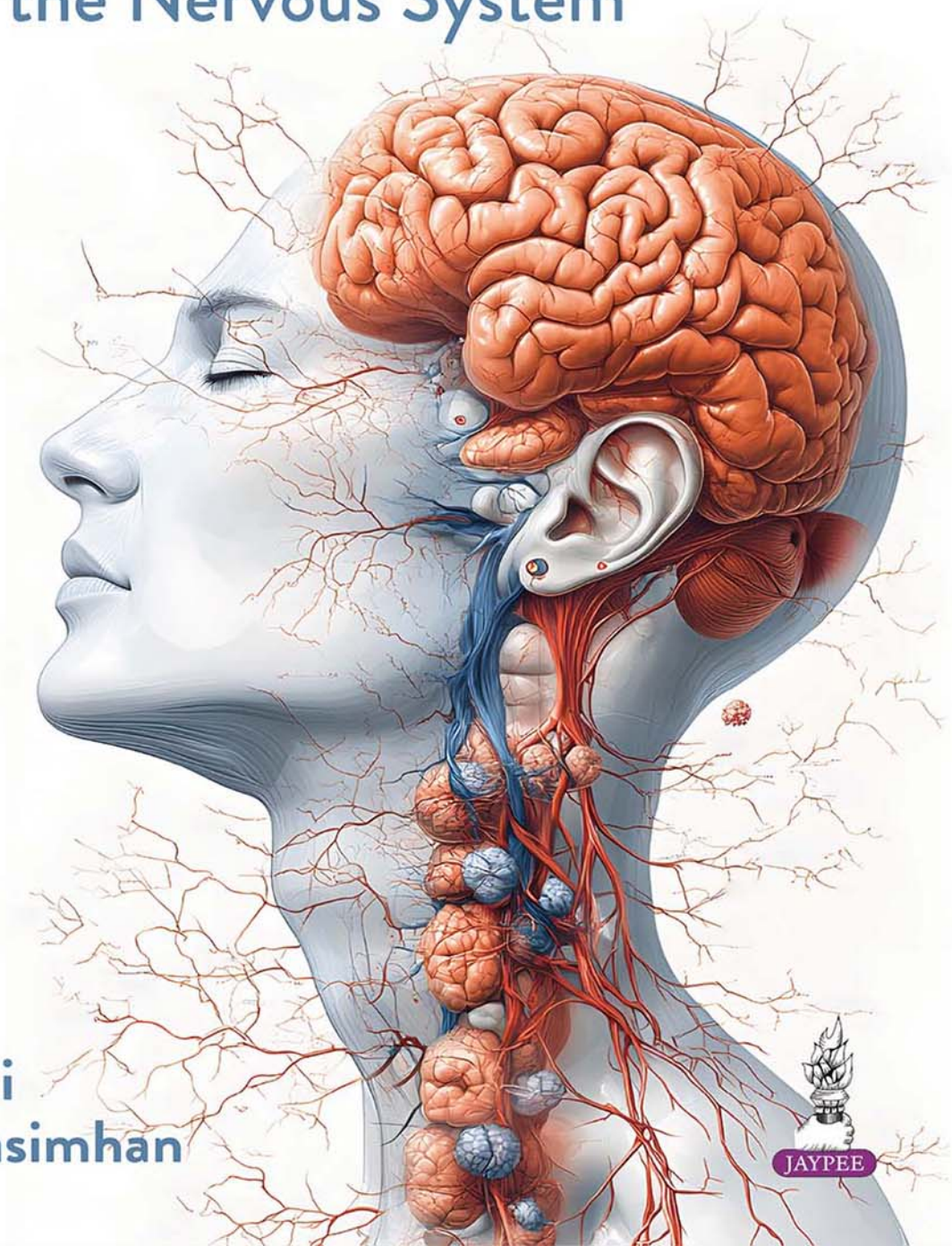
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IAN Reviews in NEUROLOGY 2025

Infections of the Nervous System



Editors
Sita Jayalakshmi
R Lakshmi Narasimhan

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13

Emerging and Reemerging Viral Neuroinfections

Rahul T Chakor, Swaleha Nadaf, Noel Gomes

ABSTRACT

Emerging infectious diseases affect a population for the first time or have existed previously but are rapidly spreading to new geographical areas. They are commonly due to RNA viruses. Rapid globalization, immunocompromised state, and environmental factors have significantly increased the spread of neurotropic viruses leading to their emergence and reemergence. These viruses are associated with significant morbidity and mortality and cause significant burden on healthcare services. Adequate clinical and diagnostic measures, development of antiviral drugs and vaccines, adequate vector control, and improving healthcare infrastructure to handle and quarantine affected patients should be prioritized by healthcare policy makers. In this chapter, we discuss in detail about the emerging and reemerging viral infections affecting the nervous system.

Keywords: Viral neuroinfections, Encephalitis, Myelitis, Zoonotic, Enzootic, Pandemic, Emerging, Reemerging, RNA, Arbovirus.

