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VIEWPOINTS

Global Landscape of Encephalitis: Key Priorities to Reduce Future Disease Burden

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Encephalitis affects people across the lifespan, has high rates of mortality and morbidity, and results in significant neurological sequelae with long-term consequences to quality of life and wider society. The true incidence is currently unknown due to inaccurate reporting systems. The disease burden of encephalitis is unequally distributed across the globe being highest in low- and middle-income countries where resources are limited. Here countries often lack diagnostic testing, with poor access to essential treatments and neurological services, and limited surveillance and vaccination programs. Many types of encephalitis are vaccine preventable, whereas others are treatable with early diagnosis and appropriate management. In this viewpoint, we provide a narrative review of key aspects of diagnosis, surveillance, treatment, and prevention of encephalitis and highlight priorities for public health, clinical management, and research, to reduce the disease burden.

Keywords. encephalitis; treatment; diagnosis; burden; vaccination.

Encephalitis is brain inflammation mostly caused by infection or host immune responses (Table 1), although often the cause is unknown. Infectious causes typically present with an acute febrile illness, accompanied by changes in personality, behavior, cognition, or consciousness, with or without new-onset seizures, and/or focal neurologic deficits. Autoimmune causes typically present sub-acutely and may have prominent psychiatric features and/or seizures and movement disorders. Encephalitis has high mortality and morbidity, similar to other acquired brain injuries with significant neurological sequelae, causing long-term impact on quality of life (QoL) and socioeconomic status.

Data show that both children and adults suffer significant sequelae following encephalitis. A systematic review of encephalitis outcomes in children reported neurodevelopmental sequelae including developmental delay, abnormal behaviour, intellectual deficit, and motor impairment in almost half of survivors [1]. Between 26% and 62% of adults suffer significant sequelae, including epilepsy, memory problems, inappropriate behavior and poor social skills, fatigue/sleep disturbance, personality changes, cognitive problems, problems with pain and other sensations, and problems with daily living skills [2].

Encephalitis has grown in importance over recent years due to the impact of climate change on vector-borne causes, greater use of immunosuppressive drugs and biologicals, and increasing identification of antibodies associated with autoimmune encephalitis [3]. The effects of Zika virus, severe acute respiratory syndrome coronavirus 2, and monkeypox infection on the brain, including encephalitis, further emphasizes the importance of this area [4, 5].

In this viewpoint, we review key aspects of diagnosis, surveillance, treatment, and prevention of encephalitis and highlight priorities for public health, clinical management, and research to reduce disease burden. This is in line with the World Health Organization (WHO) Global Action Plan on Epilepsy and Other Neurological Disorders and WHO meeting report on "Why Encephalitis Matters" [6, 7]. We present key points from the Encephalitis Society's in-depth review and gap analysis of key variables affecting global disease burden and provide further detail particularly related to diagnostics [8, 9].

AVAILABILITY OF DIAGNOSTIC TESTING

Cerebrospinal fluid (CSF) analysis is essential for diagnosing most forms of encephalitis and determining the underlying

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Table 1. Important Causes of Encephalitis, Their Distribution, Transmission Routes, and Availability of Vaccine or Treatment Measures

