversion recovery hyperintensities. These hyperintensities are predominately observed in the deep structures of the brain with frequent thalamic, basal ganglia, and cerebellum involvement.[32–34] Other neurological manifestations are less common but have been reported, including post-infectious immune-mediated syndromes like Guillain-Barré syndrome (GBS), supported by autopsy findings of demyelination.[21,26] Indeed, a large cluster of GBS cases in Fiji was temporally associated with a DENV-3 outbreak in 2014.[35] A similar cluster of GBS cases in Peru in 2023 coincided with large DENV outbreaks of all four serotypes but with an increasing prevalence of DENV-3 and DENV-4.[36] While ophthalmic dengue is more common, typically involving the posterior segment and presenting as maculopathy or retinal vasculopathy, optic neuropathy secondary to DENV infection has also been reported.[37–39] Lastly, cerebrovascular complications have been reported, commonly during the convalescent stage of infection, with an unknown incidence, though hemorrhagic stroke appears to be more common than ischemic stroke.[40]

Epidemiological trends and the impact of climate change

Since a hypothesized origination in Africa or Southeast Asia, DENV outbreaks have occurred in a broad range of subtropical and tropical climates worldwide.[41,42] Over the course of the last few decades, however, the incidence of infection has increased more than 30-fold, such that DENV now cause the greatest disease burden of any arbovirus, infecting an estimated 390 million individuals annually.[43,44] While much of the historical spread of DENV occurred due to international trade, urbanization, sanitation methods, and water storage norms, the current trend in DENV spread appears to be driven by anthropogenic climate change.[45] Increased global temperatures expand the geographic range of habitat suitability for DENV's primary vector, the *Aedes* mosquitoes. Warmer summer temperatures induce more rapid production of adult *Aedes* mosquitoes, facilitating successful colonization of susceptible regions, and warmer winters reduce winter mortality.[46] DENV also incubate more rapidly at higher temperatures, and *Aedes* mosquitoes may feed more frequently with increased temperature.[47]

Beyond rising global temperatures, other variations in climate and weather also drive the risk for DENV outbreaks. Precipitation in particular has a significant effect on the growth, population dynamics, and behavior of *Aedes* species.[48] It has been thought that while temperature defines the viable range for vector survival, humidity and precipitation serve to amplify the vector population's potential. Indeed, 80% of DENV cases from 1983 to 2001 occurred within a temperature range of 27–29.5°C and mean humidity greater than 75%.[45] In South America, seasonal DENV outbreaks have been tied to El Niño and La Niña events that bring intermittent heavy rainfall and temperature variation.[49] These events have become less predictable and of greater amplitude over time as a result of climate change, providing the potential for more severe outbreaks.[50] This has been particularly relevant in 2023, in which the Americas have experienced a record-setting surge of infections surpassing 3 million cases.[51] Other countries, including Bangladesh, also

reported record-setting years for DENV, driven by the confluence of monsoon season, El Niño, and rising temperatures.[52]

Efforts to model the future spread of DENV are challenging given the growing unpredictability of weather-related events such as El Niño. Estimates suggest, however, that the geographic range suitable for DENV will grow to include an additional 2.5 billion individuals by 2080, beyond the estimated 4 billion people already at risk.[53] Across models, the strongest predictor of increasing frequency of DENV outbreaks is the number of days a region spends at warmer temperatures.[54,55] This is worrisome given that nearly all climate change models predict global temperatures will rise by at least 2.7°F by 2100 even with as-of-yet unimplemented mitigation strategies.[56] Areas particularly anticipated to be impacted by the future spread of DENV include the southern continental United States, large cities in coastal Japan and China, and higher altitude zones of Central and South America. However, southern and West Africa are predicted to undergo the greatest increase in DENV risk as temperatures and precipitation in the regions rise, which will strain healthcare systems already under-resourced to respond to DENV outbreaks.[53,57]

As DENV spread into new regions and cause outbreaks more frequently, existing mitigation strategies are unlikely to counteract the risk sufficiently. Local vector control strategies centered around mosquito eradication are useful but require strong public health infrastructure and do not address the broader driving causes of DENV outbreaks. In the absence of effective therapeutics, significant morbidity and mortality due to DENV neuroinvasive disease will become increasingly common throughout the global population.