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INTRODUCTION

Emerging infectious diseases affect a population for the first time or have existed previously but are rapidly spreading to new geographical areas. They are commonly due to RNA viruses that have expanded their geographic range, spread from animal reservoirs, or acquired neurovirulence. Infections that declined dramatically but are again becoming health problems for a vast population are said to be reemerging. The terms emerging and reemerging have been used interchangeably, and there is no published list of these infections. In this chapter, we have attempted to present an updated review on emerging and reemerging viral neuroinfections.

VIRAL NEUROTROPISM

Viral potential to invade the central nervous system (CNS) is neuroinvasion and viral potential to cause a CNS disease is neurovirulence. Viruses with the ability to evoke neurologic diseases are referred to as "neurotropic".[1] Viral neuropathology is due to innate and adaptive immune responses. A virus that is rarely associated with neurological manifestations (e.g., influenza) is not always defined as neurotropic. Some viruses are highly neuroinvasive but hardly neurovirulent [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mumps virus], while other viruses are capable of causing severe CNS/peripheral nervous system (PNS) disease but are weakly neuroinvasive (poliovirus) or require a tissue trauma to become neuroinvasive (rabies virus).

EMERGENCE AND REEMERGENCE OF VIRAL NEUROINFECTIONS

Over 30 new infectious agents have been detected worldwide in the last three decades. Sixty percent of these are RNA viruses, half of them cause neurologic diseases, and most are zoonotic.

Factors that contribute to emergence of infectious diseases are as follows:[2-4]

- Population surge and encroachment of forest for housing purpose and other resources with increased exposure to zoonotic viruses
- *Deforestation and agriculturalization*: Kyasanur forest disease (KFD) due to increased exposure to ticks due to agriculturalization. Japanese encephalitis virus (JEV) emerged in the places where dams and canals were built to bring in water for rice cultivation.
- Climate change with ecology changes of microbes
- International travel and spread of viruses
- Mass migration due to war, natural calamities, or economic hardships
- Expansion of viruses to new geographic regions. Chikungunya spread to India and Europe from Indian Ocean islands. West Nile virus (WNV) in New York infected a variety of susceptible mosquito and bird species and established an endemic cycle.
- Spread from animal reservoirs to humans due to exposure (rabies)
- Presence of intermediate hosts for zoonoses causing CNS infections (filovirus, lyssavirus, henipavirus and coronavirus, and Nipah virus)
- RNA viruses alter their genomes by reassortment, antigenic shift, mutations, or recombination of viral genomes leading to increased neurovirulence
- Reemergence is recently seen in WNV and chikungunya virus. Virulent strains have improved the ability of a virus to enter the CNS and usually with more efficient replication in neurons and neuronal death.
- Wildlife trade and translocation, live animal and bush-meat markets, consumption of exotic foods, ecotourism, access to petting zoos, and ownership of exotic pets contribute to emergence of infectious diseases and jumping of viruses (novel SARS-CoV) from animals to human **(Table 1 and Figs. 1 to 3)**.

TABLE 1: Spectrum of neurological manifestations of neurotropic viruses.

Virus	Genus	Family	Genome	Central nervous system involvement	Peripheral nervous system involvement
HSV-I	*Simplex virus*	Herpesviridae	dsDNA	Encephalitis, myelitis, cerebellitis	
HSV-2				Encephalitis, myelitis	
VZV	*Varicellovirus*			Encephalitis, myelitis, leukoencephalopathy, cerebellitis	
EBV	*Lymphocytovirus*			Meningoencephalitis, cerebellitis, myelitis	GBS
HCMV	*Cytomegalovirus*			Encephalitis, myelitis, cerebellitis	GBS
HHV-6	*Roseolovirus*			Encephalitis, myelitis	
JCV	*Polyomavirus*	Polyomaviridae	dsDNA	Progressive multifocal leukoencephalopathy	
Poliovirus	*Enterovirus*	Picornaviridae	+ssRNA	Encephalitis, aseptic meningitis	Acute flaccid paralysis (anterior horn cell involvement)
Coxsackie-virus				Encephalitis, myelitis, cerebellitis	
ECHO				Encephalitis, myelitis	
Enterovirus 71				Myelitis, rhombencephalitis	Acute radiculomyelitis
EEE virus	*Alphavirus*	Togaviridae	+ssRNA	Mild to fatal encephalitis, hemorrhagic syndrome	
WEE virus				May be severe in neonates	
VEE virus				Mild to fatal encephalitis	
La Crosse	*Orthobunyavirus*	Bunyaviridae		Encephalitis	
JE	*Flavivirus*	Flaviviridae		Encephalitis, myelitis	
WNV				Encephalitis, meningitis, myelitis, cerebellitis	Acute flaccid paralysis
Saint Louis				Mild to severe encephalitis, myelitis	

