Encephalitis International
The brain inflammation non-profit

Encephalitis:

an in-depth review and gap analysis of key variables affecting global disease burden

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Abbreviations

ABI	Acquired brain injury
ABLV	Australian bat lyssavirus
ADEM	Acute disseminated encephalomyelitis
AES	Acute encephalitis syndrome
ALS	Amyotrophic lateral sclerosis
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMR	Region of the Americas
AR	African region
CASPR2	Contactin-associated protein-2
CFR	Case fatality rate
CMV	Cytomegalovirus
CNS	Central nervous system
CP	Cerebral palsy
CSF	Cerebrospinal fluid
D2R	Dopamine-2 receptor
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic acid
DPPX	Dipeptidyl-peptidase-like protein-6
EAN	European Academy of Neurology
EBV	Epstein Barr virus
EBVL	European bat lyssavirus
ECDC	European Centre for Disease Prevention and Control
EEEV	Eastern equine encephalitis virus
EFNS	European Federation of Neurological Societies
EFTA	European Free Trade Association
ELISA	Enzyme-linked immunosorbent assay
EMR	Eastern Mediterranean Region
EU	European Union
EUR	European Region
EV	Enterovirus
GABAaR	γ-aminobutyric acid-A receptor
GABAbR	γ-aminobutyric acid-B receptor
GAVI	Global Alliance for Vaccines and Immunisation
GBD	Global Burden of Disease
GlyR	Glycine receptor
GOS	Glasgow Outcome Scale
GP	General practitioner
HHV-6	Human herpesvirus-6
HIC	High-income country
HSE	Herpes simplex encephalitis
HSV	Herpes simplex virus
ICD	International Classification of Disease
ICU	Intensive care unit
ID	Intradermal
IHME	Institute for Health Metrics and Evaluation
IM	Intramuscular
IQR	Interquartile range
IV	Intravenous
JE	Japanese encephalitis
JEV	Japanese encephalitis virus
LCMV	Lymphocytic choriomeningitis virus
LGI-1	Leucine-rich, glioma-inactivated 1

LIC	Low-income country
LMIC	Low- and middle-income country
mGluR5	Metabotropic glutamate receptor 5
MMSE	Mini mental state examination
MND	Motor neuron disease
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MVEV	Murray Valley encephalitis virus
NMDAR	N-methyl-D-aspartate receptor
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PICU	Paediatric intensive care unit
RDT	Rapid diagnostic test
RIG	Rabies immunoglobulin
RNA	Ribonucleic acid
RR	Rate ratio
RT-PCR	Reverse transcriptase- polymerase chain reaction
SEAR	South-East Asian Region
SLEV	St. Louis encephalitis virus
SSPE	Subacute sclerosing panencephalitis
TB	Tuberculosis
TBE	Tick-borne encephalitis
TBEV	Tick-borne encephalitis virus
UMIC	Upper-middle-income country
UN	United Nations
US	United States
VEEV	Venezuelan equine encephalitis virus
VENICE	Vaccine European New Integration Collaboration Effort
VZV	Varicella zoster virus
WEEV	Western equine encephalitis virus
WFN	World Federation of Neurology
WHO	World Health Organization
WNV	West Nile virus
WPR	Western Pacific Region

1 Executive Summary

Encephalitis is a thief. In the same way that we have watched other neurological conditions and diseases rob people of their lives and loved ones, encephalitis has quietly been at work for hundreds, if not thousands, of years, robbing families of their loved ones, and even in those families where the person survives, it often robs them of the person they once knew. Encephalitis steals their capacity to remember as well as their personalities and the types of abilities we all generally take for granted: concentration, attention, thinking, judgement, and inhibition. For many there are additional outcomes such as epilepsy and levels of fatigue so great that returning to work or education are mere pipe dreams. This is of course where the person survives, but many do not.

For many years understanding of the condition has been a poor relation to that of many other neurological conditions or diseases. Encephalitis was often relegated to the silo of 'rare disease'. Yet despite many suggestions that incidence is underestimated, encephalitis has a higher incidence than motor neuron disease/ALS, bacterial meningitis, and multiple sclerosis in many countries. With new and emerging infections, our increasing understanding of the causes of the condition, improvements in treatments, and activities of global change-maker organisations, now is the time to elevate encephalitis onto a platform shared by many other conditions that receive much greater public and policy attention.

The Encephalitis Society is knocking on the door to 30 years old and over that time has developed a rounded expertise on the condition and its impact on patients and families, including those left bereaved, that does not exist anywhere else in the world. Improvements in its governance and infrastructure along with the development of a passionate and dedicated team of paid and voluntary team members means that the organisation found itself well placed to secure funding for, and commission, this report. It has been a collaborative effort including the charity’s Chief Executive and its Scientific Advisory Panel, supported by its Board of Trustees.

In this report we not only identify the issues, but we also propose a range of solutions to the impact of encephalitis around the world, ranging from epidemiology, incidence, and economic impacts through to prevention, diagnosis and treatment, and the needs of patients and families. The Encephalitis Society has the infrastructure to align and lead a collaborative initiative based on this report that will result in both quick and longer-term wins. We will bring together leading global health organisations, public health bodies, and policy makers who are

best placed to steer the findings of this report and help us build a global response that will result in preventing and reducing the impact of encephalitis around the world. Now is the time to come together and advance the fight against encephalitis and its many causes resulting in greater access and equity across healthcare in relation to encephalitis. Only then will our global communities see a reduction in its devastation and thrive in ways we can currently only dream of. This report is the first step in a global commitment to reducing the incidence of, and morbidity and mortality from encephalitis.

2 Overview

2.1 Purpose

This report is intended to inform the creation of a robust and ambitious strategic plan for The Encephalitis Society's international development over the next 10 years and to provide a sound basis to inform its key priorities and collaborations with other global leaders in the field of infectious disease. The Encephalitis Society (www.encephalitis.info) is an award-winning UK-based charity/non-profit with a global focus and has been in operation since 1994. It operates in three primary areas: providing support and information to patients and families affected by the condition; raising global awareness of the condition (its primary vehicle for this being World Encephalitis Day); and funding, promoting, and collaborating on research with academic, scientific, and medical partners around the world.

2.2 Scope

Encephalitis is inflammation and swelling of the brain, most often caused by an infection or by the body's immune defences. Encephalitis is a growing global threat due to a variety of factors such as climate change, vaccine hesitancy, co-circulation of viruses, continued unexplained cases, increasing identification of autoimmune causes, recurrence and spread of epidemics, as well as the high mortality and morbidity associated with the condition, and its economic impact for those affected and the wider community. This report provides an in-depth analysis of 12 variables where change could make an impact on the global encephalitis burden. The variables were selected by The Encephalitis Society and its expert scientific and medical advisors. These variables are:

1) Cause;
2) Incidence;
3) Morbidity and mortality;
4) Economic impact;
5) Prevention including vaccine programs, vector control, and epidemic control;
6) Diagnosis and treatment;
7) In-country neurologists and access to neurology training;
8) Surveillance;
9) New and emerging infections;
10) Advocacy;
11) Support and after-care for survivors and families; and
12) Availability of and access to information.

2.3 Methodology

For the scientific chapters (Chapters three to nine) a literature search was carried out via Pubmed for academic papers reporting on each above-mentioned variable. A comprehensive search strategy was devised for each variable separately based on search terms, keywords, and phrases (see details of specific searches in Appendix 16.1). Bibliographies of acquired articles were searched for further relevant papers. In addition, a free-text internet search for grey literature using the Google search engine was conducted. It is worth noting that as data acquisition relied largely on published data and internet searches, relevant data unavailable via these means may not be included in this report.

A traditional rather than systematic review was carried out for each pre-identified variable as a systematic review generally addresses a specific question whereas the remit of this work was very broad, hypotheses were not stated, and summary measures were not reported. In addition, systematic reviews require pre-defined article inclusion and exclusion criteria, search of multiple databases and websites including unpublished data, assessment of article quality, and two reviewers judge which articles should be included/excluded (at least for a proportion of articles retrieved). This was not considered feasible given the broad range and reach of the topics addressed in this report.

Chapters 10, 11, and 12 were composed from the observations, understanding, and lived experience of patients supported by the Encephalitis Society. This report is updated annually since its first publication in 2021.

3 Epidemiology of encephalitis

3.1 Causes

Encephalitis or inflammation of the brain is a syndrome of multiple pathogeneses and aetiologies. Encephalitis can result from direct infection of the central nervous system (CNS) or it can be immune-mediated. More than 100 different organisms have been recognised as causative agents, some of which have a worldwide distribution and others which are geographically restricted (1).

3.1.1 Causes with a worldwide distribution

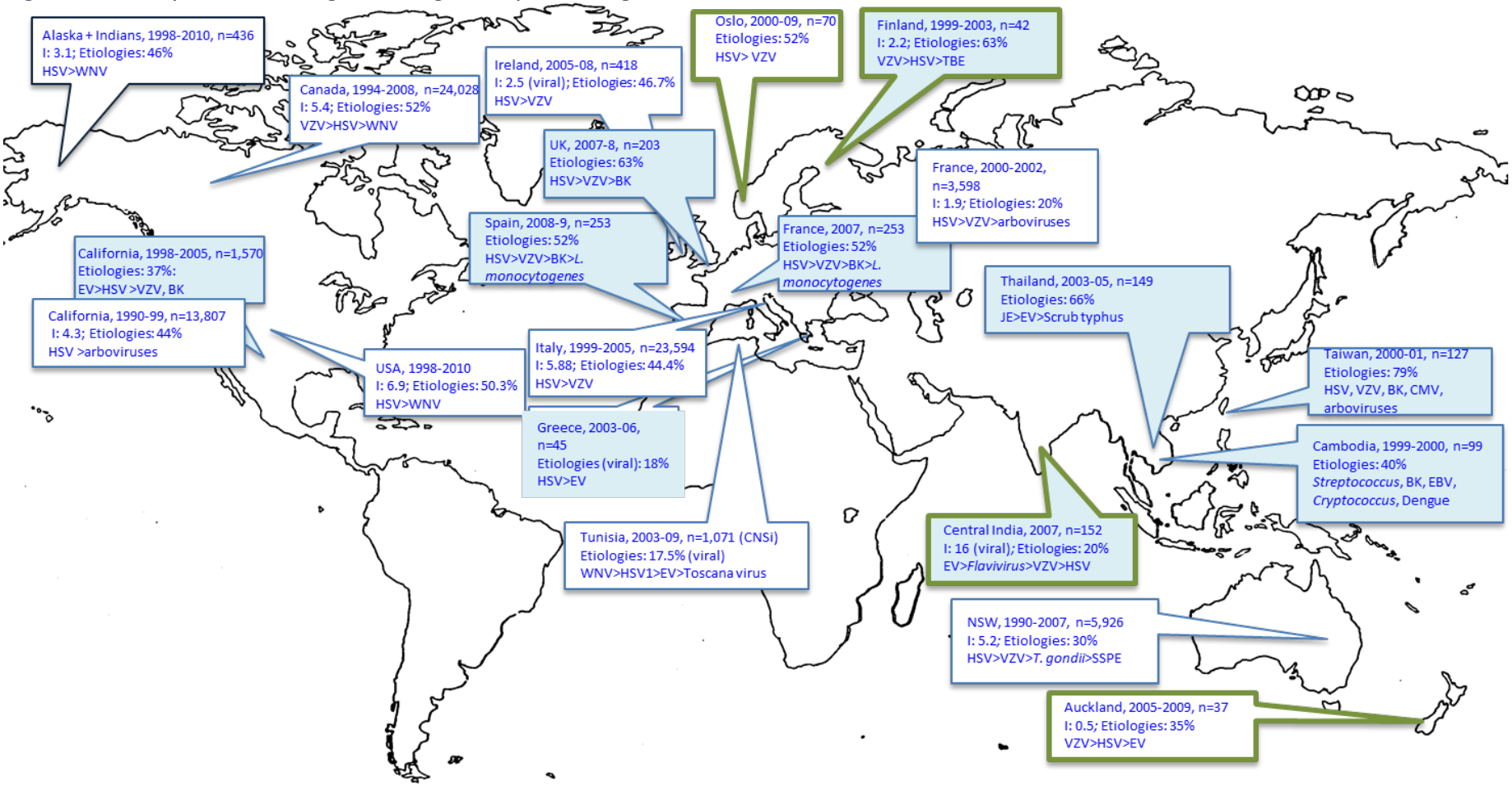
Herpes simplex encephalitis (HSE) occurs worldwide; approximately 50% to 90% of adult populations in all parts of the world are seropositive for herpes simplex virus (HSV) infections and encephalitis occurs in a minority of those infected (2). HSV is the most common reported infectious cause of encephalitis in industrialized countries (3). Boucher et al. reviewed the literature for articles on infectious causes of encephalitis published between 2000 and 2015 (4). Twenty-five studies were retrieved, including prospective and retrospective studies from tropical and temperate countries. In 65% of studies, including those from North America, Europe, Australia/New Zealand, and one from Asia, HSV was the most commonly identified aetiological agent (Figure 1). There were limited studies from Africa and South and Central America included in the review by Boucher et al.; however, studies published subsequently identified HSV as a common cause of encephalitis in Peru and Colombia (5,6). Studies from Africa are lacking and diagnostic capacity limited (see Section 6.1.3.2); however, a recent study from Senegal identified HSV as an important cause of encephalitis (7).

Varicella zoster virus (VZV) and enteroviruses (EV) were also reported by Boucher et al. as frequent causes of encephalitis in North America, Europe, Asia, and Australia/New Zealand (Figure 1). VZV is the second most common cause of encephalitis in industrialized countries, after HSV (8–11). EV71, which causes severe encephalitis in 3% of neurological presentations, has been responsible for epidemics in Southeast Asia and the Pacific since 1997 and there have been reports of a few epidemics outside Asia, notably in Australia/Oceania, United States of America (USA), Europe, Japan, and Brazil (4). Other causes of infectious encephalitis with a worldwide distribution include other herpesviruses (Epstein Barr virus [EBV], cytomegalovirus [CMV], human herpesvirus-6 [HHV-6]), mumps, measles, rubella, JC virus, human immunodeficiency virus (HIV), and lymphocytic choriomeningitis virus (LCMV; Table 1) (12).

Although viruses are responsible for the majority of encephalitis cases due to infection, bacteria, parasites, and fungi can also cause encephalitis. As with viruses, these other causes of encephalitis can be distributed worldwide or restricted geographically. *Mycobacterium tuberculosis* and *Mycoplasma pneumoniae* are two important bacterial causes of encephalitis with a worldwide distribution. A prospective French study identified *M.tuberculosis* and *Listeria monocytogenes* as the most frequently identified bacterial causes of encephalitis in 2007 (11). *M.tuberculosis* was also identified as an important cause in a UK study (13). *M.pneumoniae* is frequently associated with encephalitis, and infection with *M.pneumoniae* is established in 5-10% of paediatric encephalitis patients (14–16). However, *M.pneumoniae* is rarely found in the cerebrospinal fluid (CSF) suggesting an immunoinflammatory pathogenic mechanism rather than direct CNS infection (4).

About half of all encephalitides with known cause are thought to be immune-mediated (17). Autoimmune encephalitis may be predominantly demyelinating brain disease (e.g., acute disseminated encephalomyelitis [ADEM]), in the context of systemic autoimmune disorders (e.g., systemic lupus erythematosus), in the setting of a steroid-responsive condition associated with elevated antithyroid antibodies (e.g., Hashimoto's encephalopathy), or in association with antineuronal antibodies (18). ADEM predominantly affects children and can often be temporally linked to upper respiratory tract symptoms or an acute febrile illness in the days/weeks prior to neurological symptom onset. Granerod et al. identified viruses such as enteroviruses, EBV, HHV-6, and parainfluenza, and bacteria including *M.pneumoniae*, *Bartonella henselae*, and streptococci as the main microbes associated with ADEM worldwide (8). Different pathogenic mechanisms have been suggested for ADEM, and a subset of individuals have evidence of antibody-associated autoimmunity against myelin oligodendrocyte glycoprotein (MOG) (19). More recently, cortical encephalitis has been reported in patients with anti-MOG autoantibodies (20,21). Technological improvements have enabled the discovery over the last 15 years of autoimmune encephalitides associated with antibodies against neuronal surface targets (22) (Table 2; Figure 2). Anti N-methyl-D-aspartate receptor (NMDAR) encephalitis, first identified in 2007, is the most common of these in younger age groups, while leucine-rich, glioma-inactivated 1 (LGI-1)-antibody encephalitis appears most common in those >50 years of age (23). This will however likely change in the future with the discovery of further antibody epitopes and increasing testing specificity. Other causes include contactin-associated protein-2 (CASPR2)-antibody encephalitis, γ-aminobutyric acid-B receptor (GABAbR), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies (24). Immune-mediated causes of encephalitis have a worldwide distribution as their pathogenesis is not dependent on external factors, including vectors and climate. However, one study showed higher incidence (and possibly more severe phenotype) of anti-NMDAR encephalitis in Maori and Pacific Island children compared to children without this ancestry, which may suggest a genetic predisposition in some populations perhaps affecting distribution (25). It is highly likely that further autoimmune causes account for some of the 30-40% of cases that lack an aetiological diagnosis (18).

Figure 1 – Encephalitis aetiologies from global epidemiological studies



Adapted from Boucher et al. (4) *Blue background: prospective studies; white background: retrospective studies. Green-boxed text: studies including adults; black-boxed text: studies including children and adults.*
BK = BK virus; CMV = Cytomegalovirus; EBV = Epstein Barr virus; EV = Enterovirus; HSV = Herpes simplex virus; I = Incidence per 100,000 population; JE = Japanese encephalitis; SSPE = Subacute sclerosing panencephalitis; TBE = Tick-borne encephalitis; VZV = Varicella zoster virus; WNV = West Nile virus

Table 1 – Global distribution of viral causes of encephalitis

Virus	Distribution	Transmission
Herpes viridae		
HSV	Worldwide	Human to human
VZV	Worldwide	Human to human
EBV	Worldwide	Human to human
CMV	Worldwide	Human to human
HHV-6	Worldwide	Human to human
Cercopithecine herpes virus 1	Old world except for Madagascar	Monkey bite or scratch or spitting
Arboviruses		
WNV	North and South America, Middle East, Africa, Europe, Australia/Oceania, and Southern Asia (Kunjin)	Vector (various mosquito species [mainly Culex spp.])
JEV	Asia and South East Asia, Australia/Oceania	Vector (*Culex spp*.)
SLEV	North and South America	Vector (*Culex spp.*)
TBEV	Central and Eastern Europe, Russia	Vector (*Ixodes spp*.)
EEEV	Eastern half of North and South America, from Canada to Argentina	Vector (various mosquito species)
WEEV	Western half of North and South America from Canada to Argentina	Vector (*Culex tarsalis*)
VEEV	North and South America	Vector (*Aedes, Psorophora spp.*)
LaCV	North America	Vector (*Aedes spp.*)
TOSV	Mediterranean Basin	Vector (*Phlebotomus perniciosus* and *P.perfiliewi)*
CTFV	North America	Vector (*Dermacentor spp*.)
Others		
Rabies virus	Worldwide except for Western Europe, Japan, other islands	Carnivorous mammals, or bat bite, or scratch, or licking on wounded skin or mucosae, graft transmission possible although rare
Mumps virus	Worldwide	Human to human
Measles virus	Worldwide	Human to human
Rubella virus	Worldwide	Human to human
Henipah viruses	Nipah: Malaysia, Bangladesh, India Hendra: Australia/Oceania	Probably airborne, or contact with animal feces, from fruit bats. Pigs may be possible intermediate hosts.
JC virus	Worldwide	Human to human
HIV	Worldwide	Human to human
Enteroviruses	Worldwide	Human to human
LCMV	Worldwide	Airborne from rodent feces
Influenza	Worldwide	Human to human, airborne

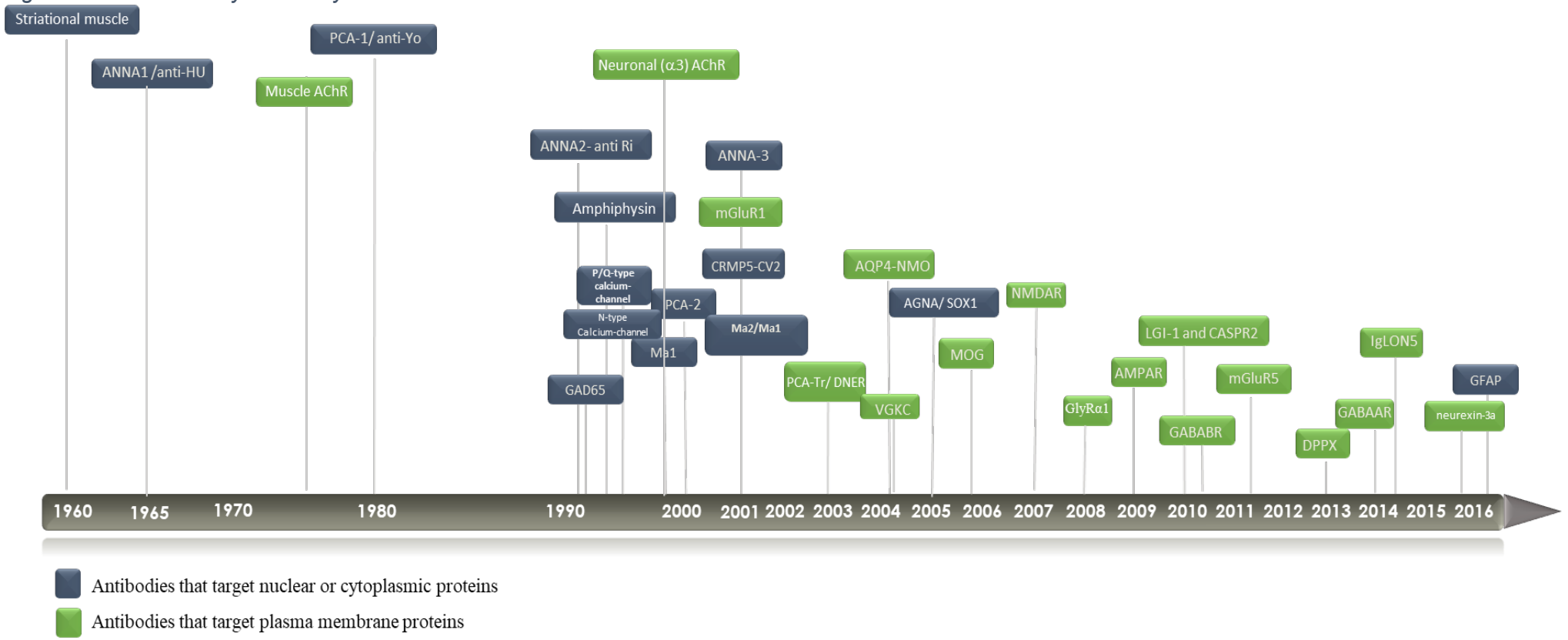
Adapted from Stahl et al. (12); *CMV = Cytomegalovirus; CTFV = Colorado tick fever virus; EBV = Epstein Barr virus; EEEV = Eastern equine encephalitis virus; HHV-6 = Human herpesvirus-6; HIV = Human immunodeficiency virus; HSV = Herpes simplex virus; JEV = Japanese encephalitis virus; LaCV = La Crosse virus; LCMV = Lymphocytic choriomeningitis virus; SLEV = Saint Louis encephalitis virus; TBEV = Tick-borne encephalitis virus; TOSV = Toscana virus; VEEV = Venezuelan equine encephalitis virus; VZV = Varicella zoster virus; WEEV = Western equine encephalitis virus; WNV = West Nile virus*

Table 2 - Autoimmune causes of encephalitis associated with antibodies against neuronal surface targets

Neuronal surface antibody target	Distribution	First reported (reference)
MOG	Worldwide	2006 (19)
NMDAR	Worldwide	2007 (26)
GlyR	Worldwide	2008 (27)
AMPAR	Worldwide	2009 (28)
GABAbR	Worldwide	2010 (29)
LGI1	Worldwide	2010 (30)
CASPR2	Worldwide	2010 (30)
mGluR5	Worldwide	2011 (31)
D2R	Worldwide	2012 (32)
DPPX	Worldwide	2013 (33)
GABAaR	Worldwide	2014 (34)
Neurexin-3α	Worldwide	2016 (35)

Adapted from Zuliani et al. (36)
AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 = Contactin-associated protein-2; DPPX = Dipeptidyl-peptidase-like protein-6; D2R = Dopamine-2 receptor; GABAaR = γ-aminobutyric acid-A receptor; GABAbR = γ-aminobutyric acid-B receptor; GlyR = Glycine receptor; LGI1 = Leucine-rich, glioma-inactivated protein-1; mGluR5 = Metabotropic glutamate receptor 5; MOG = Myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor

Figure 2 – Autoantibody discovery timeline



This figure also includes neural autoantibodies that have not been associated with encephalitis; From Lopez-Chiriboga et al. (37)
ANNA = Anti-neuronal nuclear antibody; AChR = Acetylcholine; PCA = Purkinje cell cytoplasmic antibody, CRMP5 = Collapsin response-mediator protein-5; GAD65 = Glutamic acid decarboxylase; mGluR1 = Metabotropic glutamate receptor type1; DNER = Delta/notch-like epidermal growth factor-related receptor; AQP4 = Aquaporin-4 water channel; AGNA = Anti-glia nuclear antibodies; VGKC = Voltage-gated potassium channel (Kv1)-complex; NMDA = N-methyl-D-aspartate; MOG = Myelin-oligodendrocyte glycoprotein; GlyRα1 = Glycine receptor; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid ; LGI-1 = Leucine-rich, glioma inactivated 1; CASPR2 = Contactin-associated protein-like 2; mGluR5 = Metabotropic glutamate receptor type5; GABAB = Gamma-aminobutyric acid type B; GABAA = Gamma-aminobutyric acid type A; DPPX = Dipeptidyl-peptidase-like protein-6; GFAP = Glial fibrillary acidic protein.

3.1.2 Causes which are geographically restricted

Infectious agents transmitted by vectors or animals, or that have an animal host, cause encephalitis in geographically restricted areas (Table 3). This is a result of the ecological range of the vector or the reservoir, or because of geographically or culturally specific behaviour that puts individuals at risk (1). Arboviruses are the most important of these. Most arboviral infections are asymptomatic and only a small proportion result in neurological disease. Approximately 100,000 global Japanese encephalitis virus (JEV) cases are thought to occur annually, and two reviews of global encephalitis studies have confirmed the predominance of JEV in Asia (Figure 1) (38,8,4). Japanese encephalitis (JE) is a vector-borne zoonotic disease primarily transmitted by *Culex* mosquitoes. The virus exists in a cycle between mosquitos, pigs, and/or water birds; humans are dead-end hosts. JE occurs throughout most of Asia and parts of the Western Pacific, but local transmission of JEV has not been detected in Africa, Europe, or the Americas (39). JEV transmission often occurs in rural agricultural areas associated with rice production and flooding irrigation as this is where mosquito vectors breed. Tick-borne encephalitis virus (TBEV) was more frequently reported in Eastern and Northern Europe as well as in Russia in the studies included in the review by Boucher et al. (Figure 1) (4). Tick-borne encephalitis (TBE) is caused by three subtypes of TBEV including European, Siberian, and Far-Eastern, and is endemic in central, eastern, and northern Europe; the Urals region, Siberia, and far-eastern Russia; and in forested regions of China and Japan (40). Boucher et al. reported that other arboviruses, mainly Flaviviruses and Alphaviruses, were more frequent in North American studies (Table 3) (4). These include predominantly West Nile virus (WNV), Saint Louis encephalitis virus (SLEV), and La Crosse virus. WNV, first detected in the Western hemisphere in 1999, has rapidly spread across North and South America and resulted in a massive outbreak across southern and central Europe in 2018 (41). Between 1999 and 2008 almost 30,000 cases of WNV were reported in the US; 41% of these were neuroinvasive (42). Rarer arboviral causes include Powassan virus, Eastern equine encephalitis virus (EEEV), and Western equine encephalitis virus (WEEV) amongst others (Table 3). Human rabies is a Lyssavirus and results in an acute progressive encephalitis that is almost always fatal after the onset of clinical symptoms (43). An estimated 59,000 human deaths occur each year due to rabies, mainly in Asia and Africa (44). The primary reservoir of the virus and main source of human infections are dogs. Although classical canine rabies is no longer observed in Western Europe, a few cases of rabies caused by European bat lyssaviruses has been reported (45). Apart from some viral causes of encephalitis, certain other infectious causes are also geographically restricted (Table 3). *Orientia tsutsugamushi*, the bacteria which causes scrub typhus and has been linked to encephalitis, is transmitted by mites and predominantly occurs in the Asia Pacific region (see Section 9.2.4 for more

information) (46,47). *Trypanosoma brucei* is a parasite transmitted by tsetse flies and causes sleeping sickness and encephalitis in Africa (Table 3). Parasites and fungi are rare causes of encephalitis in Europe (48).

Table 3 – Causes of encephalitis that are geographically restricted

Region	Causes	
Africa	Chikungunya virus Dengue virus Yellow fever virus HTLV WNV Rabies virus *Trypanosoma brucei* *Schistosoma*	
Asia	JEV TBEV Chandipura virus Nipah virus EV71 Chikungunya virus	Rabies virus *Orientia tsutsugamushi* *Angiostrongylus* sp.
Australia/Oceania	MVEV Kunjin virus Hendra virus ABLV JEV	Rabies virus
Europe	TBEV WNV Toscana virus Rabies virus *Anaplasma phagocytophilum* *Borrelia burgdorferi*	EBLV
Mediterranean region	Toscana virus WNV Dengue virus Rabies virus	
North America	WNV La Crosse virus SLEV EEEV WEEV California encephalitis virus Colorado tick fever virus Powassan virus Chikungunya virus Rabies virus EV71	*Rickettsia rickettsii* *Anaplasma phagocytophilum* *Borrelia burgdorferi* *Coccidioides* *Naegleria fowleri* *Acanthamoeba* spp. *Balamuthia mandrillaris* *Baylisascaris procyonis*
South and Central America	VEEV WNV EEEV SLEV Chikungunya virus Dengue virus Ilheus virus	Yellow fever virus Rabies virus HTLV *Bartonella bacilliformis* *Rickettsia* *Taenia solium*

Adapted from Boucher et al. (4)
ABLV = Australian bat lyssavirus; EBVL = European bat lyssavirus; EEEV = Eastern equine encephalitis virus; EV71 = Enterovirus 71; HTLV = Human T-cell lymphotropic virus; JEV = Japanese encephalitis virus; MVEV = Murray Valley encephalitis virus; SLEV = St. Louis encephalitis virus; TBEV = Tick-borne encephalitis virus;

VEEV = Venezuelan equine encephalitis virus; WEEV = Western equine encephalitis virus; WNV = West Nile virus

3.1.3 New and emerging infections

Boucher et al. reported that the proportion of encephalitis patients in which a cause was identified ranged from 27.5% to 79% (4). Amongst the cases of unknown cause, new and as yet undiscovered agents may be responsible. Encephalitis is a marker syndrome for new and emerging infections and numerous pathogens have been detected in these cases. Between 2011 and 2013 three breeders of variegated squirrels died in Germany from an acute encephalitis, and variegated squirrel bornavirus 1 was identified from patient brain samples and a contact squirrel (49). The effects of Zika virus, severe acute respiratory syndrome coronavirus 2 (COVID-19), and monkeypox infection on the brain, including encephalitis, further highlights this (50,51). See Chapter 9 for more information on emerging infectious encephalitides.

3.2 Incidence

It is important to understand the incidence of encephalitis as the burden of encephalitis to health services is disproportionately high (see Section 4.2.1). Incidence must be examined in the global context as climate change, increased international travel, and emerging infections raise the possibility of wider geographical spread of microbes. We aimed to understand global encephalitis incidence in order to compare how rates vary among different subgroups/exposures and enable limited resources to be focused appropriately in settings where they are most needed.

3.2.1 Global incidence of all-cause encephalitis in non-outbreak situations

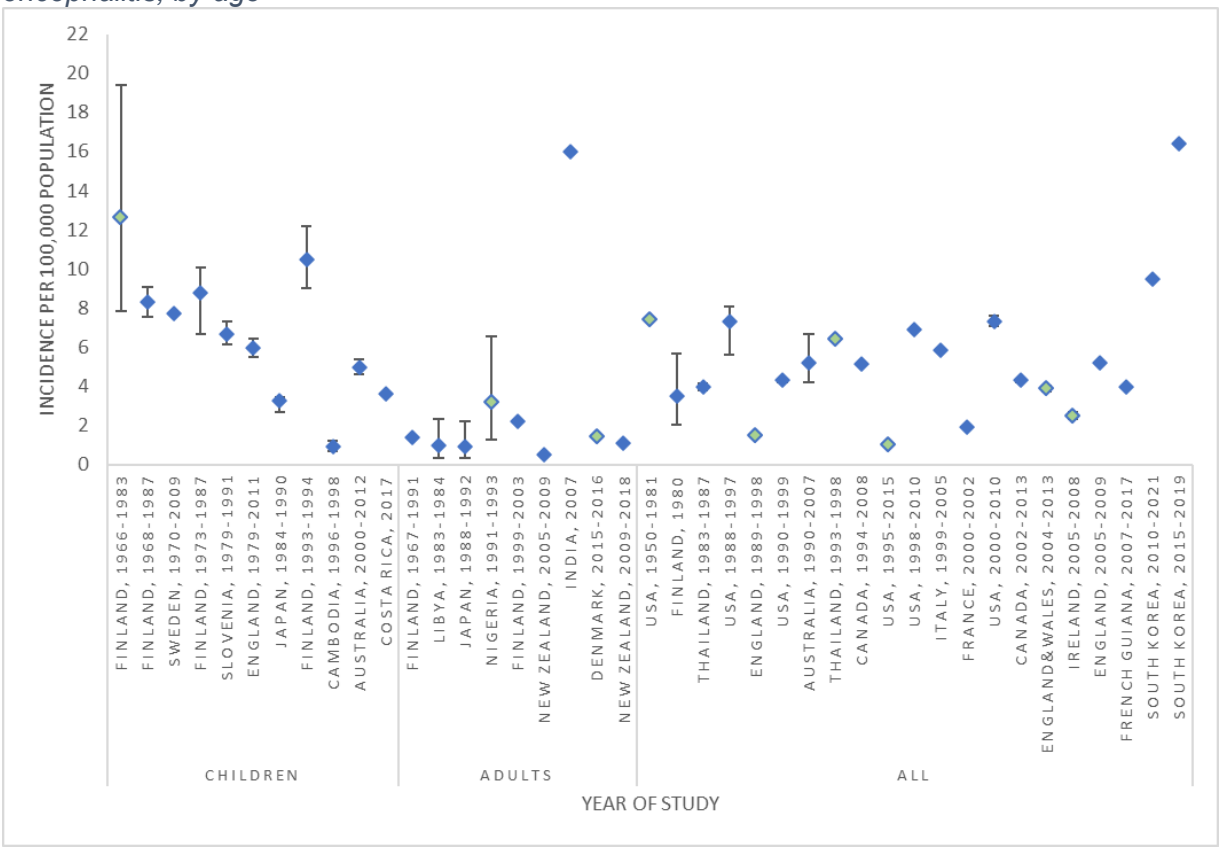
We built on data from a systematic review conducted in 2009 on the global incidence of all-cause encephalitis in non-outbreak situations (see further details on methodology in Appendix 16.1) (8). Studies restricted to a specific cause of encephalitis from the outset (e.g., JEV, HSV) were not included to keep the focus on the incidence of encephalitis in its broadest sense. In addition, outbreaks were excluded as the incidence in these situations is transient, increasing rapidly before falling again, and is thus not reflective of the true underlying incidence.

Fifty-three studies were identified that reported on the incidence of all-cause encephalitis in non-outbreak situations worldwide (9,10,17,52–102); 21 of these were included in the original systematic review conducted by Granerod et al (8). See Table A1 in the Appendix for details of all included studies. The 53 studies included 22 (41%) from Europe, 13 (24%) from North America, 11 (21%) from Asia, 4 (8%) from Australia/New Zealand, 2 (4%) from Africa, and 1

(2%) from South America, spanning the period 1950-2021 (published until March 2023). Twenty-one studies (40%) were restricted to children, 8 (15%) included adults only, and 24 (45%) included both children and adults. The commonest type of subsyndrome was unspecified (i.e., general syndrome and not specific to a cause) encephalitis/meningoencephalitis (60% of studies). Twenty-three percent of studies were restricted to immune-mediated encephalitis and 17% to infectious.

Incidence estimates reported in studies of unspecified and infectious/viral encephalitis are displayed in Figure 3 (see Table A1 for further detail) (9,10,17,52–59,62–70,73–87,96,98,100–103). The incidence ranged from 0.5 to 16 cases/100,000/year. The lowest incidence of 0.5/100,000 was reported in a study from Auckland, New Zealand where patients were identified via a database search of all patients with a request for CSF viral polymerase chain reaction (PCR) testing; medical notes were then retrieved to assess whether the patient fulfilled the criteria for encephalitis (10). The highest incidence (16/100,000) was a prospective study from India that reported on acute encephalitis syndrome (AES) and a retrospective review of claims data in South Korea (70,101). Encephalitis incidence in children appeared generally higher than that in adults (Figure 3).

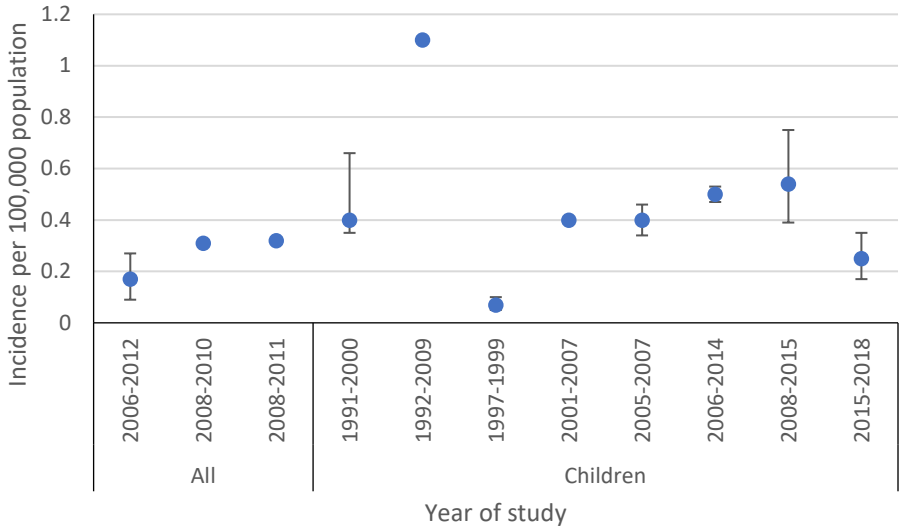
Figure 3 - Incidence per 100,000 population per year of unspecified and infectious/viral encephalitis, by age



Green represents infectious/viral encephalitis and blue represents unspecified encephalitis. The error bars represent the 95% confidence interval around the incidence estimates.