	Distribution	Transmission	Main Vaccines and/or Treatment
Causes with worldwide distribution			
Virus			
Herpesviridae			
Herpes simplex virus type 1	Worldwide	Human to human	IV acyclovir
Herpes simplex virus type 2	Worldwide	Human to human	IV acyclovir
Varicella zoster virus	Worldwide	Human to human	VZV vaccine, IV acyclovir
Epstein-Barr virus	Worldwide	Human to human	…
Cytomegalovirus	Worldwide	Human to human	Ganciclovir and foscarnet
Human herpes virus type 6 and 7	Worldwide	Human to human	…
Others			
Mumps virus	Worldwide	Human to human	MMR vaccine
Measles virus	Worldwide	Human to human	Measles containing vaccine (including MMR)
Rubella virus	Worldwide	Human to human	MMR vaccine
Human immunodeficiency virus	Worldwide	Human to human	Antiretrovirals
Enteroviruses	Worldwide	Human to human	…
Lymphocytic choriomeningitis virus	Worldwide	Airborne from rodent faeces	…
SARS-CoV-2	Worldwide	Human to human, airborne	SARS-CoV-2 vaccine
Causes that are geographically restricted			
Virus			
Flaviviridae			
Japanese encephalitis virus	Asia and South-East Asia, Australia	*Culex spp.* mosquitoes	Japanese encephalitis vaccine
Dengue virus	Africa, Mediterranean region, South and Central America	*Aedes spp.* mosquitoes	Dengue virus vaccine
West Nile virus	North and South America, Middle East, Africa, Europe, Australia and Southern Asia (Kunjin virus)	Various mosquito species (mainly *Culex spp.*)	…
Saint Louis encephalitis virus	North and South America	*Culex* spp. mosquitoes	…
Murray Valley encephalitis virus	Australia and New Guinea	*Culex* and *Aedes* spp. Mosquitoes	…
Yellow fever virus	Africa, South and Central America	*Aedes* spp. and *Haemagogus* spp. mosquitoes	Yellow fever vaccine
Tick-borne encephalitis virus	Central and Eastern Europe and parts of Asia	*Ixodes* spp. ticks	Tick-borne encephalitis vaccine
Bunyaviridae			
La Crosse virus	North America	*Aedes* spp. mosquitoes	…
Toscana virus	Mediterranean Basin	*Phlebotomus* sandflies	…
Togaviridae			
Chikungunya virus	Africa, Asia, North America, South and Central America	*Aedes* spp. mosquitoes	…
Eastern equine encephalitis virus	Eastern half of North and South America, from Canada to Argentina	Various mosquito species	…
Western equine encephalitis virus	Western half of North and South America from Canada to Argentina	Various mosquito species	…
Venezuelan equine encephalitis virus	North and South America	Various mosquito species	…
Others			
Rabies virus	Worldwide except for Western Europe, Japan and other islands	Bites from infected mammals (mostly dogs, bats)	Rabies vaccine, rabies immunoglobin
Australian bat lyssavirus	Australia	Bites from infected bats	…
European bat lyssavirus	Europe	Bites from infected bats	…
Nipah virus	Malaysia, Bangladesh, India, Australia	Probably airborne, or contact with animal feces, eg, bats.	…
Bacteria			
Orientia tsutsugamushi (Scrub typhus)	Rural areas of Southeast Asia, Indonesia, China, Japan, India and northern Australia	Laval mites (chiggers)	Doxycycline

Abbreviations: IV, intravenous; MMR, measles, mumps, rubella; SARS-CoV-2, severe acute respiratory disease coronavirus 2; VZV, varicella zoster virus.

cause. The WHO List of Essential Diagnostics, which helps countries prioritise important tests for their public health systems, recommends microscopy and culture of CSF for bacteriology, mycology, and parasitology [10]. More specifically, the tests that pertain to neurology include CSF cryptococcal antigen (cryptococcal meningitis), CSF nucleic acid amplification test (central nervous system tuberculosis), CSF bacterial culture, CSF Venereal Disease Research Laboratory test (neurosyphilis), CSF cell cytology, and CSF profile (ie, red and white blood cells, glucose, protein) [10]. However, CSF polymerase chain reaction (PCR) for viruses, which is the gold standard for the etiological diagnosis of most forms of viral encephalitis, is not included in the WHO list. We examined global access to CSF diagnostics and autoantibody testing, with a particular focus on herpes simplex virus (HSV) and autoantibody encephalitis as prompt diagnosis of these significantly improves outcomes.

CSF Diagnostics

Capacity for CSF testing was available in most (97%) countries included in a survey of 28 low- and middle-income countries (LMICs) and 9 high-income countries (HICs) in 2014; however, the exact tests varied [11]. All were able to test for white cells, protein, and glucose, whereas 6% could not obtain staining for bacteria and 7% were unable to send tests for *Mycobacterium tuberculosis*.