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Virus	Genus	Family	Genome	Central nervous system involvement	Peripheral nervous system involvement
LCMV	*Arenavirus*	Arenaviridae	–SRNA	Meningoencephalitis	
JUNV				Meningoencephalitis	
MACV				Meningoencephalitis	
NiV	*Henipavirus*	Paramyxo-viridae	–SRNA	Febrile encephalitis	
Hendra virus				Meningoencephalitis	
Measles virus	*Morbillivirus*			Meningoencephalitis, myelitis	
Mumps virus	*Rubulavirus*			Meningoencephalitis, aseptic meningitis, myelitis	
Rabies virus	*Lyssavirus*	Rhabdoviridae	–ssRNA	Acute encephalitis, myelitis	
HIV	*Lentivirus*	Retroviridae	+ssRNA (RT)	Acute or chronic encephalitis and meningitis, myelitis	
HTLV-1	*Deltaretrovirus*			Tropical spastic paraparesis/HTLV-associated myelopathy	
HTLV-2				Subacute myelopathy	
Influenza A	*Orthomyxovirus*			Cerebellitis, myelitis	
RSV				Cerebellitis	
Hepatitis A				Myelitis	
Hepatitis E					Peripheral neuropathy

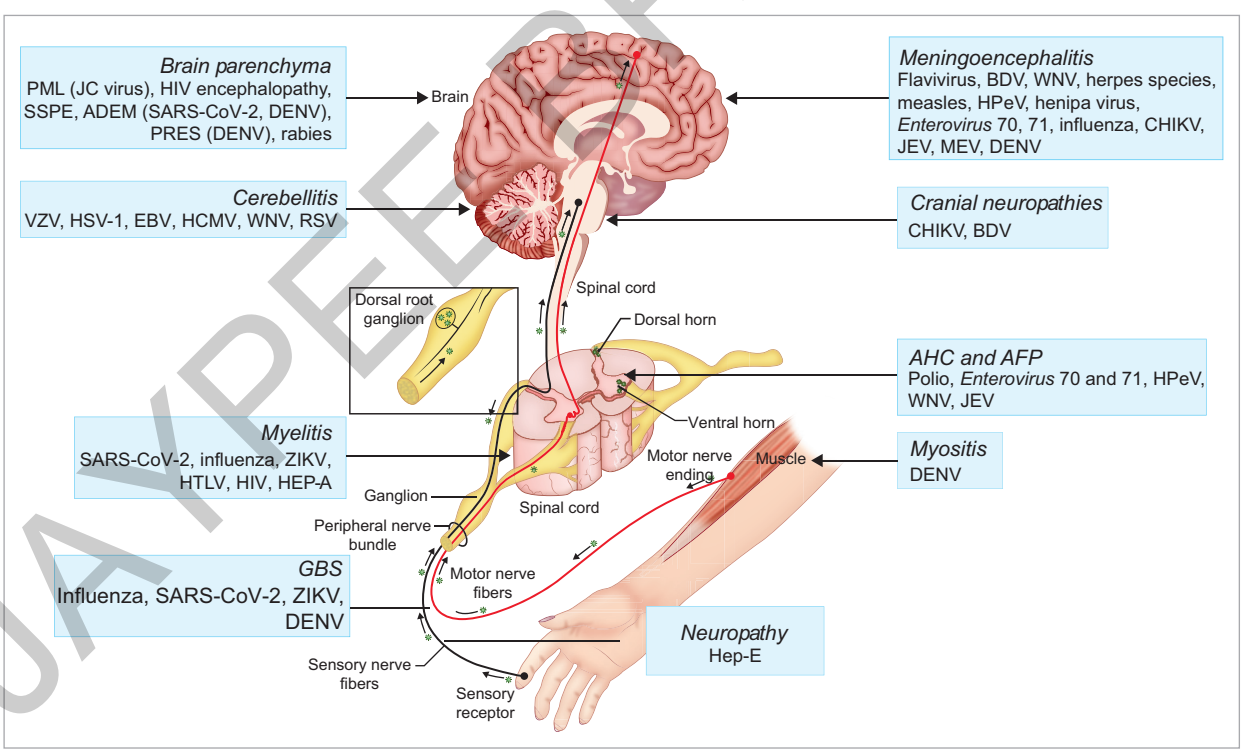
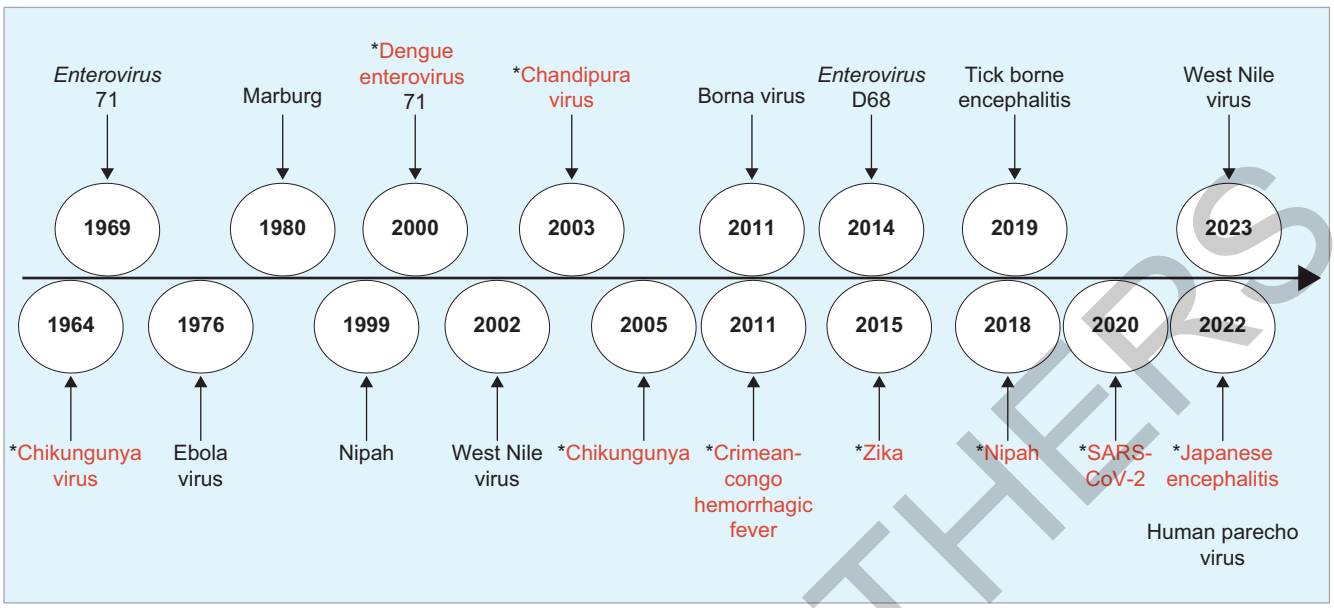