Eleven studies were identified that reported on the incidence of ADEM (60,61,71,88–95). The incidence of included studies ranged from 0.07-1.1/100,000/year (Figure 4). Most ADEM incidence studies (n=8/11, 73%) were restricted to children.

Figure 4 - Incidence per 100,000 population per year of ADEM, by age

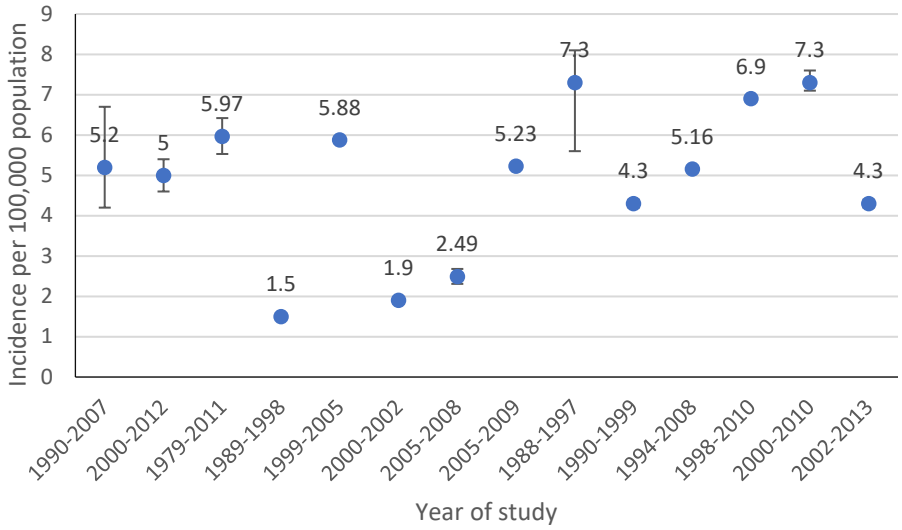


Vertical bars represent 95% confidence intervals where available

The incidence of other autoimmune encephalitis ranged from 0.055-0.8 per 100,000 (17,72,93,99). The highest incidence (0.8/100,000) was reported from a population-based retrospective study of the incidence of autoimmune encephalitis among residents of Olmsted County, USA (17). The lowest incidence (0.055/100,000) was from a retrospective Danish study and reported “antibody negative but probably autoimmune encephalitis” in children (72).

Studies were restricted to those that used a similar hospitalisation data source and coding system (n=13) to facilitate better comparison across studies (52–55,63,74–79,81,84,96). Incidence ranged from 1.5-7.3/100,000/year (Figure 5). It should be noted that lower incidence studies were restricted to viral encephalitis (rather than all-cause unspecified encephalitis) (53,84). In 11 of the 14 studies (when these outliers were excluded), the incidence ranged from 4.3-7.3/100,000/year.

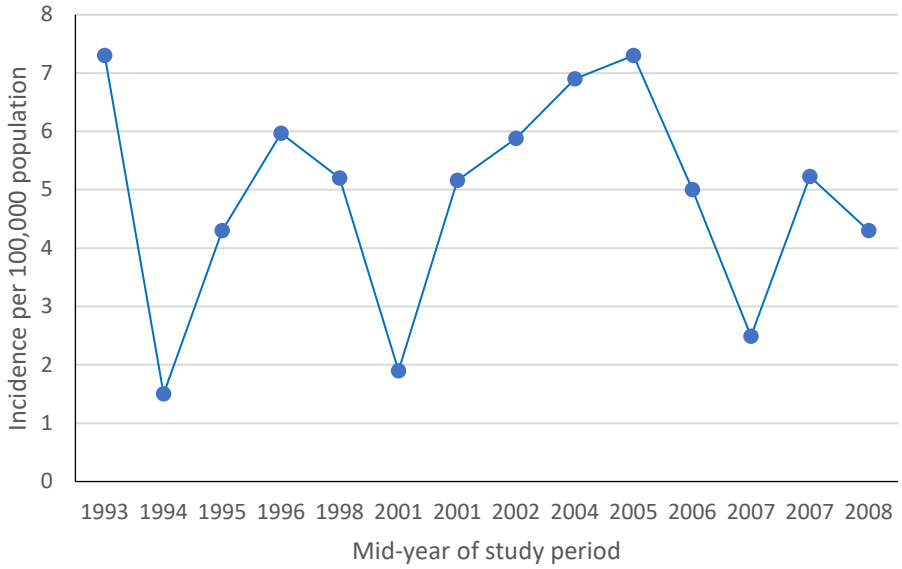
Figure 5 - Encephalitis incidence per 100,000 per year in studies using hospitalisation data



Vertical bars represent 95% confidence intervals where available

When the incidence estimates reported from studies which used hospitalisation data were plotted against the mid-year point of the study, there was no visible increase or decrease in incidence over time (Figure 6).

Figure 6 - Encephalitis incidence per 100,000 per year in studies using hospitalisation data, by mid-year of study period



3.2.2 Discussion

A wide range of incidence estimates were reported from the numerous studies included in this review. The lowest incidence of 0.07/100,000/year was reported in a German study of children

with ADEM while the highest incidence of 16/100,000 was reported in both an Indian study of AES and a retrospective review of South Korean claims data (60,70,101). Incidence may vary due to biological factors, such as the geographic distribution of causative agents and vaccination histories of study populations. It may also vary due to methodological factors such as case definitions used and differences in diagnostic testing and ascertainment strategies. Encephalitis is a complex diagnosis and symptoms often overlap with those of other neurological diseases that lack an infectious or inflammatory aetiology. Studies that use more stringent case definitions may report lower incidences than those where diagnosis is based on less specific clinical criteria. The study by Joshi et al., which reported the highest incidence, likely included some non-encephalitis cases (e.g., toxic encephalopathy, bacterial meningitis) as the case definition for AES is quite broad (70). The strategy used to ascertain cases may also impact on incidence; active case finding may result in a higher incidence estimate than a study using a passive reporting system. The study by Child et al. may have missed cases where no CSF PCR was requested as that was their main method of ascertainment (10). Thus, the studies included in this review are not directly comparable. When studies were restricted to those that used hospitalisation data only, they became more comparable. In 11 of the 14 studies (when outliers were excluded), the incidence ranged from 4.3-7.3/100,000/year. All studies that used hospitalisation data were from Europe, North America, and Australia. Studies that used hospitalisation data had a similar data source and data coding; however, some used encephalitis in the primary diagnostic coding field only and some in all diagnostic fields. Also, the diagnosis of encephalitis in hospitalisation data has not yet undergone validation so there is likely to be some misclassification if mimicker syndromes are coded using encephalitis codes. There was a lack of studies from Africa, Asia, and South America, which likely reflects the lack of resources and lack of surveillance infrastructure (i.e., national hospital data) in these parts of the world. However, incidence is likely to be higher in these countries. For example, a systematic review of the global incidence of JE reports a JE incidence of up to 3.7/100,000 in Cambodia, Indonesia, Lao People's Democratic Republic, parts of Malaysia, Myanmar, Philippines, and Timor-Lest (104). Given there are over 100 causes, the incidence of all-cause encephalitis in these parts of Asia is likely to be even higher.

Recent studies have shown that encephalitis may be more common than previously thought. The incidence of encephalitis in England, previously estimated at 1.5/100,000/year, is likely 5.23 but could be as high as 8.66/100,000/year (53,54). Importantly, in many countries encephalitis has a higher incidence than motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS), bacterial meningitis, multiple sclerosis (MS), and cerebral palsy (CP) - conditions which have much higher clinical and public profiles (105–108). When the incidence estimates reported from studies which used hospitalisation data were plotted against the mid-

year point of the study, there was no visible increase or decrease in incidence over time. Vaccination programs may have resulted in a decreased incidence in vaccine-preventable causes of encephalitis; however, increased recognition of novel causes and improved surveillance may have masked any decrease seen when incidence of all-cause encephalitis is considered.

Fourteen papers which reported on the incidence of immune-mediated encephalitis were included here. In the systematic review by Granerod et al., which included studies conducted until 2002 (published until 2009), only two such studies were included (8). This reflects the increasing recognition of and interest in these encephalitides, particularly since the identification of anti-NMDAR encephalitis in 2007. It should be noted however, that studies of general/unspecified or infectious encephalitis also report a large proportion of cases of unknown aetiology, some of which are likely to be immune-mediated.

It is worth mentioning that the Global Burden of Disease (GBD) study reports a global incidence of encephalitis of 29/100,000 population for 2017 (109). There is some doubt however about the accuracy of these figures (110). Incidence of global HIV/acquired immune deficiency syndrome in the GBD study (25.42/100,000) was reportedly lower than the global incidence of encephalitis which does not appear correct. The International Classification of Disease (ICD) codes used to estimate encephalitis incidence in the GBD study included sequelae codes but omitted HSV and VZV encephalitis codes. In addition, the incidence given for England (10.98/100,000) was over twice as high as that estimated in a very robust national study (5.23/100,000).

In conclusion, the data from this review demonstrate the difficulty in comparing incidences across studies as biological and geographical factors differ between populations and case definitions and other methodological differences exist. Incidence in parts of the world (West) is higher than previously thought. However, there is a lack of incidence studies in parts of the world where incidence is likely to be even higher (South America, Africa). We also highlight the importance of immune-mediated causes which have been increasingly recognized over the last decade.

3.2.3 Gap analysis

Table 4 – Gap analysis for encephalitis incidence

Where we are	Where we want to be
It is estimated that 500,000 cases of encephalitis occur globally each year (111) but this is thought to be an underestimate. 100,000, 60,000, and 15,000 cases of JE, rabies, and TBE,	Need for more accurate assessment of incidence as global cases of encephalitis are underestimated

respectively, are thought to occur annually (39,112,113). Given 1:1,000 cases of childhood measles are complicated by encephalitis and that 9,828,400 estimated cases of measles occurred in 2019, almost 10,000 cases of measles encephalitis likely occurred (114). Thus, just these four causes alone (of >100 possible causes) amount to 185,000 encephalitis cases per year, over a third of the total 500,000. In addition, the GBD study estimated almost 1.5 million incident cases of encephalitis in 2019 (115). However, for aforementioned reasons, we believe the GBD study is an overestimate. The true incidence likely falls between the Jmor et al. figure of 500,000 and the GBD figure of 1.5 million.	
There is a lack of incidence studies from Africa, South America, and parts of Asia. Studies from Asia tend to be restricted to JE.	Need further studies to enable better assessment of encephalitis incidence in Africa, Asia, and South America
Studies vary in incidence partly due to biological factors of study populations (e.g., geographical area and vaccination history) but also due to methodological differences between studies.	Need standardisation of case definitions, diagnostic testing, and methods of case ascertainment to enable better comparison of incidence between studies and regions
Routine surveillance systems are either sub-standard or lacking in many countries.	Need to develop/improve routine surveillance systems to facilitate assessment of accurate incidence estimates

GBD = Global Burden of Disease; JE = Japanese encephalitis; TBE = Tick-borne encephalitis; WHO = World Health Organization

4 Burden of disease

4.1 Morbidity and mortality

It is important to assess the morbidity and mortality of encephalitis worldwide to understand the burden of encephalitis on global populations. In addition, it is important to assess specific long-term needs of survivors, so that strategies for long term care, support, and rehabilitation can be designed accordingly. We aimed to understand global encephalitis morbidity and mortality to compare how rates vary among different subgroups/exposures and enable limited resources to be focused appropriately.

4.1.1 Mortality for all-cause encephalitis

4.1.1.1 Mortality rate

Mortality rate measures the number of deaths due to encephalitis in a population scaled to the size of that population per unit of time. In 2016, the WHO estimated around 104,000 deaths in all ages from encephalitis which equates to a crude mortality rate of 1.4/100,000 population (Table 5) (116). This is similar to the Institute for Health Metrics and Evaluation (IHME) estimate of 92,370 deaths for 2017 which equates to a rate of 1.2/100,000 (95% confidence interval [CI] 1.1-1.4) (109).

Table 5 - Estimates of all-age encephalitis mortality by WHO region, 2016

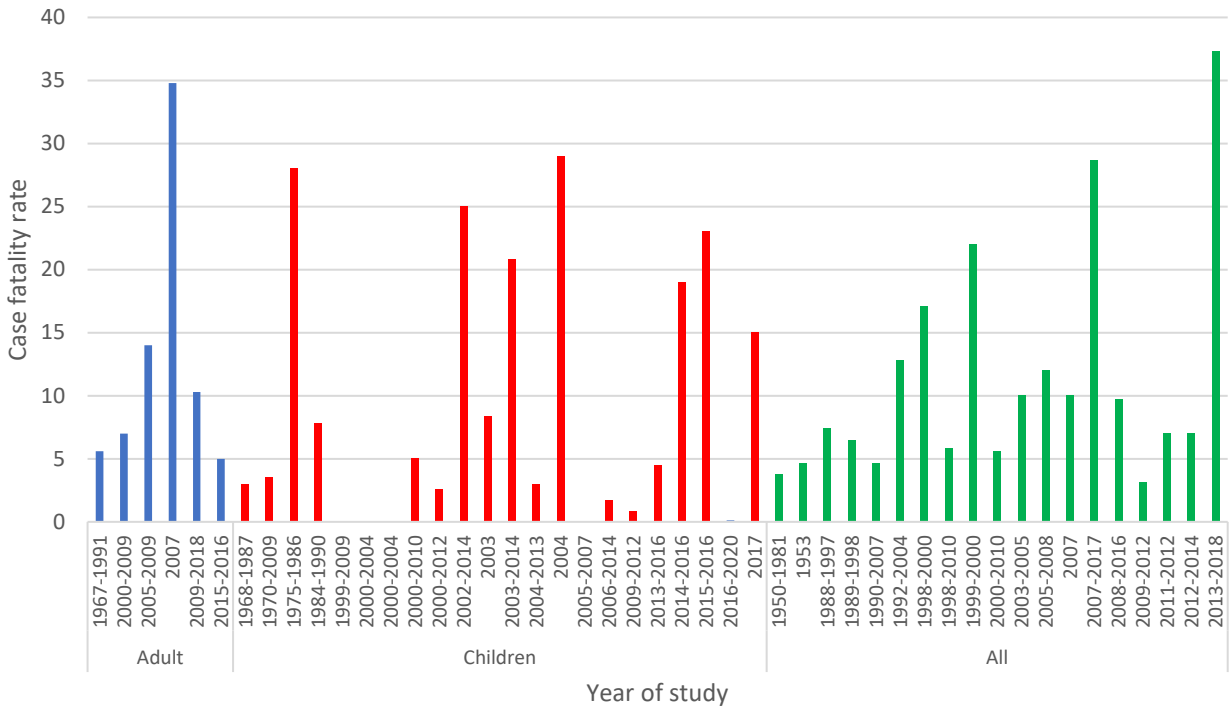
	Number deaths	% of total deaths	Crude death rate (/100,000)	Age-specific death rate (/100,000)
Global	**104,000**	**0.2**	**1.4**	**1.4**
African Region	9,000	0.1	0.9	0.9
Region of the Americas	20,000	0.3	2.0	1.6
South-East Asia Region	40,000	0.3	2.0	2.3
European Region	18,000	0.2	2.0	1.1
Eastern Mediterranean Region	6,000	0.2	0.9	1.1
Western Pacific Region	11,000	0.1	0.6	0.6

From WHO Global Health Estimates **(116)**

4.1.1.2 Case fatality rate

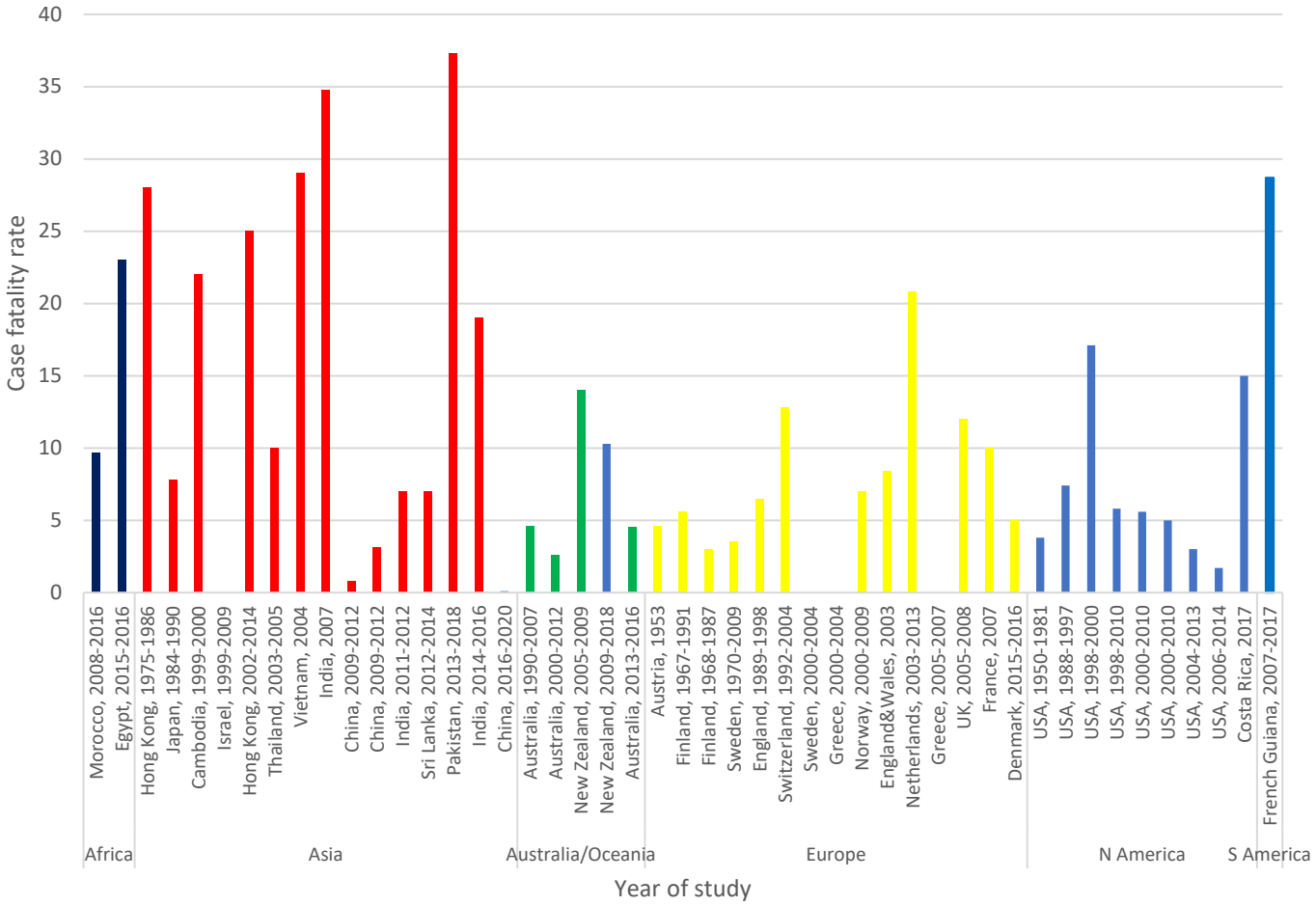
Case fatality rate (CFR) represents the proportion of deaths from encephalitis compared to the total number of people diagnosed for a certain period of time. Our search retrieved 47 studies of all-cause encephalitis that estimated case fatality; 22 (47%) included children only, 6 (13%) adults only, and 19 (40%) included all ages (Figure 7) (9–11,13,52,53,56,57,70,74,78–83,94,97,98,98,102,117–139,139–143). Fifteen (32%) studies from Europe, 15 (32%) from Asia, 9 (19%) from North America, 5 (11%) from Australia/New Zealand, 2 (4%) from Africa, and 1 (2%) from South America were included. Studies of encephalitis in the literature reported CFRs ranging from 0 to 37% (117,142). Four studies reported zero deaths; these were all studies of children, three conducted in Europe and one in Israel (117,118,127,141). The highest CFR (37.3%) was reported from a retrospective study in Pakistan that included patients with severe encephalitis admitted to the intensive care unit (142). This was followed by CFRs of 34.8%, 29%, 28%, and >25% reported in four Asian studies (India, Vietnam, and two from Hong Kong). Thirty-four (n=16/47) percent of studies reported CFRs between 5 and 10%, while 34% (n=16/47) reported CFRs <5% and 32% (n=15/47) reported CFRs >10%. See Table A2 in Appendix for details of all included studies.

Figure 7 - Case fatality rates for encephalitis studies by age and year of study



CFRs from included African, Asian, and South American studies appeared higher than those from other continents (Figure 8). In half (n=1/2) of African, 43% (n=6/14) of Asian, and the one included South American study the CFR was >20%. This is compared to one study from Europe and none from Australia/New Zealand or North America having a CFR >20%.

Figure 8 – Case fatality rates for encephalitis studies by age and continent



4.1.1.3 Discussion

These results confirm that encephalitis is associated with high mortality on a global scale. The WHO/IHME estimate of 104,000 deaths worldwide (1.4/100,000 population) from encephalitis in 2016 is likely an underestimate (116). Rabies alone is estimated to cause 60,000 deaths and JE 25,000 deaths worldwide each year yielding a total of 85,000 deaths just from these two causes of encephalitis alone (47,144). Given there are >100 different causes of encephalitis, the total number of deaths is likely to be higher than the estimate of 104,000 deaths. In addition, a recent study reported >24,000 human deaths from rabies annually in Sub-Saharan Africa alone, far higher than the 9,000 deaths due to encephalitis reported by WHO for the whole of Africa in 2016 (145). Data for the IHME estimate were based on ICD codes; these included codes for arboviruses, sequelae of viral encephalitis, and general non-pathogen-specific rubric specifying encephalitis diagnoses, but omitted codes for rabies, HSE, and other specific known causes. Thus, deaths due to encephalitis are higher than current global estimates.

The CFRs reported varied between studies; a third of included studies reported CFRs between 5 and 10%, a third reported CFRs <5%, and a third reported CFRs >10%. It is evident that CFRs from African, Asian, and South American studies were higher than those reported from Australian/New Zealand, European, and North American studies. There are some possible explanations for this. Firstly, the main factor that influences outcome appears to be the aetiological agent involved, likely a reflection of an interplay between the pathogenesis of the organism, treatment available, and host factors (1). Different organisms are present in these regions that may cause more severe disease. Second, the regions with the highest CFRs have the fewest number of neurologists per 100,000 population (see Section 7.2.1) and lowest coverage of two doses of measles-containing vaccine (see Section 5.1.3.2), both which would contribute to better protection against and treatment of encephalitis. It is important to note however, that comparison is difficult due to between-study heterogeneity, which emphasizes the need for standardised surveillance systems across the board for incidence and mortality. Some studies may have been missed as this was not a systematic review; however, this is thought to be limited as the search used for this review was very comprehensive. Data from Africa and South America were scarce. Two African studies were not included in this review as the full text could not be obtained; however, CFRs of 20% and 50% were reported in Libya and Nigeria, respectively, in the abstract (66,69). These latter studies only included a very small sample size (five and seven patients).

4.1.1.4 Gap analysis

Table 6 - Gap analysis for encephalitis mortality

Where we are	Where we want to be
WHO/IHME estimated 104,000 deaths worldwide from encephalitis in 2016. However, 60,000 and 25,000 deaths from rabies and JE, respectively, occur each year in Asia and Africa which equates to 85,000 deaths per year from these two causes alone. Thus, it is certain that the global number of deaths from encephalitis per year is higher than the estimated 104,000.	Need for more accurate assessment and better recording of mortality as global deaths from encephalitis are underestimated
Comparison is difficult due to between-study heterogeneity.	Need for standardised surveillance systems to enable more accurate assessment and comparison of mortality/case fatality
Case fatality rates are higher in Africa, Asia, and South America compared to Europe, Australia/New Zealand, and North America.	Need to facilitate prevention, treatment, and management (e.g., increase number of neurologists and coverage of two doses of measles-containing vaccine) of encephalitis in these regions
Data from Africa and South America are scarce.	Need for more research to assess mortality in Africa and South America

IHME = Institute for Health Metrics and Evaluation; JE = Japanese encephalitis; WHO = World Health Organization

4.1.2 Morbidity for all-cause encephalitis

4.1.2.1 Sequelae in children

A systematic review and meta-analysis were undertaken by Khandaker et al. to quantify the long-term (i.e., follow-up period ≥12 months) outcomes of infective encephalitis from all causes in 1,018 children (38,86–88, 95). This review comprised articles published up until April 2016. Sixteen studies were included for quantitative meta-analysis, the majority (n=13/16, 81%) from high-income countries (HICs). Almost half (n=312, 42%) of survivors had incomplete recovery/neurodevelopmental sequelae (Table 7). The most common long-term sequelae included developmental delay (35%), abnormal behaviour (18%), intellectual deficit (IQ<85; 17.5%), and motor impairment (17%). Higher rates of sequelae were reported in studies from HICs compared to low- and middle-income countries (LMICs; 47% [36-58%] versus 26% [9-47%]). Children with HSV encephalitis had a higher proportion of long-term sequelae compared to those with other infections (64% [95%CI 34-89%] versus 38% [28.0-50.0%]). A recent systematic review from 2023 similarly reported neurological sequelae in over half (51%) of children following encephalitis associated with HSV (146).

Table 7- Meta-analysis of long-term outcomes of infective encephalitis in childhood

Long-term sequelae	Number of patients followed up	Number of patients who developed sequelae	Percentage with sequelae (95% CI)

Death	584	18	**2.7** (1.7-4.5)
Severe sequelae*	520	33	**6.7** (4.5-8.8)
Incomplete recovery**	890	312	**42.0** (31.6-53.1)
Motor impairment	705	86	**17.0** (10.0-26.0)
Seizure	566	52	**10.0** (6.0-14.0)
Developmental delay	227	50	**35.0** (10.0-65.0)
Abnormal behaviour	329	61	**18.0** (8.0-31.0)
Intellectual deficit (IQ<85)	285	41	**17.5** (4.3-37.1)
Intellectual deficit (IQ<70)	302	33	**12.5** (4.6-23.4)

**Persisting sequelae which impair everyday functions; **Residual neurocognitive symptoms*
Adapted from Khandaker et al. **(147)**
CI = Confidence interval

The presence of varying degrees of neurological sequelae in children following encephalitis has been confirmed in studies published since the aforementioned systematic review (i.e., post-April 2016; Table 8) (82,134–136,148).

Table 8 – Sequelae reported in post-April 2016 studies of childhood encephalitis

Study (sample size)	Date	Country	Sequelae reported
Wickstrom et al. (n=408)	1970-2009	Sweden	26% mild and 18.25% moderate-severe sequelae
Elenga et al. (n=30)	2007-2018	French Guiana	17% severe neurological sequelae (epilepsy, quadriplegia, visual and cognitive impairments)
Ai et al. (n=255)	2009-2012	China	7.5% neurological sequelae (coma, aphasia, secondary epilepsy, cognitive impairment, blindness, ataxia, dysphasia, hearing impairment, hemiplegia)
Britton et al. (n=287)	2013-2016	Australia	27% moderate to severe neurological sequelae
Meligy et al. (n=96)	2015-2016	Egypt	74% of survivors (n=74) mild to severe/vegetative neurological sequelae

From references (82,134–136,148)

4.1.2.2 Sequelae in adults

Studies report similar outcomes in adults as children following encephalitis (Table 9). Between 26% and 62% of adults suffer significant sequelae, including epilepsy, memory problems, inappropriate behaviour and poor social skills, fatigue/sleep disturbance, personality changes, cognitive problems, problems with pain and other sensations, and problems with daily living skills (149). A UK study of mainly adults (~80%) which assessed sequelae in encephalitis survivors relative to rates within the general population showed an increased risk of all investigated outcomes, including epilepsy, depressive disorders, anxiety disorders, psychotic disorders, bipolar disorder, cognitive problems, dementia, headache, and alcohol abuse (150). The highest rate ratio (RR) was seen for epilepsy (adjusted RR 31.9; 95%CI 25.38-40.08) followed by particular psychiatric illnesses, including bipolar disorder (6.34, 3.34-12.04) and psychotic disorders (3.48, 2.18-5.57). The RR was generally highest in the first year of follow

up; this was particularly true for epilepsy (adjusted RR in first year of follow up 139.6, 90.62-215.03).

Table 9 - Sequelae reported in studies of adult/all-age encephalitis

Study	Age	Sample size	Date	Continent	Sequelae reported
Rantalaiho et al.	Adult	322	1967-1991	Europe	26% (n=85) sequelae
Hansen et al.	All	340	2000-2017	USA	50.6% (n=172) confirmed adverse clinical outcome (GOS 1-4)
Granerod et al.	All	198	2005-2008	Europe	44% (n=88) of all or 50% (88/174) of survivors severe or moderate disability (GOS 2-4)
Joshi et al.	Adult	152	2007	Asia	34% of survivors (34/99) significant cognitive disability (MMSE<25)
Mailles et al.	All	253	2007	Europe	62% (140/223) of survivors had neurological signs and 10% (22/223) behavioural disorders
Roux et al.	All	108	2007-2017	South America	46.6% (n=48) poor outcome*
Toudou-Daouda et al.*	All	31	2008-2016	Africa	9.7% temporal lobe epilepsy, 16.1% anterograde amnesia, and 19.4% severe cognitive impairment
Zhao et al.	All	1027	2009-2012	Asia	20.7% (n=213) mild, 10% (n=103) moderate, and 1.8% (n=19) severe neurological sequelae
Rathore et al.	All	80	2011-2012	Asia	18% (n=14) poor outcome**
Bodilsen et al.	Adult	89	2015-2016	Europe	62% (n=55) unfavourable outcome (GOS 1-4)

**Study relates to limbic encephalitis*
***Includes death or severe disability*
From references (9,11,13,70,80,83,123,131,137,151)
GOS = Glasgow Outcome Scale; MMSE = Mini mental state examination

4.1.2.3 Carer burden

Sequelae following encephalitis do not only affect the survivor but can have a huge impact on their families and communities. Caregiving, particularly in neurological diseases, is costly and time-consuming and has been shown to increase the risk for depression and worse physical health (152). A study of 36 parents reported greater parental distress when their child experienced higher levels of behavioural symptoms following encephalitis (153). A recent study which assessed caregiver burden in 76 individuals caring for a person with anti-NMDAR encephalitis reported a mean Zarit Burden Interview (i.e., standardised 22-item questionnaire to assess burden) score of 44 (range 17-70), reflecting moderate to severe burden (154). Caregivers of individuals with anti-NMDAR encephalitis in this study experienced higher levels of burden than those reported for dementia, stroke, and Alzheimer's (155–157).

4.1.2.4 Discussion

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 (147). In this study higher rates of sequelae were reported from HICs compared to LMICs, likely due to sequelae not being adequately assessed and recorded in the latter. A systematic review from 2010 of the global and regional risk of disabling sequelae from bacterial meningitis found that survivors in low income countries (LICs) were worst affected; the risk of major sequelae was twice as high in Africa and South-East Asia as in Europe (158). As for children, between a quarter and two thirds of adults suffer significant sequelae following encephalitis. Between-study heterogeneity exists in terms of study setting, aetiology, sample size, duration of follow-up, and variations in the reporting of the type of sequelae (i.e., one specific type or category of sequelae versus all sequelae, some include deaths as poor outcome, some reported all cases including deaths as denominator while others only survivors). There are ongoing global efforts to standardise outcome evaluation and documentation in children across diagnoses, ages, and genders (159). A systematic review which assessed the range of outcome measures used in the long-term follow-up of patients with encephalitis, concluded that most of the 37 measures used assessed a single category of sequelae using 5–8-point scales and were not validated for use in encephalitis (160). Thus, standardisation is required in the way sequelae are measured and reported to facilitate comparison between regions, causes, and to better assess the extent of sequelae post-encephalitis.

4.1.2.5 Gap analysis

Table 10 - Gap analysis for encephalitis morbidity

Where we are	Where we want to be
Data are available from high-income countries on the acute outcomes of HSE and from LMICs on the acute outcomes of JE.	Need data from LMICs on acute outcomes of encephalitis from other infectious causes
Data are available from high-income countries on the long-term outcomes of HSE.	Need data from LMICs on long-term outcomes of encephalitis Need data on long-term neurocognitive outcomes of infective encephalitis Need data on clinical predictors of long-term outcomes of infective encephalitis in children Need age stratification of follow-up studies on long-term outcomes of infective encephalitis
Evidence of significant caregiver burden associated with encephalitis	Need to consider possible interventions including psychoeducational interventions focused on coping and problem solving and educational sessions, which have shown to be

	successful in other neurological diseases (161,162)
Lack of standardized methods of outcome data collection and uniform definitions, and lack of validation of outcome measures for study population complicates comparison of studies/causes or full assessment of extent of sequelae following encephalitis (163).	Need an encephalitis-specific outcome measure to aid standardization

Adapted from Khandaker et al. (147)
HSE = Herpes simplex encephalitis; JE = Japanese encephalitis; LMICs = Low- and middle-income countries

4.1.3 Morbidity and mortality by cause

Mortality and morbidity by the main causes of encephalitis are displayed in Table 11. Rabies encephalitis is invariably fatal, while HSV and JE are often associated with a CFR of around 20%. A recent systematic review and modelling analysis however, reported JE CFR estimates were <20% after 2000 (164).

Table 11 - Mortality and morbidity by main causes of encephalitis

Cause	Case fatality	Sequelae	Reference
Infectious			
HSV	20%	70%	Piret et al.
JE	14-30%	30-60%	Simon et al.; Kumar et al.; Chow et al.; Cheng 2022
TBE			Taba et al.
European subtype	1%	26-46%	
Far Eastern subtype	6.4-33%*	N/A	
Siberian subtype	1.8-3%*	N/A	
Rabies	100%	N/A	Dacheux et al.
Immune-mediated			
ADEM	1-3%	20%	Bhatt et al.
NMDARE	5-7%	25% significant morbidity or mortality	Venkatesan et al.; Chi et al.
All-cause AE	N/A	18%	Abboud et al.

**Based on limited data*
From references (94,164–173)
ADEM = Acute disseminated encephalomyelitis; AE = Autoimmune encephalitis; HSV = Herpes simplex virus; JE = Japanese encephalitis; N/A = Not available; NMDARE = N-methyl-D-aspartate receptor encephalitis; TBE = Tick-borne encephalitis

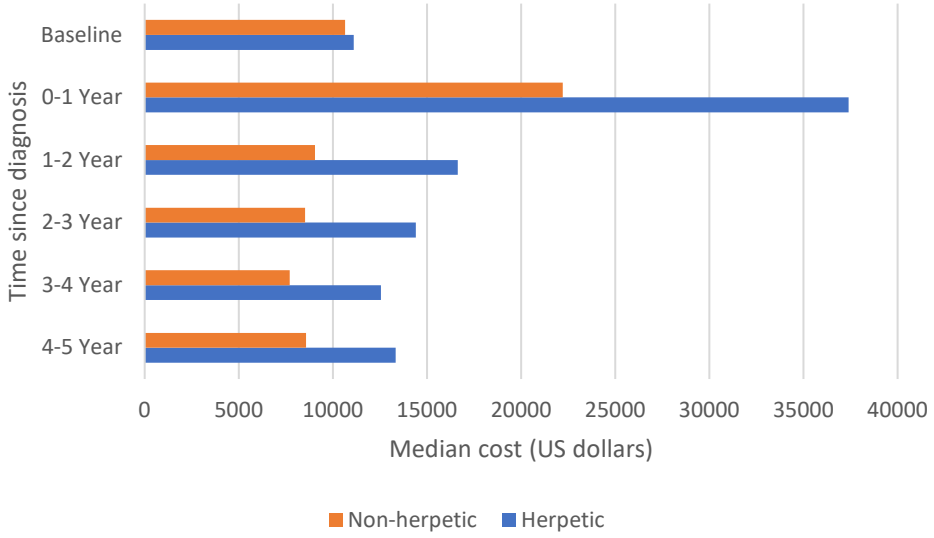
4.2 Economic burden and DALYs

4.2.1 Cost

Due to its high morbidity and mortality, encephalitis is associated with significant costs to individuals and society. An annual cost of >£23 million (US$35 million) has been estimated in England based on an incidence of 5.23 cases/100,000/year, a mean hospital length of stay of 34 days, and a bed-day cost of £261 (54). This, however, does not include the cost of intensive care, expensive investigations, in-patient rehabilitation, or long-term care and loss of productivity among many working-age survivors. Thus, the cost of encephalitis is likely

substantially higher. In a USA study, the mean charges for hospitalization for a child with encephalitis was $64,604 and for those requiring critical care was $260,012. In this study, 40% of the 7,298 children admitted with encephalitis between 2004 and 2013 were admitted to paediatric intensive care, incurring a total cost of >$750 million (132). Encephalitis-associated hospitalisations in the USA were estimated to cost $2 billion in 2010 (78). Data obtained from the Paediatric Intensive Care Audit national Network database estimated a paediatric intensive care unit (PICU) encephalitis bed cost of £414,230/year (IQR: £198,111–£882,495) for this cohort of 1,031 children with severe encephalitis admitted to the PICU in England and Wales between 2003 and 2013 (138). This is however an underestimate of the PICU cost burden of encephalitis as treatment costs and costs for procedures such as invasive ventilation were not accounted for. A study by Kiyani et al. examined the longitudinal health economic impact of viral encephalitis over a five-year period following diagnosis using a national claims database (174). Healthcare resource utilisation was investigated in 1,635 patients between 2008 and 2015, 598 with herpetic and 1,037 with non-herpetic encephalitis. The median baseline total cost for the one-year period prior to diagnosis was $10,654 for the non-herpetic viral encephalitis group and $11,097 for the herpetic encephalitis group. The cost increased by 165% to $37,403 during the first year of diagnosis for the herpetic group and by 90% to $22,207 for the non-herpetic viral encephalitis group (Figure 9). Costs decreased after two years but remained elevated in the herpetic versus non-herpetic group. The longer length of hospital stay and more admissions associated with the disease have been suggested as possible reasons for the higher costs seen with HSE (174). An analysis of Swedish registry data reported the cost of illness and death from TBE alone in Sweden in 2019 was €23.5 million (175).

Figure 9 – Annual total median costs of viral encephalitis in the USA at baseline and up to five years post-diagnosis



Adapted from Kiyani et al. (174)

Median hospital charges per autoimmune encephalitis patient (>$70,000) were nearly four times higher compared with HSE in a USA study (176). The hospital charges were significantly higher for autoimmune encephalitis patients admitted to the ICU than for those not admitted to the ICU ($173,000 versus $50,000; p<0.001). This was mainly driven by a longer length of hospital stay resulting from delayed diagnosis, prolonged treatment course, and lack of treatment response. The mean direct cost per patient with antibody-positive autoimmune encephalitis in West China was $14,219, and the authors noted a heavy financial burden of autoimmune encephalitis for Chinese patients (177).