Fungal meningitis

General epidemiology and clinical features

Fungi are ubiquitous in the environment, and of the over 100,000 species known, approximately 300 are known to be capable of CNS disease.[58] Fungal meningitis typically occurs secondary to hematogenous spread from a systemic focus of infection. However, it may also be caused by direct extension of infection through the cranial bones or sinuses, as well as direct introduction during neurosurgical procedures.[59] Additionally, many patients who develop fungal meningitis have an immunocompromized status due to human immunodeficiency virus infection, chemotherapy, or prolonged corticosteroid use as in transplant patients.[59,60] Some fungal pathogens may also invade immunocompetent hosts, resulting in meningitis due to *C. neoformans* or *C. gattii*, *Coccidioides* species *C. immitis* or *C. posadii*, and *Histoplasma*. Others such as *Candida* spp. typically emerge only with immune dysfunction.[61] Nosocomial-acquired fungal meningitis, referring to infections acquired in a hospital setting, represents a growing concern. These cases are most commonly caused by *Candida* spp. infections, followed by *Aspergillus* spp. and more distantly by *Mucorales*, *Fusarium*, and other mold species.[62] Particularly, *Candida* spp. cause the most common and potentially lethal fungal infections following neurosurgical procedures and in those with ventriculoperitoneal shunts.[63–65] This may be selected for by post-surgical antibiotic prophylaxis that eliminates competing bacterial flora.[66]

Though fungal meningitides may present acutely, such infections more often present subacutely, frequently with low-grade fever and headache. Fungal infections are also a common cause of chronic meningitis that may present with signs of increased intracranial pressure including papilledema, seizures, and nonspecific cognitive decline.[67] Patients with a chronic or subacute course may additionally present acutely with vascular complications, such as stroke or arterial dissection, which may result from vasculopathy, obstruction of venous outflow, and small vessel arteritis.[68,69] Neuroimaging may identify meningeal enhancement, particularly of the basilar cisterns, as well as complications of fungal meningitis including hydrocephalus or cerebral infarction.[67]

Medical tourism and fungal meningitis

Medical tourism, referring to international travel for the purpose of obtaining medical care, has rapidly increased in recent years as physical barriers between countries have been reduced by modern transportation. Historically, medical tourism more commonly flowed from countries with weaker healthcare infrastructure to more advanced healthcare systems in the United States and Europe. However, the directionality of medical tourism has recently shifted toward a predominance of tourists from high-income countries seeking lower-cost or more accessible medical

procedures in developing health systems.[70] This trend is driven by high local costs of healthcare, long wait times in patients' home countries, and the lack of availability of certain treatments in some regions.[71] In 2017, more than 1.4 million United States citizens, for instance, turned to medical tourism in response to rapidly increasing medical costs within the U.S. healthcare system.[72,73] Most commonly, individuals travel for cosmetic surgery, dentistry, dermatological procedures, cardiac care, and some solid organ transplants.[73] According to the International Society of Aesthetic Plastic Surgery, 10,607,227 aesthetic surgical procedures were recorded globally in 2018.[74] Most medical procedures performed in medical tourists are carried out in South America, followed by Southeast and Central Europe.[75] Concerningly, medical and surgical procedures in tourists performed overseas confer risk of infectious complications due to several factors, including lack of regulations for equipment and devices, drugs, and medical products.[76] Healthcare-related infectious complications among medical tourists are a growing concern for public health worldwide.[77]