FIG. 1: Spectrum of central and peripheral nervous system involvement by neurotropic viruses.

(BDV: borna disease virus; CHIKV: chikungunya virus; DENV: dengue virus; HCMV: human cytomegalovirus; HIV: human immunodeficiency virus; HPeV: human parechovirus; HTLV: human T-lymphotropic virus; JC: John cunningham; JEV: Japanese encephalitis virus; MEV: Murray encephalitis virus; RSV: respiratory syncytial virus; VZV: varicella zoster virus; WNV: West Nile virus; ZIKV: zika virus)

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*Outbreaks in or widespread including India.

FIG. 2: Timeline of neurotropic virus outbreak in the world.

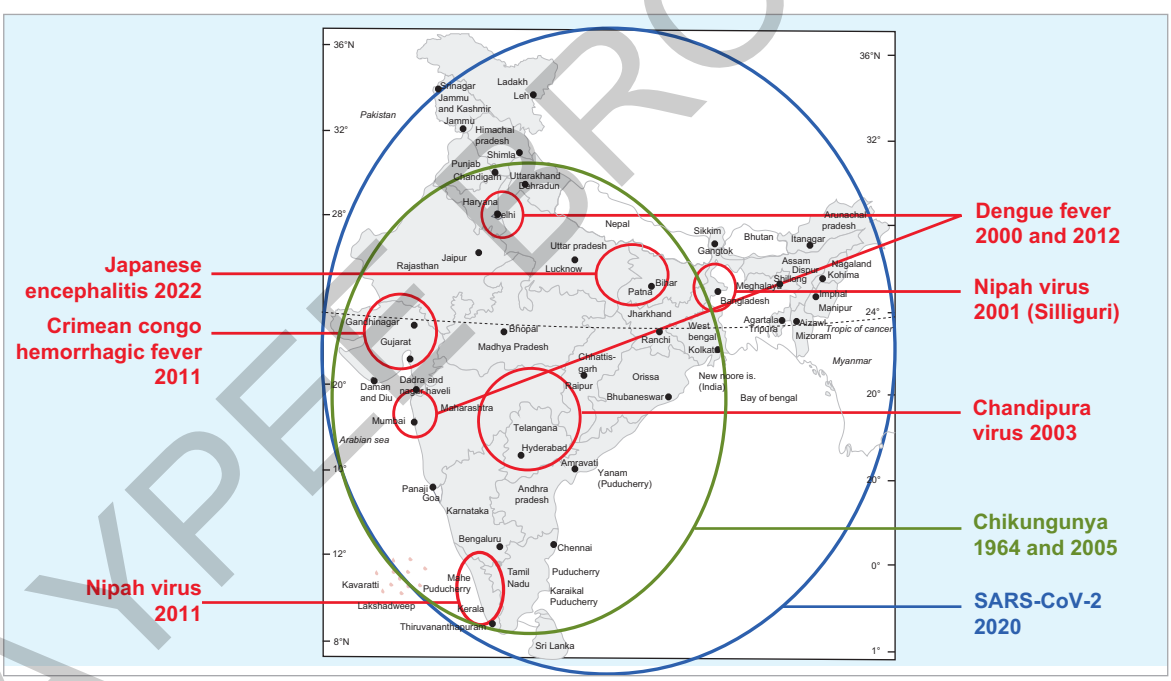


FIG. 3: Outbreaks of neurotropic viruses in India.