There are little data available on the burden of encephalitis in LICs and lower-middle-income countries. A study of children admitted to two Nepali hospitals was the first to consider the cost of AES in a low resource country (178). An economic questionnaire was used to assess the out-of-pocket costs, including medical bills, medication, and lost earnings, incurred to each family by AES. For children with severe/moderate impairment the median out-of-pocket cost to families was US $1,151, 10 times their median monthly income. For children with mild/no impairment the median cost was $524, almost five times their income. The acute admission accounted for almost three-quarters of the cost.

4.2.2 DALYs

Disability-adjusted life years (DALYs) are used to measure the burden of disability associated with a disease and represent the total number of years lost to illness, disability, or premature death within a given population. In short, DALYs are the sum of the number of years of life lost and the years lived with disability for a specific disease. One lost DALY represents one lost year of healthy life (through death or illness/disability), and total DALYs (burden of disease) measure the gap between the current health of a population and an ideal situation where everyone lives into old age in full health. DALYs combine information on incidence/prevalence, mortality, and sequelae into a composite measure.

Smit et al. evaluated the burden of TBE in Slovenia using DALYs (179). Total DALYs amounted to 3,450 or 167.8 per 100,000 population (or 3.1 per case from the individual perspective) in 2011, with a greater burden resulting from the consequences of TBE. LaBeaud et al. used updated information on incidence, mortality, average age at death, and (in survivors) the duration and impact of disability outcomes to evaluate the disease burden of arboviral causes of encephalitis, including JE and Chikungunya virus (180). Global DALYs estimates for JE ranged from 107,435 to 1,859,170 in 2005 (Table 12), with early mortality

and long-term, related chronic conditions providing the largest DALY component. The total burden of JE in Zhejiang Province, China was 14.25 DALYS per million population; a separate Chinese study reported 9.2 as the median DALY lost to JE per subject (181,182).

Table 12 – Calculated global 2005 DALY estimates and inputs for specific arboviral causes of encephalitis

	Inputs				DALYs	
	Estimated clinical cases per year	Median age (years) for symptomatic disease	Case fatality rate	Survivor's risk for multiyear or permanent disability	Non-discounted	Discounted
JEV	35-50,000	10	10-30%	30-50%	265,778-1,859,170	107,435-755,670
CHIKV	33-93,000	40	0.1-28%	5-50%	2,124-1,411,904	1,481-780,234

Adapted from LaBeaud (180)
CHIKV = Chikungunya virus; DALYs = Disability-adjusted life-years; JEV = Japanese encephalitis virus

The GBD study estimated 4.8 million DALYs related to encephalitis globally in 2019 (115). This was down from 8.48 million in 1990; however, age-standardised DALY rates increased in some parts of the world, including New Zealand, UK, Australia, Greece, Switzerland, USA, and Canada. This was attributed to more immunocompromised people in HICs (i.e., following tissue/organ transplantation), HSE being the most common cause and associated with poor prognosis, and a longer life expectancy in these parts of the world (115). Encephalitis was the fifth largest contributor to total neurological DALYS in India, just behind stroke, headache disorder, epilepsy, and CP (183). As previously noted, the encephalitis incidence estimated from the GBD Study is likely an overestimate; however, comparisons to other diseases should remain similar proportionally.

In addition to assessing disease burden, DALYs are often used to monitor health technologies. A cost-effectiveness study of routine immunisation to control JE in Shanghai showed that a program using inactivated or live attenuated JE vaccine would save 6,456 or 6,556 DALYs per 100,000 persons, respectively (184). A similar study conducted in Bali, Indonesia reported that a potential routine JE immunisation program would save 1,223 DALYs at a cost of US $31 per DALY saved, yielding it highly cost effective (185).

4.2.3 Gap analysis

Table 13 – Gap analysis for cost of encephalitis and associated DALYs

Where we are	Where we want to be
Studies report significant direct costs (e.g., hospitalisation) associated with encephalitis but data on indirect costs are lacking (e.g., lost productivity).	Need more data on direct costs from LMICs and on indirect costs from all countries

Encephalitis is associated with high DALYs, but these vary depending on input estimates.	Need more accurate input estimates including incidence/prevalence, mortality, and sequelae to more accurate assess DALYs
DALYs are mostly associated with encephalitis sequelae.	Need to reduce DALYs associated with encephalitis sequelae by implementing better tertiary prevention strategies
DALYs are often used to monitor health technologies and assess benefit of vaccination program against specific causes of encephalitis.	Need to use DALYs measure to assess further introduction of JE/TBE vaccine in endemic places where vaccine not already implemented or where disease may spread in future

DALYs = Disability-adjusted life years; JE = Japanese encephalitis; LMICs = Low- and middle-income countries; TBE = Tick-borne encephalitis

5 Prevention

5.1 Vaccines

Vaccines have had an enormous impact on global health, especially in LMICs. Smallpox became the first (and only) human infectious disease to be eradicated by vaccination in 1979 (186). There are currently vaccine programs in place for the elimination of other infectious diseases including polio and measles. Ozawa et al. used health impact models to estimate that vaccinations given between 2001 and 2020 in 73 LMICs will avert over 20 million deaths and save US $350 billion in cost of illness (187). Vaccines are available for some causes of encephalitis, including JEV, TBEV, measles, rabies, and VZV. We aimed to assess the global distribution of vaccine programs for these vaccine-preventable causes of encephalitis to determine where the gaps are.

5.1.1 Japanese encephalitis vaccination programs

5.1.1.1 Recommended practice

Four classes of vaccines are available against JEV including inactivated mouse brain-derived vaccines, inactivated Vero cell-derived vaccines, live attenuated vaccines, and live recombinant (chimeric) vaccines (188). The WHO recommends that JE vaccination is included in the national immunisation schedule of all countries where JE is recognised as a public health priority (189). Since 2006, the WHO has urged inactivated mouse brain-derived vaccines be replaced with the newer generation vaccines for safety reasons (188).

5.1.1.2 Implementation status

Heffelfinger et al. reported on JE immunisation programs in Asia and the Western Pacific in 2016 (190). Data were obtained from published literature and websites, the 2015 WHO/ United

Nations Children's Fund Joint Reporting Form on Immunization, notes and reports from JE meetings held during 2014–2016, and a survey of JE surveillance and immunisation practices administered to health officials in countries with JE virus transmission risk. Twelve of 24 countries (50%) with JEV transmission risk had a JE immunisation program in 2016, a slight increase from 46% in 2012 (190,191). Improvements were not only seen in implementation of a JE immunisation program but also in the breadth of existing programs (i.e., whether they were national or only covered some areas). The JE vaccine program covered all areas in 42% of countries in 2016 compared to 25% in 2012 (190,191). Since 2016, three further countries have implemented JE vaccination programs, including Myanmar (national), Indonesia (Bali), and the Philippines (Regions I, II, III, and the Cordillera Administrative Region; Table 14) (190,192). Now, 15 of 24 (62%) countries with JEV transmission risk have a JE immunisation program, 10 of which are national programs.

In 2016, live attenuated vaccine was used in six countries (Cambodia, China, India, Laos, Nepal, Sri Lanka), live recombinant in two (Australia, Malaysia), inactivated Vero cell culture-derived in one (Japan), and multiple vaccine types in two countries (South Korea and Thailand) (190). Mouse-brain derived vaccine was only used in Vietnam and Taiwan in 2016 compared to in five countries in 2012 (190). Since 2017, Taiwan has replaced mouse-brain derived with live attenuated vaccine (193).

Table 14 - Presence of JE immunisation program in countries with JEV transmission risk

Country	JE immunisation program	Comment
Australia*	All risk areas	Vaccination recommended for residents of the outer Torres Strait Islands or non-residents living or working there for ≥30 days during the wet season
Bangladesh	None	
Bhutan	None	
Brunei	None	
Cambodia	National	
Myanmar	National	
China	National	Excluding the provinces of Qinghai, Tibet, and Xinjiang, which do not have endemic transmission
Taiwan**	All areas	
India	Subnational	In 216 districts with endemic JE
Indonesia	Subnational	In Bali
Japan	National	
Laos	National	
Malaysia	Subnational	In Sarawak state; in peninsular Malaysia and Sabah, vaccination is provided to children aged <15 years in vicinity of outbreak
Nepal	National	
North Korea	None	JE vaccination campaign conducted in 2016

Pakistan	None	
Papua New Guinea	None	
Philippines	Subnational	Regions I, II, III, and the Cordillera Administrative Region CAR
Russia*	None	
Singapore	None	Decided not to introduce JE vaccine because only rare, sporadic human cases are reported in the country
South Korea	National	
Sri Lanka	National	
Thailand	National	
Timor-Leste	None	
Vietnam	National	

**JE virus transmission risk in well-defined, limited areas; **A survey was not administered to health officials from Taiwan. Data for Taiwan were obtained from published literature and the Taiwan CDC website*
Adapted from Heffelfinger et al. (190)
JE = Japanese encephalitis; JEV = Japanese encephalitis virus

5.1.1.3 Barriers to implementation and discussion

Recent improvements have been seen in the presence and breadth of JE vaccine programs. At present, 62% of countries with JEV transmission risk have JE immunization programs compared to 50% in 2016 and 46% in 2012. There may be further increases as it is planned to recommend introduction of the JE vaccine into the national vaccine benefit package in Bangladesh following identification of JE vaccine as the top priority vaccine in a multicriteria decision analysis (194). It should be noted that some countries with risk have decided against a program as only rare, sporadic human cases occur (e.g., Singapore) (190). However, non-functional health facilities and lack of vaccine availability are the reason for lack of a vaccine program in other countries (e.g., Papua New Guinea) (195). It is also evident that since 2012, mouse brain-derived vaccine is used in fewer countries as recommended by WHO with more countries using newer, less reactogenic vaccines with simpler dosing schedules (188,190). Lack of disease surveillance, inadequate financial resources, competing vaccine priorities, and need for technical assistance have been cited as the four main barriers for JE vaccine introduction by decision makers in JE-endemic countries (196). The introduction of the JE vaccine has resulted in a 72% reduction in JE in Nepal, reduced the risk of acquiring JE by 61% in Sarawak, Malaysia, reduced the proportion of encephalitis caused by JEV from 40% to 15% in Thailand, and reduced morbidity in China by 97% (197–200). This emphasizes the success of a vaccine program if it is properly implemented.

5.1.1.4 Gap analysis

Table 15 - Gap analysis for JE vaccination

Where we are	Where we want to be
Approximately 62% of countries with JEV transmission risk have JE immunization programs. Implementation of JE vaccination programs have improved over the years but is still patchy in some in endemic areas.	Need to improve access to health facilities, vaccine availability, financial resources, and education to enable access to JE vaccines in countries with JEV transmission risk

	Need good burden data as vaccine introduction in resource-limited settings often require prioritization of multiple public health interventions for diseases that affect populations
Vietnam continues to use mouse brain-derived vaccines despite the WHO recommendation that inactivated mouse brain-derived vaccines be replaced with the newer generation vaccines for safety reasons.	Need to replace mouse brain-derived vaccines with safer options
General vaccine hesitancy is on the rise including in countries affected by JE **(201)**.	Need to maintain confidence in vaccine programs and high JE vaccine coverage.

JE = Japanese encephalitis; JEV = Japanese encephalitis virus

5.1.2 Tick-borne encephalitis vaccination programs

5.1.2.1 Recommended practice

Five types of TBE vaccine are currently licensed in Europe and Russia (40). The WHO recommends vaccination should be offered to the whole population in areas where TBE is highly endemic (≥5 cases/100,000/year) and to targeted individuals at risk in regions with a moderate or low TBE incidence (<5 cases/100,000/year) (202). Similarly, the Central European Vaccination Awareness Group recommends universal TBE vaccination for persons aged over one year for all countries at high risk of TBE (203).

5.1.2.2 Implementation status

Different immunisation strategies exist in European countries depending on the local epidemiological situation and regional/national risk assessment. A cross-sectional survey of TBE vaccination strategies in 28 European Union (EU)/European Free Trade Association countries was conducted as a collaboration between the Vaccine European New Integration Collaboration Effort (VENICE II) and the European Centre for Disease Control (ECDC) (204). As of 2009, vaccine against TBE was recommended for the general population in eight countries (29%; 8/28; Table 17). In four of these, including Austria, Finland, Germany, and Latvia, TBE vaccine is included in the routine immunization schedule. Vaccination is recommended at national level in Austria, the Czech Republic, and Slovenia, at subnational level in Finland, and only in endemic areas in Germany, Sweden, Estonia, and Latvia. In twelve countries (42%;12/28) vaccine recommendations were developed for occupational high-risk groups, 10 countries recommend vaccine for forestry and woodcutting workers, and eight countries recommend vaccine for people going on holidays and leisure time (e.g., hiking, camping, hunting). It should be noted that Switzerland was not included in the VENICE II report but vaccination is recommended for individuals over the age of six who live or occasionally spend time in a risk area (i.e., anywhere in Switzerland apart from the cantons of Geneva and Ticino) (205). In addition, individuals travelling to an endemic area in Austria, Czech Republic,

Estonia, Finland, Denmark, Hungary, Poland, Sweden, Slovakia, or Slovenia are recommended the TBE vaccination. Travellers who are planning to camp or trek through forests in Ireland should also consider TBE vaccination.

A study by Cassimos et al. published in 2020 reported on national immunisation policies in 2019 for adults in Europe (Table 18) (206). This study used official governmental and national public health websites, ECDC, and WHO as their sources of information. They report TBE immunisation is recommended for all adults in Austria, Czech Republic, and Latvia; for high-risk groups in Bosnia and Herzegovina, Russia, and Serbia; for residents of Åland, Finland; and for residents or those who go walking in endemic areas Slovenia (206). Vaccination against TBE is recommended for all children in Austria, Czech Republic, Hungary, Poland, and Slovenia, and for specific risk groups in 17 countries (207). Although the focus has mainly been on Europe, countries outside Europe experience TBE too, namely China and Japan. The TBE immunisation policy in China 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 (208). There is currently no TBE vaccine licensed in Japan (209).

Despite many European countries having some form of TBE vaccine policy in place, vaccination rates remain suboptimal. A population survey conducted in 2015 concluded that 25% across 10 European countries (i.e., Czech Republic, Estonia, Finland, Germany, Hungary, Latvia, Lithuania, Slovakia, Slovenia, and Sweden) had at least one injection (210). The lowest vaccination rates were seen in Finland and Slovakia (~10%) and the highest in Austria (85%). A belief that vaccination is unnecessary and that there is no risk of contracting TBE are the main reasons for not receiving vaccination.

5.1.2.3 Barriers to implementation and discussion

TBE vaccines are highly effective and considered the most successful way to prevent TBE. A large proportion of European countries have some form of TBE vaccine policy in place, which is largely dependent on the local epidemiological situation and risk assessment. However, it has been suggested that prevention of TBE is suboptimal in some European countries where an increasing number of cases are occurring (211). This is likely due to underuse of vaccine in the majority of countries with TBE, even in highly endemic areas. Some Asian countries like China and Japan, also experience TBE. Historically, TBE in China was considered an occupational disease. However, since the 1990s, 70%–95% of TBE patients were non-forest-working farmers, housewives, domestic workers, students or anyone with any occupation who

entered the endemic forest areas (209). Thus, adjustments to the immunisation policy may need consideration with more TBE cases observed in people with occupations other than forest workers (208). Despite policies being in place, it is thought that vaccine uptake is limited. Only 158,000 and 255,000 doses of second-generation purified primary hamster kidney cell-derived inactivated vaccine were released on 28 November 2007 and 3 February 2008, respectively; however, the population of the endemic provinces (including the non-endemic areas) was 65.7 million (208). Japan reported its first case of TBE in 1993; since then only four further cases have been reported (between 2016 and 2018)(212). However, endemic foci of TBEV have been identified in parts of Japan, especially Hokkaido, as has undiagnosed TBE in patients with neurological disorders (212). This emphasizes the potential for more cases to occur; however, currently no TBE vaccine is licensed in Japan (209). Climate change may alter the current distribution of TBE, and low endemic countries may see an increase in TBE burden. Milder weather may prolong the exposure period to ticks and tick activity in endemic areas (40). Also, TBE endemic areas may be extended, and the distribution of vectors may increase.

5.1.2.4 Gap analysis

Table 16 - Gap analysis for TBE vaccination

Where we are	Where we want to be
Many European countries have some form of TBE vaccine policy in place; however, TBE vaccines are underused in most, even in highly endemic areas	Need to focus efforts on raising awareness (also outside endemic areas), improving surveillance and diagnostics, ensuring better vaccine uptake, and strengthening international collaborations to look beyond natural foci and national borders
There is a TBE immunization policy in place in China for people working or living in high-risk regions, especially forest workers or those who enter the forest areas for occupational reasons.	Need to consider adjustments to the immunization policy with more TBE cases observed in non-forest-working farmers, housewives, domestic workers, students, or anyone with any occupation who entered the endemic forest areas
There is currently no vaccine licensed in Japan despite some human cases of TBE reported since 1993 and endemic foci of TBEV (e.g., in dogs, rodents, ticks) in parts of the country, especially Hokkaido.	Need to ensure a vaccine is licensed in currently low endemic countries (e.g., Japan) as climate change may alter the current distribution of TBE and result in an increase in TBE burden

TBE = Tick-borne encephalitis; TBEV = Tick-borne encephalitis virus

Table 17 – TBE Vaccine recommendations in EU/EFTA countries, 2009

Country	Surveillance	Incidence per 100,000 inhabitants in 2007	TBE vaccination program	Vaccine coverage assessment
Austria	Yes	0.58	**National** – all ages	Yes
Belgium	Yes			
Bulgaria	No			
Cyprus	No			
Czech Republic	Yes	5.00	**National** – all ages **National** – forestry, woodcutting workers, military service, police, lab workers who may be exposed to TBE, border guards, forest rangers, every person working mainly outdoors	
Denmark	No		**Endemic areas** – forestry, woodcutting workers, military service, every person working mainly outdoors, outdoor sport, holiday and leisure camp	
Estonia	Yes	10.40	**National** – forestry, woodcutting workers, agriculture workers, military service, police, lab workers who may be exposed to TBE, border guards, forest rangers, every person working mainly outdoors, other **Endemic areas** – all age groups	Yes
Finland	Yes	0.38	**Subnational** – specific age groups **Subnational** – forestry, woodcutting workers, forest rangers, outdoor sport, holidays and leisure time, mushroom/berry collectors	
France	No	0.01		
Germany	Yes	0.29	**National** – lab workers who may be exposed to TBE, forest rangers **Subnational** – other **Endemic areas** – all age groups, forestry, woodcutting workers, agriculture workers, every person working mainly outdoors	Yes
Greece	Yes	0.01		
Hungary	Yes	0.70	**National** – forestry, woodcutting workers, agriculture workers **Endemic areas** – outdoor sport, holidays and leisure time	
Iceland	No			
Ireland	No			
Italy	Yes	0.03	**Endemic areas** – every person working mainly outdoors, outdoor sport, holiday and leisure camp	
Latvia	Yes	7.50	**National** – forestry, woodcutting workers, military service, police, lab workers who may be exposed to TBE, border guards, forest rangers **Endemic areas** – specific age groups, other	Yes
Lithuania	Yes	6.89		

Malta	No			
The Netherlands	No		**Endemic areas** - recreational activities in forested areas such as camping and hiking or working in forestry occupations, as well as long-term travellers to endemic areas	
Norway	Yes	0.30	**Endemic areas** – outdoor sport, holidays and leisure time	
Poland	Yes	0.61	**National** – forestry, woodcutting workers, agriculture workers, military service, border guards, forest rangers, holidays and leisure time	Yes
Portugal	No			
Romania	Yes	1.44		
Slovakia	Yes	1.06	**National** – forestry, woodcutting workers, agriculture workers, military service, police, lab workers who may be exposed to TBE, forest rangers, every person working mainly outdoors, other **Endemic areas** – outdoor sport, holidays and leisure time, mushroom/berry collectors	
Slovenia	Yes	9.90	**National** – all ages **National** – forestry, woodcutting workers, agriculture workers, military service, police, lab workers who may be exposed to TBE, border guards, forest rangers, every person working mainly outdoors, outdoor sport, holidays and leisure time, mushroom/berry collectors	Yes
Spain	No			
Sweden	Yes	1.97	**Endemic areas** – all age groups	
United Kingdom	No		**National** – lab workers who may be exposed to TBE	

From VENICE/ECDC report (204)*; EFTA = European Free Trade Association; EU = European Union; TBE = Tick-borne encephalitis*

Table 18 - National vaccination policies for adults in Europe, 2019

	Measles	Tick-borne encephalitis	Rabies
Albania	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Austria	Recommended for all adults	Recommended for all adults	Not mandatory-not recommended
Belarus	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Belgium	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Bosnia Herzegovina	Not mandatory-not recommended	Recommended for specific groups	Mandatory for specific groups
Bulgaria	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Croatia	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Cyprus	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Czech Republic	Not mandatory-not recommended	Recommended for all adults	Recommended for specific groups
Denmark	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Estonia	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Finland	Not mandatory-not recommended	Recommended for specific groups	Not mandatory-not recommended
France	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Germany	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Greece	Recommended for all adults; recommended for specific groups	Not mandatory-not recommended	Not mandatory-not recommended
Hungary	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Iceland	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Ireland	Recommended for all adults; recommended for specific groups	Not mandatory-not recommended	Not mandatory-not recommended
Italy	Recommended for all adults; recommended for specific groups	Not mandatory-not recommended	Not mandatory-not recommended
Latvia	Not mandatory-not recommended	Recommended for all adults	Not mandatory-not recommended
Liechtenstein	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Lithuania	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Luxembourg	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Malta	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Moldova	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Monaco	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Montenegro	Not mandatory-not recommended	Not mandatory-not recommended	Mandatory for specific groups
Netherlands	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
North Macedonia	Not mandatory-not recommended	Not mandatory-not recommended	Mandatory for specific groups
Norway	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Poland	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Portugal	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended

Romania	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Russia	Mandatory for specific groups; recommended for specific groups	Recommended for specific groups	Not mandatory-not recommended
Serbia	Not mandatory-not recommended	Recommended for specific groups	Mandatory for specific groups
Slovakia	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Slovenia	Not mandatory-not recommended	Recommended for specific groups	Not mandatory-not recommended
Spain	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Sweden	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
Switzerland	Recommended for all adults	Not mandatory-not recommended	Not mandatory-not recommended
Ukraine	Not mandatory-not recommended	Not mandatory-not recommended	Not mandatory-not recommended
United Kingdom	Recommended for all adults	Not mandatory-not recommended	Recommended for specific groups

From Cassimos et al. (206)

5.1.3 Measles vaccination programs

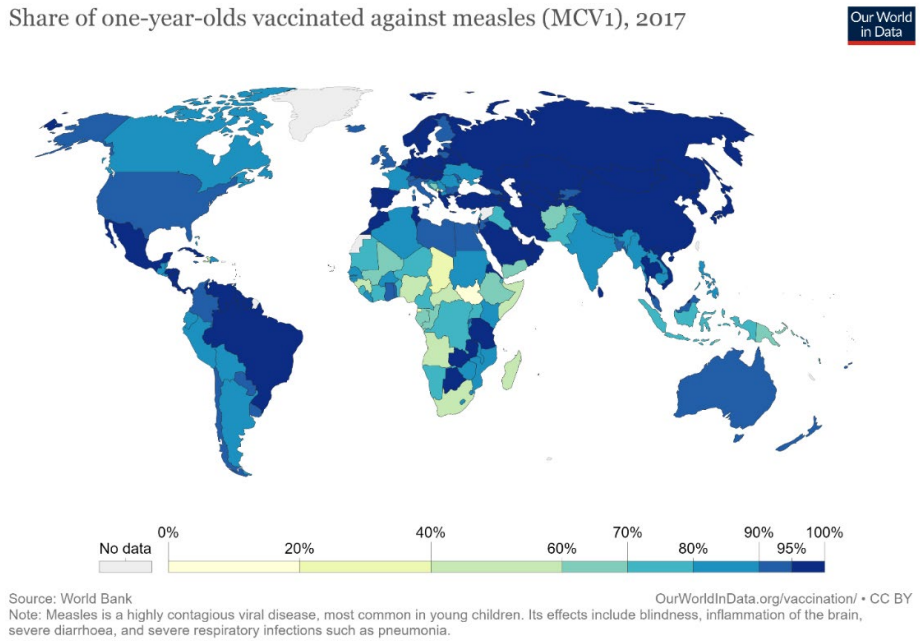
5.1.3.1 Recommended practice

Despite the availability of a safe and effective vaccine, measles still infects hundreds of thousands of people globally. Approximately 90,000 deaths occur every year due to measles; 87% are in children under the age of five years (213). It is estimated that 1-3 in 1,000 children who contract measles will develop encephalitis; 10–15% of those children will die and a further 25% will be left with permanent neurological damage (214). The WHO recommends 95% vaccination coverage with two doses of measles-containing vaccine in each country to protect the population from measles (215).

5.1.3.2 Implementation status

The WHO estimated that in 1980 only 16% of one-year olds received the first dose of a measles-containing vaccine (MCV1); this increased to 86% in 2018. As a result, deaths due to measles decreased by 84% between 2000 and 2016. Coverage of MCV1 by country in 2017 is displayed in Figure 10. The lowest coverage is seen in sub-Saharan Africa (e.g., 20% in South Sudan and 37% in Chad), some Pacific Islands including Papua New Guinea (62%), and unstable countries such as Afghanistan (62%) and Iraq (71%) (213). A study on the trends of measles vaccine coverage in 204 countries from 1990 to 2019 reported only 74 (36%) reached the recommended MCV1 coverage rate of 95% (216).

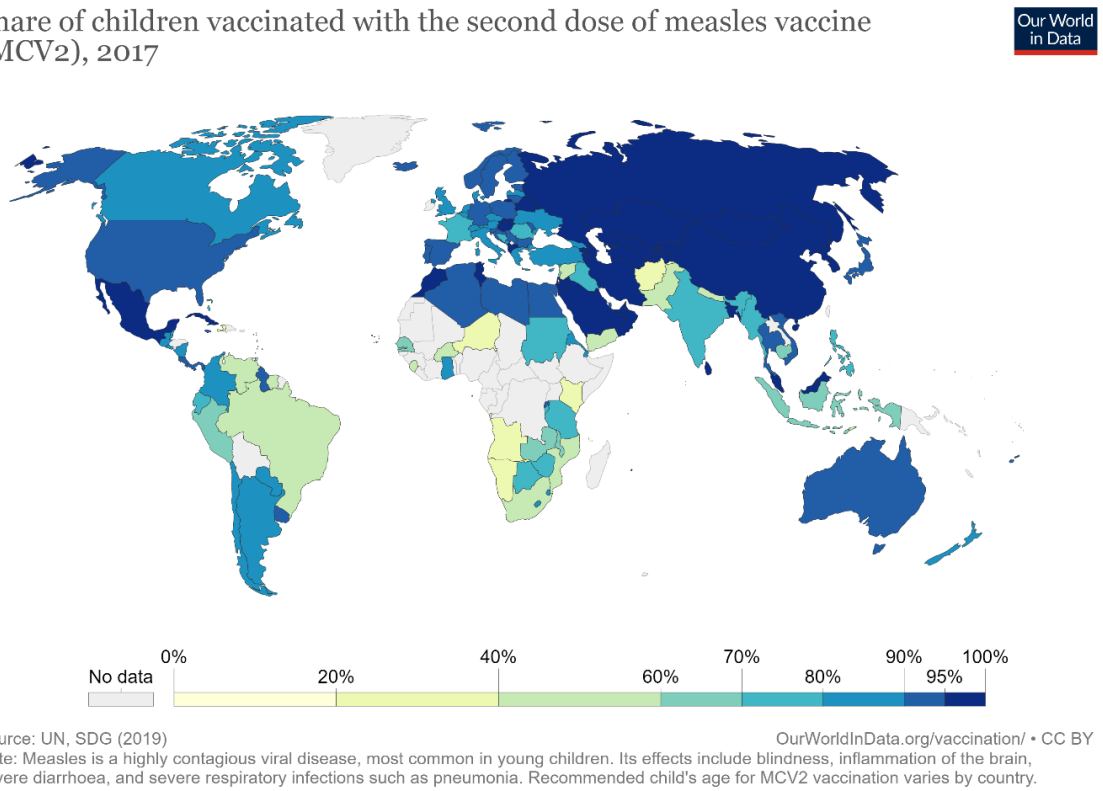
Figure 10 - Global coverage of first dose of measles-containing vaccine in one-year olds, 2017



From Vanderslott et al. (213)

A higher level of protection is achieved with two doses of a measles-containing vaccine (MCV2). The WHO estimated that 183 Member States had included a second dose as part of routine immunisation by the end of 2021 resulting in an average global coverage of 71% (217). Coverage of MCV2 by country is displayed in Figure 11. In 2017, coverage was lowest in Angola (30%), Namibia (32%), Kenya (35%), Niger (38%), and Afghanistan (39%). Furthermore, many countries in sub-Saharan Africa have yet to introduce MCV2 as part of routine immunisation (213). Only 36 (18%) countries reported a rate of MCV2 over 95% in a study on the trends of measles vaccine coverage in 204 countries from 1990 to 2019 (216).

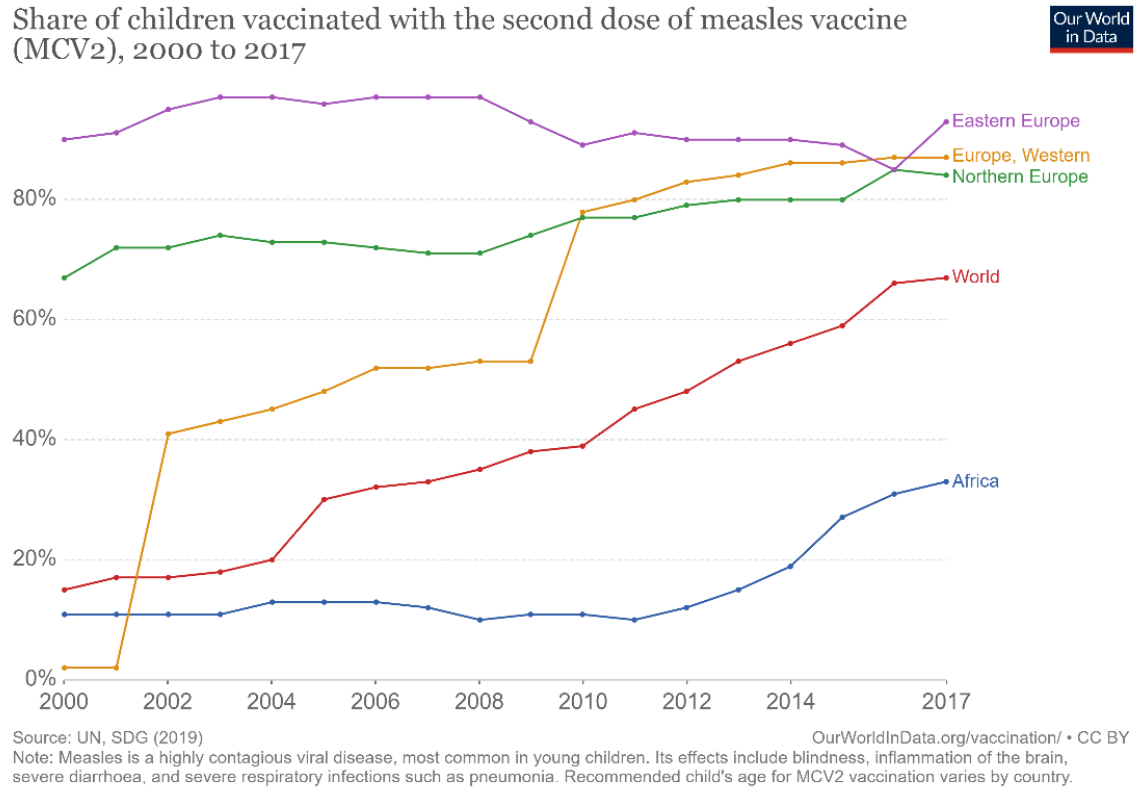
Figure 11 – Global coverage for second dose of measles-containing vaccine, 2017



From Vanderslott et al. (213)

A substantially higher proportion of European children have been vaccinated with two doses of a measles-containing vaccine than African children (Figure 12).

Figure 12 – Proportion of children given second dose measles vaccine in Europe and Africa

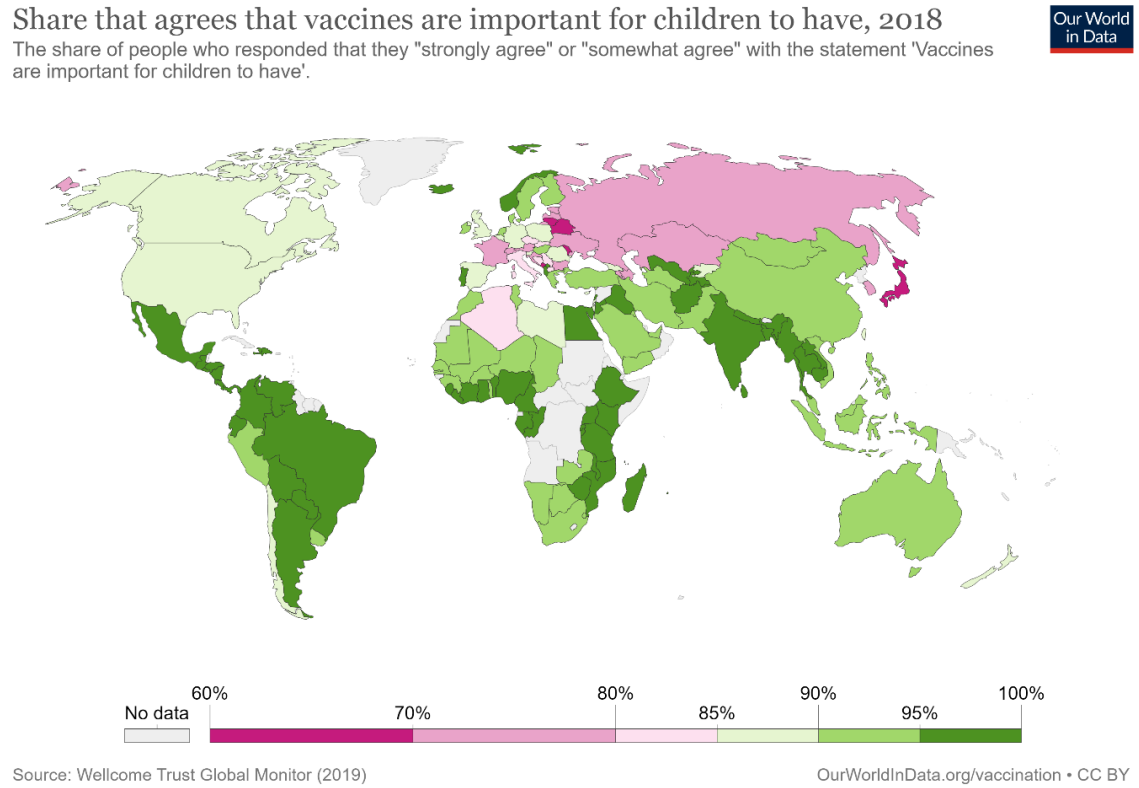


5.1.3.3 Barriers to implementation and discussion

5.1.3.3.1 Barriers to implementation

A survey on peoples' attitudes to science and major health challenges, including attitudes to vaccination, was conducted by The Wellcome Trust in 2018 and included >140,000 people from 140 countries (218). The survey found that >90% of the world's population believe childhood immunisation is important. Despite support for vaccination being generally high, some differences were observed between northern and southern countries. Vaccination support was highest across South Asia (98%), South America (97%), Northern Africa (94%), and Southern Africa (92%). Although still high, vaccination support was lower across North America (87%), Western Europe (83%), and Eastern Europe (80%; Figure 13). Countries with the lowest support for childhood immunisation include Belarus (61%), Japan (66%), Moldova (66%), Montenegro (68%), and Lithuania (69%).

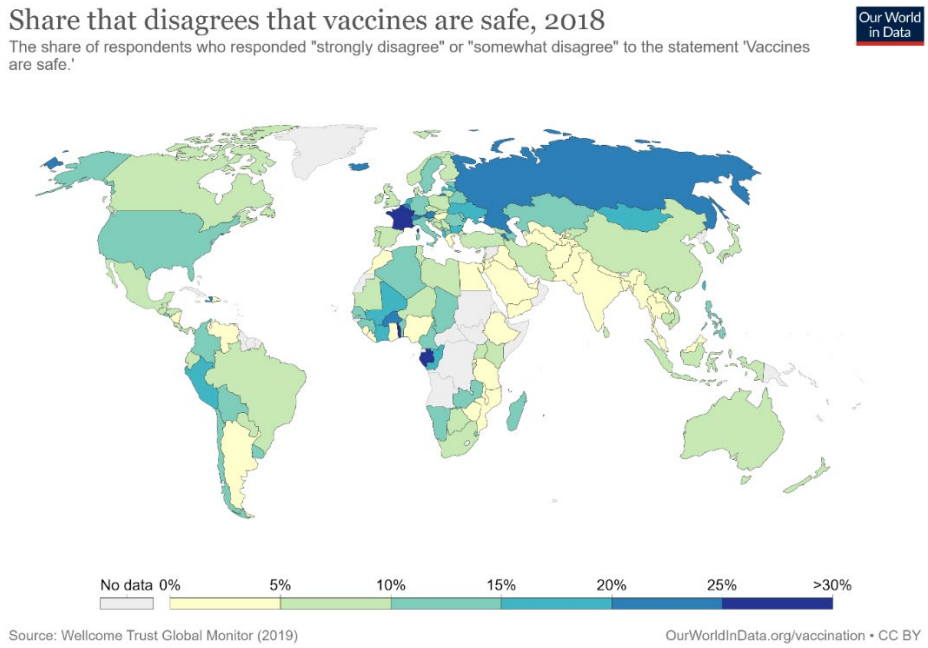
Figure 13 – Proportion of respondents by country who believe childhood immunisation is important, 2018



From Vanderslott et al. (213)

When asked about perceived safety of vaccines, only 7% of respondents strongly or somewhat disagreed with the statement 'vaccines are safe' (213,218). This ranged from <1% in Bangladesh to 33% in France. Apart from France, other countries with high mistrust of vaccine safety included Gabon (26%), Togo (25%), Russia (24%), Switzerland (22%), Austria (21%), Belgium (21%), and Iceland (21%; Figure 14).