Infections acquired through medical tourism represent a growing concern for clinicians, as exemplified by a recent fungal meningitis outbreak impacting United States tourists seeking medical care internationally.[78] In May 2023, the United States Centers for Disease Control and Prevention (CDC) identified a number of patients in Texas who experienced fungal meningitis after receiving spinal epidural anesthesia for cosmetic surgery in northern Mexico.[79] This prompted an extensive investigation and closure of the clinics, during which nearly 200 residents across more than 25 U.S. states were determined to be at risk as a result of potential exposure during procedures at the clinics. The infections were suspected to have been transmitted during epidural anesthesia, either as a result of contaminated medications or inadequate sanitary measures. When elevated CSF β-D-glucan levels were observed across multiple cases, an outbreak of fungal meningitis was suspected.[80] Later that month, *Fusarium solani*, a filamentous fungus typically only capable of causing meningitis in immunocompromized patients,[81] was identified as the culprit pathogen.[82,83]

Notably, the outbreak was similar to two other fungal meningitis outbreaks in North America. In Durango, Mexico, another cluster of patients with *F. solani* meningitis was identified following receipt of epidural anesthesia. The public health response identified 1801 potentially exposed patients, of whom 80 developed fungal meningitis. Despite the immunocompetency of the exposed population, the case fatality rate exceeded 50%.[80,84] Historically, these outbreaks recall the largest healthcare-associated fungal meningitis outbreak in the United States in 2012–2013, which resulted from injections of contaminated methylprednisolone acetate, a steroid medication.[85] During that outbreak, 751 patients developed fungal meningitis, spinal or paraspinal infection, and/or peripheral osteoarticular infection with a mortality rate of 8.5%.[86] In this instance, the identified pathogen was the brown-black soil fungus *Exserohilum rostratum*, similarly an exceedingly rare cause of disease in humans under normal circumstances.[87]

In each of these cases, contaminated medications or medical equipment contributed to outbreaks with severe morbidity and mortality from pathogens typically unknown as major causes of human disease. In some instances, meningitis resulted despite the absence of instrumentation within the CNS, underscoring the possible neurotropic potential of these fungi following access to specific tissue sites.[88] As norms and regulations for medical tourism continue to be defined, understanding and addressing risks for severe CNS infections acquired during travel will be essential for the maintenance of public health.

Antimicrobial-resistant meningitis

Trends in antibiotic-resistant bacterial meningitis

Bacterial meningitis contributes significantly to global morbidity and mortality, leading to death in 8%–15% of cases even with treatment and permanent disabling sequelae in more than 20%.[89] The clinical features and etiologic epidemiology of acute bacterial meningitis have been reviewed at length elsewhere[90]; generally, the most common causes in adults have been *Streptococcus pneumoniae* and *Neisseria meningitidis*.[91] Historically, *Haemophilus influenzae* additionally caused a substantial proportion of acute bacterial meningitis cases, but introduction of the *H. influenza* type b conjugate vaccines substantially reduced its burden.[92] Vaccines for *S. pneumoniae* and *N. meningitidis* have also been introduced with substantial success; however, inequitable

vaccine access has resulted in a persistently elevated burden of disease due to these pathogens in resource-constrained settings.[93,94] Furthermore, emerging increases in antimicrobial resistance among these pathogens may undermine additional progress in addressing the burden of bacterial meningitis globally.

In general terms, antibiotic resistance refers to the ability of a bacterium to elude the bactericidal or bacteriostatic effect of a particular antibiotic. In the context of CNS infections, antimicrobial resistance poses a particular challenge given the poor penetration of most antibiotics through the BBB. This results in a necessity to employ higher concentrations of antibiotics for CNS infections to achieve a minimal inhibitory concentration in the CSF, which often results in greater treatment toxicity or less efficacy when second-line agents must be used.[95,96]

The recognition of penicillin-resistant strains of *S. pneumoniae* dates back to 1967, with increasing reports worldwide of treatment failure in *S. pneumoniae* meningitis due to penicillin resistance through the 1970s to 1990s.[97–99] Empiric treatment with third-generation cephalosporins (e.g., ceftriaxone) for bacterial meningitis, as recommended by European guidelines for management of acute bacterial meningitis, has become a successful strategy in mitigating the risk of treatment failure for penicillin-resistant strains.[98,100] However, optimal treatment paradigms for multidrug-resistant *S. pneumoniae* (i.e., to both penicillin and cephalosporins) are less well defined but largely include additional empiric treatment with vancomycin or rifampicin.[100,101]