EMERGING AND REEMERGING VIRAL NEUROINFECTIONS

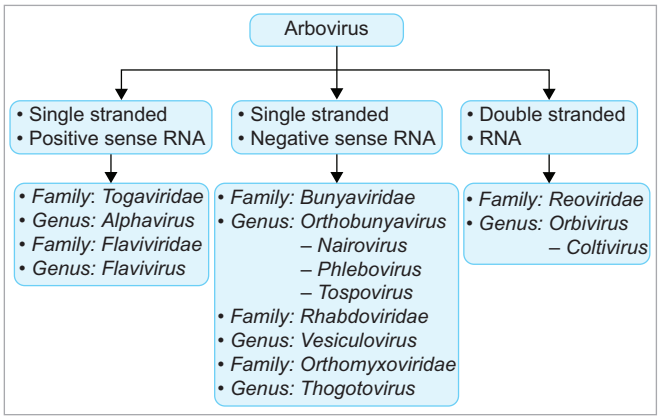
Emergence/reemergence of several viral infections has been reported from India and worldwide in the past few decades. We discuss such neuroinfectious viruses according to their taxonomical classification in the following text.

Arboviruses

Arboviruses are small RNA viruses that consist of four families: Flaviviridae, Togaviridae, Bunyaviridae, and Reoviridae **(Flowchart 1)**.

They have a common mode of transmission through the bite of hematophagous arthropods (mosquitoes, ticks, midges, sandflies). They are maintained in avian and

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FLOWCHART 1: Classification of arboviruses.

mammalian reservoirs, with man being an accidental host except dengue virus (DENV), which is anthroponotic.

Flaviviridae Family

Flaviviruses mainly infect mammals and birds and primarily spread through arthropod vectors (ticks and mosquitoes) **(Box 1)**.

- *Japanese encephalitis B virus (JEV)* is a single-stranded RNA virus. JEV is transmitted by *Culex tritaeniorhynchus* mosquitoes, through pigs and water birds breeding on rice paddy fields and other water sources.

  Epidemiology: JEV is endemic in south and southeast Asia. Outbreaks of JE occurred in West Bengal, Andhra Pradesh, Bihar, Tamil Nadu, Uttar Pradesh, Assam, Karnataka, and Puducherry.

  Clinical manifestation: The incubation period is about 5–15 days. Symptomatic cases are uncommon. Only 20% of symptomatic patients develop a fatal encephalitis. Most have mild flu-like illness. Nausea, vomiting, and abdominal pains are followed by encephalitis with seizures, focal deficits, and coma. MRI shows involvement of thalamus and basal ganglia. JE can also present as acute flaccid paralysis. Fatality is observed in 20–30% of the cases. Neurological sequelae are extrapyramidal syndrome, epilepsy, and mental retardation in children.
- *DENV* is a single-stranded positive RNA, with four known serotypes, DENV-1 to DENV-4. DENV is transmitted by Aedes mosquitoes.

  Epidemiology: Dengue is an urban disease that has spread to rural areas of India. The resurgence of dengue can be linked to urbanization, population explosion, increased density of the mosquito vector with no effective mosquito control, reinfestation with *Aedes aegypti* of a new geographical area, water storage pattern in houses, storage of junk in open spaces that trap rainwater, and introduction of a new serotype of the virus. Dengue has become an annual epidemic in many parts of southeast Asia.[4,5]

  Clinical manifestation: The incubation time is 3–14 days. Dengue infections are usually mild, asymptomatic, or severe like dengue hemorrhagic fever or dengue shock syndrome (DHF/DSS). Patients initially present with fever, headache, myalgia, arthralgia (breakbone fever), and rash. Dengue is not primarily a neurotropic virus and encephalopathy is a more common finding. Encephalopathy could be due to hypotension, hepatic/renal failure, and metabolic acidosis. In about 10%, there is meningitis and encephalitis. Dengue encephalitis can involve bilateral thalami, basal ganglia, midbrain, pons, and cerebellum with foci of hemorrhages within. Acute disseminated encephalomyelitis (ADEM), posterior reversible encephalopathy syndrome (PRES), ischemic strokes or hemorrhages, and long segment myelitis are known. Involvement of the PNS can cause Guillain–Barré syndrome (GBS) and myositis.
- *Zika virus (ZIKV)* is an enveloped RNA flavivirus transmitted by *Aedes aegypti* mosquitoes from mother to fetus, through sexual contact, transfusion of blood and blood products, and organ transplantation.

  Epidemiology: In 1947, ZIKV was discovered in the Zika forest in Uganda, Africa. The first larger outbreak was reported in 2007 on Yapisland, Micronesia, after which the virus quickly spread to countries in

BOX 1 Flavivirus classification.

