The Global Burden of Neuroinfectious Diseases

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Overview

Infectious diseases of the nervous system are of global health significance, and have a particularly high impact in resource-limited settings, where neglected tropical neuroinfectious diseases cause significant morbidity and mortality on vulnerable populations (1). Over 100 infectious organisms can damage the nervous system, either through direct mechanisms or through post-infectious inflammatory responses, and have significant acute neurological effects as well as often devastating neurological sequelae in survivors. The three most significant global infectious diseases-malaria, tuberculosis, and Human Immunodeficiency Virus (HIV)- have significant neurological complications. Emerging and re-emerging neuroinfectious diseases are of growing concern, with major work needed to enhance surveillance and identification of pathogens in vertebrate and invertebrate hosts, as well as in humans. Estimating the global burden of neurotropic infectious diseases is a challenging task as there is a derth of epidemiological studies. There are several major challenges to understanding neuroinfectious disease burden, amongst them are that individuals often present with nonspecific clinical syndromes, traditional microbiological techniques are often not timely, and are insensitive and nonspecific, and risk factors in different regions of the world are constantly changing due to epidemiological transitions, demographic changes, and other factors.

Neuroinfectious diseases in the Global Burden of Disease Report 2015 (2)

Neuroinfectious diseases captured in the Global Burden of Disease Report 2015 include bacterial meningitis, encephalitis, and tetanus (2). Importantly, acute neurological complications of several neuroinfectious diseases and their sequelae are not captured in the Global Burden of Disease study. Overall trends show a marked decrease in mortality of bacterial meningitis, with Hemophilus influenza being the most significant (age standardized mortality rate decreased by 41.1% (-48.3 to -31.4). HIV incidence reached its peak in 1997, and HIV deaths have been declining since the mid-2000s. The number of people living with HIV/AIDS has been steadily increasing, and reached 38·8 million in 2015 which is of particular relevance given the age-related neurological effects of HIV including HIV-associated cognitive impairment, cerebrovascular disease, and peripheral neuropathy. Malaria deaths decreased by 37·4% (27·8–47·0), falling to 730,500 (555,800–904,000) in 2015. Age-standardized death rates due to malaria fell slightly more rapidly (43·1%, 34·7–51·8) during this time. Tuberculosis, which killed fewer people than HIV/ AIDS in 2005 essentially matched HIV/AIDS's toll by 2015, causing 1·1 million deaths (0·91 million to 1·4 million) (2).

Bacterial meningitis

Bacterial meningitis is a devastating disease that is associated with substantial morbidity and mortality. In those who survive, neurological sequelae including hearing loss, epilepsy, strokes, and neurocognitive impairment are reported to occur in up to half of survivors of bacterial meningitis (3). Low-income and middle-income countries account for 98% of the estimated 5·6 million disability-adjusted life years attributed to meningitis globally and bacterial meningitis ranks among the top ten causes of death in children younger than 14 years in high-income countries (4). H influenzae, S pneumoniae, and N meningitidis are the predominant causes of bacterial meningitis, but their relative contribution differs over time, by location, and by age group (5-6). Other important causes of meningitis in resource-limited countries are Enterobacteriaceae (especially non-typhoidal salmonella species) in children in sub-Saharan Africa (7-8) and Streptococcus suis in adults in southeast Asia (9). A major epicenter of recurring meningitis outbreaks is across the sub-Saharan Africa, involving 19 contiguous countries that constitute the 'meningitis belt' where historically the causative agent has been serogroup A meningococcus. Conjugate meningococcal vaccine against serotype A (MenAfriVac) was developed between 2001 and 2009 and deployed in 2010 (10). Thus far, over 250 million individuals have been immunized across the meningitis belt. The public health benefits of MenAfriVac have already been demonstrated by a sharp decline in reported cases of meningococcal disease in the countries where it has been introduced. However, serogroup replacement following mass meningitis vaccination has been noted, and in 2015 an epidemic with a novel strain of serogroup C was recorded in Niger and Nigeria for the first time since 1975. This has posed a serious challenge toward elimination of meningococcal meningitis epidemics in the African (10).

Japanese Encephalitis

Japanese encephalitis (JE) is the leading vaccine-preventable cause of encephalitis in Asia, with an estimated 68,000 annual cases worldwide (11). The natural reservoirs of JE virus (JEV) are pigs and wading birds, and the virus is transmitted to humans by *Culex* mosquitos, primarily in rural agricultural settings (12). The majority of infections are asymptomatic; < 1% of infected individuals develop clinical disease, and the most commonly recognized manifestation is acute encephalitis. Other presentations include aseptic meningitis, seizures, or acute flaccid paralysis. The fatality rate is 20–30%, and 30–50% survivors are left with neurologic sequelae (13). Twenty-four countries in the World Health Organization (WHO) South-East Asia and Western Pacific regions have endemic JE transmission, exposing more than 3 billion people to risks of infection. The global incidence of JE is unknown due to the variability in the quality of JE surveillance and the availability of diagnostic laboratory testing which varies throughout the region. A study evaluated the worldwide incidence of JE, and found that approximately 33,900 (50%) cases occur in China (excluding Taiwan) and approximately 55,000 (81%) occur in areas with well established or developing JE vaccination programmes, while approximately 12,900 (19%) occur in areas with minimal or no JE vaccination programmes (14). Approximately 51,000 (75%) of these cases occur in children aged 0–14 years, which gives an estimated overall annual incidence of 5.4 per 100 000 in this age group. The results of the study suggest that the actual incidence of JE is nearly 10 times higher than reflected in recent reports to

WHO. While there is no treatment for JE, though there are several classes of JEV vaccines are available, including inactivated, live attenuated and live recombinant versions (15-16).