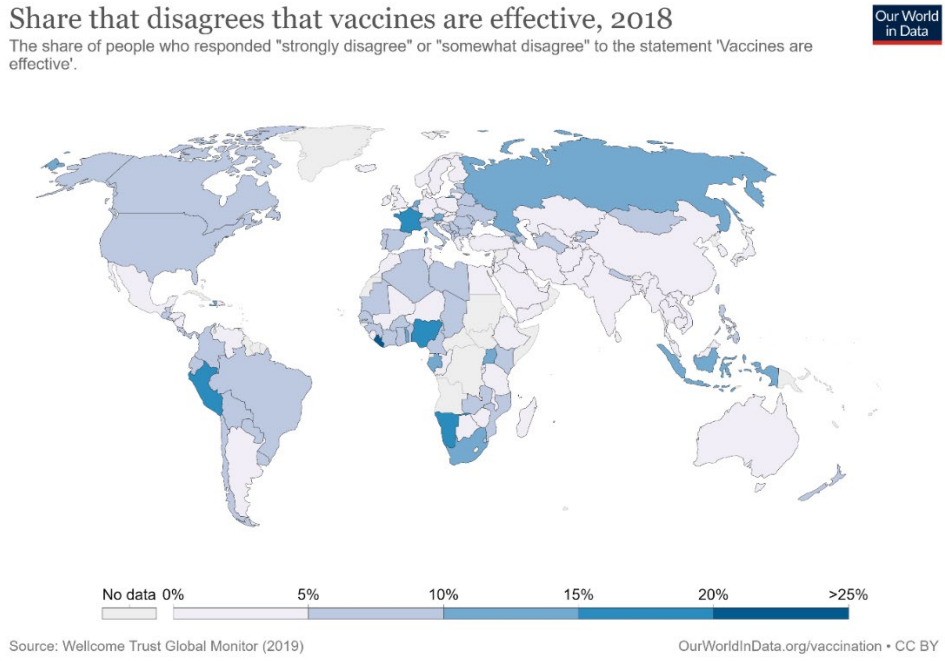
Figure 14 – Proportion of respondents by country who disagree that vaccines are safe, 2018



From Vanderslott et al. (213)

When asked about perception of vaccine effectiveness, only 5% of respondents strongly or somewhat disagreed with the statement 'vaccines are effective' (213,218). This ranged from <1% in Bangladesh and Egypt to 28% in Liberia. Skepticism of vaccine effectiveness was also high in France (18%), Namibia (16%), Nigeria (16%), and Peru (15%; Figure 15).

Figure 15 - Proportion of respondents by country who disagree that vaccines are effective, 2018



From Vanderslott et al. (213)

5.1.3.3.2 Discussion

Despite the availability of vaccine, cases of measles are increasing at an alarming rate. This is important as approximately 90% of people who are not already immune will become infected following exposure to the measles virus (218). In LMICs, it is estimated that 1 or 2 in every 1,000 children with measles will die from the disease or its complications (218). Global vaccine coverage has not reached sufficient levels to prevent outbreaks. The WHO recommends 95% vaccine coverage of two doses of measles-containing vaccine to protect the population against measles. Many countries in sub-Saharan Africa have yet to introduce a second dose, and in many other countries coverage remains low. In 2021, an estimated 9 million cases and 128,000 deaths from measles occurred worldwide, 22 countries experienced large and disruptive outbreaks, and almost 61 million doses of measles vaccine were postponed or missed in 18 countries due to COVID-19 (219). Measles remains an imminent threat in every region of the world due to declines in vaccine coverage, weakened measles surveillance, continued interruptions and delays in immunisation activities due to COVID-19, and persistent large outbreaks in 2022. Efforts must focus on improving routine immunisation and health systems and overcoming vaccine hesitancy.

5.1.3.4 Gap analysis

Table 19 - Gap analysis for measles vaccination

Where we are	Where we want to be
The average global coverage of second dose of measles-containing vaccine was estimated at 71% in 2021. Many countries in sub-Saharan Africa have yet to introduce a second dose, and in other countries coverage remains low (e.g., Angola, Namibia, Kenya, Niger, Afghanistan).	Need to increase the number of countries, especially in Africa, offering a second dose of measles-containing vaccine as part of routine immunization Need to increase the coverage of measles-containing vaccine to 95% in each country Need to focus efforts on improving routine immunisation and health systems and overcoming vaccine hesitancy

5.1.4 Rabies vaccination programs

5.1.4.1 Recommended practice

Rabies CNS involvement manifests as classic or furious encephalitic rabies in 80% of cases as opposed to paralytic rabies (220). To date, no effective therapy for rabies CNS involvement has been developed and most cases result in death. Vaccination against rabies can be used to protect against exposure to rabies (i.e., pre-exposure vaccination) or to prevent the development of clinical symptoms once exposure has occurred (i.e., post-exposure prophylaxis [PEP]). Rabies transmitted by dogs is most common in LMICs, whereas rabies transmitted by bats account for the few cases seen in industrialized countries. Pre-exposure

vaccination with cell-culture- or embryonated-egg-based vaccine is recommended for individuals living in or travelling to countries or areas at risk and people at high risk of exposure to rabies, including laboratory staff working with rabies virus, veterinarians, animal handlers, and wildlife officers. The WHO recommends intradermal (ID) administration of rabies vaccine for pre-exposure prophylaxis (221). Prompt PEP may be required in countries or areas at risk of rabies following an animal bite or other contact with an animal suspected to be rabid. PEP includes wound washing, vaccination with rabies vaccine, and administration of rabies immunoglobulin (RIG) where indicated (44). The WHO and partner organisations have set a target for global elimination of dog-mediated rabies by 2030.

5.1.4.2 Implementation status

National rabies vaccination policies for adults exist in some European countries (Table 18). Rabies vaccine is recommended for specific risk groups in the Czech Republic and UK, and is mandatory for specific risk groups in Bosnia Herzegovina, Serbia, Montenegro, and North Macedonia. In other European countries rabies vaccine is not recommended or mandatory. In the USA, individuals at high risk of exposure, such as vets, animal handlers, and laboratory workers, should be offered rabies vaccination (222).

The vast majority of rabies cases/deaths worldwide occur in Asia and Africa (44). A survey of 35 key personnel at the national, county, sub-county, and health facility levels in five counties of Kenya was conducted (44). Results showed considerable variability in the availability of rabies vaccine and immunoglobulin within Kenya, administration of PEP via the intramuscular (IM) route rather than intradermally (i.e., one ID dose is 0.1 mL of vaccine while one IM dose is an entire vial of vaccine irrespective of vial size), and a high cost of rabies PEP and immunoglobulin to patients with bites (44). A further study which assessed patient characteristics associated with initiation and completion of rabies PEP in Vietnam between 2014 and 2016 showed that only 70% and 41% of patients with animal exposures completed two and five doses, respectively, of their IM vaccine course (223).

Sreenivasan et al. reported the results of a standardized assessment of rabies PEP procurement, forecasting, distribution, monitoring, and reporting in 23 LMICs in Asia and Africa (43). Data on administration route, cost, and accessibility of rabies vaccine and immunoglobulin in the public sector by country are displayed in Table 20. Almost 60% of countries (13/22) have a national program or guidelines for rabies control and prevention; these included seven countries in Asia and six in Africa. Rabies vaccine was available in all countries; however, accessibility and cost varied widely. Vaccine was widely accessible in

36% (8/22), accessible in 32% (7/22), and limited in 32% of countries (7/32; Table 20). Rabies vaccine was only widely accessible in one African country and limited in five. Almost 90% of countries with wide access to vaccine had a national rabies control program or guidelines. Rabies vaccine was reported to be consistently provided for free in the public sector in 43% (10/23) of countries. RIG was less accessible than vaccine; 65% (15/23) of countries had limited access of which 11 were in Africa. RIG was only widely accessible in two countries. Approximately half of countries (12/23) used the IM route exclusively for rabies vaccination; 10 of these were in Africa. A further five Asian countries reported using both IM and ID administration.

Table 20 - Administration route, cost, and accessibility of rabies vaccine and rabies immunoglobulin in the public and non-private sectors of Asian and African countries, 2017–2018

Country	National program/ guidelines	Route of administration	Vaccine accessibility*	Vaccine cost to patient	RIG accessibility	RIG cost
Cameroon		Intramuscular	Accessible	$13-17/dose	Limited	-
Chad		Intramuscular	Limited	$13/dose	Limited	-
Côte d'Ivoire		Intramuscular	Accessible	$13/dose	Limited	-
Ethiopia	Yes	Subcutaneous Intramuscular	Limited	$2-4/course $13/dose	Limited	-
Ghana		Intramuscular	Limited	Free	Limited	-
Kenya	Yes	Intramuscular	Accessible	$12-15/dose	Limited	$70/vial
Madagascar	Yes	Intradermal	Accessible	Free	Limited	Free
Mali		Intramuscular	Limited	$20/dose	Limited	-
Malawi (Blantyre district only)		Intramuscular	Information not available	Free	Limited	-
Nigeria	Yes	Intramuscular	Limited	Free	Limited	-
South Africa	Yes	Intramuscular	Widely accessible	Free	Widely accessible	Free
Tanzania	Yes	Intramuscular	Accessible	$13	Limited	-
Bangladesh	Yes	Intradermal	Widely accessible	Free	Accessible	Free - $15/vial
Bhutan	Yes	Intradermal	Widely accessible	Free	Accessible	Free
India	Yes	Intradermal Intramuscular	Accessible	Free	Limited	Free
Nepal		Intradermal Intramuscular	Accessible	Free	Limited	-
Sri Lanka	Yes	Intradermal	Widely accessible	Free	Accessible	Free
Pakistan		Intradermal Intramuscular	Limited	Free	Limited	Free
Cambodia		Intradermal Intramuscular	Limited	Free - $15/dose	Limited	$37/ patient
China	Yes	Intramuscular	Widely accessible	$50/course	Widely accessible	$25-50/ vial
Mongolia		Intramuscular	Widely accessible	Free	Limited	Free
Philippines	Yes	Intradermal	Widely accessible	Free	Accessible	$28-32/vial
Vietnam	Yes	Intradermal Intramuscular	Accessible	$7-13/dose	Accessible	$15-27/vial

**Widely accessible = vaccine or RIG available for free or at a subsidized cost at the central level, provincial, state or regional level, and at least one health facility in every district, county or zone; Accessible = vaccine or RIG available at the central level and provincial, state, or regional level but not in every district, county or zone, or available in every district but at a cost to patients (greater than US$ 5/dose); Limited accessibility = vaccine or RIG only available at the central level (regardless of cost) or being sporadically available at lower levels because of budget constraints or stock outs*
Adapted from Sreenivasan et al. (43)

Dog-mediated rabies in Latin American countries has decreased significantly over the last three decades but only 37% of countries surveyed in 2013/4 reported sufficient funds to sustain their rabies control program, which includes the use of PEP (224). A situational analysis of rabies in the Caribbean (conducted via survey and literature review) showed that pre-exposure rabies vaccination for at-risk groups (e.g., vets and laboratory personnel) was routinely conducted and vaccine was available for PEP in all endemic countries in 2014//5 (225). RIG for PEP however was only available in five of 10 endemic Caribbean countries; it was not available in Belize, Dominican Republic, Guyana, Suriname, and Trinidad despite these countries being endemic for rabies. It was also available in three non-endemic Caribbean countries, including Bonaire, Bermuda, and Guadeloupe.

5.1.4.3 Barriers to implementation and discussion

Rabies vaccine is effective yet an estimated 59,000 human deaths still occur each year due to rabies (44). Data shows the availability and cost of rabies vaccine and PEP varies between and within countries and is often limited in the places that need it the most. In Africa in particular, vaccine is widely limited, RIG is less accessible than vaccine, and rabies vaccination is most often given via the IM route. The WHO recommends pre-exposure rabies vaccine be administered intradermally as 60-80% less vaccine volume is used via this route, which lowers the vaccination cost, extends supplies, and prevents shortages (226). Monoclonal antibodies for PEP might be preferable to RIG in terms of supply, cost, and efficacy (227). Almost 90% of Asian and African countries which reported wide access to rabies vaccine had a national rabies control program or guidelines. This highlights the importance of developing and ensuring such programs or guidelines are in place within endemic countries. PEP is almost 100% effective in preventing rabies when given appropriately and in a timely manner (43). However, it is evident that prompt provision of PEP remains a challenge in rabies endemic areas due to lack of steady supply of PEP for bite patients that seek care, delays in receiving PEP due to long distances bite patients have to travel to access health care, lack of affordability of PEP, or poor health care seeking by bite patients due to a lack of knowledge about the risk of rabies and its prevention (44). Efforts need to focus on shifting these barriers to reach the WHO target for global elimination of dog-mediated rabies by 2030 (44). It should be noted that mass vaccination of dogs is a key

component of national rabies elimination programmes and has been successful in eliminating dog-transmitted rabies in Europe, North and Latin America, and Japan (228).

5.1.4.4 Gap analysis

Table 21 - Gap analysis for rabies vaccines

Where we are	Where we want to be
Rabies vaccine is effective, yet an estimated 59,000 human deaths still occur each year due to rabies, mainly in Asia and Africa. In Africa in particular, vaccine is widely limited, and RIG is less accessible than vaccine.	Need to increase provision of readily available vaccine across all countries where rabies is endemic, as well as educate people about dog bite prevention. Canine vaccination programs should also be implemented in endemic areas.
A national rabies control program or guidelines are available in almost 90% of Asian and African countries which reported wide access to rabies vaccine.	Need to ensure development and implementation of such programs or guidelines in all rabies endemic countries, which will increase government buy-in and funding
PEP is almost 100% effective in preventing rabies when given appropriately and in a timely manner, but prompt provision of PEP remains a challenge in rabies endemic areas.	Need to increase supply of PEP for bite patients that seek care, minimize delays in receiving PEP due to long distances bite patients have to travel to access health care, make PEP more affordable, and educate people about the risk of rabies and its prevention and the importance of seeking health care if bitten
In Africa in particular, rabies vaccination is predominantly given via the IM route.	Need to shift pre-exposure rabies vaccine administration from IM to ID in line with the WHO guidelines as 60-80% less vaccine volume is used via the ID route, thus lowering vaccination cost, extending supplies, and preventing shortages

ID = Intradermal; IM = Intramuscular; PEP = Post-exposure prophylaxis; RIG = Rabies immunoglobulin; WHO = World Health Organization

5.1.5 Varicella zoster virus vaccination programs

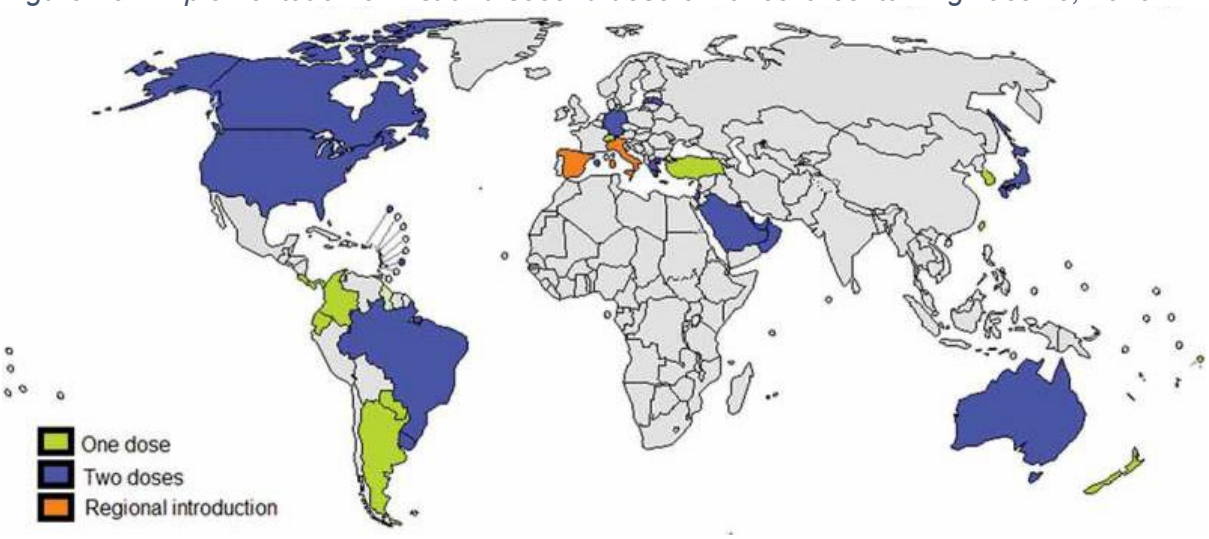
5.1.5.1 Recommended practice

VZV affects ~140 million individuals annually despite the availability of a safe, well-tolerated, and effective vaccine (229). Approximately 4.2 million severe complications requiring hospitalisation and ~4,200 deaths from VZV infections occur per year (230). The greatest disease burden has been reported in children, which represent 90% of cases, 70% of hospitalisations, and 50% of deaths (229). It is estimated that 2-4 per 1,000,000 individuals who contract VZV will develop encephalitis (231); 9–20% of those individuals will die and a further 33% will be left with neurological complications (232). The WHO recommends ≥80% vaccination coverage with two doses of varicella-containing vaccine in each country to reduce the mortality and morbidity from VZV (230).

5.1.5.2 Implementation status

The vaccine effectiveness of the varicella vaccine is estimated at 55-87% for one dose and 84-98% for two doses *(233)*. However, despite the established efficacy, the varicella vaccine it is not universally part of routine immunisations having only been recommended in 36 countries, predominantly HICs *(234)*. Implementation of the first and second dose of varicella vaccine by country in 2019 is displayed in Figure 16. Many countries around the world, particularly in Africa and Asia, have yet to recommend the varicella vaccine as part of routine immunisation.

Figure 16 - Implementation of first and second dose of varicella-containing vaccine, 2019



From Varela et al. (234)

5.1.5.3 Barriers to implementation and discussion

There are several known barriers specific to the implementation of universal varicella vaccination. VZV is frequently perceived to have a low risk of complications with only immunocompromised children or those with underlying medical conditions being at risk (235). This is supported by a survey on parental attitudes to varicella vaccination in preschool and school children which was conducted in Hong Kong in 2015 and included >3,000 parents (236). The survey found that VZV infection being considered a “minor infection” was a key reason that parents did not vaccinate their children. Another key barrier is the potential impact that vaccination programmes could have on the epidemiology of VZV infections (235). In populations where varicella vaccinations have reduced natural infections from VZV, natural boosting of immunised individuals would also likely be reduced (235). This may lead to a shift in infections from young children to older age groups, who are at high risk from complications, resulting in increased morbidity and mortality, despite an overall decline in the number of VZV cases (237). Having reduced natural immunity may also led to an increase in the risk of viral

reactivation in individuals with latent VZV through natural infection (238). This has been postulated as a key reason to why the UK is yet to implement universal varicella vaccination (235,239). Lastly, cost-effectiveness analyses show little economic support for universal varicella vaccination, and funds for vaccination programmes are often highly limited (235). However, it should be noted that the burden of VZV brain infection is likely underestimated which may affect cost-benefit analyses.

Thus, despite the availability of a vaccine for VZV, many countries around the world have chosen not to recommended or include it in within their routine vaccinations. This is important as an effective vaccination program has been shown to reduce hospitalisations and complications at least three-fold with the greatest reduction in children under four years of age (234,240). VZV is the second leading cause of viral encephalitis, accounting for 5% of total cases within the UK and other HICs, and is highly preventable with the varicella vaccine (13). However, currently global vaccine coverage must significantly increase to reach levels to prevent outbreaks. The WHO recommends 80% coverage of two doses of varicella containing vaccine to protect the population against VZV. Many countries in Africa, Asia and Eastern Europe have yet to introduce or recommend vaccination.

5.1.5.4 Gap analysis

Table 22 - Gap analysis for varicella vaccination

Where we are	Where we want to be
Currently, 36 countries around the world recommend the varicella. Many countries in Africa, Asia and Eastern Europe have yet to introduce or recommend the varicella vaccine.	Need to increase the number of countries, which offer or recommend the varicella vaccine to be taken Need to increase the coverage of varicella vaccine to 80% in each country Need to focus efforts on improving routine immunisation and health systems and overcoming vaccine hesitancy

5.1.6 Vaccines in travelers

Travelers are advised to have a medical consultation prior to departure to acquire knowledge on disease risk in the country/ies they plan to visit and necessary steps to prevent illness, including vaccination. Specific vaccinations that may be recommended to prevent travel-associated encephalitis include for example JE, TBE, and rabies vaccine. The WHO recommends TBE vaccination in travelers to endemic areas, particularly if their visits include outdoor activities (241). JE vaccination is recommended for travelers spending extensive time in JE endemic areas (242). However, despite the availability of vaccine, cases of travel-associated encephalitis still occur. In 2014/15, three cases of JE were diagnosed in British travelers; all suffered severe, life-threatening illness and have been left with life-changing

neurological sequelae (243). Similarly, 38 cases of TBE were documented in 2012 in Central/ Western Europe among international travelers (205). Reasons individuals contract travel-associated encephalitis include failure to vaccinate due to poor travel advice and cost of vaccination. A survey of travelers from Canada, Germany, Sweden, and UK to TBE-endemic regions reported only 69% had heard of TBE, 32% had heard of TBE vaccine, and most sought information online rather than through family doctors or travel clinics (241). A survey of 85 travelers identified cost and 'lack of perceived necessity' as barriers to patient acceptance of pharmacist-provided recommendations for international travel and showed JE and rabies were the vaccines with the lowest acceptance (244). Efforts to increase awareness of travel risk and available vaccines and reduce costs associated with receiving advice and vaccination are needed to reduce the occurrence of travel-related encephalitis.

5.1.6.1 Gap analysis

Table 23 - Gap analysis for vaccines in travellers

Where we are	Where we want to be
Despite the availability of vaccine, cases of travel-associated encephalitis still occur.	Need efforts to increase awareness of travel risk and available vaccines Need efforts to reduce costs associated with receiving advice and vaccination

5.1.7 Other vaccines in development

Further vaccines are in development that may prevent encephalitis from other causes in the future. Several vaccine candidates against Chikungunya virus have shown promising safety and immunogenicity results in Phase 1 and 2 clinical trials (245,246). Valneva recently announced successful completion of the Phase 3 pivotal trial of its single-shot chikungunya vaccine candidate, VLA1553, and is currently seeking Food and Drug Administration (FDA) approval for use in adults (247).

A live attenuated vaccine against Venezuelan equine encephalitis virus (VEEV) was developed in 1961 and has been used exclusively for laboratory and military personnel at risk of contracting VEEV and to immunize horses. This vaccine however is associated with adverse events, serological nonresponse, and lacks full coverage of VEEV (248). There are currently no vaccines against EEEV, VEEV, or WEEV licensed for human use; however, several vaccines are currently under development to protect against these encephalitic alphaviruses.

The rapid development and implementation of vaccines against SARS-CoV-2 in response to the COVID-19 pandemic have shown how much can be achieved when there is financial commitment, determination, and engagement of the global scientific community. Novel

vaccine platforms (e.g., mRNA), adoptive case-driven trial designs, and a rolling review process by regulators have facilitated this process (249). Lessons should be learned and applied to the development of future vaccines, including those against other causes of encephalitis.

5.2 Vector control

Vaccines are the most effective intervention for the aforementioned causes of encephalitis. However, other measures exist that could help reduce disease burden. Use of protective clothing and repellents to avoid mosquito and tick bites and avoiding the consumption of unpasteurized milk or dairy products in TBE risk areas (as infected dairy animals can shed TBEV in their milk) may reduce the burden of TBE (250). Mosquito nets have only proved effective in one study of JE; several other studies have shown no effect (188). Mass dog vaccination has resulted in elimination of canine rabies in Malaysia, Japan, Taiwan, Singapore, and across Western Europe (251). There is however little evidence that interventions apart from vaccination of humans, for example vaccination of pigs, environmental management for vector control, and chemical control of vectors, reduces JE disease burden (188). It is important to intensify efforts to prevent and control vector-borne diseases as climate change is likely to increasingly impact vector-borne disease transmission and spread (252).

5.3 Epidemic control

Encephalitis can either occur sporadically or in outbreaks. Encephalitis itself might be epidemic (e.g., arboviruses) or may occur as a feature of disease epidemics for which encephalitis is a rare complication (e.g., COVID-19) (1). The control of encephalitis outbreaks, or epidemic control, is dependent on the underlying aetiology and availability of a vaccine. For example, a vaccination campaign can be considered (but its value has not been studied) if a JE outbreak occurs in an area where JE vaccination has not yet been introduced (253). Factors such as outbreak size, response timeliness, population affected, and program capacity should be taken into account, and the use of live vaccines are recommended for rapid production of protective antibodies (253). Following the outbreak vaccination campaign, introduction of JE vaccine into the routine immunisation schedule is recommended. In Nipah virus outbreaks, where a vaccine is not available, successful epidemic control measures have included isolation of pig farms known to harbour Nipah virus, evacuation of farmers/pig handlers, and the culling of pigs to limit further transmission (254).

For disease outbreaks where encephalitis is a complication (e.g., influenza, COVID-19, measles), different epidemic control strategies can be adopted. Public health interventions such as self-isolation and social distancing have been implemented to reduce the spread of the coronavirus epidemic and thus the subsequent occurrence of resulting encephalitis cases (255). Similar non-pharmaceutical interventions have been used to control influenza outbreaks, as well as vaccination or prophylaxis with antiviral drugs (255,256).

6 Diagnosis and treatment

6.1 Diagnostics

6.1.1 Overview of diagnostic tests

Numerous diagnostic tests are available for the aetiological diagnosis of encephalitis (257). CSF culture can be used for the diagnosis of bacterial encephalitis, while CSF microscopy is helpful for detection of acid-fast bacilli in tuberculous (TB) encephalitis. Serological techniques provide diagnostic support for some causes of encephalitis (e.g., arboviruses); however, when an organism is detected outside the CNS it can be difficult fully to attribute causality. The gold standard for the aetiological diagnosis of most viral encephalitides is CSF PCR. The CSF can also be examined for the presence of microbe-specific intrathecal antibodies present in excess of that predicted by passive transfer from the periphery indicating a local infectious or inflammatory process in the CNS. CSF biochemistry, microbiological tests performed on samples from outside the CNS, and neuroimaging results can provide important supporting diagnostic information in the absence of a lumbar puncture (LP). The diagnosis of ADEM relies primarily on magnetic resonance imaging (MRI). Serological tests are used to identify the precipitant infection of ADEM and test for autoantibody encephalitis. Metagenomics includes sequencing the total deoxyribonucleic acid (DNA)/ribonucleic acid (RNA) from a sample to enable the identification of genetic material from any (known or unknown) microorganism present in the specimen that might be causing encephalitis. This method might have a role to play in undiagnosed encephalitis but has yet to be implemented on a routine basis (258).

6.1.2 Recommended practice

The 3rd WHO Model List of Essential Diagnostics was published in 2021 (updated from 1st edition in 2018) to help countries prioritize important diagnostic tests for their populations (259). The intention is for countries to use this list to decide which diagnostic tests to select and where to use them, depending on their epidemiology, resources, and infrastructure. The

list does not specifically refer to encephalitis but recommends types of tests that can be used for the diagnosis of many communicable and non-communicable diseases, including encephalitis. The WHO List of Essential Diagnostics recommends microscopy and culture of CSF specimens for bacteriology, mycology, and parasitology. More specifically, the tests that pertain to neurology include CSF cryptococcal antigen (for cryptococcal meningitis), CSF nucleic acid amplification test (CNS TB), CSF bacterial culture, CSF Venereal Disease Research Laboratory test (neurosyphilis), CSF cell cytology, and CSF profile (i.e., red and white blood cells, glucose, protein) (259,260). Despite numerous diagnostic tests being available for the diagnosis of encephalitis, we focus on global access to the following four: 1) CSF examination, including microscopy/culture, 2) CSF HSV PCR, 3) MRI, and 4) autoantibody testing for the aetiological diagnosis of encephalitis.

6.1.3 Implementation status

6.1.3.1 CSF examination

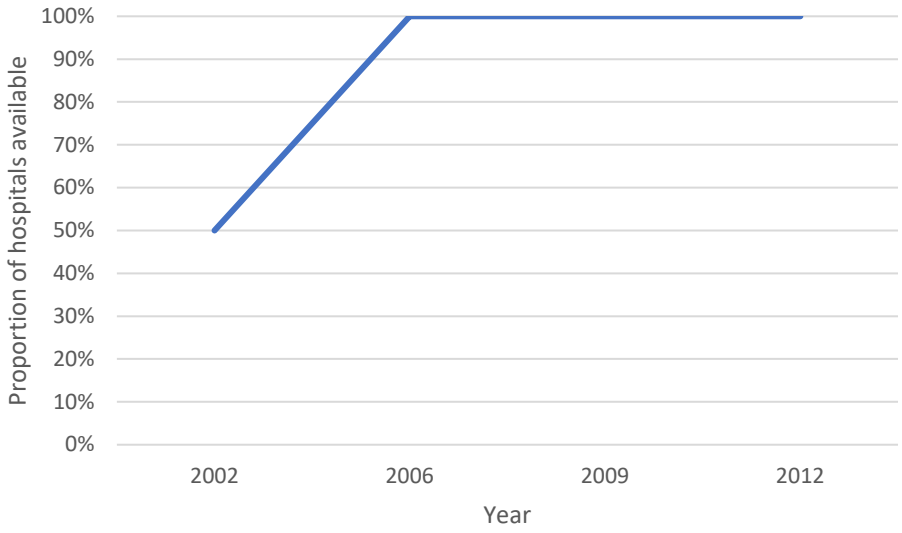
The vast majority of laboratories in HICs (i.e., Europe, North America, Australia/New Zealand) are able to conduct CSF investigations, including microscopy and culture. However, these basic diagnostic techniques are often superseded by more sophisticated laboratory diagnostic methods including PCR in these regions. A large survey was conducted of physician respondents engaged in neurology practice worldwide in 2014 to assess the availability of neurodiagnostic tests (261). Thirty-seven countries (n=119, 31% response rate) responded including eight (22%) LICs (Bangladesh, Burkina Faso, Ethiopia, Haiti, Myanmar, Somalia, Uganda, Zimbabwe), seven (19%) lower-middle-income countries (Bhutan, Ghana, India, Lao People's Democratic Republic, Nigeria, Pakistan, Zambia), 13 (35%) upper-middle-income countries (UMICs; Albania, Botswana, Brazil, Cuba, Iran, Jamaica, Jordan, Macedonia, Mexico, Namibia, Panama, Peru, South Africa), and nine (24%) HICs (Canada, Czech Republic, Iceland, Israel, Japan, Kuwait, the Netherlands, United States[1]). CSF studies were reported available in most (n=36, 97%) survey countries, except one LIC which was not specified. All 36 countries could test for white cells, protein, and glucose; 6% (n=2, Bangladesh, Ethiopia) could not obtain staining for bacteria; 17% (n=6, Burkina Faso, Bangladesh, Ethiopia, Jordan, Peru, Albania) were unable to send tests for *M.tuberculosis*; 33% (n=12) were unable to obtain an opening pressure; 36% (n=13) were unable to obtain HSV PCR; and 53% (n=19) were unable to obtain oligoclonal bands for intrathecal antibody

[1] One country was missing from the paper, hence only eight countries were identified here.

testing. Bacterial culture was named by Haiti as the number one diagnostic test they would like that was not currently available.

Numerous studies have assessed the adoption of recommended practices and basic technologies for global health in Kenya, particularly in the context of children. A national survey of 14 hospitals covering 13 Kenyan districts reported 92.9% (n=13) of hospitals were able to do CSF microscopy in 2002 (262). A study which evaluated resources for providing effective paediatric/neonatal care in Kenyan district hospitals over an 11-year period (2002–2012) found that in 2002 only half (7/14) of hospitals could offer microscopy, Gram stain, and culture of CSF. This increased to 100% in 2006 (8/8), 2009 (17/17), and 2012 (22/22; Figure 17) (263).

Figure 17 – Proportion of hospitals in Kenya where microscopy, Gram stain, and culture for CSF available by year, 2002-2012



From English et al. (263)

Apart from the Kenyan studies, a survey was conducted of the availability and types of laboratory tests offered in clinical laboratories (public and non-public) in Kampala, Uganda (264). Data were obtained from 95% (907/954) of public and private laboratories in 2011. The study recorded the Availability Index (i.e., weighted the percentage of laboratories that offered a test by the laboratory-wide test volumes of those laboratories) of various tests, and CSF analysis was categorised as a minimal availability test (≤15%).

6.1.3.2 HSV PCR

Although no systematic review or survey specifically assessing the global availability of HSV PCR could be identified, studies of encephalitis in Europe, Australia/New Zealand, and the

USA have shown widespread use of CSF HSV PCR as a first-line diagnostic test in cases of suspected encephalitis (11,13,136,140). This has also been reiterated in guidelines for the management of encephalitis produced by countries covering these regions (265–267).

Fewer data are available from Asia, Africa, and Latin America. In Asia, anecdotal evidence suggests CSF HSV PCR is generally available in Middle Eastern countries, some Southeast Asian countries including Singapore and Hong Kong, and at many larger sites in India (T Solomon 2020, personal communication) (268,269). Availability is however more sporadic in other Asian countries and is often not available routinely in government hospitals but can be available via private laboratories for those who can afford it. Studies of encephalitis from Sri Lanka, Vietnam, Taiwan, and Thailand have shown the availability of CSF HSV PCR; however, these research studies are often done in larger tertiary referral centres (120,130,270,271). Some CSF investigations were conducted locally (biochemistry, Gram stain, direct acid-fast bacilli smear examination) in a study of adults with presumed CNS infection who presented to a tertiary referral hospital in Manado, North Sulawesi, Indonesia between 2015 and 2017 but CSF HSV PCR was conducted retrospectively on samples sent to a larger institute in Jakarta (272). A study conducted in rural Nepal between 2014 and 2016 sent collected CSF samples to a collaborating laboratory in Sweden for HSV PCR testing (273). Similarly, samples from adults with CNS infection admitted to a tertiary referral hospital in Kathmandu, Nepal between 2009 and 2011 were investigated locally for CSF biochemistry, Gram stain, and culture but sent to the Oxford University Clinical Research Unit in Vietnam for molecular analysis (274).

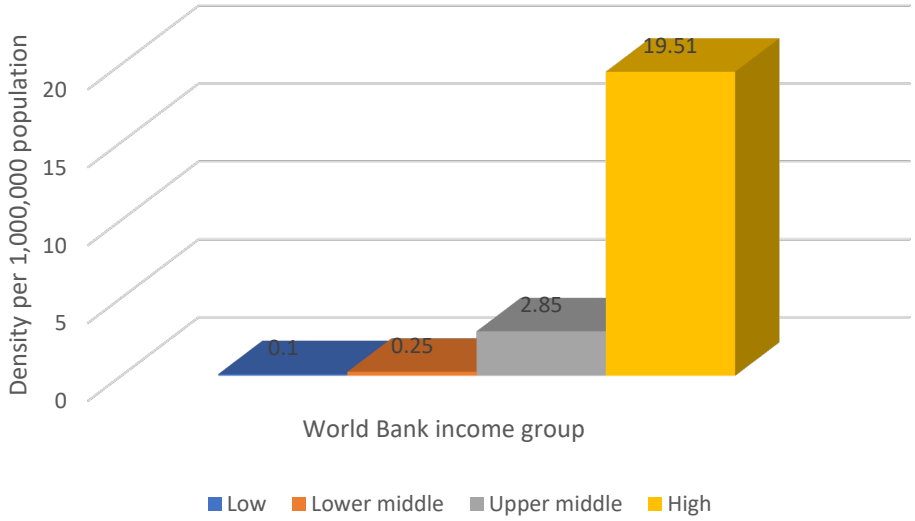
In Africa, anecdotal evidence suggests CSF HSV PCR is not routinely available at most hospitals in Zambia, Mozambique, and Nigeria and only available for research purposes in Malawi (B Michael 2020, personal communication). A study of children with fever and altered consciousness (including encephalitis) conducted in Sudan in 2011 did not search for herpes immunoglobulin or conduct CSF PCR for viruses (275). Similarly, basic laboratory examinations and CSF analysis were carried out locally in a paediatric prospective study to assess the causes of acute neurologic diseases, including encephalitis, in the Democratic Republic of the Congo between 2015 and 2016; however, molecular analysis for the diagnosis of viral CNS infection was not available (276). When respondents in the aforementioned McLane et al. study were asked to list the top three diagnostic tests they would like that were not already available in their practice, PCR for CNS pathogens including HSV was mentioned by Ghana, Zambia, Ethiopia, Botswana, and Bangladesh (261). This study also reported 36% (13/36) of participating countries were unable to obtain HSV PCR; however, the exact countries are not specified in the paper.

Information from Latin America on the availability of laboratory testing in encephalitis is also lacking. Anecdotal evidence suggests CSF PCR is generally available in Brazil, but there is some within-country variation (D Brown 2020, personal communication). Bastos et al. reported that the tertiary public health hospital for infectious diseases in Manaus receives 90% of all CSF samples from patients in the Amazonas state and is the only hospital which performs viral molecular diagnosis (277). In Peru, a prospective study was conducted at 12 hospitals located in different settings (city, Amazon, Andes, and coast) between 2009 and 2012 (5). CSF glucose, protein, and cell count with differential were determined at local laboratories; however, CSF HSV PCR was not available in most Peruvian hospitals and samples were referred to the US Naval Medical Research Unit-6 in Lima for further testing. Following this study, improved diagnostic assays for CSF were identified as a major need through interviews with 48 neurologists across Peru (278). No participating laboratory was able to perform all the following assays: basic CSF chemistries (cell count, glucose, and protein), culture, PCR, immunoglobulin assays, and additional advanced diagnostic testing. Routine CSF biochemistry and culture were performed by most laboratories; however, some relied on private local laboratories for these assays. At present, a reference centre for CSF diagnostics is being developed at the only reference centre for neurological diseases in Peru, with the ultimate aim for CSF PCR testing capacity at regional hospitals.

6.1.3.3 MRI

A baseline country survey on medical devices was carried out in 145 WHO Member States in 2010 (279). The response rate was as follows: 81.2% (26/32) in low, 75.8% (25/33) in lower middle, 78.9% (30/38) in upper middle, and 70.7% (29/41) in high income groups. Results demonstrated a higher density of MRI scanners per million population in high income ; Figure 18).