Mosquito-borne flavivirus:
- Dengue virus serotype 1 (DENV-1)
- Dengue virus serotype 2 (DENV-2)
- Dengue virus serotype 3 (DENV-3)
- Dengue virus serotype 4 (DENV-4)
- Japanese encephalitis virus (JEV)
- West Nile virus (WNV)
- Spondweni virus (SPOV)
- Zika virus (ZIKV)
- Yellow fever virus

Tick-borne flavivirus:
- Mammalian tickborne virus
- Tick-borne encephalitis virus (TBEV)

No known vector-borne flavivirus:
- Modoc virus (MODV)

Insect-specific flaviviruses:
- Classic insect-specific flavivirus (cISFV)
- Cell fusion agent virus (CFAV)

Divergent flaviviruses:
- Tamana bat virus (TABV)

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southeast Asia. As of January 2025, a total of 151 ZIKV disease (ZVD) cases were reported from Gujarat, Karnataka, and Maharashtra.[4]

Clinical manifestation: The incubation time is 3–14 days. Symptoms are mild with fever, headache, rash, conjunctivitis, and muscle and joint pain. Neurological complications such as GBS and myelitis can occur. ZIKV can cause congenital malformations, such as microcephaly.

- *West Nile virus* belongs to the genus *Flavivirus* and is transmitted by culex mosquitoes. WNV directly infects neurons in deep nuclei and gray matter of the brainstem and spinal cord.

  Epidemiology: The first isolation of WNV was in 1937 in the West Nile district of Uganda. Since 1999, there were a large number of outbreaks in North America and Southern and Eastern Europe. Cases are reported from Kerala.[6]

  Clinical manifestation: Most infections are subclinical. The incubation time is 2–14 days. Fever, headache, fatigue, and myalgia are followed by neurological complications in <1% of cases. Meningitis, encephalitis, and motor neuron involvement with acute, asymmetric flaccid paralysis (AFP) are similar to poliomyelitis.
- *Powassan virus*[7] is a tick-borne single-strand positive-sense RNA flavivirus reported from the northeastern United States. Fever and headache are followed by encephalitis and cerebellitis.

Togaviridae Family

Togaviridae family contains two genera, *Alphavirus* and *Rubivirus*. Chikungunya (CHIKV), Eastern equine encephalitis, Western equine encephalitis, and Sindbis virus are alphaviruses. Rubella virus, which causes German measles (rubella), is a *Rubivirus*.

- *Chikungunya virus* causes endemic infections transmitted by *Aedes* mosquitoes.

  Epidemiology: The first outbreak was at the border region between Mozambique and Tanzania in 1952. In India, well-documented outbreaks occurred in 1963 and 1964 in Kolkata and southern India, respectively. Reemergence of CHIKV was recorded in India during 2005–2006 after a hiatus of 32 years.[4]

  Clinical manifestation: High fever, headache, maculopapular rash, and painful arthralgia with a typical incubation time of 3–7 days. Encephalopathy, encephalitis, cerebellitis, encephalomyelopathy, myeloneuropathy, encephalomyeloneuropathy, ADEM, uveitis, optic neuritis, cranial neuropathies, and myositis are described.

Bunyaviridae Family

- *Toscana virus*[7] that belongs to the *Phlebovirus* genus is transmitted by the sandfly.

  Epidemiology: It is seen usually in the summer months in the Mediterranean region.

  Clinical features: Mild meningoencephalitis with a self-limited course.
- *Crimean Congo hemorrhagic fever (CCHF)*[7] is a negatively stranded RNA virus of the genus *Nairovirus* transmitted via Ixodes ticks or crushing of the infected tick.

  Epidemiology: It was first recognized in Crimea (USSR) in 1944 and later in Congo. In India, the first outbreak was in Gujarat in 2011.

  Clinical features: Fever, headache, myalgia, and gastrointestinal symptoms are rarely followed by encephalitis.

Mononegavirales Order

Mononegavirales order encompasses several families of nonsegmented, negative-sense, single-stranded RNA viruses, namely Paramyxoviridae (measles, mumps), Bornaviridae, Filoviridae (Ebola virus), and Rhabdoviridae (rabies virus) **(Table 2)**.

Paramyxoviridae Family

Paramyxoviridae family includes the henipavirus, parainfluenza and mumps, pneumovirus (respiratory syncytial virus) and *Morbillivirus* (measles virus).

- *Nipah* virus is a type of zoonotic henipavirus. Fruit bats are the natural hosts for Nipah virus and pigs are intermediary hosts.

  Epidemiology: It is endemic in southeast Asia. In 1999, the Nipah virus was first isolated from the cerebrospinal fluid (CSF) of an encephalitis patient from the Sungai Nipah village. It was associated with major encephalitic outbreaks in Bangladesh.[3,4] Outbreaks have been concentrated in the states of West Bengal and Kerala, particularly in the Malappuram and Kozhikode districts. Clinical manifestations include acute encephalitis, fever, and headaches.
- *Measles* is a single-stranded RNA virus belonging to the genus *Morbilliform*.