Zika virus

Zika virus is an arthropod-borne virus which is an emerging infectious disease with the potential to spread to new areas where the Aedes mosquito vector is present (17-20) Clinical manifestations of Zika virus infection occur in approximately 20 percent of patients and include acute onset of low-grade fever with maculopapular pruritic rash, arthralgia (notably small joints of hands and feet), or conjunctivitis (nonpurulent). Neurotropism of Zika virus has been demonstrated in vivo and in vitro (21-25). Zika virus infection has been associated with neurologic complications; these including congenital birth defects, Guillain-Barré syndrome, myelitis, and meningoencephalitis (26-28). Zika virus was first isolated from a rhesus monkey in 1947 in Uganda (29). The virus subsequently spread across equatorial Africa and Asia, where it was associated with sporadic infections. The first major recognized outbreak occurred in the Yap Islands of Micronesia in 2007; more than 70 percent of the population ≥3 years of age was infected, resulting in an estimated 5000 infections among the total population of 6700 (30-32). Another larger outbreak occurred in French Polynesia in 2013 to 2014, which affected about two-thirds of the population, resulting in approximately 32,000 infections (33-34). During the outbreak in French Polynesia, Guillain Barre Syndrome and microcephaly were epidemiologically linked with the Zika virus outbreak. Zika virus infections were subsequently detected in Brazil in May 2015 (33). Molecular analyses have suggested that the virus may have been introduced earlier, in late 2013 or early 2014 (34). As of the beginning of March 2017, eighty-four countries, territories or subnational areas with evidence of vector-borne ZIKV transmission (35). Thirty-one countries or territories have reported microcephaly and other central nervous system (CNS) malformations potentially associated with ZIKV infection, or suggestive of congenital infection and twenty three countries or territories have reported an increased incidence of Guillain Barré syndrome (GBS) and/or laboratory confirmation of a ZIKV infection among GBS cases.

Poliomyelitis

Although poliomyelitis no longer poses a worldwide public health threat, small areas of endemic wild-type poliovirus still exist in parts of Asia and Africa, and concerningly, there has been a recent rise in the number of wild type poliomyelitis cases in 2016 (36). Given the availability of an inexpensive oral polio vaccine (OPV) and the success of the Pan American Health Organization polio eradication program in the Americas, the World Health Assembly resolved in 1988 to eradicate polio globally by the year 2000 (37). This goal proved more challenging than originally foreseen, and important obstacles remain including the poor access to children in remaining endemic areas due to insecurity and co-circulation of oral poliovirus vaccine-derived polioviruses (cVDPV). Nonetheless, great progress has been made: the incidence of paralytic polio worldwide has been reduced by more than 1000-fold (38). Surveillance is a cornerstone of the polio eradication initiative for poliomyelitis cases consists of detection of acute flaccid paralysis cases in children and adolescents ≤15 years of age that are compatible with

poliomyelitis. Stool collected from AFP cases and close contacts within 14 days of onset are tested by cell culture in a regional Global Polio Laboratory Network laboratory for the presence of polioviruses and other enteroviruses. This global surveillance system serves as possible model for future surveillance systems of other neuroinfectious diseases.

Neurological complications of HIV/AIDS

The landscape of global HIV is changing with increased access to combined antiretroviral therapy (cART). In sub-Saharan Africa, the world's most affected region, the number of people on treatment has more than doubled in the last 5 years and since 2003 annual AIDS-related deaths have decreased by approximately 43% globally (39). Along with these achievements, significant challenges remain including an alarming number of new HIV infections worldwide, particularly among young women, accounting for 20% of the 2.1 million new HIV infections among adults in 2015 (39). The total number of people living with HIV is massive—approximately 37 million (Figure 2). HIV-associated neurological syndromes continue to cause significant morbidity and mortality globally, and are classified as (1) those due to primary HIV infection, (2) secondary to opportunistic infection (OIs) or immune reconstitution, or (3) associated with antiretroviral treatment. The widespread implementation of cART in resource-rich settings has transformed the presentation, manifestations, and epidemiology of the neurological aspects of HIV (40). Neurological disorders associated with HIV demonstrate geographic variability, with Europe and Northern America having high rates of cognitive sequelae and peripheral neuropathy, likely due to an aging HIV positive population. In contrast, in resource-limited settings, there remains a large portion of patients with CNS OIs and those with adverse effects from older generation neurotoxic medications. Though, these differences may be partly mediated by limited ascertainment of cognitive dysfunction and peripheral neuropathies in environments with a dearth of specialists.

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