In contrast to *S. pneumoniae*, antibiotic resistance in meningococcal disease caused by *N. meningitidis* is historically infrequent. However, in 2020, isolates of *N. meningitidis* serotype Y resistant to penicillin and ciprofloxacin were detected in the United States.[102] The CDC subsequently reviewed 2097 samples collected between 2011 and 2020 and identified 33 isolates resistant to penicillin, 11 of which were also resistant to ciprofloxacin.[102] Similarly, infrequent rates of *N. meningitidis* resistance to penicillin, rifampicin, cefotaxime, and ciprofloxacin have been reported in other countries.[103] This is of particular relevance in the African meningitis belt, where overall rates of invasive meningitis disease have fallen following more widespread vaccine introduction, yet non-vaccine serotypes have been increasing in prevalence. Due to this, the potential for antimicrobial resistance in this high-incidence region has increased.[104,105]

Herpes simplex 1 anti-viral resistance

HSV-1 encephalitis is the most common infectious cause of encephalitis, representing 30–40% of encephalitis cases with an identified etiology.[106] Prior to the introduction of acyclovir, mortality from HSV-1 encephalitis approached 70% but has dramatically improved to below 10% in recent decades.[107] Presenting clinical features are relatively nonspecific but include altered mental status, fever, headache, and seizures as in several other encephalitis syndromes. However, PCR testing in combination with supportive MRI features has greatly improved the time to diagnosis and therapeutic outcomes as a result.[108]

HSV-1 resistance to acyclovir, first observed in 1982, is reported in up to 0.5% of immunocompetent patients and 10% of immunocompromised patients; however, acyclovir resistance in the setting of HSV-1 encephalitis is rarely tested or reported.[109–112] Acyclovir resistance occurs due to thymidine kinase mutation in 95% of cases, while DNA polymerase mutations are less commonly reported.[109] The mutations that drive acyclovir resistance likely reduce the pathogen's ability to establish latency and reactivation, which may limit the clinical impact of acyclovir resistance, especially in cases of encephalitis.[109] Nonetheless, acyclovir resistance should be considered in patients with HSV-1 encephalitis who do not respond to acyclovir, as alternative agents (i.e., foscarnet) have led to clinical improvement in these rare instances.[111,113]

Multidrug-resistant Mycobacterium tuberculosis *and tuberculous meningitis*

TBM represents the most severe form of TB, resulting in mortality in approximately 20% of patients and severe neurological sequelae in nearly 50%.[114–116] Prevalence of TBM varies between high and low TB prevalence regions, generally accounting for about 5% of all extrapulmonary TB cases and 1% of all TB cases.[117] It occurs following the hematogenous spread of *M. tuberculosis* to the CNS via the choroid plexus, with subsequent rupture of tubercles into the subarachnoid space. This results in the formation of

a dense exudate that concentrates in the basal cisterns and infiltrates the meningeal vasculature, leading to obstructive hydrocephalus and tissue infarction in a high proportion of cases.[118,119] In addition to expectant management of its complications, TBM requires urgent initiation of intensive anti-tubercular therapy with adjunctive dexamethasone. Delays in treatment, along with more severe initial presentation, portend a worsened prognosis.[120] Unfortunately, increasing rates of resistance to first- and second-line anti-tubercular medications threaten to complicate management of this already challenging disease. Indeed, the presence of drug resistance in TBM has been found strongly to predict death.[121]