  Epidemiology: Decreased immunization and vaccination hesitancy are the most important factors leading to reemergence. Measles virus affects the CNS either during active infection or after the infection has become inactive. Neurological syndromes include primary measles encephalitis (PME) and acute

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TABLE 2: Classification of mononegaviruses.

Mononegavirales classification				
Order	**Family**	**Subfamily**	**Genus**	**Virus**
Mononegavirales	*Bornaviridae*		*Bornavirus*	• Newcastle disease • Hendra • Sendai • Mumps • Measles
	Filoviridae		• *Cuevavirus* • *Ebolavirus* • *Marburgvirus*	
	Nyamiviridae		*Nyavirus*	
	Rhabdoviridae		• *Cytorhabdovirus* • *Ephemerovirus* • *Lyssavirus* • *Novirhabdovirus* • *Nucleorhabdovirus* • *Perhabdovirus* • *Sigmavirus* • *Sprivivirus* • *Tibrovirus* • *Tupavirus* • *Vesiculovirus*	
	Paramyxoviridae	• Penumovirinae • Paramyxovirinae	• *Metapneumovirus* • *Pneumovirus* • *Aquaparamyxovirus* • *Avulavirus* • *Ferlavirus* • *Henipavirus* • *Respirovirus* • *Rubulavirus* • *Morbillivirus*	

postinfectious measles encephalomyelitis (APME) which occur in 1–3/1,000 cases (similar incidence in India). Measles inclusion body encephalitis (MIBE) is rare (<1 per 1,000,000 cases in India) and subacute sclerosing panencephalitis (SSPE) incidence is 1:10,000 to 20,000 measles cases.[8]

Clinical features: In PME, the measles virus directly infects the CNS during acute measles infection. It occurs in immunocompetent, unvaccinated, or partially vaccinated measles infected patients. The presentation is usually during the exanthema phase with features of raised intracranial tension along with encephalitis. In APME, the encephalitis is immune mediated with pathogenesis likely being molecular mimicry. The patient can present with encephalitis, myelitis, ataxia, optic neuritis, and cranial neuropathies. MIBE, also known as subacute immunosuppressive measles encephalitis, is seen in immunocompromised hosts. Symptoms occur within days to months after measles infection or vaccination. Patients present with encephalopathy, seizures, focal motor deficits, dysphagia, ataxia, visual loss, and autonomic dysfunction. The neuropathological findings show inclusion bodies in neurons and glial cells and focal necrosis without inflammation. A 4-fold rise in the measles antibody in CSF from baseline is seen. The diagnosis can be confirmed on brain biopsy, by detecting measles virus RNA. SSPE is a slowly progressive panencephalitis, which is caused by persistence of the measles virus which mutates and leads to neurovirulence. The usual age of presentation ranges from 8 to 11 years. The latent period is 1–15 years following primary measles infection. Jabbour staging for SSPE is behavioral changes and forgetfulness (Stage I), movement disorder and myoclonus (Stage II), decerebrate/decorticate rigidity (Stage III), and coma/vegetative state (Stage IV). About 50% of patients have necrotizing chorioretinitis. CSF shows mildly elevated proteins, intrathecal IgG synthesis, and IgM and IgG anti-measles antibodies in CSF and serum. EEG shows high voltage generalized long interval periodic waves (Rademaker complex).

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MRI brain shows hyperintensities in cerebral cortex, periventricular white matter, and brainstem.

Treatment: In PME, treatment is mainly supportive. Ribavirin has been tried but not approved. In APME, corticosteroids, intravenous immunoglobulin (IVIg), and plasmapheresis, along with supportive measures, are recommended. In MIBE, treatment is supportive. In SSPE, supportive care and symptomatic management are advised. Trials with few drugs like Isoprinosine and interferon alpha have shown some benefits.

Bornaviridae Family

Bornaviridae family includes Borna virus, a nonsegmented RNA virus. Its most likely natural route of entry is nerve endings in the nasal and pharyngeal mucosa.

Epidemiology: In the 1700s, borna disease was first described in European farm horses. There are no known cases of Borna disease virus (BDV) in India.[2]

Clinical manifestations: Encephalitis, fever, cerebellar symptoms, myoclonus, and cranial neuropathies.

Filoviridae Family

Filoviridae family has *Ebola and Marburg viruses* which are among the most virulent pathogens known to man with a case fatality rate of above 90%.

Epidemiology: Ebola outbreak was first reported in 1976 in the Democratic Republic of Congo followed by multiple outbreaks in Sudan and Uganda.[7] There have been no reported cases of Ebola or Marburg in India.

Clinical presentation: Fever, headache, and myalgia followed by hemorrhagic manifestations. Neurological manifestations include encephalitis, encephalopathy, and seizures.