The availability of CSF viral PCR is variable. Across Europe, North America, and other HICs, CSF PCR for HSV and varicella zoster virus (VZV) is widely used as the first-line aetiological test for suspected encephalitis [12–14]. Despite availability, CSF PCR is not always used optimally. A repeat CSF PCR was only carried out in 14% of US patients with suspected HSV encephalitis and an initial negative test [15]. Availability varies in Asia where CSF HSV PCR is reported from large tertiary referral centers in Sri Lanka, Vietnam, Taiwan, and Thailand but is often not available in smaller hospitals [16–19]. In other Asian countries it may only be accessible through private laboratories for those who can afford it. Data are sparse for Africa and Latin America, with CSF HSV PCR likely limited outside of research and some large or private settings. CSF HSV PCR is not routinely available at most hospitals in Zambia, Mozambique, and Nigeria and is only available for research purposes in Malawi. It was not available at all in Sudan, Democratic Republic of Congo, Ghana, Ethiopia, and Botswana [11, 20, 21]. In Latin America, CSF PCR is available in Brazil but with in-country variation and CSF samples from regional Peruvian hospitals were sent to the capital Lima for CSF HSV PCR testing [22]. Although there is no specific treatment for dengue encephalitis, PCR testing for dengue is available in many Asian and Latin American countries. A manual to improve sentinel surveillance of neuroinvasive diseases caused by arboviruses was recently launched in Brazil, resulting in 11 state and 5 reference laboratories being qualified for CSF PCR testing for dengue, Zika and chikungunya viruses [23].

Access to PCR, however, remains largely insufficient in most LMICs and is often limited to human immunodeficiency virus (HIV) and tuberculosis [24]. Contributing factors include lack of basic microbiology laboratories, skilled staff, inability to promptly report results, and absence of accreditation and quality assurance, which can reduce the engagement of clinicians in sending samples [25]. CSF analysis relies on a lumbar puncture, which is not always performed due to lack of training, equipment, and laboratory capacity [26]. Emerging point-of-care diagnostics, such as multiplex CSF PCR panels, offer an efficient and promising means to rapidly and accurately diagnose encephalitis globally in adults and children. A recent meta-analysis showed acceptable-to-high sensitivities and high specificities for identifying bacterial and some viral causes, including HSV-2 and enteroviruses, of central nervous system infections [27]. However, sensitivities for HSV-1 (75.5%–78.2%) were suboptimal.

Antibody Testing

Testing for anti-neuronal autoantibodies is widely available in Europe, North America, and Australia. However, variation in testing methods provide different levels of sensitivity and specificity [28–30]. Recent studies have reported autoantibody testing availability in larger tertiary referral centres in Sri Lanka, Thailand, and Vietnam; however, there is a lack of data from Africa and South America where availability of these tests are likely lacking despite the occurrence of cases [31–33]. A worldwide survey reported that neurologists treating >5 cases of autoimmune encephalitis per year were more likely to test antibodies in both serum and CSF, pursue empiric immunotherapy, and continue immunotherapy despite no response and negative antibodies at two weeks [34]. In areas where antibody tests are unavailable, treatment initiation relies on clinical judgement, often requiring neurological input which is often most lacking in these same areas [35]. Flavivirus encephalitis is often diagnosed through detection of antibodies in CSF and/or serum. Testing for Japanese encephalitis virus (JEV) and dengue antibodies is available across much of Asia through the WHO diagnostics laboratory network.

Key Priorities

In low-resource settings, existing healthcare infrastructure should be strengthened, laboratory training programs implemented, affordable rapid diagnostic tests developed, and partnerships between public and private organizations encouraged (Table 2).

SURVEILLANCE

Surveillance is important for understanding the epidemiology and global burden of encephalitis. It enables rapid response

Table 2. Key Priorities in the Diagnosis, Treatment, Prevention, and Surveillance of Encephalitis