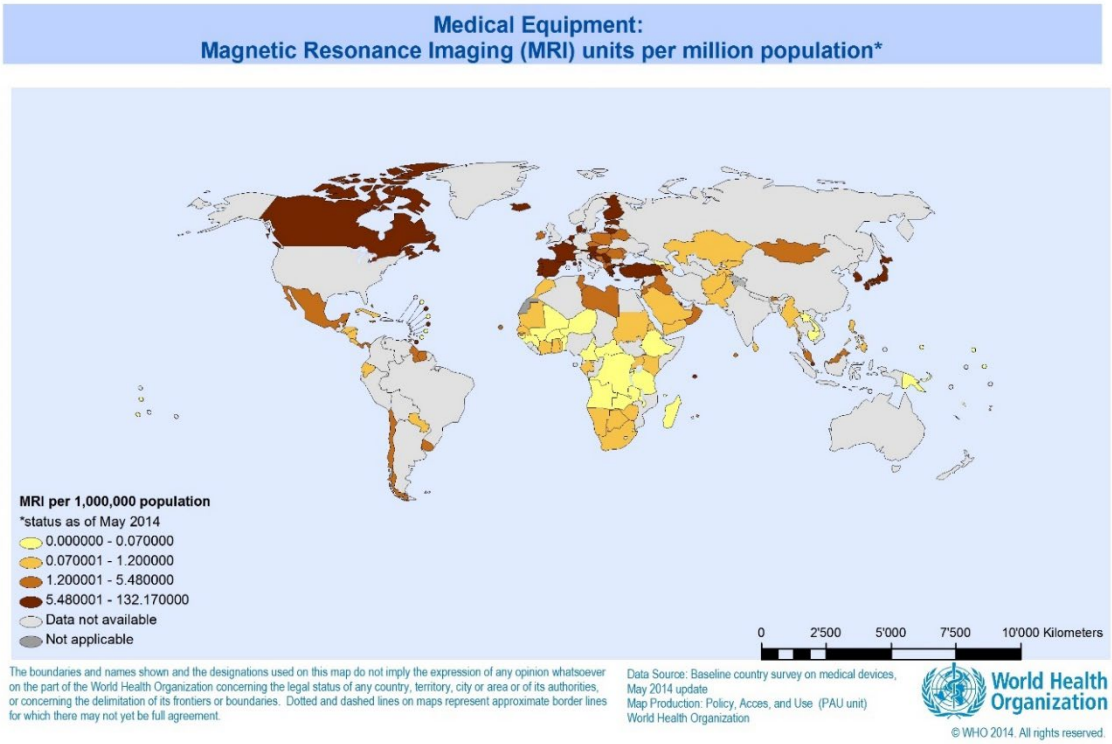
Figure 18 – Density of MRI scanners by income group, 2011



From reference (279)*; MRI = Magnetic resonance imaging*

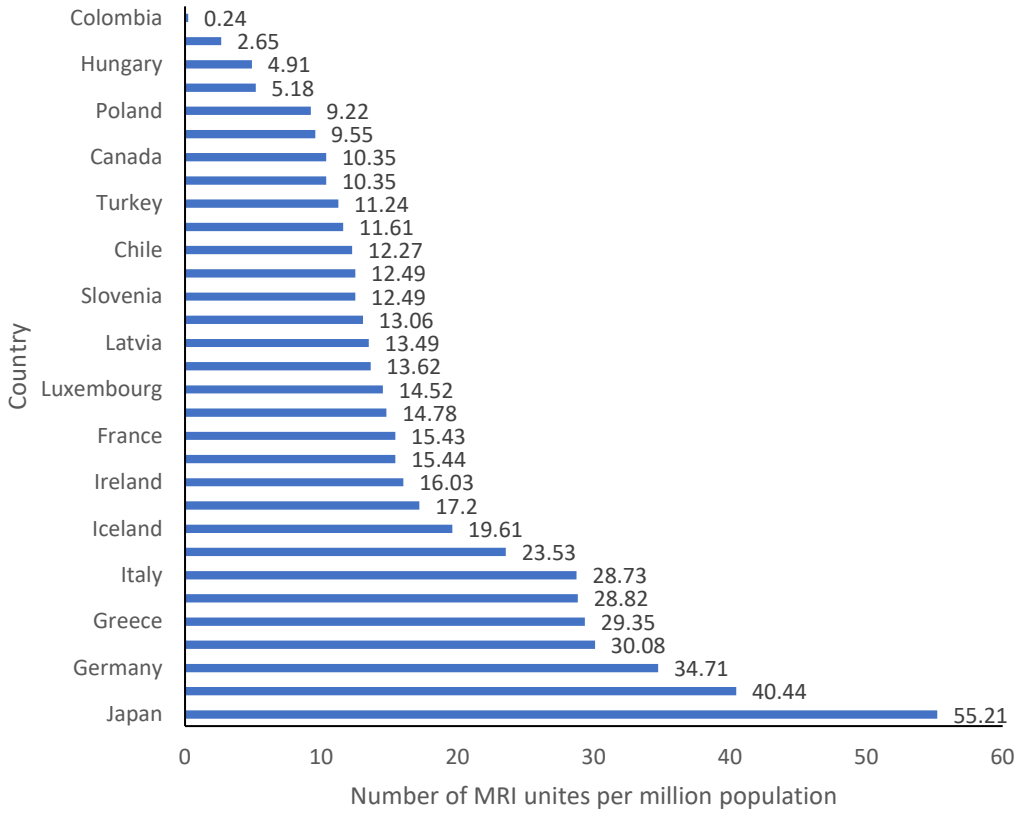
A 2014 update of the aforementioned WHO baseline country survey on medical devices showed that many African countries, some Caribbean islands, Georgia, Papua New Guinea, Laos, and Cambodia had the lowest number of MRI units per million population (0.00-0.07/million; Figure 19).

Figure 19 – MRI units per million population by country, 2014



The presence of MRI scanners was assessed in Organisation for Economic Co-operation and Development (OECD) countries in 2019. The majority of OCED members are HICs with a high Human Development Index (measure of economic development and welfare). The availability of MRI scanners in OCED countries ranged from 0.24 per million population in Colombia to 55.21 per million in Japan (Figure 20). The second and third highest number of MRI scanners per million population was seen in the US (40.44/million) and Germany (34.71/million), respectively. Apart from Colombia, Hungary and Poland had the lowest number of MRI scanners per million population amongst OCED countries (280).

Figure 20 – MRI units per million population in selected OECD countries as of 2019



From reference (280)

Ogbole et al. carried out a one-year survey between 2015 and 2016 (using both interview and online search) to assess the availability of MRI in the West African region (281). In 2016 there were 84 MRI units in West Africa; more than two-thirds of these were in Nigeria. All Nigerian MRI scanners were situated in urban areas, most were within the private (63%) rather than public health sector, and most (77.6%) were low-field strength (rather than high-field strength) systems. Despite Nigeria having the largest actual number of MRI scanners, Ghana had the highest number of MRI units per million population in West Africa (0.48 units/million compared

to 0.30 units/million in Nigeria). This compares to 5.16/million MRI scanners in Libya, the North African country with the highest number of MRI units per million population, and 0.87 units/million in Namibia in the Southern African region (281). When respondents in the aforementioned McLane et al. study were asked to list the top diagnostic test they would like that was not already available in their practice, MRI was mentioned by Pakistan, Cuba, Namibia, and Israel (261).

6.1.3.4 Autoantibody test

The discovery of novel autoimmune encephalitides associated with antibodies against neuronal surface targets has exploded over the last decade. Autoantibody testing is widely and routinely available in most of Europe, the USA, and Australia (S Irani 2020, personal communication). However, variation in testing methods provide different levels of sensitivity and specificity (282–285). Data from Africa and Asia are scarce but anecdotal evidence suggests that autoantibody testing is limited in these parts of the world (S Irani 2020, personal communication). A study of patients with limbic encephalitis in Morocco noted limited access to systemic immunological tests, antineuronal antibodies, and HSV PCR (131). We have already shown a lack of more basic tests for the diagnosis of encephalitis in Africa, thus it can be expected that autoantibody testing is not readily available or performed. Some recent studies however, have shown the availability of autoantibody testing in larger tertiary referral centres in India, Sri Lanka, Thailand, and Vietnam (286–289). A narrative review of autoimmune encephalitis in Latin America reported that CSF and blood samples for suspected cases of autoimmune encephalitis are usually sent to Europe or the USA for analysis (290).

6.1.4 Barriers to implementation and discussion

The global inequity in the availability of laboratory tests for the aetiological diagnosis of encephalitis is stark. Basic CSF microscopy and culture are the most widely available of the four test types evaluated; however, these tests are predominantly for non-viral causes of encephalitis (which also cause meningitis) and most cases of encephalitis are viral or autoimmune. CSF analysis also relies on performance of an LP which is not always carried out due to lack of training, experience, sterile LP kits, and limited laboratory capacity (291). A recent retrospective study in Kenya reported an LP ordered in a median of 66% (range 38%–95%) of children with meningitis and LP findings documented in laboratory or clinical records in a median of 58% (range 15%–79%) (292). This suggests that a LP is not ordered in some children with meningitis, or they may be ordered and never carried out. As meningitis is more

widely known and occurs in epidemics across sub-Saharan Africa LPs for encephalitis might be even lower.

The availability of CSF HSV PCR is variable; however, these data show that it is lacking in places that need it. For example, samples from studies in Peru and Indonesia were referred for CSF HSV PCR as testing was not available locally, but HSV was identified as a common cause of encephalitis in both these countries (Peru n=45/313, 14.4%; Indonesia n=7/74, 9.5%) (5,272). This confirms the importance of diagnosing HSE as treatment is available and the outcome is better if treatment is instigated early in the illness. Despite slowly increasing, access to nucleic acid tests remains largely insufficient in LICs and remains limited to predominantly HIV and tuberculosis (293). Lack of availability of testing can be due to numerous factors. Some hospitals in some resource-limited countries lack even basic microbiology laboratories (294). Other laboratories have all the relevant instruments and reagents to carry out specific diagnostic tests but lack skilled staff. Further laboratories are able to amplify DNA but unable to report the results in a timely manner, and many laboratories neglect accreditation and quality assurance (294). Other factors apart from laboratory characteristics and capabilities may play a role. For example, clinician preference was recorded as the main reason further diagnostic testing was not performed in children with acute neurological illness or injury in the Democratic Republic of the Congo suggesting that there are significant gaps in knowledge of appropriate and necessary diagnostic strategies which can be improved through education (276). It is worth noting that even in areas where CSF HSV PCR is readily available it might be used sub-optimally, for example a study in the USA reported CSF HSV PCR was only repeated in 14.2 % of patients with an initial negative result (295).

The global inequity in MRI availability is stark, with a much higher number of MRI units per million population in high-income compared to lower income countries. Japan, the country with the highest number of MRI scanners per million population, has 115 times more than Ghana, the country in West Africa with the highest density of scanners per million population. Even within OCED, which includes predominantly HICs, the availability varies from 0.24 units per million population in Colombia to 55.21 in Japan. The number of available MRI units in Africa is very small for the population. This is largely due to cost, poor infrastructure, shortage of healthcare workers, lack of capacity in the existing workforce, and substandard facilities (281). The price of an MRI scanner ranges from $150,000 to several million not including installation and maintenance costs, with the cost of single scan of up to $4,000 (296). The MRI units that are available are often located in urban areas and often accessible within the private, rather than public, healthcare sector. However, the latter serve only a minority of the population

(297). It has been suggested that greater cooperation between the private and public healthcare sectors is required for future improvement of MRI use across the African region (281). Most developed countries use high magnetic field MRI machines while low magnetic field MRI machines are more widely available in West Africa. Although the basic imaging functions of these machines still play an important role in the management of neurological conditions in West Africa, the high cost is restricting access to more advanced imaging capability that comes with high magnetic field MRI (281). It is worth noting that even the presence of an MRI scanner does not ensure appropriate and timely scans are conducted in patients with suspected encephalitis, as other factors such as skilled technical staff to carry out the scan and knowledgeable medical staff to order the scan are required.

Antibody testing is widely available in Europe, North America, and Australia. Standardised, commercial diagnostic kits are available for the most common subtypes of autoantibody encephalitis; however, expensive kits or reagents, training, ongoing quality measures, pre-analytic pipelines, and sophisticated laboratory equipment are required for analysis and interpretation, severely limiting their availability in LMIC (298). Two case reports of NMDAR encephalitis from Kenya and South Africa and one case series from Chile were identified that confirm that these types of encephalitis do occur in this part of the world and are likely under-recognized (299,300). Similarly, a recent systematic review of autoantibody encephalitis in Asia included 24 studies with 263 patients (301). In areas where antibody tests are available, doctors need to recognize and be aware of autoantibody encephalitis to ensure specimens are sent for diagnosis. Bedside assessment and clinical judgement remain critical in the diagnosis of immune-mediated encephalitis as treatment is available, effective, and often empiric based on presenting features. A worldwide survey of over 1,000 neurologists from 94 countries on their approach to autoimmune encephalitis found that those treating >5 cases per year were more likely to send antibodies in both serum and CSF, pursue empiric immunotherapy, and continue immunotherapy despite no response and negative antibodies at two weeks (302). In areas where antibody tests are unavailable, treatment initiation relies solely on bedside assessment and clinical judgement. Coincidentally, this usually requires specialized neurological input, but antibody tests are mostly lacking in areas where there is also a lack of neurologists (see Section 7.2.1). Lack of necessary treatment may also be an issue in lower income countries. A high index of clinical suspicion combined with better access to autoantibody testing and availability of required therapy is needed.

We can only draw conclusions based on the data retrieved. However, this report is also intended to highlight inadequacies in information systems. A systematic survey is required to

assess the availability of these diagnostic test types globally. For a summary of barriers to implementation of these different diagnostic methods see Table 24.

Table 24- Summary of barriers to implementation of various diagnostic tests for encephalitis

Diagnostic test	Barriers to implementation
CSF analysis	-Laboratories in LMICs are often sparsely distributed -Access may be limited by economic or geographical factors -Clinical laboratories are often under resourced -Amenities such as electrical supply and water may be unreliable -Shortage of skilled technical personnel, especially in rural areas - Due to their high cost or lack of robustness, some specific diagnostic tests may not be available to the majority population -Some manufacturers may be reluctant to supply countries if return on their investment is likely to be low or where it may be difficult to establish effective mechanisms for product distribution or technical support -Weak regulation has also contributed to the sub-optimal provision of diagnostic services and in some countries, tests of unknown or dubious quality are sold without hindrance
CSF HSV PCR	-Lack of basic microbiology labs in hospitals in some resource-limited countries -Lack of skilled staff to carry out tests -Lack of laboratory accreditation and appropriate quality assurance and quality control -Lack of timely reporting in labs able to amplify DNA -Clinician preference -Gaps in knowledge of appropriate and necessary diagnostic strategies
MRI	-High cost -Poor infrastructure -Shortage of healthcare workers -Lack of capacity in the existing workforce -Substandard facilities -MRI units that are available are often located in urban areas and often accessible within the private, rather than public, healthcare sector
Autoantibody testing	-Lack of awareness -Lack of neurologists -Lack of availability of antibody tests

CSF = Cerebrospinal fluid; DNA = Deoxyribonucleic acid; HSV = Herpes simplex virus; LMICs = Low- and middle-income countries; MRI = Magnetic resonance imaging; PCR = Polymerase chain reaction; Adapted from McNerney et al. (303)

6.1.5 Gap analysis

Table 25 - Gap analysis for diagnostic tests in encephalitis

	Where we are	Where we want to be
CSF examination	Some kind of CSF examination is available in most countries but exactly what this consists of varies greatly.	-Need investment and participation from regional and local governments to sustain new diagnostic and treatment capacity -Need to increase lab capacity by training lab technicians, installing basic equipment, and implementing more advanced diagnostics -Need recognition at national and international level of importance of clinical laboratory services in health system -Need education, supervision and technical improvements and quality assurance networks to revitalize lab services as sub-standard services waste resources and result in clinical mismanagement and inaccurate health information -Need collaboration between laboratory professionals and clinicians to ensure effectiveness of lab services in guiding patient management -Need to ensure budget for laboratory equipment also covers servicing, repair, spare parts, and training in maintenance -Need to incorporate routine CSF testing in WHO essential diagnostics list
CSF HSV PCR	Widely available in Europe, North America, and Australia/New Zealand; variable availability in Asia often in larger tertiary referral centres; limited availability in Africa and South America, mainly only for research purposes.	-Need to emphasize importance of laboratory testing -Need to balance the allocation of financial resources -Need to strengthen the existing health care infrastructure -Need to routinely monitor test quality -Need to establish system for laboratory accreditation -Need to implement laboratory training programs -Need to encourage partnerships between public and private organizations -Need to develop affordable, rapid diagnostic tests -Need systematic survey to collect information on availability of CSF HSV PCR testing globally -Need to incorporate CSF PCR in the WHO essential diagnostics list
MRI	Low number of MRI units in African countries, often located in urban areas and in the private sector.	Need better cooperation between public and private healthcare sectors for future improvement in MRI use across African region
Antibody testing	Widely available in Europe, North America, and Australia but likely limited in Asia, Africa, and South America despite the occurrence of cases in these areas.	Need systematic survey to collect information on availability of autoantibody testing globally

Adapted from (303,304)*; CSF = Cerebrospinal fluid; HSV = Herpes simplex virus; MRI = Magnetic resonance imaging; PCR = Polymerase chain reaction; WHO = World Health Organization*

6.2 Treatment

6.2.1 Recommended practice

The WHO List of Essential Medicines was first published in 1977 and most recently updated in 2021 for both adults (22nd version) and children (8th version) (305). This list aids prioritization of key health products that should be widely available, accessible, and affordable throughout health systems, particularly in LMICs. JE and TBE vaccine are included in the WHO Essential Medicines list and their availability in terms of preventing encephalitis is discussed in Sections 5.1.1.2 and 5.1.2.2. Treatment for encephalitis is largely supportive but specific treatment is available for herpesvirus encephalitis, and non-viral and immune-mediated causes (3). Aciclovir is the first-line treatment for HSE. The WHO List of Essential Medicines includes aciclovir for both children and adults but does not specifically refer to encephalitis or specify the route of administration. Thus, despite the availability of other treatments for encephalitis, we focus on the availability of aciclovir for the treatment of encephalitis worldwide.

6.2.2 Implementation status

It has been shown that in the absence of aciclovir treatment the case fatality from HSE is up to 70%; aciclovir treatment has reduced this to below 20% but survivors still have significant sequelae (306). Early administration is key to improved outcomes. As HSV is the most common cause of encephalitis in Western countries, intravenous (IV) aciclovir is commenced upon suspicion of a case, often even prior to laboratory results being available. Aciclovir is widely available in HICs across Europe, North America, and Australia/New Zealand but often administered sub-optimally and not in accordance with recommended guidelines. A study of encephalitis patients in a tertiary referral centre in the UK showed that only 53% of patients had received aciclovir despite the recommendation to start empirical treatment with aciclovir upon clinical suspicion of encephalitis (307). Furthermore, a pragmatic cluster randomised controlled trial of a tailored intervention to improve the initial management of suspected encephalitis showed that less than a third of patients at participating UK hospitals were prescribed aciclovir within the recommended six hours of admission (308). Outside of the UK, one third of adults (n=241) admitted with encephalitis in the Houston area were not started on IV aciclovir upon suspicion of encephalitis (295).

Data suggests aciclovir availability across Asia is variable. Studies from India, Pakistan, Japan, and Sri Lanka report treatment of encephalitis with aciclovir (120,309,310). However, these studies are often conducted in larger tertiary referral centres, so aciclovir is perhaps less available in smaller rural hospitals and within-country variation likely exists. Other Asian studies have reported lack of aciclovir availability. A study conducted at a tertiary referral

hospital in Vietnam between 1996 and 2008 reported that patients with suspected HSE were prescribed oral aciclovir due to IV aciclovir being largely unavailable during the study period (311). After 2005, IV aciclovir was only given to patients who could afford to pay for their medications pending HSV PCR results. Similarly, a South American study that recruited patients from 12 hospitals between 2009 and 2012 reported treatment with IV aciclovir was not available in most Peruvian hospitals (5). However, a systematic review of herpes zoster in Latin America reported treatment with IV aciclovir in Argentina and Brazil (312).

Anecdotal evidence suggests that aciclovir is available only in African cities, and in Lusaka, Zambia the IV formulation is only available in private pharmacies rather than government-funded hospitals and is very costly at $40/dose or $120/day (D Saylor 2020, personal communication). IV aciclovir was not available in a study in Senegal, and patients with HSE were instead given oral aciclovir or valaciclovir with high mortality rates (313). Data on aciclovir availability in Africa is lacking. Thus, the availability of other drugs, which might indicate how likely a country is to have aciclovir, was considered. The WHO Atlas of African Health Statistics report based on 2013-2017 Service Availability and Readiness Assessment surveys assessed the availability of 33 essential medicines in African countries (Table 26) (314). On average, only 40% of essential medicines were available in African countries; this ranged from 26% in Ethiopia to 73% in Kenya. Similarly, the Neurology Atlas 2017 assessed the availability of anticonvulsants, often used as supportive therapy in encephalitis and on the WHO Essential Medicines list, in countries worldwide (315). Only 55% (n=68/123) and 70% (n=65/132) of countries reported the availability of at least one anticonvulsant at all times in the primary care or hospital setting, respectively. The proportion with at least one anticonvulsant available in the primary care setting was lower in Africa, Southeast Asia, and the Western Pacific (≤50%) and also in LIC (42% compared to 79% in HIC).

Table 26 – Proportion of available essential medicines available by African country

	Essential medicines* (%)
Zimbabwe	48
Zambia	43
Ethiopia	26
Benin	41
Burkina Faso	38
Chad	44
Mauritania	35
Niger	41
Sierra Leone	31
Burundi	29
Uganda	35
Kenya	73
Tanzania	
Seychelles	63
Liberia	44

Democratic Republic of Congo	20
Togo	39
Regional average	**40.6**

[*]Includes Amlodipine tablet or alternative calcium channel blocker; Amoxicillin syrup/suspension or dispersible tablet; Amoxicillin tablet; Ampicillin powder for injection; Aspirin cap/tab; Beclometasone inhaler; Beta blocker (e.g., bisoprolol, metoprolol, carvedilol, atenolol); Carbamazepine tablet; Ceftriaxone injection; Diazepam injection; Enalapril tablet or alternative ACE inhibitor e.g., lisinopril, ramipril, perindopril; Fluoxetine tablet; Gentamicin injection; Glibenclamide tablet; Haloperidol tablet; Insulin regular injection; Magnesium sulphate injectable; Metformin tablet; Omeprazole tablet or alternative such as pantoprazole, rabeprazole; Oral rehydration solution; Oxytocin injection; Salbutamol inhaler; Simvastatin tablet or other statin e.g., atorvastatin, pravastatin, Fluvastatin; Thiazide (e.g., hydrochlorothiazide); Zinc sulphate tablets, dispersible tablets or syrup
From WHO Atlas of African Health Statistics 2018 (314)

6.2.3 Barriers to implementation and discussion

Aciclovir is widely available in Europe, North America, and Australia/New Zealand; however, use is often suboptimal and not always in line with available guidance for maximum patient benefit. Delays in starting aciclovir therapy might relate to failure to consider HSE promptly or awaiting HSV PCR laboratory results unnecessarily. When aciclovir is instigated promptly, treatment length might be too short (316).

Aciclovir availability appears variable in Asia, with India, Japan, Pakistan, and Sri Lanka reporting availability but most likely in larger tertiary referral centres and with within-country variation. The price of aciclovir in Pakistan is 18 times higher than the international reference price resulting in significant out-of-pocket payments impacting affordability (317). A study from Vietnam only reported the availability of oral rather than the recommended IV aciclovir for HSE (311); however, oral aciclovir does not result in adequate CSF concentration to achieve antiviral efficacy (318). Aciclovir availability was lacking in a Peruvian study; however, the high prevalence of HSE identified in this study (n=45/313, 14.4%) highlights the need for increased availability of IV aciclovir for the treatment of HSE in Peru and likely other South American countries. A subsequent study designed to set up a research network for encephalitis among twelve hospitals in five Peruvian cities indicated the lack of availability of IV aciclovir in Peru (278). IV aciclovir was purchased in bulk through a US hospital pharmacy; however, a national shortage led to a search for other suppliers. Shipping and manufacturing delays were amongst the challenges that occurred in the aciclovir supply chain, and the authors are currently exploring possibilities for acquiring and maintaining aciclovir supplies in Peru (278).

Data on aciclovir availability from Africa are sparse but the lack of availability of other more 'basic' medication indicates this is also the likely situation for aciclovir. For example, the availability of supportive therapy with anticonvulsants was only 70% globally in the hospital setting and <50% in the primary care setting in Africa, Southeast Asia, and the Western Pacific (315). The availability of these drug types in the primary care setting is important as patients

in these regions often consult primary care physicians for neurological care in the absence of neurologists (see Section 7.2.1). LICs generally 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 (319). Furthermore, poor procurement practices often afflict the inefficient and bureaucratic public sector supply system in Africa leading to unavailable or costly drugs.

6.2.4 Gap analysis

Table 27 – Gap analysis for aciclovir use

Where we are	Where we need to be
IV aciclovir is widely available in most countries in Europe, Australia/New Zealand, and USA although use can be sub-optimal.	Need to promote adherence to available guidance and education on importance of early instigation of aciclovir in suspected encephalitis Need to educate on how to recognize suspected encephalitis
Variable aciclovir availability across Asia, limited availability in South America and lack of data on availability in Africa but from other essential medicines can presume lack of availability.	Need efforts to improve availability of essential medicines in health facilities, prescribing practices, dispensing practices, quality of medicines, and access to drug information resources Need systematic survey needed to assess global availability of aciclovir Need to reduce aciclovir cost to facilitate availability in low-resource settings including Africa Need to incorporate routine IV aciclovir in the WHO essential medicines list

USA = United States of America

7 In-country neurologists and access to neurology training

7.1 Recommended practice

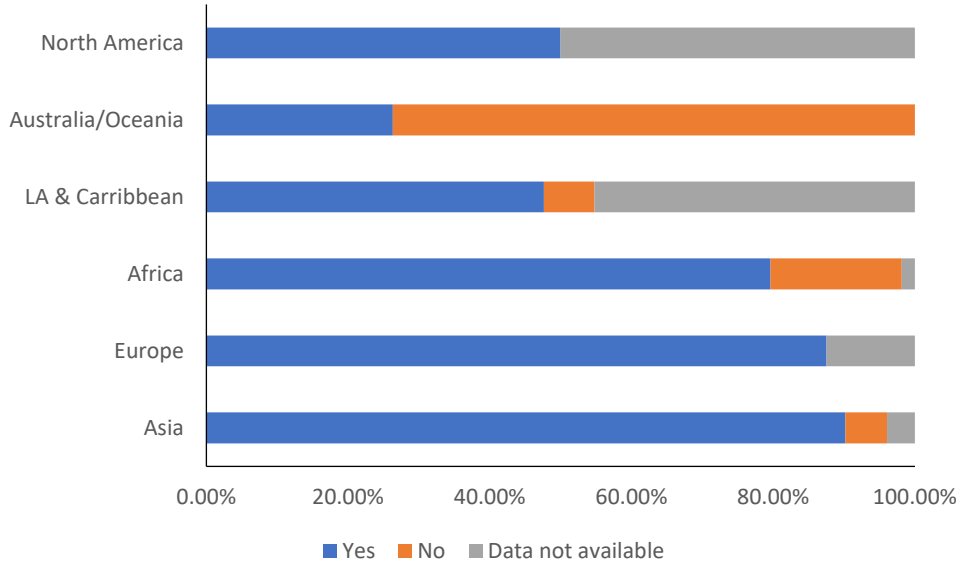
Neurological disorders account for a large proportion of the global burden of disease, and the number of people living with neurological disorders is growing worldwide (320). We reported in Section 3.2 that encephalitis incidence is higher than previously thought and in many countries surpasses that of MND/ALS, bacterial meningitis, MS, and CP (105–108). Neurology healthcare professionals are needed to care for and manage the growing number of people with neurological disorders. The WHO recommends at least one neurologist per 100,000 population (321). We assessed the global presence of neurologists and neurology training.

7.2 Implementation status

7.2.1 Presence of neurologists

A recent review by Hillis et al. summarizes country-level data on the presence of neurologists and neurology training from eight published surveys (322–330). Most surveys were conducted by the World Federation of Neurology (WFN) and the European Federation of Neurological Societies (EFNS; now European Academy of Neurology [EAN]); one was conducted at a neurology course in sub-Saharan Africa. Within each continent, the majority of countries reported the presence of a neurologist with the exception of Latin America and the Caribbean and Australia/Oceania where only 48% (20/42) and 26% (5/19; Figure 21) of countries, respectively, reported the presence of a neurologist. Three Caribbean countries reported no neurologist (Antigua and Barbuda, British Virgin Islands, and St. Vincent and the Grenadines) and 19 of 42 (45%) countries in Latin America and the Caribbean had no data available. Fourteen of 19 (74%) countries in Australia/Oceania reported no neurologist (Figure 21); these comprised the countries of the Pacific Islands (e.g., Samoa, Papua New Guinea, Tuvalu – see Table A3 for full list of countries). Nineteen percent (10/54) of African countries reported no neurologist. Of note, 50% (2/4) of countries in North America reported no data on the presence of neurologists; these included Bermuda and Greenland. These survey data show a paucity of neurologists in LMICs (322). Of countries with data available, 11% (3/28), 27% (13/49), 21% (10/48), and 6% (4/63) of LICs, lower-middle-income countries, UMICs, and HICs, respectively, had no neurologist (322). The HICs that reported lack of a neurologist included Antigua and Barbuda, British Virgin Islands, Nauru, and Northern Mariana Islands.

Figure 21 – The proportion of countries in each region that reports having at least one neurologist



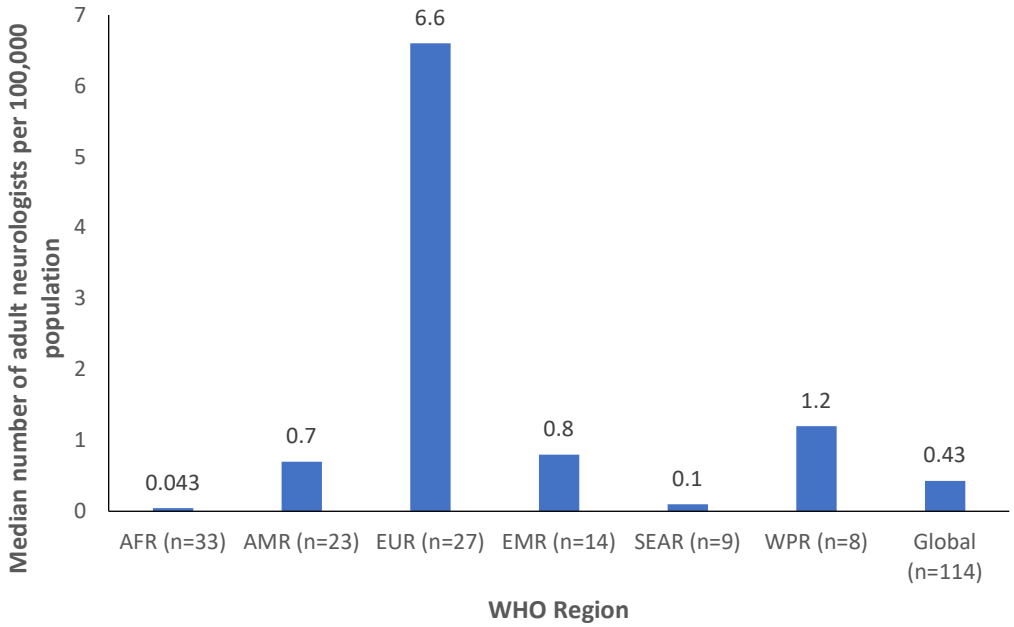
Data obtained from Hillis et al. (322)

Information on the presence or absence of neurologists in specific countries is significant, but it is also very important to quantify this. For example, even though neurologists are present it has been estimated that there is only one neurologist per five million people in Myanmar and one per two million in Lao (331). Thus, neurology in these countries is severely under-resourced. The Neurology Atlas 2017 (and previously 2004) was a collaboration between the WHO and WFN to better assess the resources available within countries to cope with the growing burden of death and disability caused by neurological diseases (315). In brief, relevant information was collected from a questionnaire administered to 132 countries and two territories covering 94% of the world population. Data were collected from 36 countries (77%) in the African Region (AR), 25 (71%) in the Region of the Americas (AMR), 18 (86%) in the Eastern Mediterranean Region (EMR), 33 (62%) countries in the European Region (EUR), 10 (91%) countries in the South-East Asian Region (SEAR), and 12 (44%) in the Western Pacific Region (WPR). For detailed methodology see the Neurology Atlas report (315).

The global median of the total neurological workforce (including adult neurologists, paediatric neurologists, and neurosurgeons) was estimated at 3.1 per 100,000 population among the 114 countries who responded (315). The largest number was reported in EUR (9/100,000) whereas the lowest number was reported in AR (0.1/100,000) and SEAR (0.3/100,000). When participating countries were grouped into World Bank income groups, LICs and HICs reported a median of 0.1 and 7.1 neurological workforce per 100,000 population, respectively. The global median number of adult neurologists is 0.43 per 100,000 population. AFR and SEAR have the lowest number of adult neurologists (medians 0.04 and 0.1/100,000, respectively)

whereas the highest number is seen in EUR (median 6.6/100,000). For the median number of adult neurologists by WHO region see Figure 22.

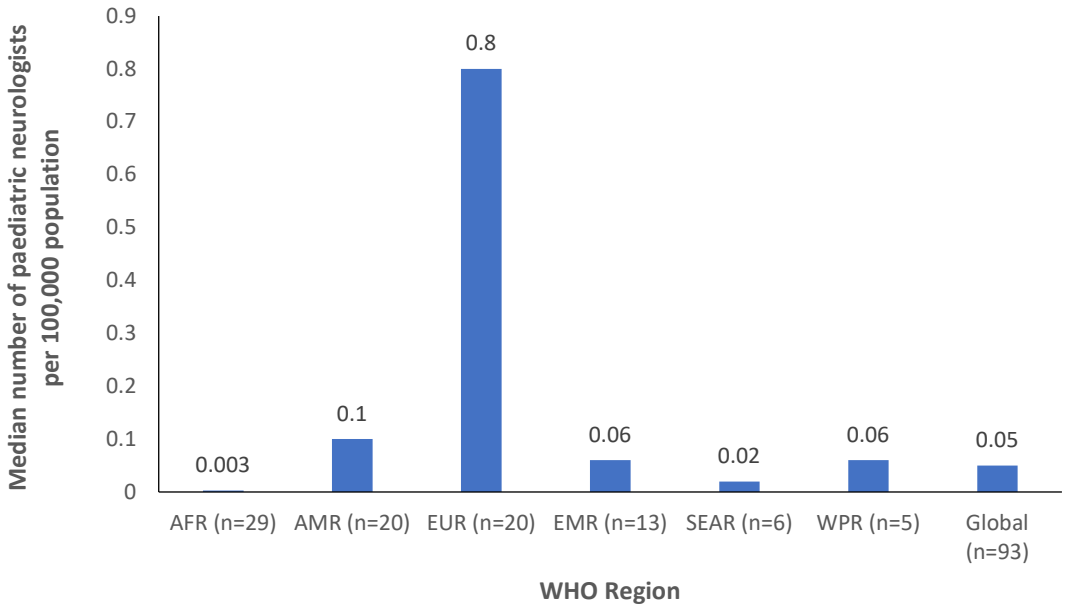
Figure 22 - Median number of adult neurologists per 100,000 population by WHO region



From Neurology Atlas 2017 (315)
AR = African Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South-East Asia Region; WPR = Western Pacific Region

The global median number of paediatric neurologists was over eight times lower than that reported for adult neurologists (0.05 per 100,000 population among 93 countries that responded) (315). The pattern by region; however, was the same as that seen for adult neurologists (highest in EUR and lowest in AFR and SEAR; Figure 23).

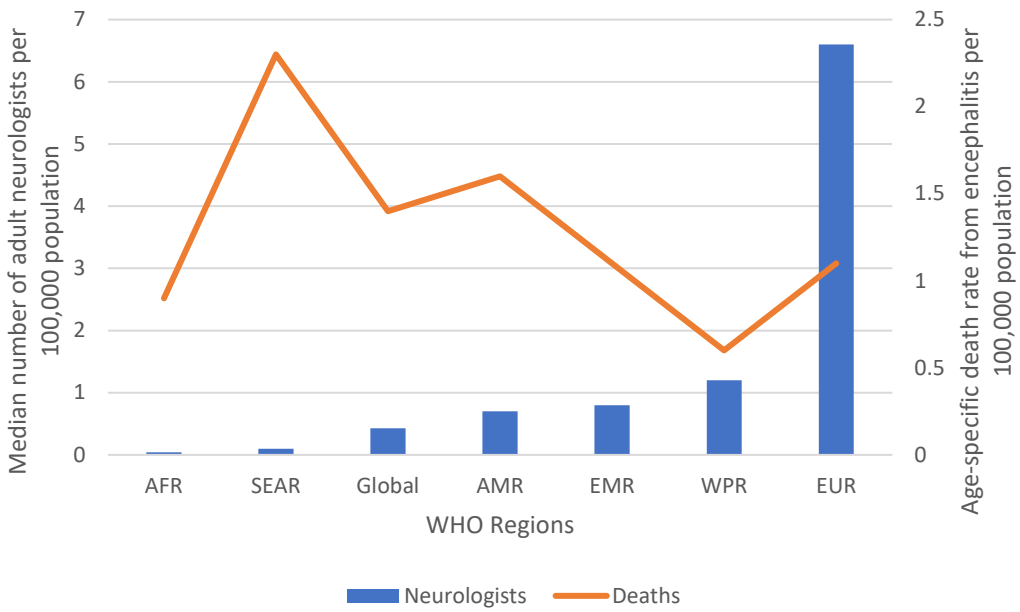
Figure 23- Median number of paediatric neurologists per 100,000 population by WHO region



From Neurology Atlas 2017 (315)
AR = African Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South-East Asia Region; WPR = Western Pacific Region

The age-specific death rate from encephalitis, as estimated by the WHO in 2016, by the median number of adult neurologists per 100,000 population for each WHO region is displayed in Figure 24 (116,315). The highest death rate from encephalitis was reported in SEAR, also one of the regions with the lowest number of adult neurologists. A visible trend of lower encephalitis mortality rates in regions with a higher number of neurologists is evident.

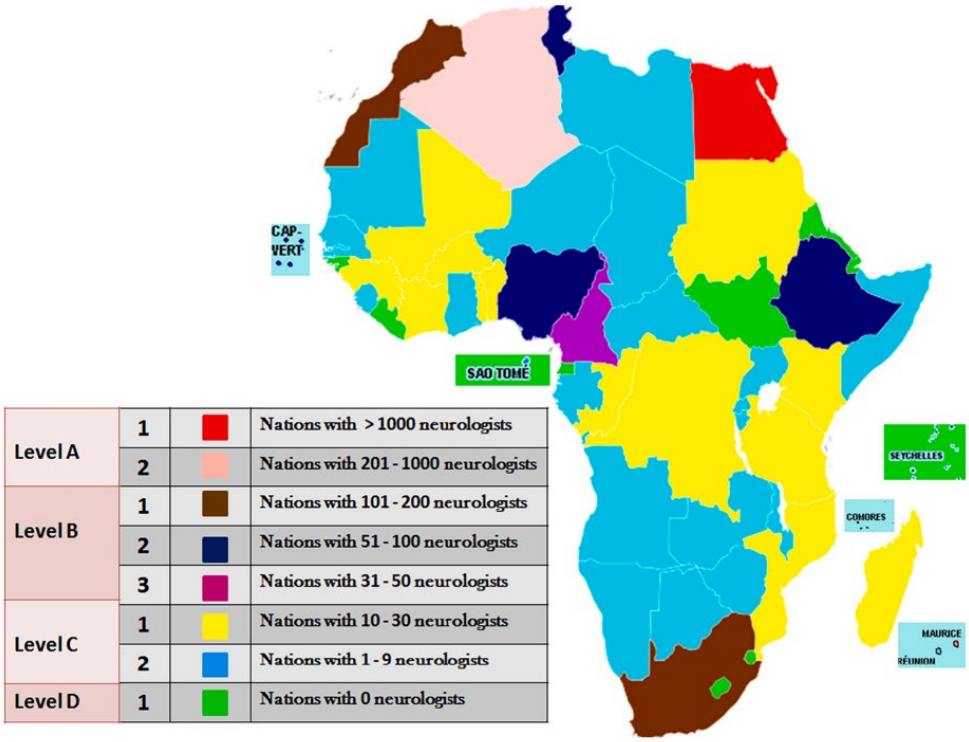
Figure 24 – Global mortality for encephalitis and number of adult neurologists by WHO region



Almost all countries (111/114, 97%) reported neurologists practicing in the capital city. Only 23% of countries overall reported neurologists in rural regions; this was 45% in HICs versus 0% in LICs. Of 105 countries that responded, only 20% reported the availability of specialist neurology units, 16% specialized neurorehabilitation services, and 17% general rehabilitation units offering neurological rehabilitation (315). The exact countries where rehabilitation services or neurologists in rural areas are unavailable were not specified. Primary care physicians may offer neurological care in 91% of responding countries (n=96/106), ranging from 78% in EMR to 100% in SEAR.