Specifically, multidrug-resistant TB (MDR-TB) refers to *M. tuberculosis* resistant to both isoniazid and rifampicin.[122] Various other drug resistance patterns in TB are recognized, including monoresistance to isoniazid or rifampicin, polyresistance beyond isoniazid and rifampicin, and extensive drug resistance (i.e., fluoroquinolone or second-line drug resistance).[123] Drug-resistant TB infections occur as a result of either primary transmission of circulating drug-resistant *M. tuberculosis* or development of mutations conferring resistance after initial infection and attempted treatment.[124] The emergence of MDR-TB poses a major challenge to worldwide TB control and threatens to worsen outcomes in TBM. A systematic review and meta-analysis of TB patients primarily in Asia found MDR-TB and isoniazid monoresistance in 5.2% and 9.4% of patients, respectively.[125] Similarly, a multi-center European cohort identified MDR-TB/TBM in 3.5% of patients, and 14.1% displayed resistance to at least one anti-tubercular drug.[126] Drug resistance, especially MDR-TB, in TBM is associated with a high rate of mortality, ranging from 67% to 100%.[121,127] While intensified treatment regimens for TBM, including higher dose rifampicin and the addition of levofloxacin, demonstrate some promise in improving survival in patients with isoniazid-resistant TBM, MDR-TB remains a highly morbid and difficult-to-treat condition.[128]

Antimicrobial use and emergence of resistance in a global context

Though antimicrobial resistance is a naturally occurring phenomenon, the evolution and spread of resistance to specific medications has recently been accelerated by overuse of antimicrobials in community, hospital, and agricultural contexts.[129–131] Indeed, across all contexts, the rate of antibiotic consumption directly correlates with the rates of emerging antimicrobial resistance due to the increased selective pressure medication overuse induces.[132,133] In the United States, for instance, one study of outpatient antibiotic prescribing found that likely 30% of 154 million outpatient antibiotic prescriptions were inappropriate in 2010–2011.[134] Such trends have only accelerated, as antibiotic consumption globally increased by 65% between 2010 and 2015. This was primarily driven by increased rates of use in low and middle-income counties (LMICs) that are quickly converging with the longstanding history of overuse in high-income countries (HICs).[135] As urbanization and density of transportation networks continue to grow in LMICs, rates of antimicrobial resistance now exceed 50% in some settings,[136] and LMICs now have the highest rates of resistance for many pathogens.[137] Coupled with surveillance systems inadequate for monitoring antimicrobial resistance and poor sanitation infrastructure, this allows for a high incidence of community-level transmission of antimicrobial-resistant pathogens through wastewater and food processing networks.[138] International travel further compounds this issue, as individuals are able to transmit highly resistant pathogens bidirectionally between different settings.[139]

In addition to overuse of medications in healthcare settings, human-environment interactions also contribute substantially to the increasing prevalence of antimicrobial resistance. In 2017, for instance, 73% of all antimicrobial use occurred in animals,[140] and use of antibiotics has displayed a robust correlation with antimicrobial-resistant colonization of common livestock.[141] At least part of this trend is driven by increasing global demand for animal protein,[142] which has resulted in a shift from small-scale agriculture (particularly in middle-income countries) to large-scale industrial agricultural practices that more commonly utilize antimicrobials to promote growth and longevity in livestock.[143] After selection occurs for resistance genes in livestock, drug-resistant pathogens may then propagate in manure and surface soil, which can then runoff into waterways utilized for human consumption and hygiene.[144,145] Food products serve as a route for spread of antimicrobial-resistant pathogens to humans, either through direct consumption of contaminated meat or during food processing.[146] Consumption

of contaminated water or food products may then colonize both human and animal gastrointestinal tracts, further enhancing transmission of antibiotic-resistant pathogens within local networks.[147]