	Current Situation	Key Priorities
Global availability of diagnostic testing for encephalitis	Some CSF testing is available for most countries, but varies significantly in the exact tests available.	International recognition of importance of clinical laboratory service in health system Investment to sustain new diagnostic capacity Education, supervision, technical improvement, and quality assurance for lab services Incorporate routine CSF testing in WHO Essential Diagnostic List Universal diagnostic algorithms Coordinated effort to train providers to perform lumbar punctures Culturally appropriate information campaigns to educate the public on the safety of lumbar punctures
	CSF HSV PCR is widely available in Europe, North America, and Australia. Its availability varies in Asia and is very limited in African and South American countries.	Systematic survey to collect information on availability of CSF HSV PCR testing globally Strengthen existing healthcare infrastructure, implement laboratory training programs, develop affordable, rapid diagnostic tests, and encourage partnerships between public and private organisations Further education of clinicians on diagnosis of suspected encephalitis Incorporate CSF PCR in the WHO Essential Diagnostic List
	No readily available data on autoantibody testing accessibility globally, however likely to be limited in Asian, African, and South American countries	Systematic survey to collect information on the availability of autoantibody testing globally
Surveillance	Surveillance systems for all-cause encephalitis exist in HICs including notification systems, hospitalisation data, and laboratory reports; however, cases are still under-reported.	Strengthen these surveillance systems by validation of codes in hospitalisation data, encouraging notification of cases, strengthening laboratory diagnosis, and standardisation of case definitions Implementation of surveillance systems for all-cause encephalitis in lower income countries
	Surveillance systems exist in LMICs, but these are more focussed on vaccine-preventable causes of encephalitis such as JE. JE surveillance has improved in countries at risk of JE transmission, but challenges remain.	Implement JE surveillance systems in all areas where JE is a public health priority. This could involve integration with other infrastructure, ie, polio-measles surveillance. Ensure complete case reporting, correct classification, presence of immunisation program monitoring data, and adequate monitoring of JE vaccination coverage following vaccine introduction
	Most European countries conduct TBE surveillance but differences in case definitions and laboratory diagnosis make international comparisons difficult.	Improve surveillance throughout Europe to obtain homogenous, comparable data Encourage uniform use of diagnostic methods for detection of TBE pathogens Recommend use of standard EU case definition for TBE
	Rabies surveillance is particularly lacking in Asia and Africa.	Implement and strengthen rabies surveillance across all risk areas to meet WHO target of rabies elimination by 2030
Global availability and use of IV acyclovir for treatment of HSV encephalitis	IV acyclovir is widely available in most countries in Europe, Australia, and USA; however, its administration can be sub-optimal.	Educate and promote adherence to the guidelines, for early initiation and adequate duration of IV acyclovir in patients with suspected encephalitis
	Variable IV acyclovir availability across Asia, lack of data for African countries	Systematic survey to assess global availability of IV acyclovir Reduce IV acyclovir costs to facilitate availability in low-resource settings Incorporate routine acyclovir in the WHO Essential Medicines List Improve availability of essential medicines Algorithms for empiric therapy
Global vaccination programmes for preventable causes of encephalitis	Approximately 63% of countries with JEV transmission risk have a JE immunisation programme.	Improve access to health facilities, vaccine availability, financial resources, and education to enable access to a JE vaccine in all countries with JEV transmission risk
	Many European countries have some form of TBE vaccine policy in place; however, low rates of TBE vaccine uptake are seen in some highly endemic areas.	Focus on raising awareness, improving surveillance and diagnostics, and promote better vaccine uptake in endemic areas and at-risk populations
	TBE immunisation policy in China only for people working or living in high-risk regions	Consider adjusting immunisation policy as more TBE observed in non-forest working occupations and increase awareness and uptake of vaccine
	No vaccine licensed in Japan, despite cases reported since 1993, with endemic foci	Ensure a vaccine is licensed in low endemic countries, ie, Japan —as TBE distribution likely to be altered by climate change, causing increasing TBE burden

Table 2. Continued

	Current Situation	Key Priorities
	Average global coverage of a second dose of measles-containing vaccine is estimated at 71% in 2019. Many countries in sub-Saharan Africa have yet to introduce a second dose.	Increase the number of countries offering a second dose of measles-containing vaccine as part of routine immunisation Increase coverage of measles-containing vaccine to 95% in each country Focus efforts on education and overcoming vaccine hesitancy
	Variability in availability and cost of rabies vaccine and rabies immunoglobulin in Asian and African countries	Increase provision of readily available vaccine and supply of post-exposure prophylaxis across all countries where rabies is endemic Enhancement of governmental programs to increase rabies vaccination programs for dogs Educate people about dog bite prevention and importance of seeking health care if bitten
	Currently, only 36 countries worldwide have recommended a VZV vaccine Many countries in Africa, Asia and Eastern Europe have yet to introduce or recommend a VZV vaccine	Increase the number of countries which offers or recommend a varicella vaccine Increase the coverage of two doses of a varicella vaccine to 80% in each country

Abbreviations: CSF, cerebrospinal fluid; EU, European Union; HIC, high-income countries; HSV, Herpes simplex virus; IV, intravenous; JE, Japanese encephalitis; JEV, Japanese encephalitis virus; LMIC, low- and middle-income countries; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TBE, tick-borne encephalitis; VZV, Varicella zoster virus; WHO, World Health Organization.

to encephalitis outbreaks, monitoring epidemiological trends, guiding public health policy, and monitoring the impact of prevention and control measure. The WHO suggests that monitoring vaccine impact in settings where JE vaccine has been introduced is a research priority [36]. The WHO Recommended Surveillance Standards also includes measles, rabies, and other causes of encephalitis with a vaccine available. In some HICs, encephalitis is a notifiable disease.