A more recent survey of 50 African countries conducted in 2020 showed an improvement in the number of neurologists; however, it is still insufficient to fill the gaps (321). Almost three-quarters (n=36/50; 72%) of countries reported one to 30 neurologists per country and 10 (20%) reported having no neurologist (Figure 25).

Figure 25 - Number of neurologists by African country



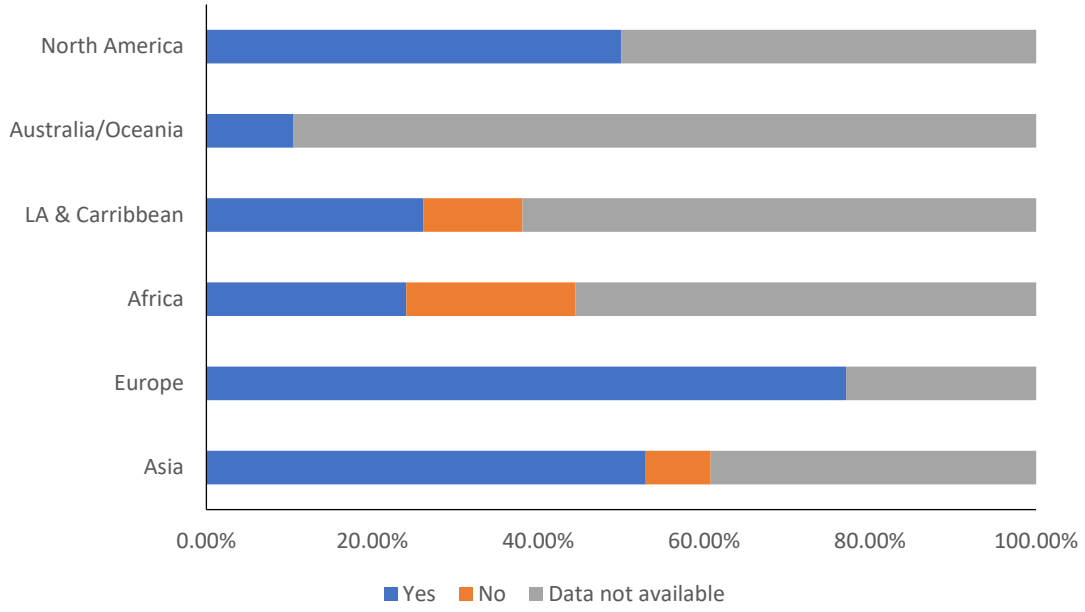
Data obtained from Kissani et al. (321)

Even though the number of neurologists reported in Europe are highest, variations exist. A recent survey conducted by the Association of British Neurologists reported the number of full-time neurology consultants involved in patient care is 1.1 per 100,000 in the UK compared to one per less than 25,000 in other HICs such as France and Germany (332).

7.2.2 Neurology training

The review by Hillis et al. also investigated the presence of neurology trainees, a marker of the presence of a neurology training program within a country (322). A similar pattern was seen with neurology trainees as neurologists. Of countries with data available, 58% (7/12), 24% (6/25), 10% (3/29), and 9% (4/46) of LICs, lower-middle-income countries, UMICs, and HICs, respectively, reported no trainees (322). Within each continent, the majority of countries reported they had a trainee with the exception of Africa, Latin America and the Caribbean, and Asia where 20% (11/54), 12% (5/42), and 8% (4/51) of countries, respectively, reported the presence of no trainee (Figure 26). Data on trainees was not available from 89% (17/19), 62% (26/42), and 56% (30/54) of countries in Australia/Oceania, Latin America and the Caribbean, and Africa, respectively (Figure 26).

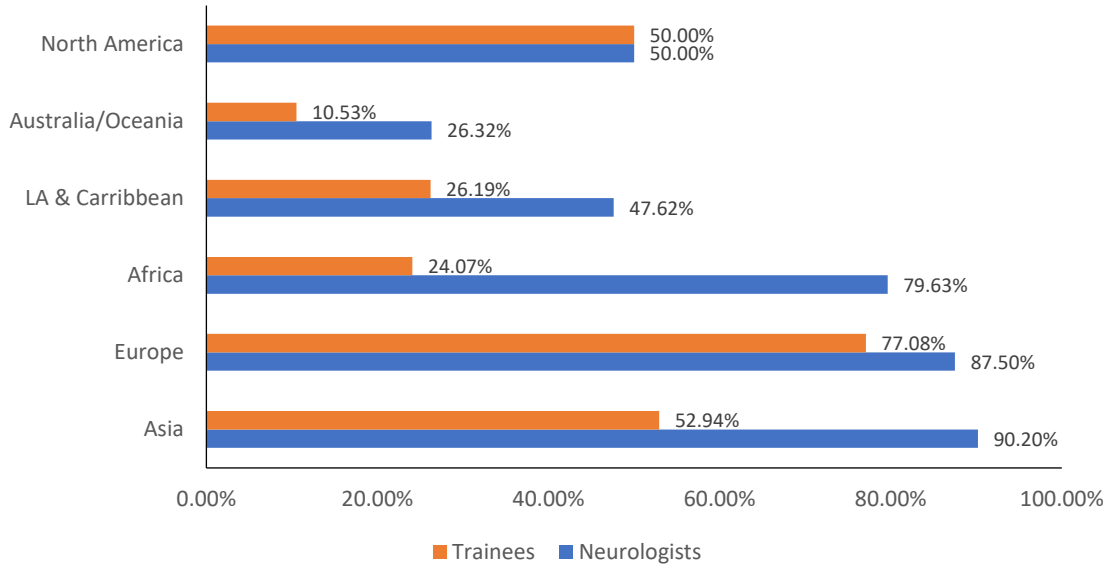
Figure 26 - Proportion of countries with neurology trainees by continent



Data obtained from Hillis et al. (322)

For the vast majority of continents, the proportion of countries with trainees was lower than the proportion with neurologists (Figure 27).

Figure 27 - Proportion of countries with neurologists versus neurology trainees by continent



Data obtained from Hillis et al. (322)

7.3 Barriers to implementation and discussion

These data demonstrate that the available resources for neurological disorders globally are insufficient. The complete absence of neurologists is evident in a few Caribbean, some African, and most countries that constitute the Pacific Islands. Despite most countries in Asia and Africa reporting the presence of neurologists, the actual number of neurologists is very low. The number of paediatric neurologists in particular is strikingly low across all regions, which is significant as the incidence of encephalitis is higher in children that adults (54,96). A lack of neurology in rural areas and lack of neurorehabilitation services were also evident (333). In the absence of neurologists, many countries consult primary care physicians for neurological care; however, their level of training and expertise is unknown. Data from India and Peru suggest some patients with encephalitis are managed by internists, infectious disease specialists, or a combination of healthcare providers (278,302). The presence of a neurologist at an epilepsy clinic in rural Tanzania compared to a clinic mainly attended by nurses resulted in a reduced disease burden, emphasising the importance of specialist care (334). Neurology trainees, a marker of neurology training programs, were scarcer than neurologists. One reason for the lack of neurology training programs is the lack of neurologists to develop and support them (322). No trainees were reported in some African, Latin American and Caribbean, and Asian countries; however, data on this were lacking from the majority of countries. Recent initiatives have seen the first postgraduate neurology training program started in Zambia in October 2018; the program was developed and is directed by a Johns Hopkins faculty neurologist (335). Such initiatives could serve as a model for neurology training in other LICs. Virtual platforms may offer a way to improve neurology training in areas with low neurological workforce (336). A recent cross-sectional survey of medical students and post-graduate trainees in internal medicine and paediatrics across Africa showed fear and discomfort with the subject of neurology (337). This highlights the need for strategies, including enhancing neurological educational, diagnostic, and treatment capacity, to mitigate so-called neurophobia.

Two comprehensive data sources were identified which provided detailed information on the global presence of neurologists and neurology trainees (315,322). The Neurology Atlas 2017 gathered data from key experts in the area of neurology identified by the WFN in 132 countries and two territories, representing 94% of the world population. Most of the surveys included in the review by Hillis et al. were also conducted through the WFN (322). As a confederation of national neurological societies, the WFN is well positioned to collect data from their member countries. However, surveys conducted by the WFN and EFNS/EAN omit countries without neurological societies and might be biased toward countries with more established neurology

infrastructure (315). Also, countries that received surveys but did not respond were perhaps those with worse infrastructure. Thus, it is likely the global estimates presented here are an overestimate. A further limitation of Neurology Atlas 2017 is the fact that one key person in each country was the source of information. However, this individual was not only the WFN liaison officer, but could also consult other neurologists within the country and had access to both official and unofficial sources of information (315). Despite the limitations, the Neurology Atlas 2017 is considered a comprehensive compilation of neurological resources (315).

7.4 Gap analysis

Table 28 – Gap analysis for presence of neurologists and/or neurology training

Where we are	Where we want to be
Available resources for neurological disorders globally are insufficient given the increasing number of patients with neurological disorders.	Need to increase neurological services and training in order to care for these patients
There is a complete absence of neurologists in a few Caribbean, some African, and most countries that constitute the Pacific Islands. Even in Asian and African countries reporting the presence of neurologist, the actual number of neurologists is very low.	Need to increase number of neurologists, especially in LMICs and rural areas
Neurology trainees, a marker of neurology training programs, were scarcer than neurologists. No trainees were reported in some African, Latin American and Caribbean, and Asian countries; however, data on this were lacking from the majority of countries.	Neurology training programs need to be developed across many areas, particularly Africa Need neurologists to develop and support training programs Need to strengthen data on the availability of these resources by country
There is an evident lack of neurorehabilitation services.	Need to consider increased access to neurorehabilitation services

LMICs = Low- and middle-income countries

8 Surveillance

8.1 Recommended practice

Surveillance, or the systematic collection, analysis, and interpretation of health-related data, is important for understanding the epidemiology and global burden of encephalitis and implementing the appropriate disease prevention and control measures. Surveillance also enables detection of and rapid response to encephalitis outbreaks, monitoring epidemiological trends over time, guiding public health policy, and monitoring the impact of any prevention and control measure (291). The latter is particularly important, and the WHO suggests that monitoring vaccine impact in settings where JE vaccine has been introduced is a research

priority. The WHO recommends enhanced or minimal JE surveillance depending on the availability of resources within a country. National, case-based surveillance for JE and AES with laboratory confirmation comprises enhanced surveillance. The alternative minimal recommended surveillance includes sentinel surveillance with laboratory confirmation of JE in all JE-endemic countries (188). The WHO position paper suggests AES surveillance is important in the absence of JE confirmatory testing for monitoring vaccine programs and to understand all causes of encephalitis. The WHO Recommended Surveillance Standards (Second Edition) also includes measles and rabies, other causes of encephalitis with a vaccine available. In some HICs encephalitis is notifiable by law with a requirement to notify every case.

8.2 Implementation status

8.2.1 All-cause syndromic surveillance

Case ascertainment for encephalitis in higher income countries predominantly relies on routine laboratory reports, notifications, hospitalisation data, and mortality data (1). Surveillance of encephalitis using either of these systems alone; however, is incomplete. National hospitalisation data are available in Europe, North America, and Australia as is evident in Section 3.2.1. Cases of complex syndromes such as encephalitis might be over- or under-ascertained using hospital-only data. Cases of meningoencephalitis may for example be coded as meningitis rather than encephalitis, and patients with NMDAR encephalitis who present with psychiatric symptoms might be classified as such. Hospitalisation data can also include non-encephalitis cases misdiagnosed as encephalitis due to overlapping symptoms (54). Statutory notifications are grossly underreported with only 10, nine, and eight cases of acute encephalitis notified for England and Wales in 2019, 2020, and 2021, respectively (338).

The European Network for Diagnostics of ‘Imported’ Viral Diseases carried out a survey of existing surveillance systems for encephalitis in Europe in 2004 (339). The survey found that bacterial causes of meningitis/encephalitis were thoroughly investigated in all 27 EU Member States; however, notification of viral cases varied between countries because of non-standardised or not enforced reporting policies. The distribution of relevant viral causes of encephalitis reported in the surveillance systems varied greatly and depended on the diagnostic tests carried out and/or notification regulations. Only six countries (Austria, Czech Republic, Hungary, Poland, Slovakia, and Slovenia) could provide pathogen-specific data on common causes of encephalitis (e.g., HSV) and endemic causes (e.g., TBEV). Furthermore, other countries could only report pathogen-specific data for major arboviral causes of encephalitis including TBEV (Baltic States, Germany, Finland) and WNV (Romania). Just over

half (n=15, 56%) of the 27 European countries provided information on unexplained neurological illnesses of possible infectious aetiology.

8.2.2 JE surveillance

Surveys were administered to health officials from 24 countries with endemic JE to obtain information on JE surveillance programs in 2016 (190). This was supplemented with data from relevant meetings, reports, and websites. Twenty-two of 24 (92%) countries carried out some form of JE surveillance; 14 (58%) national, 2 (8%) subnational in all JE risk areas, and 11 (46%) sentinel surveillance (Table 29). The latter also included five that also carried out national or subnational surveillance. Twenty-two countries (92%) used JE case definitions; however, the exact definition used varied between countries (from the WHO AES definition to country-specific case definitions). All countries that carried out JE surveillance reported use of JE-specific diagnostic testing in serum and/or CSF to confirm some/most suspected cases.

Table 29 - JE surveillance in countries with JEV transmission risk, 2016

Country	Surveillance program	Age groups included	Laboratory confirmation
Australia	All risk areas	All	Yes
Bangladesh	Sentinel (4 sites)	All	Yes
Bhutan	Sentinel (5 sites)	<15 years	Yes
Brunei	National	All	Yes
Burma	National	All	Yes
Cambodia	Sentinel (6 sites)	<15 years	Yes
China	National and sentinel (27 sites)	All	Yes
Taiwan	All areas	All	Yes
India	All risk areas and sentinel (223 sites)	All	Yes
Indonesia	Sentinel (34 sites)	All	Yes
Japan	National	All	Yes
Laos	National and sentinel (3 sites)	All	Yes
Malaysia	National	All	Yes
Nepal	National	All	Yes
North Korea	National	<15 years	Yes
Pakistan	None	-	-
Papua New Guinea	Sentinel (1 site)	<15 years	Yes
Philippines	Sentinel (9 sites)	All	Yes
Russia	None	-	-
Singapore	National	All	Yes
South Korea	National	All	Yes
Sri Lanka	National	All	Yes
Thailand	National and sentinel (40 sites)	All	Yes
Timor Leste	National	All	Yes
Vietnam	National and sentinel (8 sites)	All	Yes

Adapted from Heffelfinger et al. (190)

It is worth noting that these JE systems are not always stand-alone surveillance systems. Cambodia successfully integrated JE surveillance into an established, working system for bacterial meningitis surveillance (340). Similarly, successful surveillance was established for acute meningitis-encephalitis syndrome in China and Bangladesh in 2006 and 2007, respectively, and for AES in India in 2007 using the polio-measles surveillance infrastructure and laboratory networks (341).

8.2.3 TBE surveillance

TBE surveillance is not always uniform or mandatory across Europe despite being endemic in several European countries (Table 30; Figure 28). ECDC conducted a survey in EU/EFTA countries which aimed to assess the surveillance of TBE across Europe between 2000 and 2010. Of 30 participating countries, 20 (67%) had developed a TBE surveillance system, with comprehensive surveillance in 18 countries. National surveillance was conducted in 18 countries, sub-national surveillance in one, and in Italy surveillance was practically only implemented in endemic regions. Reporting was mandatory in 16 countries, voluntary in one, and undefined in three countries. Surveillance data were generally derived from reporting by hospital physicians, reporting by general practitioners, and laboratory reporting. A TBE surveillance case definition was used in 10 countries.

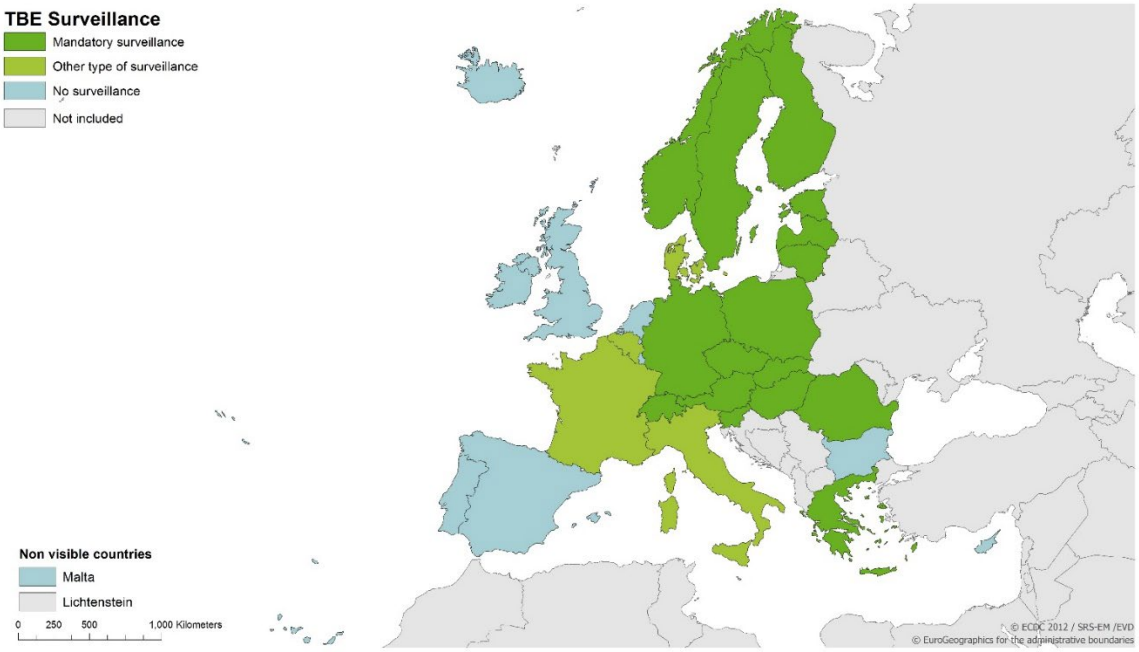
Table 30 – TBE surveillance in EU/EFTA countries, 2000-2010

	Type of surveillance	System operating	Type of reporting	Type of data recorded	Cases routinely reported	Case definition	Provision of surveillance data	Estimated sensitivity of surveillance
Austria	Comprehensive	National	Mandatory	Case-based	Cases with CNS infection	Yes	Aggregated (2000-01); case-based (2002-10)	National, fair sensitivity
Belgium	Sentinel	National	Voluntary	Case-based	All cases	N/A	N/A	N/A
Czech Republic	Comprehensive	National	Mandatory	Case-based	Cases with CNS infections	Yes	No, summary figures for this report	National, fair sensitivity
Denmark	Comprehensive	National	Not well-defined	Case-based	All cases	No	Case-based (2001-10)	National, fair sensitivity
Estonia	Comprehensive	National	Mandatory	Case-based	All symptomatic cases (including tick-borne fever)	Yes (since 2004)	Aggregated (2000–2007), case-based (2008–-2010)	National, fair sensitivity
Finland	Comprehensive	National	Mandatory	Case-based	All cases	Yes	Case-based (2000-10)	National, fair sensitivity
France	Other (National Reference Centre for Arboviruses)	National	Not well-defined	Case-based	Cases with CNS infection	No	N/A	N/A
Germany	Comprehensive	National	Mandatory	Case-based	All cases	Yes	No, summary figures for this report	N/A
Greece	Comprehensive	National	Mandatory	Case-based	Cases with CNS infection	Yes	N/A	National, fair sensitivity
Hungary	Comprehensive	National	Mandatory	Case-based	Cases with CNS infection	No	Aggregated (2000-10)	National, overall low sensitivity
Italy	Comprehensive	Other	Not well-defined	Case-based	All symptomatic cases (including tick-borne fever)	No	Aggregated (2001-10)	Regional, fair sensitivity
Latvia	Comprehensive	National	Mandatory	Case-based	All cases	No	Aggregated (2000–2006); case-based (2007–2010)	National, fair sensitivity
Lithuania	Comprehensive	National	Mandatory	Case-based	All cases	No	Case-based (2010)	National, fair sensitivity
Norway	Comprehensive	National	Mandatory	Case-based	All cases	Yes (2008)	N/A	National, fair sensitivity
Poland	Comprehensive	National	Mandatory	Case-based	Cases with CNS infections	Yes (2005)	Case-based (2000-10)	50-75%

Romania	Comprehensive	Sub-national	Mandatory	Case-based	Cases with CNS infections	Yes (2008, revised in 2011)	Case-based (2008-2010)	Regional, fair sensitivity
Slovakia	Comprehensive	National	Mandatory	Case-based	All cases	No	Aggregated (2000), case-based (2001–2010)	National, important regional differences in sensitivity
Slovenia	Comprehensive	National	Mandatory	Case-based	Cases with CNS infections	No	No, summary figures for this report	National, fair sensitivity
Sweden	Comprehensive	National	Mandatory	Case-based	Cases with CNS infections	Yes (2004)	Case-based (2005-10)	National, fair sensitivity
Switzerland	Comprehensive	National	Mandatory	Case-based	All symptomatic cases (including tick-borne fever)	Yes (1988, revised in 2007)	N/A	National, fair sensitivity

**As of 2010, Bulgaria, Cyprus, Iceland, Ireland, Luxembourg, Malta, the Netherlands, Portugal, Spain, and United Kingdom had not developed TBE surveillance systems.*

Figure 28 – TBE surveillance in Europe



From ECDC report (342)

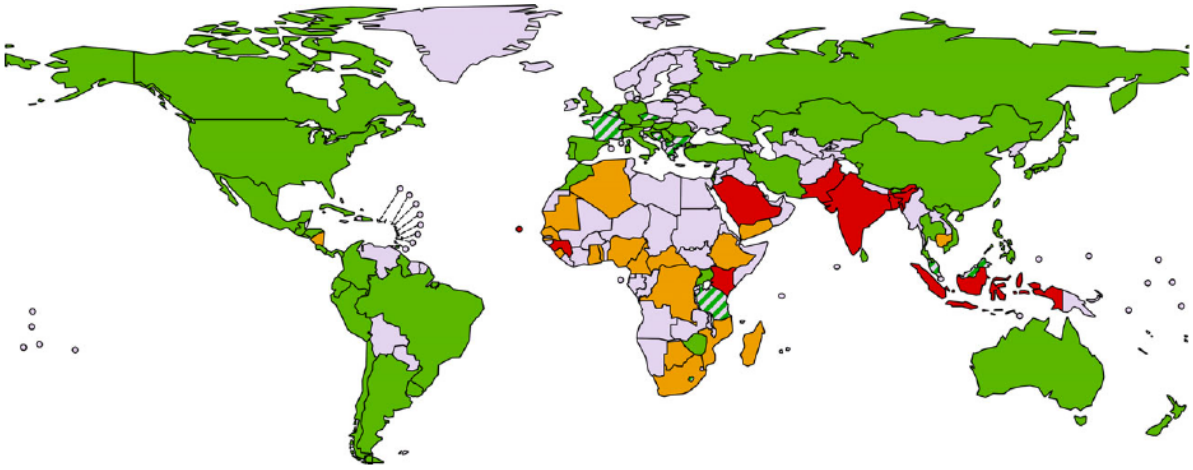
Since 2012, ECDC has required all 28 EU Member States, Iceland, and Norway to report their TBE data annually to the European Surveillance System (TESSy) database using the EU case definition (343).

8.2.4 Rabies surveillance

A global survey of human rabies surveillance was carried out between 2011 and 2013 via governmental medical, veterinary, and public health services, research organisations, and the private industry sector (344). Responses were received from 91 countries (24 in Africa, 23 in Asia, 22 in Europe, 20 in the Americas, and two in Oceania), and included approximately half (n=38/81, 47%) of countries with a high risk of rabies infection. Rabies was notifiable by law in 83 (91%) participating countries. Rabies was not notifiable in eight Asian (n=5) and African (n=3) countries; however, the exact countries were not specified. Sixty-three (of 71 countries where rabies notifiable and who provided information on case definitions) countries reported availability of a case definition to guide the notification of human cases; however, only 33 included suspected, probable and confirmed cases as recommended by the WHO (345). Specific legislation (e.g., national mandate, provincial law) for data collection on human rabies cases was reported in 58 of 67 (87%) countries where rabies was notifiable and information provided; all countries without specific legislation were in Africa (n=6) and Asia (n=3). The majority of countries (n=44/64, 69%) integrated rabies reporting with other surveillance

systems, mainly national notifiable disease structures. Nineteen respondents (16 from Africa) judged the collection of case data for surveillance purposes in their country to be ineffective (Figure 29). In total, rabies was not notifiable, or surveillance was ineffective in 27 of 91 (30%) countries surveyed. The equivalent in high-risk countries was 55% (n=21/38).

Figure 29 – Rabies surveillance, 2011-2013



Green = human rabies is notifiable and surveillance is effective; Orange = human rabies is notifiable, but surveillance is ineffective; Grey/green striped = human rabies is notifiable, but no information on effectiveness was supplied; Red = human rabies is not notifiable; Grey = no survey data available. From Taylor et al. (251)

A 2020 scoping review that assessed the current situation and gaps on rabies morbidity and mortality, integrated rabies surveillance programmes, and existing prevention and control strategies in Africa reported coordinated surveillance for rabies in seven of 18 African countries (39%), including Cameroon, Ivory Coast, Malawi, Senegal, Tanzania. South Africa, and Zimbabwe (228).

8.3 Barriers to implementation and discussion

It is evident from the literature that encephalitis surveillance exists and has improved over the years but there is still a way to go. HICs, in Europe, USA, and Australia/New Zealand, have surveillance systems including national hospitalisation data, notification systems, and laboratory reports; however, under-reporting is common in many countries. In the UK, 97% of hospitalised cases were not formally reported in the routine notification system (53). Hospitalisation data will include most cases of encephalitis but cases with a milder presentation may be missed (1). In addition, hospitalisation data are limited by unknown accuracy of coding, lack of specific diagnostic criteria, and lack of timeliness (1). Many European countries have implemented surveillance systems for the systematic collection of

TBE information, enabling the extent of TBE endemic regions and general surveillance trends to be described (342). However, some important differences (case definition, laboratory diagnosis, clinical syndromes reported) exist in these surveillances systems that might complicate interpretation and international comparisons (342). The requirement, since 2012, for all EU Member States, Iceland, and Norway to annually report their TBE data to the ECDC European Surveillance System database using the EU case definition represents a step forward in this area; however, comparison between regions/countries is still dependent on the accuracy and consistency of national/regional surveillance systems (343,346).

In LMICs where resources are more scarce surveillance strategies are often targeted at vaccine-preventable causes. JE surveillance programs have expanded in recent years; over 90% of countries with JE transmission risk conducted JE surveillance in 2016 compared to three quarters in 2012. It is likely these surveillance programs relate only to people living in-country and not travellers who might be affected. This represents substantial progress, but challenges remain including incomplete case reporting, case misclassification, lack of monitoring data for immunisation programs, and suboptimal monitoring of vaccine coverage following introduction (190). Surveillance of vaccine-preventable causes of encephalitis is particularly important to assess burden, inform vaccination strategies, monitor vaccine safety, and monitor the impact and effectiveness of vaccines (190). The WHO also suggests AES surveillance is important to understand other causes of encephalitis and also to demonstrate the impact of the vaccination program in the absence of JE confirmatory testing (190). AES surveillance could be incorporated into other well-established surveillance systems, such as those for poliomyelitis, acute flaccid paralysis, or meningitis surveillance. This has been done in some countries and gives technical and logistical benefits of existing infrastructure and investments.

The WHO target is to eliminate dog-mediated rabies by 2030. The means are there to achieve this but relies on many factors including strong surveillance systems. In countries where rabies was a notifiable disease, there was high variability in rabies surveillance systems. The Taylor et al. survey found that rabies was not notifiable or surveillance was ineffective in 27 of 91 (30%) countries surveyed, including 55% (n=21/38) of high risk countries, predominantly in Africa and Asia (251). Respondents cited lack of specific anti-rabies legislation, lack of rabies policy, poor awareness, lack of funds in the health system, lack of accountability for doctors, and priority given to other diseases as barriers to human rabies becoming a notifiable disease. Significant underreporting (e.g., in rural areas away from major hospitals), inadequate follow-up of unconfirmed cases to determine outcome or diagnostics to confirm cases, inadequate financial investment in surveillance systems, lack of enforcement or implementation of the

legislation and guidance, human rabies deaths occurring at home and away from health centres, poor recognition of rabies by some health workers, rabies being neglected by politicians due to competing priorities, lack of coordination between veterinary and medical authorities, inadequate training of medical staff in surveillance and case definitions, and lack of understanding on when and how to seek treatment by bite victims were cited as reasons for rabies surveillance being ineffective (251). An evaluation of rabies surveillance in southern Vietnam recommended simplification of the report forms, training staff, and improvements in the timeliness of reporting and data usage for better implementation of rabies surveillance (347). It is worth noting that for vector-borne and zoonotic diseases, surveillance should be a multi-pronged approach and also include environmental, entomological, and veterinary surveillance.

8.4 Gap analysis

Table 31 – Gap analysis for presence of encephalitis surveillance

What we know	Where we want to be
Surveillance systems for all-cause encephalitis exist in HICs including notification systems, hospitalisation data, and laboratory reports; however, cases are still under-reported.	Need to strengthen these surveillance systems by validation of codes in hospitalisation data, encouraging notification of cases, strengthening laboratory diagnosis, and standardisation of case definitions Need 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 still remain.	Need to implement JE surveillance systems in all areas where JE is a public health priority. This could involve integration with other infrastructure, i.e., polio-measles surveillance. Need to ensure complete case reporting, correct classification of cases, 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.	Need to improve surveillance throughout Europe to obtain homogenous, comparable data Need to encourage uniform use of diagnostic methods for detection of TBE pathogens Need to recommend use of standard EU case definition for TBE
Rabies surveillance is particularly lacking in Asia and Africa.	Need to implement and strengthen rabies surveillance across all risk areas to meet WHO target of rabies elimination by 2030

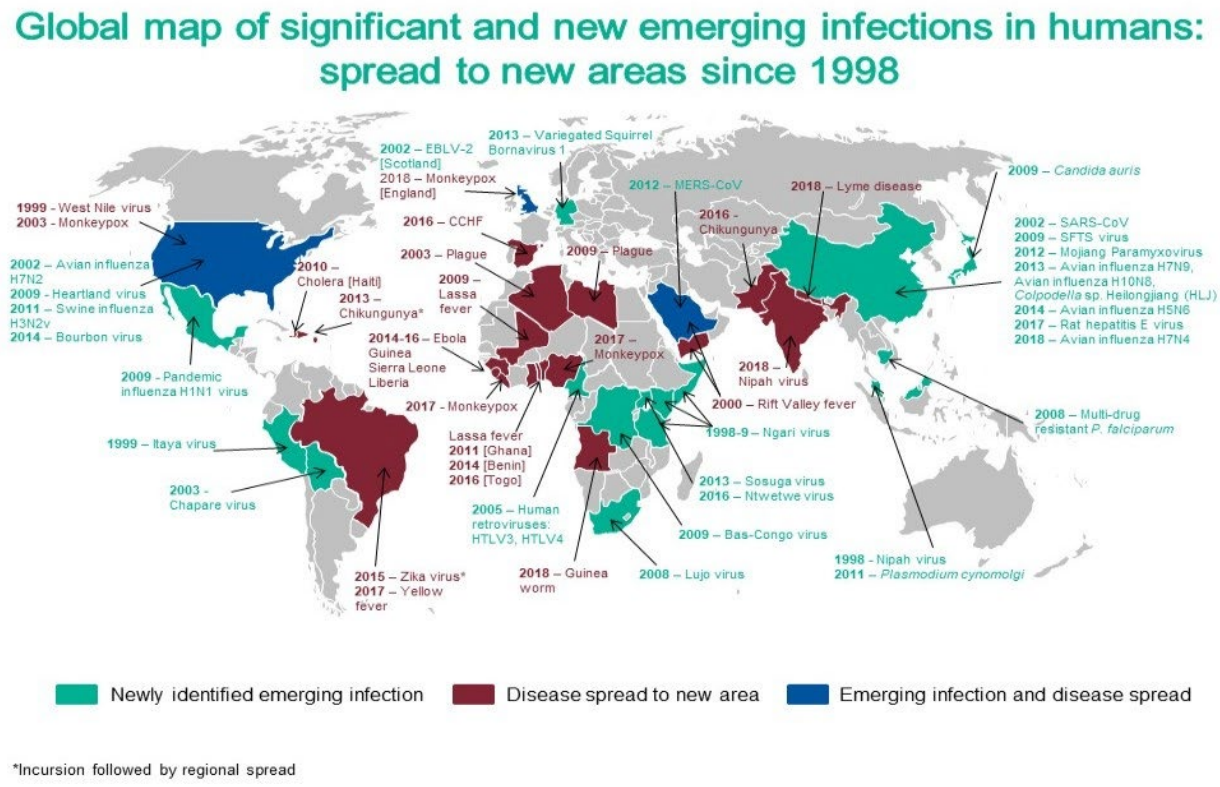
EU = European Union; HICs = High-income countries; JE = Japanese encephalitis; LMICs = Low- and middle-income countries; TBE = Tick-borne encephalitis

9 New and emerging infections

9.1 Introduction

Novel Infectious diseases have been emerging for thousands of years and will continue to do so in the future as a result of climate change, rapid urbanization, changing land-use patterns, and increasing interaction between humans, animals, and their environment (One Health) (348,349) (Figure 30). Approximately 60-80% of emerging infections are thought to be derived from an animal source (348). Many emerging infections can present as encephalitis, and there is potential to detect many more amongst the current pool of unknown causes. Recent years have seen the emergence and spread of arboviruses, such as Powassan, chikungunya, TBEV, and more recently JEV in Australia, and the unique role of bats in the transmission of novel viruses to humans, some of which can cause encephalitis (e.g., Nipah virus and likely SARS-CoV-2) (350). WHO monitors the spread of diseases globally and maintains a list of diseases with epidemic or pandemic potential (351). We aimed to assess the global situation in terms of emerging/re-emerging pathogens included in the WHO list that can cause encephalitis, including chikungunya, Nipah virus infection, and novel coronavirus (COVID-19). Importantly, we also considered scrub typhus, an emerging cause of encephalitis in South Asia for which effective treatment is available.

Figure 30 - Global map of significant and new emerging infections in humans: spread to new areas from 1998 to February 2019



From PHE (348)

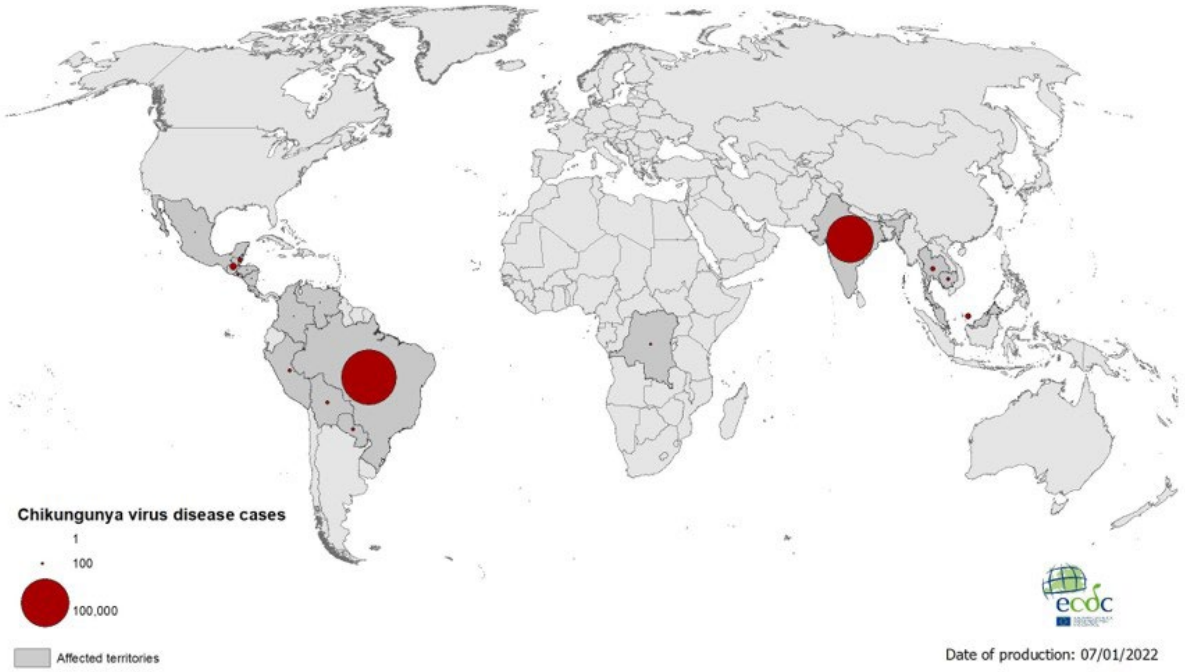
9.2 Selected examples

9.2.1 Chikungunya virus

Chikungunya, a mosquito-borne viral disease, was first recognised in 1952 during an outbreak in southern Tanzania; however, clinical descriptions suggest that chikungunya outbreaks may date as far back as the 1600s (352). Historically, chikungunya was considered a mild febrile self-limiting disease, possibly complicated by chronic disabling arthritis of the joints, restricted to Africa and Asia (353). Over the last decade however, a new face of chikungunya has emerged with rapid global expansion and accumulating evidence for neurological consequences. The last year has seen large outbreaks across South America, particularly in Paraguay (354).