These trends, both overuse in medical and agricultural settings, are also reshaping the environmental landscape from which resistant pathogens emerge. Resistance genes are ubiquitous and evolutionarily ancient among bacteria in the environment, which provides fertile soil for rapid emergence of antimicrobial resistance in the environment once selective pressure is introduced.[148,149] In both humans and animals, many antibiotics are excreted into the environment without chemical modification,[150] which can drive selection for resistant pathogens even at low concentrations.[151] Therefore, both direct contamination of the environment via runoff of human and animal waste laden with resistant pathogens and deposition of antibiotics into the environment serve to increase the prevalence of antimicrobial resistance in soil. Indeed, soils treated with manure or utilized for agricultural production have been found to display an increased prevalence of antibiotic resistance genes and bacteria with higher minimum inhibitory concentrations than other environments.[152] Similarly, wildlife have been found to harbor extended-spectrum beta-lactamase-producing bacteria, but only after such bacteria were identified in livestock.[153] Environmental contamination in turn then drives an increased risk of both human and animal disease. For instance, outbreaks of multidrug-resistant *Acinetobacter*, a previously drug-susceptible organism prevalent in soil and water, have occurred in hospital settings following environmental exposure in military personnel and survivors of earthquakes.[149,154,155] As a whole, these findings underscore the mutually reinforcing nature of medical overuse, agricultural practices, and the environment as they contribute to the rising threat of antimicrobial resistance. These trends indicate the need for broader interventions and regulation of antimicrobial use in addition to a continued commitment to vaccine development and distribution.

Conclusion

Emerging neuroinfectious diseases, of which we discuss arboviral diseases, fungal meningitis, and antimicrobial-resistant infections, present substantial challenges for which global health systems are inadequately prepared, underscoring the necessity to improve preventative frameworks for infectious diseases. Though we present a limited subset of neuroinvasive infections, the discussed trends are applicable to an even broader range of neuroinfectious diseases, including severe parasitic infections such as cerebral malaria and neurocysticercosis that are increasing in prevalence with climate change and global movement of populations.[156,157] Addressing such emerging threats must involve strengthening local public health systems for infectious disease monitoring and treatment, a commitment to equitable therapeutic and vaccine development, and prevention of environmental degradation.

Global infectious disease infrastructure has historically focused on preventing spread of "tropical" pathogens into HICs in service of health security rather than improving systems of care and disease monitoring to address pathogen endemicity locally.[158] Pandemic preparedness, however, requires an economically inefficient process centered on diffuse distribution of infrastructure and investment in surveillance capacity that may never be utilized on a broader global scale.[159] This underscores the reality that while any individual pathogen has a low risk of inciting an epidemic or pandemic, the aggregate risk across all emerging pathogens is quite high.[160] An increased dedication to developing laboratory and clinical infrastructure in diverse global contexts recognizes that policies of disease containment are insufficient to halt the spread of emerging pathogens in a globalized society.

Similarly, vaccine development often favors economic incentives over social value, placing a disproportionate emphasis on addressing diseases that impact HICs.[161] Rather than relying on goodwill from private companies responsive to market forces, open science collaborations between governments, researchers, and philanthropic organizations may contribute to the development of therapeutics that anticipate disease threats.[162] Importantly, such approaches allow for central decision making that encourages cooperation between diverse governments and private companies, as well as creating sharable knowledge that can be scaled through investments in local production capacity and public health networks.[163]

Lastly, curtailing the emergence of neuroinfectious diseases requires an urgent commitment to

preventing further environmental degradation and climate change. Exploitation of wild habitats brings humans into contact with novel vectors that transmit previously un-encountered diseases.[164] A "One Health" framework, which recognizes the necessity to combine multi-disciplinary approaches spanning ecology, veterinary science, laboratory science, epidemiology, and agriculture to mitigate the threat of zoonotic diseases, is essential to confronting these emerging threats.[165,166]

As a whole, addressing the emergence of neuroinfectious diseases requires investment in global public health infrastructure that is collaborative and centered on a holistic understanding of pathogen emergence and spread. In addition to improved disease surveillance must be sustained investment in novel therapeutics made widely available in LMICs through support of local production capacity and facilitatory trade agreements that recognize the interconnected nature of global health.

Declarations

Ethics approval and consent to participate

Not applicable. This study did not include human or animal participants.

Consent for publication

Not applicable.

Author contributions

Jackson A. Roberts: Conceptualization; Writing – original draft.

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No datasets are associated with this publication.

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