All-cause Syndromic Surveillance

Many HICs have surveillance systems including national notification systems and reporting of hospitalization and laboratory data; however, under-reporting is common [37]. Routine hospitalisation data are limited by unknown accuracy of coding, lack of specific diagnostic criteria, and lack of timeliness. The lack of surveillance in many countries makes it difficult to truly understand encephalitis incidence.

Japanese Encephalitis

Surveillance strategies in LMICs are often targeted at vaccine-preventable causes. JE surveillance programs have expanded from 75% of countries with JE transmission risk conducting surveillance in 2012 to 92% (22/24) in 2016 [38]. Over half (14/22, 58%) were national surveillance programs and 22 (92%) countries used JE case definitions; however, the exact definition used varied between countries. All countries that carried out JE surveillance used JE-specific diagnostic testing in serum and/or CSF to confirm some/most suspected cases. This represents substantial progress, but challenges remain including incomplete case reporting, case misclassification, and lack of monitoring data for immunisation programs [38]. Acute encephalitis syndrome surveillance could be incorporated into other well-established surveillance systems, which gives technical and logistical benefits of existing infrastructure. Cambodia successfully integrated JE surveillance into an established, working system for bacterial meningitis [39].

Tick-borne Encephalitis

Many European countries have surveillance systems for the systematic collection of tick-borne encephalitis (TBE) information; however, some important differences (case definition, laboratory diagnosis, clinical syndromes) exist that complicate interpretation and international comparisons. Of the 30 countries participating in a European survey between 2000 and 2010, 20 (67%) had developed a TBE surveillance system [40]. National surveillance was conducted in 18 (90%) countries, reporting was mandatory in 16 (80%) countries, and surveillance data were generally derived from reporting by physicians and laboratories. A TBE surveillance case definition was used in 10 (50%) countries. However, the requirement, since 2012, for all EU Member States, Iceland, and Norway to annually report their TBE data to the European Surveillance System database using the EU case definition represents a step forward [41].

Rabies

A strong surveillance system is required to achieve the WHO target of elimination of dog-mediated rabies by 2030 [42]. A global survey of human rabies surveillance between 2011 and 2013 found that rabies was not notifiable or surveillance was ineffective in 27 of 91 (30%) countries, including 55% (n = 21/38) of high-risk countries, predominantly in Africa and Asia [43]. Respondents cited numerous barriers to human rabies becoming a notifiable disease, including lack of specific anti-rabies legislation, lack of rabies policy, poor awareness, lack of funds and accountability, and priority given to other diseases.

Reasons for rabies surveillance being ineffective included issues relating to poor recognition of rabies and death occurring away from health centers. Furthermore, inadequate financial investment in surveillance systems and lack of enforcement of guidance further contributes [44]. A 2020 scoping review in Africa reported surveillance for rabies in seven of 18 African countries (39%), including Cameroon, Ivory Coast, Malawi, Senegal, Tanzania, South Africa, and Zimbabwe [45].

Key Priorities

Surveillance systems for all-cause encephalitis should be strengthened by validation of codes in hospitalization data, encouraging notification, strengthening laboratory diagnosis, standardization of case definitions, and vector surveillance. Surveillance for vector-borne and zoonotic diseases should be multi-pronged including environmental, entomological, and veterinary surveillance.

AVAILABILITY AND USE OF SPECIFIC TREATMENT

Specific treatments are available for some important causes of encephalitis, including doxycycline for scrub typhus, immunotherapy for autoimmune encephalitis, and acyclovir for HSV and VZV. We focus here on the global availability of intravenous (IV) acyclovir. Empirical treatment with IV acyclovir is recommended for patients with suspected encephalitis in most HICs, until the diagnosis is either confirmed or excluded [46]. In settings where there are outbreaks from other causes, especially arboviruses, acyclovir is often reserved for those in whom there is a strong clinical suspicion of HSV. Prompt treatment with IV acyclovir has been shown to reduce the case fatality of HSV encephalitis from 70% to 10%–20% [47]. Oral acyclovir is not suitable as it does not result in adequate CSF concentration, though oral valaciclovir may be an alternative which requires further investigation [48]. The WHO List of Essential Medicines includes acyclovir for both adults and children but does not specifically refer to encephalitis or specify the route of administration [49].