Since 2004, chikungunya virus caused large epidemics, spreading to the Pacific Islands in 2011, and the Americas in 2013 (355,356). This rapid global expansion has been the result of adaptation of the virus to other vector species (i.e., *Aedes Albopictus* in addition to *Ae. Aegypti*), expansion of mosquito vectors to more temperate climates, and increased air travel exporting chikungunya virus to other countries and possibly provoking autochthonous transmission by local *Aedes* populations (352,356). To date, autochthonous transmission has been reported in 114 countries over the tropical and sub-tropical areas of Africa, Asia, Oceania, the Americas, and Europe with millions infected (352) (Figure 31). The 2005/2006 outbreak on Réunion Island, which resulted in a cumulative incidence rate of 34%, demonstrated the explosive capacity and swift dissemination that chikungunya virus is capable of (357). In this outbreak, the incidence of chikungunya-associated encephalitis contributed to a two-fold increase of the regional overall incidence of all encephalitis (14.6 versus 6.0 cases per 100,000 persons per year at baseline) (358). Neurological involvement ranging from 0.1% to 16.3% has been reported in case series during epidemics, with encephalitis and myelitis the most important neurological presentations of chikungunya infection (351,355).

Figure 31 - Geographical distribution of Chikungunya virus disease cases reported worldwide, 2021



From ECDC website (359)

Neurological presentations of chikungunya are severe and often result in a poor neurocognitive outcome. The case fatality among patients with a neurological presentation in the 2005/2006 Réunion Island outbreak was 10%. Treatment is symptomatic as no efficacious medical countermeasures exist despite >75% of the world population living in areas at risk of chikungunya virus transmission (352). Thus, prevention is of utmost importance and currently involves preventing mosquito bites and transmission from viraemic patients, and vector control through targeted limited spraying and destruction of breeding sites. The rapid detection of outbreaks is key to ensure prompt initiation of control measures. Current diagnostic strategies predominantly rely on reverse transcriptase (RT)-PCR and antibody detection by enzyme-linked immunosorbent assay (ELISA); however, these diagnostic technologies require complex instrumentation, sophisticated laboratories, and trained personnel rendering them not accessible or affordable to patients at the lower healthcare system levels where most chikungunya outbreaks occur (361). Rapid Diagnostic Tests (RDTs) are available and have the potential to overcome some of these challenges; however, the landscape of chikungunya RDTs is fragmented and coordinated efforts are needed to ensure that patients in chikungunya-endemic areas have access to appropriate RDTs (361).

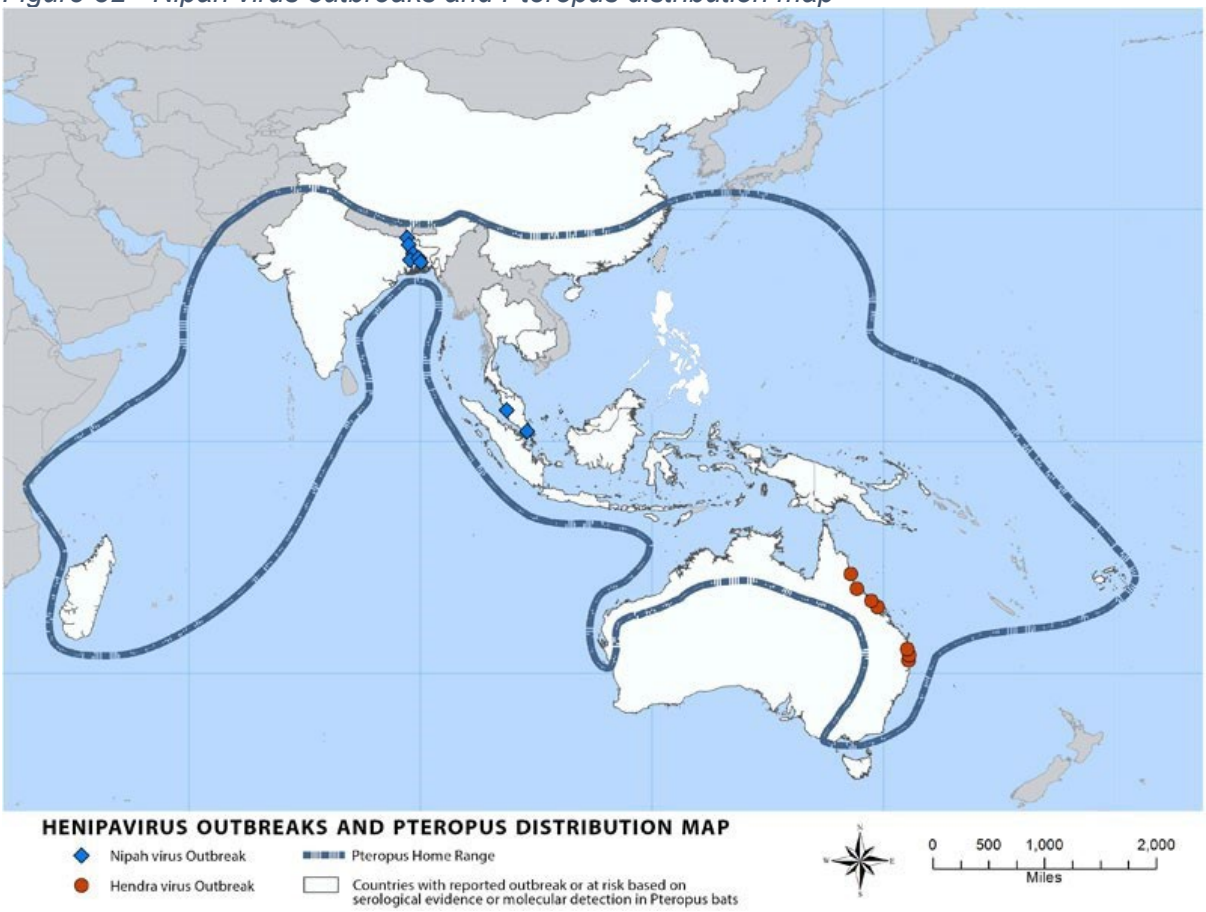
As previously mentioned, a Phase 3 pivotal trial of Valneva's single-shot chikungunya vaccine candidate, VLA1553, has been successfully completed and FDA approval for use in adults in currently being sought (247). Future research should focus on diagnostics, drug and vaccine development, vector control programs, and surveillance activities to enable any explosive increase in chikungunya cases to be mitigated.

9.2.2 Nipah virus

Nipah virus was first identified in Malaysia and Singapore in 1999 following an outbreak of respiratory and neurological disease in pigs and encephalitis in humans (362). Since then, further sporadic and unpredictable outbreaks have occurred in Bangladesh, India, and the Philippines (363). Symptoms in humans range from mild to severe and initially include fever, headache, and respiratory symptoms; encephalitis and potentially death may follow. Nipah virus infection is associated with a high case fatality rate (40-75%) (362).

Nipah is a zoonotic disease, and the animal host reservoir is the fruit bat (genus *Pteropus*) (363). Infected fruit bats can spread the disease to humans or other animals, including pigs. Humans can become infected through close contact with an infected animal or its body fluids. Fruit bats have a flying range that can cover vast areas, hence there is concern that outbreaks can affect further areas in the future (364) (Figure 32). Human-to-human transmission has been documented, accounting for 75% and 51% of cases in the India and Bangladesh outbreaks, respectively, raising further fears of Nipah's pandemic potential (364).

Figure 32 - Nipah virus outbreaks and Pteropus distribution map



From Dhaked et al. (365)

Despite the threat posed by Nipah virus, medical countermeasures do not exist. Intensive supportive therapy, where available, is the current standard of care for severe respiratory and neurological complications (366). Current prevention strategies focus on raising disease awareness in affected areas and behaviour modifications to prevent spill-over from bats (364). Rapid detection of Nipah outbreaks is required for prompt initiation of appropriate control measures. Various assays have been developed for laboratory confirmation of Nipah virus infections, with ELISA and RT-PCR the preferred methods (364). Currently available tests could be improved by validation of methods and standardization across laboratories. Further investment in strategies that can facilitate access to suitable diagnostics in all areas where Nipah virus outbreaks are likely to occur is important (364).

There is a diverse pipeline of medical countermeasures in development, including small molecules and antivirals, monoclonal antibodies, and vaccines, that have the potential to control future Nipah outbreaks (366). It is important to continue and progress these efforts given the high case fatality associated with the disease coupled with the potential for further spread. Investment in a combined portfolio of several medical countermeasures, including

surveillance systems, and active data exchange between developers of human and animal medical countermeasures should be encouraged (366).

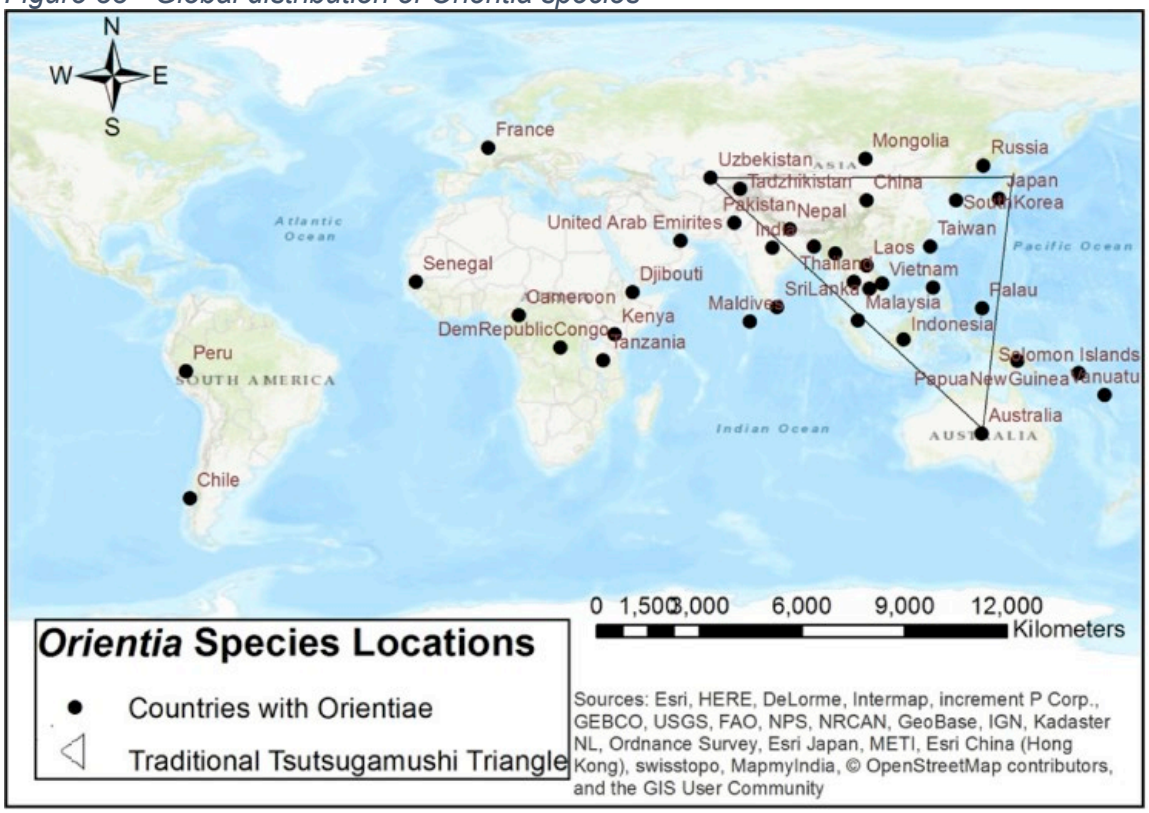
9.2.3 COVID-19

Since the first cases of SARS-CoV-2 were reported in Wuhan, China in 2019, the world has seen a global COVID-19 pandemic with >750 million cases, almost seven million deaths, and an unprecedented burden on economic and healthcare systems (367). Although COVID-19 predominantly affects the respiratory system, neurological disorders, such as stroke, Guillain-Barre syndrome, myelitis, and encephalitis, have been increasingly reported (368). A systematic review and meta-analysis reported the pooled incidence of encephalitis in COVID-19 patients was relatively low at 0.215% (range 0.008-0.904); however, this still equates to a significant number of cases (i.e., approximately based on 0.215% of 750 million COVID-19 cases worldwide since the start of the pandemic) (368). The incidence of encephalitis increases significantly in COVID-19 patients who are severely ill and require ITU care (6.7%). In addition, mortality in patients who suffer encephalitis as a complication of COVID-19 is four times higher than the general population of COVID-19 patients (13.4% versus 3.4%) (368). Encephalitis syndromes seen with COVID-19 are heterogeneous, including acute and post-infectious presentations, likely representing varied underlying neuropathogenesis (369). Response to treatment depends on the specific CNS manifestation. Various treatments have been used for COVID-19-associated encephalitis; one survey reported IV methylprednisolone/oral prednisone (36.11%), IV immunoglobulin (27.77%), and aciclovir (16.66%) as common treatment options (370). Several studies have confirmed the efficacy of IV immunoglobulin in severe cases of COVID-19 (371,372).
In December 2020, approximately one year after the initial case was reported, the UK became the first country to approve a COVID-19 vaccine (i.e., Pfizer-BioNTech) that has been tested in a large clinical trial (373). Further vaccines have been developed and as of December 2022, 11 vaccines against COVID-19 have been granted emergency use listing by WHO with others still in preclinical and clinical development (374). The extraordinary success of the COVID-19 vaccines shows what can be achieved in the event of a true global emergency and sufficient resources. The COVID-19 pandemic has changed the future of vaccine science, as new vaccine manufacturing methods (e.g., messenger RNA) have been validated and it has been demonstrated that the development process can be accelerated substantially without compromising safety (375). Lessons from the coronavirus pandemic should be applied to preparedness efforts against Nipah virus and other pathogens of pandemic potential (366).

9.2.4 Scrub typhus

Scrub typhus, a disease caused by the rickettsia/bacteria *Orientia tsutsugamushi*, is spread to humans through bites of infected chiggers or larval mites. Although first described as early as the third century A.D., scrub typhus shot into prominence during the second world war when millions were affected in the China-Burma-India corridor of military action (46). Since then, scrub typhus has reemerged with a different geographical distribution and varied clinical presentation (376). Scrub typhus is endemic in the Asia–Pacific region (i.e., 'tsutsugamushi triangle') but has recently spread to Chile, Peru, and West Africa (Figure 33) (46).

Figure 33 - Global distribution of Orientia species



From Tilak et al. (46)

The most common symptoms of scrub typhus include fever, headache, body aches, and sometimes rash. The first sign of the disease prior to symptom development is the formation of a black crust or eschar close to the site of the vector bite (377). Eschars are present in 7-97% of patients with scrub typhus (46). Nervous system involvement occurs in up to one fifth of patients and can include encephalitis, meningitis, and less frequently opsoclonus, myoclonus, parkinsonism, and Guillain-Barre syndrome (378). Scrub typhus has emerged as an important cause of encephalitis in children in India. A prospective cohort study conducted

at a tertiary care public hospital reported scrub typhus in 18.8% (n=66/352) of children with AES (379). Other studies in India have reported ranges from 12.5% in Notheast India to 63% in Gorakphur (380,381). Seasonal outbreaks of AES have been occurring over numerous years in eastern Uttar Pradesh during the monsoon and post-monsoon months, affecting mainly children from rural areas and resulting in high case fatality (15-25%) (382). Scrub typhus has increasingly been identified as an important, and even main aetiology of these outbreaks. Moderate to severe disability is frequent amongst survivors of AES caused by scrub typhus (382). Of 146 survivors of AES caused by scrub typhus, 38.4% (n=56) had mild disability and 13% (n=19) had moderate to severe disability.

The gold standard for diagnosing rickettsial infections is immunofluorescence. However, the required fluorescence microscope is not easily available, the test is expensive and time-consuming, technical expertise is required, and cell culture facilities are ideally needed for sustaining rickettsial antigens (383). Serum IgM ELISA is the most widely used test for diagnosis; however, CSF IgM ELISA may be preferable but this requires further evaluation in larger studies (383,384). It is important however not to await laboratory confirmation when there is clinical and epidemiological suspicion as scrub typhus can successfully be treated with doxycycline, tetracycline, and azithromycin, and most of the neurological manifestations of scrub typhus, including encephalitis, respond to these antibiotics (377,378). Thus, it is important to consider scrub typhus high on the list of differential diagnoses among patients in endemic areas presenting with acute febrile illness, especially in the setting of multi-organ dysfunction and presence of an eschar (378).

There are ongoing efforts to develop a prophylactic vaccine against scrub typhus despite the availability of antibiotics (377). Poor cross-reactive immunity and the short life span of protective immunity results in frequent reinfection, and antibiotic resistance is a concern with the profuse use of antibiotics.

9.3 Discussion

Changes in climate, land use, proximity to animals, and human behaviours have and will continue to result in the emergence/re-emergence of numerous pathogens that cause encephalitis. Scrub typhus has re-emerged as a main cause of encephalitis in children in India, and Chikungunya virus has spread westwards since 2004 resulting in large epidemics with neurological involvement in a significant proportion of cases. Nipah virus outbreaks are restricted to Asia thus far, but there is real concern given the vast flying range of the bat vector, potential of human-to-human transmission, and high case fatality. The emergence of SARS-

CoV-2, which can result in encephalitis, has shown the devastating impact a global pandemic can have on individuals, economic, and health systems. This emphasizes the importance of pandemic preparedness and efforts to reduce the risk of emergence/re-emergence of dangerous pathogens.

A reduction in activities which contribute to environmental change, such as deforestation, intensive agricultural practices, biodiversity loss, and interactions with animals and live animal markets, would lower the risk of emerging zoonoses and spillover events (385). If a novel zoonoses or mutation does emerge, rapid and early identification is key to limit spread (369). As has been demonstrated by the coronavirus pandemic however, containment alone may prove difficult. A worldwide collaborative response, including international collaborative efforts of identification, classification, and knowledge sharing, is required to tackle a global disease that has spread (369). Expansion of global surveillance will reduce the risk of large-scale outbreaks of encephalitis in the future (350). The One Health approach is gaining global recognition as an effective way to fight health issues at the human-animal-environment interface (386,387). This approach applies global collaboration at the local level to achieve better public health outcomes, from addressing the impact of climate and environmental change through to the implementation of surveillance and early warning systems to detect emerging pathogens with the potential to cause future pandemics (385).

9.4 Gap analysis

Table 32 - Gap analysis for new and emerging infections

Where we are	Where we want to be
Novel Infectious diseases have been emerging for thousands of years and will continue to do so in the future. Some of these cause encephalitis and are included in the WHO list of diseases with epidemic or pandemic potential.	Need increased investment in outbreak response to help mitigate the threat from future emerging infections Need efforts to develop universal vaccines (e.g., against all strains of influenza viruses, flaviviruses, or coronaviruses) Need rapid and early identification of novel zoonoses or mutations to limit spread Need to improve and expand global surveillance Need One Health approach to fight health issues at the human-animal-environment interface Need a better understanding of disease ecology and investigations into infectious agents in wildlife to potentially prevent outbreaks in livestock and people
Chikungunya virus has spread westwards since 2004 resulting in large epidemics with neurological involvement in a significant proportion of cases.	Need to understand more about the epidemiology of Chikungunya, especially granular data on disease incidence and age-specific infection rates Need to standardise procedures used to characterise this disease

	Need to better understand chikungunya disease dynamics with appropriate granularity and better insights into the duration of long-term population immunity to assist in the planning and success of vaccine development efforts pre and post licensure Need to improve surveillance and rapid outbreak detection Need coordinated efforts to ensure patients in chikungunya-endemic areas have access to appropriate rapid diagnostic tests Need to continue efforts to develop medical countermeasures
Nipah virus outbreaks are restricted to Asia thus far, but there is real concern given the vast flying range of the bat vector, potential of human-to-human transmission, and high case fatality.	Need to establish or reinforce surveillance systems to ensure rapid detection of Nipah outbreaks and prompt initiation of appropriate control measures Need to increase efforts on behaviour change communication interventions to increase awareness of disease risks Need to validate and standardise laboratory diagnostic methods for Nipah Need to invest in strategies to facilitate access to suitable diagnostics in all areas where Nipah outbreaks are likely to occur Need to continue and increase efforts to develop medical countermeasures
The world has experienced a global COVID-19 pandemic with an unprecedented burden on individuals, economic, and healthcare systems.	Need to apply lessons from the coronavirus pandemic to preparedness efforts against other pathogens of pandemic potential
Scrub typhus is increasingly recognised as an important cause of encephalitis in children in India.	Need to consider scrub typhus high on the list of differential diagnoses among patients in endemic areas presenting with acute febrile illness as effective treatment is available

10 Advocacy

10.1 Introduction

The WHO defines advocacy for health as “a combination of individual and social actions designed to gain political commitment, policy support, social acceptance, and systems for a particular health goal or program” (388). At an organisation level, advocacy should concentrate on problem identification, acquisition of evidence for problem solving, and communication of knowledge to the public, decision-makers, opinion leaders/influencers, and key stakeholders in governments and institutions to enable support and implementation of actions. At an individual level, advocacy should concentrate on empowering the individual to engage in planning and monitoring health services. Communities and organisations could together successfully advocate for accessible and high-quality healthcare.

Advocacy goals for encephalitis include better protection against preventable types of encephalitis, better diagnosis and treatment, and better support and after-care for survivors of encephalitis and their families. Encephalitis professionals and those with personal experience are the strongest advocates for change, and it is essential that all involved in the management of encephalitis (health professionals, individuals affected, families, and patient organisations) contribute towards this advocacy. In addition, the commitment of decision-makers and the community is necessary. A joint effort is required to improve the lives of those affected by encephalitis. The specific advocacy goals for prevention, diagnosis and treatment, and after-care and support in encephalitis are displayed in Table 33.

Table 33 - Advocacy goals for encephalitis

Advocacy area	Goals
Prevention	-Encephalitis prioritized as a health issue in endemic areas and as a travel-related condition -More accurate data available on global burden of encephalitis -Policies accessible and funding available to support introduction and optimization of vaccine schedules and educational campaigns -Increased vaccine awareness and promotion of uptake -Increased accuracy of information on risk, burden, and preventative measures for infectious encephalitis -National and local policies to control vectors involved in transmitting specific causes of encephalitis (e.g., dogs in rabies, mosquitos in JE)
Diagnosis and treatment	-Development of diagnosis and treatment guidelines for encephalitis -Improved supply of free/affordable immunotherapies -Routine provision of evidence-based information on safety netting by health professionals -Provision of training for health professionals on all types of encephalitis -Inclusion of encephalitis and immunotherapies used for the treatment of autoimmune encephalitis on the insurance approved list -Implementation of health and social care assessments at discharge for detection of after-effects and for implementation of rehabilitation programmes
After-care and support	-Ensuring that healthcare and social services for after-care and support are accessible to affected individuals and families in a timely manner -Availability of educational programmes for the self-management of symptoms - Signposting of suitable after-care support by health services -Presence of a suitable legal framework that supports the rights of those with ongoing after-effects, impairments, and disabilities

10.2 Recommended practice

Advocacy is a powerful way to engage a diverse range of people with the encephalitis cause and promote change. However, recommended approaches for advocacy in encephalitis do not exist. Rather, key theoretical elements of a successful advocacy campaign include:

- Develop a deeper understanding of the issue;
- Know who has the power to change matters;
- Decide who the allies and enemies are and involve them;
- Develop a plan with clear advocacy goals and strategies;

- Communicate with the public, stakeholders, and decision makers.

10.3 Implementation status

It is difficult to assess the status of encephalitis advocacy as it varies by campaign, type of encephalitis, and region. At present, advocacy campaigns focus on prevention of vaccine-preventable infectious encephalitis including JE in Asia, rabies in Asia and Africa, TBE in Europe, and measles globally. Campaigns which relate specifically to diagnosis and treatment or after-care are generally included in larger, over-arching health campaigns (e.g., United Nations [UN] Sustainable Development Goals 2015) and/or as part of larger organisations (e.g., Neurological Alliance, UK Acquired Brain Injury Forum in the UK).

10.4 Barriers to implementation and discussion

Numerous barriers exist with regards to encephalitis advocacy. There is a lack of data on incidence, prevalence, and cost (human and financial) of encephalitis making it difficult to establish the real burden and acquire quantitative evidence to support advocacy campaigns. A lack of awareness among the public with regards to disease frequency and severity of the consequences is another barrier to encephalitis advocacy. Other conditions have a higher public profile despite having less impact and this greatly influences prioritisation among social, financial, and political programmes and strategies. Growing vaccine hesitancy in populations due to misinformation affects the success of advocacy campaigns. There is a lack of funding to support global and local advocacy campaigns, and a general lack of importance attributed to encephalitis resulting in it often being omitted from medical training and awareness programmes. Finally, the nature of the illness and the fact that incidence, diagnosis, and treatment differ by cause is a barrier to encephalitis advocacy.

10.5 Gap analysis

Table 34 - Gap analysis for encephalitis advocacy

	Where we are	Where we want to be
Prevention	Encephalitis is not perceived as a travel-related condition and the associated burden is not recognised	Need to increase recognition of encephalitis as a travel-related condition and its associated burden
	Vaccines against preventable causes of encephalitis are expensive for travellers	Need access to affordable vaccines for travellers
	Coverage or implementation of vaccine programmes in endemic areas are insufficient	Need affordable vaccines and access to information resources about the disease and vaccination in endemic areas
	Surveillance strategies and preventive programmes for vector-borne encephalitis (e.g., mosquitos, strained dogs) are insufficient and inadequate	Need implementation of global and local surveillance strategies and preventive measures and programmes for vector-borne encephalitis

	Vaccine hesitancy and anti-vaccine movements may hamper vaccine coverage	Need a high level of community engagement and widespread communication about vaccine safety and the incidence of encephalitis in vaccinated and unvaccinated population to improve vaccine uptake
Diagnosis and treatment	There is insufficient training on encephalitis in medical school and in some medical professions, encephalitis training does not exist at all.	Need comprehensive and up-to-date medical training
	Guidelines for the management of encephalitis that are recognised by medical councils and organisations do not exist	Need for management guidelines to be recognised and recommended by medical councils globally
	There is lack of treatment for encephalitis that is free, affordable, and approved by insurance	Need for free or affordable treatment or treatment approved by insurance
After-care and support	Services to support families and survivors and information on how to access these services are lacking	Need for affordable services to support families and survivors and for them to know how to access these services
	Legal frameworks that support the rights of disabled people are often inconsistent or even absent	Need for legal framework in each country that supports the rights of disabled people

11 Support and after-care for survivors and families

11.1 Introduction

Encephalitis survivors may acquire brain injuries to varying degrees and manifestations. This can make returning to school, work, family, and social life difficult (389). In some cases, encephalitis also increases the risk of death from other causes (390). An acquired brain injury (ABI) after encephalitis is specific to the individual and often hidden, subtle and inconsistent, and lifelong. Affected individuals may look identical to what they did before with effects being cognitive, emotional, behavioural, and social rather than physical (i.e., hidden). In addition, affected individuals may appear to function at the same level as previously in most respects and better on some days than others (i.e., subtle and inconsistent). The affected individual may also be perceived to perform better than others, but not as well as they did before the illness (i.e., individual). If encephalitis occurs in childhood, there is the possibility of a delayed onset of difficulties where the effects of the injury to the brain (ABI) are only apparent later in life due to the part of the brain affected not yet being developed at the time of illness. Consequently, these individuals may be discharged from hospital before the full extent of their disability has been recognised and addressed. As physical disabilities are rarer than mental

disabilities encephalitis, affected individuals may not be perceived as disabled by employers, school, services, and the wider public. Others may need care in their homes or care homes for the rest of their lives.

ABI following encephalitis affects entire families. Families must first come to terms with the illness and its consequences and subsequently find ways to cope. The impact of encephalitis on the lives of three families of JE survivors has been described in the following ways: “strange”, “scary”, “devastating”, “shock”, “it is not anything you imagine”, and “this is for life” (243). In addition, the carer role is often assumed by family members and has a significant impact on physical and psychological health, finances, employment, family relationships, and overall quality of life (391).

Support after encephalitis is needed for both affected individuals and their families. Affected individuals require suitable, multistage, multidisciplinary, and personalised rehabilitation and/or psychological support to come to terms with the illness and its after-effects, to learn to manage their difficulties, and to re-integrate within social and family life. Families and carers also have support needs. Some may be bereaved and require specific bereavement support, while others may need to cope with becoming a carer and the resulting change of dynamics within their families. Provision of support and rehabilitation; however, is often suboptimal and even non-existent in some countries where people affected rely mainly on family members to help with daily activities (392).

Despite the evident impact on individual lives, the true burden of disability following encephalitis remains unknown. There is no simple and reliable way of measuring the disability burden, and also it is unfamiliar to health and social care providers as well as decision makers. In a WHO document which presents the GBD estimates and projections of neurological disorder, meningitis is included irrespective of cause whereas only one type of encephalitis (i.e., JE) is included (392). Survivors of encephalitis face discrimination and stigma associated with their acquired disability. Article 25 of the UN Convention on the Rights of Persons with Disabilities reinforces the right of persons with disability to attain the highest standard of health care, without discrimination (393). This is however, not always achieved.

11.2 Recommended practice

The type of support required following the acute illness is dependent on the type and degree of disability, family and social support network, financial means, age, resilience, provision of local support and rehabilitation services, culture/religion, and education. It is widely

recognised that specialist, multi-stage, person-centred, and interdisciplinary rehabilitation is beneficial and that specialist rehabilitation is highly cost-efficient (394). The needs of each affected individual should ideally be assessed at different stages in their recovery, and support and rehabilitation should be tailored accordingly. Rehabilitation includes not only physical medicine, pharmacology, and nutrition, but also psychology and behaviour, education and counselling, occupational and vocational advice, social and supportive services, architecture and engineering, and other interventions (392). Specifically, neurorehabilitation should aim to optimise functional recovery, disability management, and adaptation to loss and change (395). WHO advocates community rehabilitation as an addition to existing rehabilitation models and for rehabilitation to look beyond medical needs/care (392).

It is important that disability following encephalitis is addressed not only from a medical perspective (resulting in individual treatment) but also from a social perspective which requires social action to reintegrate the individual into society. Education and awareness campaigns aimed at the general public, services, policy makers, and healthcare professionals (especially primary care) are needed to eliminate stigma and discrimination and improve overall quality of life.

Support for families is variable. Families need specialised bereavement support in the event of loss of life which needs to take into account different ages, emotional needs, and cultural and religious backgrounds. Support needs of families in which a carer role is assumed should consider all aspects of day-to-day life including financial needs, employment, emotional needs, mourning the loss of the person as they knew them, respite care, and daily activities. These activities undertaken to support the affected individual range from practical interventions such as help with eating, washing, and cooking to assistance on how to cope with challenging behaviour and loss of memory. Thus, different interventions should be widely available for caregivers of individuals affected by encephalitis as they are for other conditions such as stroke (i.e., psychoeducational interventions focused on coping and problem-solving) or dementia (i.e., educational sessions) (154). The support provided to caregivers is important as it has a strong influence on the management of the affected individual (153).

Universal rehabilitation guidelines do not exist, but the World Federation for Neurorehabilitation Position Paper 2015 (395) calls for:

- Long-term, coordinated efforts by governments, non-governmental organisations, international organisations, and other interested partners to facilitate investment in, and the provision of, rehabilitation equipment and the funding of education and training programmes for health professionals.

- The development of a core set of standards to constitute minimum requirements for the establishment of credible neurorehabilitation units.
- Implementation of community-based rehabilitation services with tailored and culturally sensitive education for families and carers.

Key features of support and after-care can include (but are not limited to):

- Provision of information about the illness to enable individuals to understand what happened to them and help them come to terms with the illness.
- Provision of information about recovery so individuals know what to expect.
- Provision of information on expectations from families/carers following hospital discharge.
- Provision of practical advice such as who to contact in case of an emergency.
- Provision of information regarding relevant patient organisations.
- Ensure referrals are in place for follow-up appointments or rehabilitation in the community.
- Ensure social care assessments are in place where there are social care requirements.
- Ensure family doctors/general practitioners (GPs) receive a discharge letter with recommendations for follow-up and referral.
- Ensure transfer to suitable rehabilitation if discharge to home is not possible (e.g., specialised ABI care homes rather than dementia care homes).
- Ensure community rehabilitation if discharge to home is an option.
- Ensure psychological support for affected individuals.
- Ensure psychological support for carers and families.
- Ensure plans are in place for gradual return to work or school.
- Ensure the availability of respite care for carers from caring responsibilities.
- Provide bereavement support.
- Ensure easy access to legal redress for substandard health care.
- Ensure presence of national and legal frameworks that embed the rights of disabled people.

11.3 Implementation status

The majority of affected individuals/families in contact with the Encephalitis Society report inadequate care provision. There are no guidelines for the universal implementation of support and rehabilitation for people affected by encephalitis and their families/carers. The support received varies considerably depending on location, financial means, and cultural practices.

In general, access to support services is often resource-dependent at both a national and individual level.

Services are more widely available in higher income settings and for wealthier individuals compared to low-resource settings or for individuals living in poverty. Whilst clinicians and healthcare professionals play an important role in support and after-care, it is often families and communities, alongside civil society and faith/community groups, who provide the majority of care needed.

11.4 Barriers to implementation and discussion

Despite improvements in the diagnosis and treatment of encephalitis, information about its after-effects is lacking. The focus is on the acute stage of the illness and affected individuals and their families are often left with little information about effects post-discharge. The lack of knowledge regarding the after-effects of encephalitis combined with the often invisible and subtle changes following some brain injury often results in patients leaving hospital without any follow-up appointment or referral. Thus, these individuals return home and attempt to resume life as before without realising that this is not always possible. They are usually faced with a lack of follow-up support when it is realised that they cannot function as before. Often the ABI is confused with being a result of stress, overprotective behaviours of parents in the case of children, and even in cases where there is an understanding family doctor, there are often no services available or there is a long-waiting time.

There is also a lack of rehabilitation services that provide multidisciplinary and personalised treatment plans. Availability of services depend on geographical location; some areas have full provision and others only specific professionals, for example occupational therapists. Neuropsychological services are non-existent in many areas, and long waiting lists sometimes delay much-needed intervention. Another barrier to implementation is the nature of the illness itself with various types of encephalitis having different outcomes and affected individuals having different needs. Ideally, rehabilitation for affected individuals would consist of medical, psychological, and social support. The lack of or inadequate communication between health professionals (acute and rehabilitation team), affected individuals, and families/carers is a substantial barrier to implementation.

According to WHO (396), current barriers to strengthen and extend rehabilitation in countries include:

- Under-prioritisation by government amongst competing priorities;

- Absence of rehabilitation policies and planning at the national and sub-national levels;
- Limited coordination between ministries of health and social affairs where both are involved in rehabilitation;
- Non-existent or inadequate funding;
- Dearth of evidence of met and unmet rehabilitation needs;
- Insufficient numbers of rehabilitation professionals and lack of skills;
- Absence of rehabilitation facilities and equipment;
- Lack of integration into health systems.

11.5 Gap analysis

Although most issues identified in Table 35 are not encephalitis specific, they are highly relevant to improving support and after-care for survivors and families after an encephalitis diagnosis.

Table 35 - Gap analysis for support and after-care for survivors and families

	Where we are	**Where we want to be**
Lack of information	Lack of information about expectations following discharge	Need provision of information at discharge about what to expect
Inexistent /inadequate discharge plans	Discharge plans inadequate without patient participation	Need agreement on discharge plans between healthcare professionals and affected individual/caregiver
Lack of follow-up appointment/referrals	Discharge without a follow-up appointment or with extensive waiting time	Need a timely follow-up appointment to be set-up at discharge
Lack of understanding of ABI following encephalitis by GP/family doctor	GP often unaware of ABI following encephalitis	Need to ensure awareness amongst GPs/family doctors of ABI following encephalitis and the existence of services to enhance recovery
Lack of services available and/or long waiting times	No community rehabilitation available or long waiting times No support for carers and their families (e.g., family therapy)	Need multidisciplinary community rehabilitation teams
Lack of support to help with returning to work/education	People advised to return to school/work often resulting in failure	Need adequate support in place for a phased and gradual return to school/work
Lack of care home specialised in ABI	Older adults recovering from encephalitis sent directly to dementia care homes	Need adequate provision for rehabilitation of older people
Cost	High cost of health care reduces access for those in need	Need affordable healthcare services
Policy and legislation	Inconsistent or absent policies, lack of sanctions for failure to deliver, and voices of people with disabilities are largely silent in critical decisions affecting their lives	Need stronger policies Need available services Need planned improvements for access and inclusion Need to involve children and adults with disabilities in decisions affecting their lives Need comprehensive regulatory framework with inclusion of specific objectives regarding the rights of children with disabilities in

		education, health and social services, and monitoring of the allocation of funds for their implementation
Finances	Lack of affordable public or private health financing and insurance, and unequitable access to public health programmes	Need cover for people with disabilities and measures to make the premiums affordable where private health insurance dominates healthcare financing
Human resources	Limited training on disability for healthcare professionals, limited use of evidence-based guidelines, and limited training on ABI following encephalitis	Need to integrate education on disability into undergraduate studies and continuing education for all healthcare professionals Need evidence-based guidelines for assessment and treatment
Data and research	Infrequent inclusion of people with disability in healthcare surveillance Some research exists on needs, barriers, and health outcomes for people with disabilities Limited research looking at recovery and rehabilitation	Need to include individuals with disabilities, special needs, or developmental retardation in healthcare surveillance Need more research on the needs, barriers, and health outcomes for people with disabilities Need more research on the needs of people with encephalitis and their recovery and rehabilitation
Bereavement	Lack of trained psychosocial support for bereavement	Need more widely available psychosocial support for bereavement
Service delivery	Limited modifications and adjustments made to facilitate health access Variable information, training, and peer support Sporadic use of community-based rehabilitation Lack of targeted interventions based on need	Need broad range of modifications and adjustments (reasonable accommodation) to facilitate access to healthcare services Need to empower individuals with disabilities to maximize their health by providing information, training, and peer support Need detailed responsibilities for all professionals in the health, education, and social protection system developed for the identification and referral of children with disabilities Need community-based rehabilitation to facilitate access to existing services for disabled people Need identification of groups that require alternative service delivery models, for example, targeted services or care coordination to improve access to health care

ABI = Acquired brain injury; GP = General practitioner

12 Information

12.1 Introduction

Accurate, up-to-date, and accessible information is essential for managing encephalitis adequately and improving the quality of life of people directly or indirectly affected by this condition. Both professionals and people affected/families require extensive knowledge about the condition and its effect. However, as needs vary, information must be tailored to the

specific characteristics of the audience and their stage on encephalitis journey. Whilst in hospital, affected individuals and their families need information about the illness and its course. At discharge, information is required on recovery, possibility of relapse, range of after-effects, potential impact on individual lives, and who to contact if needed.