IV acyclovir is widely available in HICs across Europe, North America, and Australia; however, there is some evidence of suboptimal administration that is not in accordance with guidelines. Studies in the United Kingdom showed that only 53% of patients with suspected encephalitis received IV acyclovir, less than one-third were prescribed within 6 hours of admission, and the duration of treatment for some was too short [50–52]. Acyclovir availability appears variable in Asia, with Japan, India, Pakistan, and Sri Lanka reporting availability but most likely in larger tertiary referral centers and with in-country variation [16, 53, 54]. A high prevalence of HSV encephalitis was identified (n = 45/313, 14%) in a Peruvian study resulting in IV acyclovir being made available on their list of essential medications. Data on acyclovir availability from Africa are sparse, but the lack of availability of other more "basic" medications indicates this is likely also the case for acyclovir. IV acyclovir was not available in a study in Senegal: patients with HSE were given oral acyclovir or valaciclovir instead with resulting high mortality rates [55]. LMICs often experience poor availability of essential medicines in health facilities, substandard-quality treatments, frequent stock-outs, and suboptimal prescription and use of medicines, poor transportation systems, lack of drug storage facilities, and weak manufacturing capacity [56].

Key Priorities

In low-resource settings, better data are needed on the availability of IV acyclovir, and greater access to the drug is needed to improve outcomes from HSV and VZV encephalitis. In HICs where acyclovir is available, there should be greater adherence to guidelines that recommend prompt initiation of treatment in suspected cases (Table 2).

PREVENTION THROUGH VACCINATION

Vaccines have led to major reductions in disease burden for some causes of encephalitis, including JEV, tick-borne encephalitis virus (TBEV), rabies, measles, and VZV.

Japanese Encephalitis

The WHO recommends JE vaccine be included in the national immunisation schedule for countries where JE is recognized as a public health priority [38]. Since 2006, newer vaccines have been recommended, rather than the inactivated mouse brain-derived vaccines, which are reactogenic [36]. In 2022, 15 (62%) of 24 countries with JEV transmission risk had a JE immunization program, an improvement from 42% in 2012 [38, 57]. The introduction of the JE vaccine has resulted in a substantial reduction in disease burden in at-risk areas; however, there is further room for improvement. Some countries with risk have decided against a program as only rare, sporadic human cases occur (eg, Singapore) [38]. Under-functioning health facilities and lack of vaccine availability are the reasons for lack of a vaccine program in other countries (eg, Papua New Guinea) [58]. Some programs (eg Vietnam) continue to use mouse-brain derived vaccines despite the change in WHO guidance [38].

Tick-borne Encephalitis

Five types of TBE vaccine are currently licensed in Europe and Russia [59]. These vaccines are highly effective (95%–99%), and the WHO recommends vaccination of the whole population in highly endemic areas (≥5 cases/100 000/year) and vaccination of individuals at risk in areas with moderate/low TBE incidence (<5 cases/100 000/year) [60]. Within Europe, different immunization strategies exist depending on local epidemiology and regional and national risk assessments. A study of vaccination

programs for adults in Europe showed TBE vaccine is recommended for all adults in Austria, Czech Republic, and Latvia, and for high-risk groups in parts of Finland, Russia, Serbia, Slovenia, and Bosnia Herzegovina [61]. There is, however, some evidence that suboptimal vaccination rates have contributed to the recent rise in European TBE cases [62]. Historically, TBE in China was considered an occupational disease and the TBE immunisation policy recommends vaccination for people working or living in high-risk regions, especially forest workers or those who enter the forest areas for occupational reasons, including military personnel [63]. However, since the 1990s, more cases have been observed in people with other occupations suggesting an adjustment to the immunisation policy might need consideration. Despite policies being in place, it is thought that vaccine uptake is limited [64]. Japan recorded its first case of TBE in 1993; since then, only 3 further cases have been reported. Despite few cases, endemic foci of TBE virus have been identified in parts of Japan, especially Hokkaido. Currently no TBE vaccine is licensed in Japan [63].

Rabies

Across Asia and Africa, where most rabies cases and deaths occur, there is considerable variation in the availability and cost of pre- and post-exposure vaccination, and access to rabies immunoglobin (RIG) [42]. An assessment of rabies post-exposure prophylaxis procurement, distribution, monitoring, and reporting in 23 LMICs in Asia and Africa reported rabies vaccine was only widely accessible in 1 African country and limited in 5 [65]. RIG was less accessible than vaccine: 65% (15/23) of countries had limited access, of which 11 were in Africa. Approximately half of countries (12/23) administered a rabies vaccine intramuscularly despite the WHO recommendation for an intradermal route, which uses 60%–80% less vaccine volume; 10 of these were in Africa [66]. Lack of awareness following potential exposure and long distances to access healthcare were highlighted as challenges for prompt provision of post-exposure prophylaxis [42]. It should be noted that mass vaccination of dogs is a key component of rabies elimination programs [45].

Measles

Measles vaccine is safe and highly effective. Yet, 90 000 deaths due to measles occur every year, and 1–3 in 1000 children with measles will develop concurrent encephalitis [67]. One in 25 000 children develop subacute sclerosing panencephalitis (SSPE), a fatal neurodegenerative condition, years after the acute infection. The incidence of SSPE is significantly higher (1 in 5000) in children who acquire measles before the age of 1 [67]. Thus, the WHO recommends 95% vaccination coverage with 2 doses of measles-containing vaccine (MCV2) in every country [68]. The WHO estimated that 183 member states have included a second dose as part of routine immunisation by the end of 2021 resulting in an average global coverage of 71% [69]. In 2017, coverage was lowest in Angola (30%), Namibia (32%), Kenya (35%), Niger (38%), and Afghanistan (39%). Furthermore, many additional countries in sub-Saharan Africa have yet to introduce MCV2 as part of routine immunisation [70]. Between 1990 and 2019, only 36 (n = 204; 18%) countries reported >95% coverage of MCV2 [71]. Parental attitudes toward immunizations are an important contributor to low immunization rates in Western countries, in part due to the now discredited supposed link to autism [70].

Varicella Zoster

It is estimated that 2–4 per 1 000 000 individuals who contract VZV develop concurrent encephalitis; 9%–20% of those individuals die and many are left with neurological sequelae [72, 73]. VZV vaccines are 84%–88% effective after 2 doses [74]. In some countries VZV vaccination is recommended in certain groups, such as older adults. However, since 2014, the WHO has recommended all countries aim for ≥80% vaccine coverage with 2 doses [75]. Only 36 countries have followed this recommendation, mostly HICs [76]. Potential barriers to wider implementation of the program include perceived low risk of complications, hypothetical risks of a reduction in natural immunity in older persons, and cost-effectiveness considerations [77].

Vaccines are the most effective intervention for the aforementioned causes of encephalitis. However, other measures exist that could help reduce disease burden. Widespread vaccination of dogs has successfully eliminated canine rabies in countries including Malaysia, Japan, Taiwan, and Singapore, and across Western Europe [44]. Use of protective clothing and tick repellents are recommended to avoid tick bites and reduce risks of TBE [78]. Effective vector control will be increasingly important due to the impact of climate change on vector-borne disease transmission [79].

Key Priorities

Efforts should focus on improving access to vaccine availability and campaigns to overcome misapprehensions driving vaccine hesitancy (Table 2).

CONCLUSION

Encephalitis affects people across the lifespan, has high rates of mortality and morbidity, and results in significant neurological sequelae with long-term consequences to QoL and wider society. The true incidence is unknown due to inaccurate reporting systems. The disease burden is unequally distributed being highest in LMICs where resources are limited. Here countries often lack diagnostic testing, have poor access to essential treatments and neurological services, and limited surveillance and vaccination programmes. Many types of encephalitis are

vaccine preventable, whereas others are treatable with early diagnosis and appropriate management. Addressing the key priorities including better diagnostic capacity and surveillance, equity of vaccine access and uptake, appropriate management and longer-term care will help improving disease control and reduce the disease burden of this often-devastating condition.

Notes

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