Patients may initially present to a GP, paramedic, or nurse or accident and emergency personnel before encephalitis is suspected and a neurologist or infectious disease specialist becomes involved. In some areas however, patients may never see a neurologist even after encephalitis is suspected. This reinforces the importance of incorporating encephalitis into the medical school curriculum and providing regular training updates for healthcare professionals. Following discharge, a range of professionals may be directly or indirectly involved, including medical, healthcare, social care, educational, and legal professionals, benefits or disability advisors, and employers. Extensive and accurate information regarding the illness will enable them to provide better input to help improve patient quality of life. Knowledge about encephalitis is also important in circumstances apart from dealing with a diagnosis of or patient with encephalitis. This refers to preventable types of encephalitis and also in care of disability resulting from encephalitis, public/employer education of inclusion and non-discriminatory disability practices.

Overall, there is lack of information regarding encephalitis and its effects among professionals, affected individuals and their families/carers, and the general public. A survey of adults in five countries (UK, USA, Germany, India, and Australia) revealed that 81% of the worldwide general public do not know what encephalitis is (397). Survey participants were asked to describe in their own words what they understood the word encephalitis to be/mean, and answers were converted by The Encephalitis Society into ‘yes I have heard of encephalitis and know what it is’ or not and the statistic calculated. Sample sizes and 2018 field work dates varied by country. Frackowiak et al. presented one medical student’s experience in the UK and argued that encephalitis is insufficiently covered as a topic during undergraduate training with a profound impact on how junior doctors deal with encephalitis cases (398). Encephalitis at medical school is briefly described in the context of meningitis, but important factors such as the need for an urgent LP, early diagnosis, and prompt treatment to avoid or minimise death and disability are omitted. Students learn about HSV as a cause of encephalitis, but the multitude of other possible aetiologies are not included. Students are left with an understanding that encephalitis is so rare they will probably never encounter an encephalitis case. Despite a lack of information, when it is available it has a significant impact. Some quotes from Encephalitis Society members who have used the information produced by the Society

include: “When your packet arrived we both cried. It felt like a big hug from someone who understood what happened.”; **“**Great to have clear information so accessible!”; “I really struggled to come to terms with the issues the encephalitis left me with to the point I knew how I was going to commit suicide, then my wife stumbled across the society online, we then saw the head with the possible after effects. As I ticked them off one by one it struck me that I was normal for the illness, which meant so much to me and honestly it saved my life. I still have issues but I'm better at managing them thanks to you and Preston hospital’s pain clinic.”; “It’s nice to find somewhere that answers the questions as you navigate acute illness and recovery. There are limited resources here, so I’ve found this extremely helpful.”; “Thanks to this wonderful Society for their information. It became our bible.”

12.2 Recommended practice

Provision of appropriate, up-to-date, and accessible information by healthcare and health information systems, and the dissemination of this information comprises a substantial part of health literacy which is needed to empower people to improve their health (Table 36) (399). There is however, no recommended practice regarding the compilation and dissemination of information related to encephalitis. Although encephalitis can affect anyone globally, the information should be tailored to the specific audience, incidence, local health system, economic setting, and cultural background. Different approaches may be required, and these should be piloted. Patient involvement in information development is crucial, as is community awareness. Any knowledge gaps should be identified. The inclusion of all types of encephalitis within the medical training curriculum and subsequent professional development, widely available professional guidelines, and free access to professional resources is key to better awareness among health professionals.

Table 36 - Role of encephalitis information resources

Information area	Role
Prevention (infectious encephalitis)	*General public*: Awareness of endemic areas; Likelihood of the condition and severity of the consequences if acquired; Awareness of vaccines and preventive measures *Travel health professionals*: Likelihood of the condition and severity of consequences if acquired
Diagnosis	*Health professionals*: Awareness of signs and symptoms; Importance of lumbar puncture; Awareness of diagnostic algorithm
Treatment effects	*Health professionals*: Awareness of timely access to treatment *Affected individuals*: Awareness of expectations and the impact on day-to-day life *General public*: Awareness of acquired brain injury following encephalitis

	Health professionals: Emphasis on the importance of individual assessments; Awareness of the brain injury following encephalitis *Social care professionals*: Awareness of the brain injury following encephalitis
Recovery and rehabilitation	*Affected individuals*: Awareness of the need for rehabilitation and self-help strategies; Signposting to appropriate services *Families/carers*: Awareness of the role of rehabilitation; Service signposting for affected individuals and carers *Professionals*: Awareness of rehabilitation after encephalitis and the importance of self-help strategies; Service signposting regarding support for carers and family members
Other information	*Bereaved families*: Service signposting *General public*: Awareness of the condition and resulting brain injury *Families of affected children*: Awareness of immediate and long-term effects following brain development; Service signposting *Education professionals*: Awareness of brain injury following encephalitis; Resources for support strategies; Awareness of the impact on families/ carers/ other children

12.3 Implementation status

Global implementation of effective information practice is generally low and varies depending on geographical area, type of encephalitis, and local economic and political priorities. Information regarding recovery, rehabilitation, and self-help is mostly non-existent (Table *37*). WHO provides information regarding JE, TBE, and rabies; however, information remains limited regarding other causes. The UK-based Encephalitis Society is the only patient organisation globally that provides information on prevention, diagnosis, treatment, effects, support, and after-care of encephalitis; however, this is not available to, or adapted for, all countries affected by encephalitis.

Table 37 - Implementation status depending on encephalitis type and setting

	High-income	Low-income
Infectious		
Vaccine-preventable	Some information depending on the geographical area/hospital type	Little/no information but depends on campaign/outbreaks
Other infectious	Some information depending on the geographical area/hospital type	Little/no information
Autoimmune	Some information depending on the size/speciality of hospital available	Little/no information

12.4 Gap analysis

Table 38 – Gap analysis for provision of information

Issue	Where we are	Where we want to be
Awareness of available vaccines for certain types of encephalitis	Low population awareness of vaccines and presence of vaccine hesitancy/anti-vaccination movement (objections/concerns about safety)	Need high population awareness of and confidence in available vaccines
Awareness of preventive measures for encephalitis apart from vaccination	Low population awareness and confusion over efficacy	Need high population awareness of and confidence in available preventative strategies apart from vaccination
Awareness of the severity of the illness	Low awareness in the general population and amongst travel and health professionals	Need high awareness in the general population and amongst travel and health professionals
Awareness of signs and symptoms of encephalitis among health professionals	Low awareness of signs and symptoms and confusion with psychiatric conditions or alcohol or drug intoxication	Need high awareness of signs and symptoms and differential diagnoses
Seeking help	Some reluctance to seek help depending on the local medical system (e.g., private or state) Limited availability of medical services and high cost of transport in low-income countries	Need health-seeking behaviours based on the presence of signs and symptoms Need affordable transport/financial support for transport
Safety-netting information (advice on potential course of illness and actions to take)	Lack of context/culturally appropriate information	Need culturally appropriate/context suitable safety-netting information readily available
Training of health professionals	All types of encephalitis not included in core training curriculum Insufficient training /experience on performance of lumbar puncture Insufficient training on the effects of encephalitis	Need to include all types of encephalitis in core training curriculum Need training/ support in performing a lumbar puncture Need training on effects of encephalitis
Materials/resources for health professionals	Context/culturally appropriate and condition-specific information not provided Lack of guidelines for managing encephalitis and its possible effects	Need culturally appropriate/context suitable and condition-specific materials and resources readily available Need widely available guidance for managing encephalitis and its effects

Service signposting	Lack of services to signpost to and limited awareness of the need to signpost	Need signposting from health facilities to services available for people with sequelae and their families and for bereavement Need sufficient knowledge on the services needed for different after-effects
Legal redress	Lack of legal framework Lack of knowledge about how/when to seek redress Financial barriers to legal engagement	Need law to allow for legal redress in the cases of poor standard health care and need for citizens to access financial support for legal redress

13 Conclusion

Encephalitis is a global problem with high death rates and often wreaks devastation on the lives of those affected. The condition does not share the same platforms and awareness among the general public and policy makers as does other comparable conditions such as meningitis and sepsis.

It is likely that encephalitis is more common than many government agencies and policy makers realise. This is in part due to variations in how data are collected and the methodologies used, if indeed it is collected at all in some countries. Surveillance systems for non-vaccine preventable encephalitides often do not exist in many countries and where they do, reporting can be poor.

Many types of encephalitis are vaccine-preventable, or morbidity and mortality can be significantly reduced with early diagnosis and treatment. The outcomes for patients and the economic costs associated with that are also poorly understood. Identification, diagnosis, and treatment are problematic in some countries due to a lack of neurologists, lack of training, lack of access to diagnostics, and lack of access to what are, in some cases, cheap treatments. Prevention is hindered by a lack of vaccination programs in some countries, public confidence is an increasing problem, and variable quality of travel health information to travellers. Much can be done in terms of advocacy around the condition for patients and their families in terms of the training of health, social care, and education professionals; improved after-care and support, and greater awareness of encephalitis as a travel-related condition and the associated preventative strategies that could be accessed. A range of factors affect information for people affected by the condition including availability, accuracy, cultural appropriateness, and signposting.

This report attempts to detail the most important areas for attention in efforts to reduce the incidence, death, and often life-changing disabilities associated with the condition: cause; incidence; morbidity and mortality; economic impact; prevention; diagnosis and treatment; neurology training; surveillance; new and emerging infections; advocacy; support and information for patients.

This report will now be used to commence dialogue with key stakeholders who can influence many of the areas identified such as surveillance and prevention, along with those who can have influence on in-country policy and practice. These discussions will form part of the ongoing international focus and strategy of the Encephalitis Society. It is recognised that this

report may provide opportunities for some quick wins however real change will require a collaborative approach to ensure that the tools, resources, systems, and commitment to effect real change are in place to mitigate the burdens presented by this too-often devastating disease.

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16 Appendix

16.1 Methodology appendix

Search terms for:

Cause:
"Encephalitis AND cause"; "encephalitis AND etiology"; "encephalitis AND aetiology"; "encephalitis AND agent"; "encephalitis AND autoimmune"; "encephalitis AND antibody"; "encephalitis AND antibodies"; "encephalitis AND infection"; "encephalitis AND unknown"

Incidence:
"Encephalitis AND incidence"; "encephalitis AND admission rates;" "encephalitis AND epidemiology"; "acute disseminated encephalomyelitis/ADEM and incidence; "autoimmune encephalitis AND incidence"

Morbidity and mortality:
"Encephalitis AND mortality"; "encephalitis AND case-fatality"; "encephalitis AND case fatality"; "encephalitis AND Africa AND mortality"; "encephalitis AND outcome"; "encephalitis AND outcome AND child"; "encephalitis AND sequelae"; "encephalitis AND effect"; "encephalitis AND morbidity"; "encephalitis AND caregiver burden"; "encephalitis AND carer burden"; "Japanese encephalitis/JE AND mortality"; "Japanese encephalitis/JE AND case-fatality"; "Japanese encephalitis/JE AND case fatality"; "Japanese encephalitis/JE AND outcome"; "Japanese encephalitis/JE AND sequelae"; "Japanese encephalitis/JE AND effect"; "Japanese encephalitis/JE AND morbidity"; "herpes/HSV AND mortality"; "herpes/HSV AND case-fatality"; "herpes/HSV AND case fatality"; "herpes/HSV AND outcome"; "herpes/HSV AND sequelae"; "herpes/HSV AND effect"; "herpes/HSV AND morbidity"; "tick-borne encephalitis/TBE AND mortality"; "tick-borne encephalitis/TBE AND case-fatality"; "tick-borne encephalitis/TBE AND case fatality"; "tick-borne encephalitis/TBE AND outcome"; "tick-borne encephalitis/TBE AND sequelae"; "tick-borne encephalitis/TBE AND effect"; "tick-borne encephalitis/TBE AND morbidity"; "rabies AND mortality"; "rabies AND case-fatality"; "rabies AND case fatality"; "rabies AND outcome"; "rabies AND sequelae"; "rabies AND effect"; "rabies AND morbidity"; "acute disseminated encephalomyelitis/ADEM AND mortality"; "acute disseminated encephalomyelitis/ADEM AND case-fatality"; "acute disseminated encephalomyelitis/ADEM AND case fatality"; "acute disseminated encephalomyelitis/ADEM AND outcome"; "acute disseminated encephalomyelitis/ADEM AND sequelae"; "acute disseminated encephalomyelitis/ADEM AND effect"; "acute disseminated encephalomyelitis/ADEM AND morbidity"; "anti-NMDA

encephalitis/NMDA AND mortality"; "anti-NMDA encephalitis/NMDA AND case-fatality"; "anti-NMDA encephalitis/NMDA AND case fatality"; "anti-NMDA encephalitis/NMDA AND outcome"; "anti-NMDA encephalitis/NMDA AND sequelae"; "anti-NMDA encephalitis/NMDA AND effect"; "anti-NMDA encephalitis/NMDA AND morbidity"

Economics/cost and DALYs:
"Encephalitis AND DALY"; "encephalitis AND economic"; "encephalitis AND cost"; "encephalitis AND burden of disease"; "encephalitis AND disease burden"; "encephalitis AND cost effective"

Prevention including vaccine programs, vector control, and epidemic control:
"Encephalitis AND vaccine programs"; "encephalitis AND program"; "Japanese encephalitis AND vaccine"; "Japanese encephalitis AND vaccination"; "Japanese encephalitis AND immunisation;" "Japanese encephalitis AND immunization"; "Tick-borne encephalitis AND vaccine"; "Tick-borne encephalitis AND vaccination"; "Tick-borne encephalitis AND immunisation"; "Tick-borne encephalitis and immunization"; "MMR AND encephalitis"; "measles AND vaccination"; "measles AND immunisation"; "measles AND immunization"; "rabies AND vaccine"; "rabies AND vaccination"; "rabies AND immunisation"; "rabies AND immunization"; "encephalitis AND vector"; "encephalitis AND vector control"; "encephalitis AND prevention"; "encephalitis AND arbovirus"; "encephalitis AND outbreak"; "encephalitis AND outbreak control"; "encephalitis AND epidemic control"; "encephalitis AND control"

Diagnosis:
"Encephalitis AND diag*"; "encephalitis AND lab*"; "encephalitis AND cerebrospinal fluid/CSF"; "encephalitis AND CSF examination"; "encephalitis AND CSF analysis"; "encephalitis AND tests"; "encephalitis AND PCR"; "encephalitis AND molecular*"; "encephalitis AND molecular assay"; "encephalitis AND molecular diag*"; "encephalitis AND nucleic acid test"; "encephalitis AND nucleic acid detection"; "encephalitis AND MRI"; "encephalitis AND MRI availability"; "encephalitis AND MRI use"; "encephalitis AND antibody test"; "encephalitis AND antibody assay"; "autoimmune encephalitis AND diagnostic"; "encephalitis AND autoantibody"; "encephalitis AND essential diagnostic"; "encephalitis AND NMDAR"

Treatment:
"Acyclovir/aciclovir availability"; "acyclovir/aciclovir availability AND encephalitis"; "acyclovir/aciclovir AND Africa"; "acyclovir/aciclovir AND encephalitis"; "acyclovir/aciclovir AND avail*"; "acyclovir/aciclovir AND encephalitis AND Asia"; "acyclovir/aciclovir AND

encephalitis AND Africa"; "encephalitis AND essential medicine"; "encephalitis AND essential medicine AND Africa"

In-country neurologists and access to neurology training:
"Neurologists by country"; "neurology training"; "neurology AND training"; "neurologist"; "neurology presence"; "presence of neurologist"

Surveillance:
"Encephalitis AND surveillance;" "encephalitis AND reporting;" "encephalitis AND report"; "encephalitis AND statistics"; "encephalitis AND routine"; "encephalitis AND monitor"; "encephalitis AND data;" "Japanese encephalitis/JE/JEV AND surveillance;" "Japanese encephalitis/JE/JEV AND reporting;" "Japanese encephalitis/JE/JEV AND report"; "Japanese encephalitis/JE/JEV AND statistics"; "Japanese encephalitis/JE/JEV AND routine"; "Japanese encephalitis/JE/JEV AND monitor"; "Japanese encephalitis/JE/JEV AND data;" "Tick-borne encephalitis/TBE/TBEV AND surveillance;" "Tick-borne encephalitis/TBE/TBEV AND reporting;" "Tick-borne encephalitis/TBE/TBEV AND report"; "Tick-borne encephalitis/TBE/TBEV AND statistics"; "Tick-borne encephalitis/TBE/TBEV AND routine"; "Tick-borne encephalitis/TBE/TBEV AND monitor"; "Tick-borne encephalitis/TBE/TBEV AND data"; "rabies AND surveillance;" "rabies AND reporting;" "rabies AND report"; "rabies AND statistics"; "rabies AND routine"; "rabies AND monitor"; "rabies AND data"

New and emerging infections:
"Encephalitis AND emerging infect*;" "encephalitis AND novel infect*;" "encephalitis AND emerging;" "encephalitis AND re-emerging;" "encephalitis AND new infect*;" "encephalitis AND Nipah;" "encephalitis AND chikungunya;" "encephalitis AND scrub typhus;" "encephalitis AND orientia*;" encephalitis AND bush typhus;" "encephalitis AND covid*;" "encephalitis AND corona*"

16.2 Tables

Table A1 - Details of included incidence studies

Study	Date	Country	Continent	Encephalitis type	Age	Incidence per 100,000 (95%CI)
Beghi et al	1950-1981	USA	North America	Viral encephalitis	All	7.4
Rantakallio et al	1966-1983	Finland	Europe	Infectious encephalitis	Children	12.6 (7.86-19.41)
Rantalaiho et al	1967-1991	Finland	Europe	Acute encephalitis	Adult	1.4
Koskiniemi et al	1968-1987	Finland	Europe	Acute encephalitis	Children	8.3 (7.56-9.09)
Wickstrom et al	1970-2009	Sweden	Europe	Encephalitis	Children	7.7
Rantala et al	1973-1987	Finland	Europe	Encephalitis	Children	8.8 (6.7-10.1)
Cizman et al	1979-1991	Slovenia	Europe	Acute encephalitis	Children	6.7 (6.13-7.32)
Iro et al	1979-2011	England	Europe	Encephalitis	Children	5.97 (5.52-6.41)
Ponka et al	1980	Finland	Europe	Encephalitis	All	3.5 (2.06-5.67)
Radhakrishnan et al	1983-1984	Libya	Africa	Encephalitis	Adult	1 (0.32-2.31)
Chunsuttiwat et al	1983-1987	Thailand	Asia	Encephalitis	All	4 (3.83-4.18)
Ishikawa et al	1984-1990	Japan	Asia	Acute encephalitis	Children	3.3 (2.71-3.47)
Kusumi et al	1988-1992	Japan	Asia	Encephalitis	Adult	0.9 (0.37-2.2)
Khetsuriani et al	1988-1997	USA	North America	Encephalitis	All	7.3 (5.6-8.1)
Davison et al	1989-1998	England	Europe	Viral encephalitis	All	1.5 (1.46-1.54)
Trevejo et al	1990-1999	USA	North America	Acute encephalitis	All	4.3 (4.2-4.4)
Huppatz et al	1990-2007	Australia	Oceania	Encephalitis	All	5.2 (4.2-6.7)
Nwosu et al	1991-1993	Nigeria	Africa	Infectious encephalitis	Adult	3.19 (1.28-6.56)
Leake et al	1991-2000	USA	North America	ADEM	Children	0.4 (0.35-0.66)
Pavone et al	1992-2009	Italy	Europe	ADEM	Children	1.1
Koskiniemi et al	1993-1994	Finland	Europe	Acute encephalitis	Children	10.5 (9-12.18)
Heinrich et al	1993-1998	Thailand	Asia	Viral encephalitis	All	6.4
Kulkarni et al	1994-2008	Canada	North America	Encephalitis	All	5.16 (5.09-5.22)
Dubey et al	1995-2015	USA	North America	AIE Infectious encephalitis excluding unknowns	All	0.8 1

Chhour et al	1996-1998	Cambodia	Asia	Encephalitis	Children	0.92 (0.69-1.22)
Pohl et al	1997-1999	Germany	Europe	ADEM	Children	0.07 (0.05-0.1)
Vora et al	1998-2010	USA	North America	Encephalitis	All	6.9
Kupila et al	1999-2003	Finland	Europe	Aseptic encephalitis	Adult	2.2
Barbadoro et al	1999-2005	Italy	Europe	Encephalitis	All	5.88 (5.87-5.89)
Mailles et al	2000-2002	France	Europe	Encephalitis	All	1.9 (1.84-1.96)
George et al	2000-2010	USA	North America	Encephalitis	All	7.3 (7.1-7.6)
Britton et al	2000-2012	Australia	Oceania	Encephalitis	Children	5 (4.6-5.4)
Van Landingham et al	2001-2007	USA	North America	ADEM	Children	0.4
Parpia et al	2002-2013	Canada	North America	Encephalitis	All	4.3 (4.2-4.4)
Kadambari et al	2004-2013	England & Wales	Europe	Viral meningo-encephalitis	All	3.9 (3.74-4.06)
Yamaguchi et al	2005-2007	Japan	Asia	ADEM	Children	0.4 (0.34-0.46)
Kelly et al	2005-2008	Ireland	Europe	Viral encephalitis	All	2.49 (2.31-2.68)
Child et al	2005-2009	New Zealand	Oceania	Encephalitis	>14	0.5
Granerod et al	2005-2009	England	Europe	Encephalitis	All	5.23
Jackson et al	2006-2012	Canada	North America	ADEM	All	0.17 (0.09-0.27)
Bhatt et al	2006-2014	USA	North America	ADEM	Children	0.5 (0.47-0.53)
Joshi et al	2007	India	Asia	AES	Adult	16
Roux et al	2007-2017	French Guiana	South America	Encephalitis	All	4
Xiong et al	2008-2010	China	Asia	ADEM	All	0.31
Chen et al	2008-2011	China	Asia	ADEM	All	0.32
Boesen et al	2008-2015	Denmark	Europe	ADEM	Children	0.54 (0.39-0.75)
Boesen et al	2011-2017	Denmark	Europe	Anti-NMDA Anti-GAD65 Antibody negative but probable AIE	Children	0.07 (0.03-0.17) 0.055 (0.021-0.15) 0.055 (0.021-0.15)
Bodilsen et al	2015-2016	Denmark	Europe	Viral encephalitis	>15	1.4
Marienke et al	2015-2018	Netherlands	Europe	Antibody-mediated AIE ADEM	Children	0.15 (0.095-0.235) 0.25 (0.17-0.35)
Sevilla-Acosta et al.	2017	Costa Rica	North America	Acute encephalitis	Children	3.6
Kim et al	2010-2021	South Korea	Asia	Encephalitis	All	9.48
Lee et al	2015-2019	South Korea	Asia	Encephalitis	All	16.4

Liem et al	2009-2018	New Zealand	Oceania	Encephalitis	Adult	1.1

ADEM = Acute disseminated encephalomyelitis; AES = Acute encephalitis syndrome; AIE = Autoimmune encephalitis; CI = Confidence interval; GAD65 = Glutamate decarboxylase; NMDARE = N-methyl-d-aspartate receptor encephalitis; USA = United States of America

Table A2 – Details of included mortality studies

Study	Date	Country	Continent	Encephalitis type	Age	CFR (%)	Raw data CFR
Andleeb et al	2013-2018	Pakistan	Asia	Encephalitis	All	37.3	28/75
Bhatt et al	2006-2014	USA	North America	ADEM	Children	1.7	
Bodilsen et al	2015-2016	Denmark	Europe	Viral encephalitis	Adult >15	5	5/89
Britton et al	2000-2012	Australia	Oceania	Encephalitis	Children	2.6	
Child et al	2005-2009	New Zealand	Oceania	Encephalitis	Adult >14	14	
Davison et al	1989-1998	England	Europe	Viral encephalitis	All	6.5	
Fowler et al	2000-2004	Sweden	Europe	Acute encephalitis	Children	0	0/93
Galanakis et al	2005-2007	Greece	Europe	Encephalitis	Children up to 15	0	0/42
George et al	2000-2010	USA	North America	Encephalitis	All	5.6	
Granerod et al	2005-2008	UK	Europe	Encephalitis	All	12	24/203
Grinschgl et al	1953	Austria	Europe	Viral ME	All	4.6	14/304
Hon et al	2002-2014	Hong Kong	Asia	Encephalitis	Children	>25	≥12/46
Huppatz et al	1990-2007	Australia	Oceania	Encephalitis	All	4.6	
Ilias et al	2000-2004	Greece	Europe	Encephalitis	Children	0	0/18
Ishikawa et al	1984-1990	Japan	Asia	Acute encephalitis	Children	7.8	20/256
Joshi et al	2007	India	Asia	AES	Adult	34.8	n=53
Khetsuriani et al	1988-1997	USA	North America	Encephalitis	All	7.4	
Koskiniemi et al	1968-1987	Finland	Europe	Encephalitis	Children (1mo - 16yr)	3	14/462
Le et al	2004	Vietnam	Asia	Acute encephalitis	Children	29	57/194
Lohitharajah et al	2012-2014	Sri Lanka	Asia	Encephalitis/ME	All	7	7/99
Mailles et al	2007	France	Europe	Encephalitis	All	10	26/253
Beghi et al	1950-1981	USA	North America	Viral encephalitis	All	3.8	
Olsen et al	2003-2005	Thailand	Asia	Encephalitis and ME	All	10	15/149
Quist-Paulsen et al	2000-2009	Norway	Europe	Encephalitis	Adult	7	5/70
Rantalaiho et al	1967-1991	Finland	Europe	Acute encephalitis	Adult	5.6	18/322
Rao et al	2000-2010	USA	North America	Encephalitis	Children <21	5	4/76
Rathore et al	2011-2012	India	Asia	Encephalitis	All	7	37/526

Roux et al	2007-2017	French Guiana	South America	Encephalitis	All	28.7	
Schmidt et al	1992-2004	Switzerland	Europe	Encephalitis of unknown aetiology	All	12.8	5/39
Sevilla-Acosta et al	2017	Costa Rica	North America	Encephalitis	Children	15	6/40
Srey et al	1999-2000	Cambodia	Asia	Encephalitis syndrome	All	22	22/99
Toudou-Daouda et al	2008-2016	Morocco	Africa	Limbic encephalitis	All	9.7	3/31
Vora et al	1998-2010	USA	North America	Encephalitis	All	5.8	
Wong et al	1975-1986	Hong Kong	Asia	Encephalitis	Children <14	28	16/57
de Blauw et al	2003-2013	The Netherlands	Europe	Encephalitis	Children <18	20.8	25/121
Iro et al	2003	England & Wales	Europe	Encephalitis	Children	8.4	87/1031
Zhao et al	2009-2012	China	Asia	Viral encephalitis	All	3.1	34/1107
Britton et al	2013-2016	Australia	Oceania	Encephalitis	Children	4.5	13/287
Ai et al	2009-2012	China	Asia	Viral encephalitis	Children	0.8	2/255
Meligy et al	2015-2016	Egypt	Africa	Viral encephalitis	Children	23	22/96
Wickstrom et al	1970-2009	Sweden	Europe	Encephalitis	Children	3.5	x/408
Misra et al	2014-2016	India	Asia	AES	Children	19	15/79
Bagdure et al	2004-2013	USA	North America	Encephalitis	Children	3	230/7298
Glaser et al	1998-2000	USA	North America	Encephalitis	All	17.1	50/293
Milshtein et al	1999-2009	Israel	Asia	Acute encephalitis	Children	0	0/44
Li et al	2016-2020	China	Asia	Viral encephalitis	Children	0.1	43/39279
Liem et al	2009-2018	New Zealand	Oceania	Encephalitis	Adults ≥15	10.3	14/136

ADEM = Acute disseminated encephalomyelitis; AES = Acute encephalitis syndrome; CFR = Case fatality rate; ME = Meningoencephalitis; UK = United Kingdom; USA = United States of America

Table A3 - Presence of neurologists and trainees by country

Country	Neurologist present?	Trainee present?	Income group	Continent
Benin	Yes		Low	Africa
Burkina Faso	Yes	Yes	Low	Africa
Burundi	Yes	No	Low	Africa
Central African Republic	Yes	No	Low	Africa
Chad	No		Low	Africa
Comoros	Yes		Low	Africa
Congo, Dem. Rep.	Yes		Low	Africa
Eritrea	Yes		Low	Africa
Ethiopia	Yes	Yes	Low	Africa
Guinea	Yes		Low	Africa
Guinea-Bissau	No		Low	Africa
Liberia	No		Low	Africa
Madagascar	Yes	Yes	Low	Africa
Malawi	Yes	No	Low	Africa
Mali	Yes		Low	Africa
Mozambique	Yes	Yes	Low	Africa
Niger	Yes		Low	Africa
Rwanda	Yes	No	Low	Africa
Senegal	Yes	Yes	Low	Africa
Sierra Leone	Yes		Low	Africa
Somalia			Low	Africa
South Sudan	Yes	No	Low	Africa
Tanzania	Yes		Low	Africa
The Gambia	Yes		Low	Africa
Togo	Yes		Low	Africa
Uganda	Yes	No	Low	Africa
Zimbabwe	Yes		Low	Africa
Afghanistan	Yes		Low	Asia
Korea, Dem. People's Rep. (North Korea)			Low	Asia
Nepal	Yes		Low	Asia
Haiti		No	Low	Latin America & the Caribbean
Cabo Verde	No		Lower middle	Africa
Cameroon	Yes	Yes	Lower middle	Africa
Congo, Rep.	Yes	Yes	Lower middle	Africa
Côte d'Ivoire	Yes		Lower middle	Africa
Dijibouti	Yes	No	Lower middle	Africa
Egypt, Arab Rep.	Yes	Yes	Lower middle	Africa
Ghana	Yes		Lower middle	Africa
Kenya	Yes	No	Lower middle	Africa
Lesotho	No		Lower middle	Africa
Mauritania	Yes		Lower middle	Africa
Morocco	Yes	Yes	Lower middle	Africa
Nigeria	Yes	Yes	Lower middle	Africa
São Tomé and Principe	No		Lower middle	Africa

Sudan	Yes	No	Lower middle	Africa
Swaziland	No		Lower middle	Africa
Tunisia	Yes	Yes	Lower middle	Africa
Zambia	Yes	No	Lower middle	Africa
Armenia	Yes	Yes	Lower middle	Asia
Bangladesh	Yes	Yes	Lower middle	Asia
Bhutan	No		Lower middle	Asia
Cambodia	No		Lower middle	Asia
India	Yes	Yes	Lower middle	Asia
Indonesia	Yes		Lower middle	Asia
Kyrgyz Republic	Yes		Lower middle	Asia
Lao PDR	Yes		Lower middle	Asia
Mongolia	Yes		Lower middle	Asia
Myanmar	Yes	Yes	Lower middle	Asia
Pakistan	Yes	Yes	Lower middle	Asia
Philippines	Yes	Yes	Lower middle	Asia
Sri Lanka	Yes	Yes	Lower middle	Asia
Syrian Arab Republic	Yes	Yes	Lower middle	Asia
Tajikistan	Yes		Lower middle	Asia
Timor-Leste			Lower middle	Asia
Uzbekistan	Yes		Lower middle	Asia
Vietnam	Yes		Lower middle	Asia
West Bank and Gaza	Yes		Lower middle	Asia
Yemen, Rep.	Yes	Yes	Lower middle	Asia
Kosovo			Lower middle	Europe
Moldova	Yes	Yes	Lower middle	Europe
Ukraine	Yes		Lower middle	Europe
Bolivia	Yes	Yes	Lower middle	Latin America & the Caribbean
El Salvador		No	Lower middle	Latin America & the Caribbean
Guatemala	Yes	Yes	Lower middle	Latin America & the Caribbean
Honduras	Yes	Yes	Lower middle	Latin America & the Caribbean
Nicaragua	Yes	No	Lower middle	Latin America & the Caribbean
Kiribati	No		Lower middle	Oceania
Micronesia, Fed. Sts.	No		Lower middle	Oceania
Papua New Guinea	No		Lower middle	Oceania
Samoa	No		Lower middle	Oceania
Solomon Islands	No		Lower middle	Oceania
Tonga	No		Lower middle	Oceania
Vanuatu	No		Lower middle	Oceania
Algeria	Yes	Yes	Upper Middle	Africa
Angola	Yes		Upper Middle	Africa
Botswana	No		Upper Middle	Africa
Equatorial Guinea	No		Upper Middle	Africa
Gabon	Yes		Upper Middle	Africa
Libya	Yes	No	Upper Middle	Africa
Mauritius	Yes		Upper Middle	Africa
Namibia	No		Upper Middle	Africa
South Africa	Yes	Yes	Upper Middle	Africa

Azerbaijan	Yes	Yes	Upper Middle	Asia
China	Yes		Upper Middle	Asia
Georgia	Yes	Yes	Upper Middle	Asia
Iran, Islamic Rep.	Yes	Yes	Upper Middle	Asia
Iraq	Yes	Yes	Upper Middle	Asia
Jordan	Yes	Yes	Upper Middle	Asia
Kazakhstan	Yes	Yes	Upper Middle	Asia
Lebanon	Yes	Yes	Upper Middle	Asia
Malaysia	Yes		Upper Middle	Asia
Maldives	No		Upper Middle	Asia
Thailand	Yes	Yes	Upper Middle	Asia
Turkey	Yes	Yes	Upper Middle	Asia
Turkmenistan	Yes		Upper Middle	Asia
Albania	Yes	Yes	Upper Middle	Europe
Belarus	Yes	Yes	Upper Middle	Europe
Bosnia and Herzegovina	Yes	Yes	Upper Middle	Europe
Bulgaria	Yes	Yes	Upper Middle	Europe
Macedonia	Yes	Yes	Upper Middle	Europe
Montenegro	Yes	Yes	Upper Middle	Europe
Romania	Yes	Yes	Upper Middle	Europe
Russian Federation	Yes	Yes	Upper Middle	Europe
Serbia	Yes	Yes	Upper Middle	Europe
Argentina	Yes	Yes	Upper Middle	Latin America & the Caribbean
Belize	Yes	No	Upper Middle	Latin America & the Caribbean
Brazil	Yes	Yes	Upper Middle	Latin America & the Caribbean
Colombia			Upper Middle	Latin America & the Caribbean
Costa Rica	Yes		Upper Middle	Latin America & the Caribbean
Cuba			Upper Middle	Latin America & the Caribbean
Dominica			Upper Middle	Latin America & the Caribbean
Dominican Republic	Yes	Yes	Upper Middle	Latin America & the Caribbean
Ecuador			Upper Middle	Latin America & the Caribbean
Grenada			Upper Middle	Latin America & the Caribbean
Guyana	Yes		Upper Middle	Latin America & the Caribbean
Jamaica			Upper Middle	Latin America & the Caribbean
Mexico	Yes	Yes	Upper Middle	Latin America & the Caribbean
Panama	Yes	No	Upper Middle	Latin America & the Caribbean
Paraguay	Yes	Yes	Upper Middle	Latin America & the Caribbean
Peru			Upper Middle	Latin America & the Caribbean
St. Lucia			Upper Middle	Latin America & the Caribbean
St. Vincent and the Grenadines	No		Upper Middle	Latin America & the Caribbean
Suriname	Yes		Upper Middle	Latin America & the Caribbean
Venezuela	Yes	Yes	Upper Middle	Latin America & the Caribbean
American Samoa	No		Upper Middle	Oceania
Fiji	No		Upper Middle	Oceania
Marshall Islands	No		Upper Middle	Oceania
Palau	No		Upper Middle	Oceania
Tuvalu	No		Upper Middle	Oceania

Seychelles	Yes		High	Africa
Bahrain	Yes	Yes	High	Asia
Brunei Darussalam	Yes		High	Asia
Cyprus	Yes	No	High	Asia
Hong Kong SAR, China	Yes	Yes	High	Asia
Israel	Yes	Yes	High	Asia
Japan	Yes	Yes	High	Asia
Korea, Rep. (South Korea)	Yes	Yes	High	Asia
Kuwait	Yes	No	High	Asia
Macao SAR, China	Yes		High	Asia
Oman	Yes	No	High	Asia
Qatar	Yes	Yes	High	Asia
Saudi Arabia	Yes	Yes	High	Asia
Singapore	Yes	Yes	High	Asia
Taiwan, China	Yes	Yes	High	Asia
United Arab Emirates	Yes	No	High	Asia
Andorra	Yes		High	Europe
Austria	Yes	Yes	High	Europe
Belgium	Yes	Yes	High	Europe
Channel Islands			High	Europe
Croatia	Yes	Yes	High	Europe
Czech Republic	Yes	Yes	High	Europe
Denmark	Yes	Yes	High	Europe
Estonia	Yes	Yes	High	Europe
Faroe Islands			High	Europe
Finland	Yes	Yes	High	Europe
France	Yes	Yes	High	Europe
Germany	Yes	Yes	High	Europe
Gibraltar			High	Europe
Greece	Yes	Yes	High	Europe
Hungary	Yes	Yes	High	Europe
Iceland	Yes	Yes	High	Europe
Ireland	Yes	Yes	High	Europe
Isle of Man			High	Europe
Italy	Yes	Yes	High	Europe
Latvia	Yes	Yes	High	Europe
Liechtenstein			High	Europe
Lithuania	Yes	Yes	High	Europe
Luxembourg	Yes	Yes	High	Europe
Malta	Yes		High	Europe
Monaco	Yes		High	Europe
Netherlands	Yes	Yes	High	Europe
Norway	Yes	Yes	High	Europe
Poland	Yes	Yes	High	Europe
Portugal	Yes	Yes	High	Europe
San Marino	Yes		High	Europe
Slovak Republic	Yes	Yes	High	Europe
Slovenia	Yes	Yes	High	Europe
Spain	Yes	Yes	High	Europe
Sweden	Yes	Yes	High	Europe
Switzerland	Yes	Yes	High	Europe
United Kingdom	Yes	Yes	High	Europe
Antigua and Barbuda	No		High	Latin America & the Caribbean
Aruba			High	Latin America & the Caribbean
Barbados	Yes		High	Latin America & the Caribbean
British Virgin Islands	No		High	Latin America & the Caribbean
Cayman Islands			High	Latin America & the Caribbean
Chile	Yes	Yes	High	Latin America & the Caribbean
Curaçao			High	Latin America & the Caribbean

Puerto Rico			High	Latin America & the Caribbean
Sint Maarten			High	Latin America & the Caribbean
St. Kitts and Nevis			High	Latin America & the Caribbean
St. Martin			High	Latin America & the Caribbean
The Bahamas	Yes		High	Latin America & the Caribbean
Trinidad and Tobago	Yes		High	Latin America & the Caribbean
Turks and Caicos Islands			High	Latin America & the Caribbean
Uruguay	Yes	Yes	High	Latin America & the Caribbean
Virgin Islands (U.S.)			High	Latin America & the Caribbean
Bermuda			High	North America
Canada	Yes	Yes	High	North America
Greenland			High	North America
United States	Yes	Yes	High	North America
Australia	Yes	Yes	High	Oceania
French Polynesia	Yes		High	Oceania
Guam	Yes		High	Oceania
Nauru	No		High	Oceania
New Caledonia	Yes		High	Oceania
New Zealand	Yes	Yes	High	Oceania
Northern Mariana Islands	No		High	Oceania