Rhabdoviridae Family

Rhabdoviridae family has Chandipura virus (CHPV). It is transmitted by sandflies, mosquitoes, and ticks.

Epidemiology: It was first identified in 1965 after isolation from the blood of two patients from Chandipura village in Maharashtra.[4]

Clinical features: Fever, encephalitis, and bleeding tendencies with rapid progression to death.

Human Herpes Viruses

Human herpes viruses are a family of DNA viruses that include HSV, varicella zoster virus (VZV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) **(Table 3)**.

Three of the eight human herpes viruses, types HSV-1, HSV-2, and VZV, persist in the peripheral sensory ganglia for lifetime. HSV-1 has a predilection for the development of encephalitis and HSV-2 generally causes meningitis. Most cases of HSV encephalitis are caused by HSV-1. HSV-2 commonly causes encephalitis in neonates and the immunocompromised individuals. HSV-1 has also been associated with autoimmune N-methyl-D-aspartate (NMDA) encephalitis. VZV can cause encephalitis and cerebellitis in children. It can cause CNS vasculitis, and necrotizing retinitis and giant cell arteritis in immunocompromised hosts. VZV myelitis can present like acute transverse myelitis or can involve anterior horn cells causing polioclastic illness. Ramsay Hunt syndrome and other cranial neuropathies are known with VZV infection. Human herpes virus 6 (HHV-6) has been associated with new-onset seizures in children. CMV infection can cause diffuse encephalitis, ventriculoencephalitis, transverse myelitis, and sacral radiculitis, especially in immunocompromised patients with HIV and organ transplant.

TABLE 3: Classification of human herpes viruses.

Formal taxonomic name	Alternative common name	Viral subfamily
Human herpes virus 1	Herpes simplex virus 1	*Alphaherpesvirinae*
Human herpes virus 2	Herpes simplex virus 2	*Alphaherpesvirinae*
Human herpes virus 3	Varicella zoster	*Alphaherpesvirinae*
Human herpes virus 4	Epstein–Barr virus	*Gammaherpesvirinae*
Human herpes virus 5	Human cytomegalovirus	*Betaherpesvirinae*
Human herpes virus 6	HHV-6 variant A or B	*Betaherpesvirinae*
Human herpes virus 7	HHV-7	*Betaherpesvirinae*
Human herpes virus 8	Kaposi's sarcoma associated herpesvirus	*Gammaherpesvirinae*

Polyoma Viruses

Polyoma viruses[3] are small DNA viruses that remain latent in healthy individuals but may become pathogenic in immunocompromised individuals. Two polyoma viruses, John Cunningham (JC) and BK, are human pathogens. BK occasionally causes disease in renal transplant patients, while JC causes progressive multifocal leukoencephalopathy (PML) in immunocompromised individuals.

Epidemiology: BK viruses are prevalent in 3% of post-transplant patients in India. JC virus infects more than 80% of population during early childhood. The infection is asymptomatic at the time but can cause PML in immunocompromised patients.

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Clinical features: Patients can present with ataxia, visual disturbances, and focal deficits. MRI shows white matter hyperintensities in parietal, occipital, and brainstem regions.

Human Immunodeficiency Virus

Human immunodeficiency virus type 1 (HIV)[3] is a human retrovirus with a unique ability to reverse transcribe its RNA genome into a complementary DNA that integrates into the human genome.

Epidemiology: HIV-1 emerged in the late 1970s. A 2023 report highlights that over 2.5 million people are living with HIV in India.

Clinical features: HIV continues to cause neurocognitive dysfunction in approximately 20% of persons. CNS manifestation of HIV includes HIV encephalopathy, vasculitis, acute aseptic meningitis or meningoencephalitis, and HIV-associated vacuolar myelopathy. HIV can make patients prone to various opportunistic infections such as tuberculosis (TB), CMV, and PML. HIV can involve PNS causing distal sensory predominant axonal polyneuropathy, acute/chronic inflammatory demyelinating polyradiculoneuropathy, and myositis.

Orthomyxoviridae Family

Orthomyxoviridae family, known for causing influenza (flu), includes viruses like influenza A, B, and C. Antigenic shifts can cause widespread diseases across geographical borders.

Influenza A Subtype (Table 4)

- *H1N1* virus is transmitted through contact with the respiratory secretions of an infected person.

  Epidemiology: In India, the state of Maharashtra was the worst affected, followed by Karnataka.

  Clinical features: Mild respiratory tract illness to severe complications such as pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death are reported. Encephalopathy, acute necrotizing encephalitis, PRESS syndrome, and GBS were reported in children.
- *H5N1 avian influenza* transmission is through droplets of infected chicken.

  Epidemiology: Highly pathogenic H5N1 avian influenza emerged in Hong Kong in 1997. Infection was acquired by humans directly from chicken. The outbreak was contained with effective culling of more than 1.5 million chicken. Epidemics of the highly pathogenic avian bird flu (H5N1) among Indian poultry birds were reported in the states of Maharashtra, Gujarat, and Madhya Pradesh.

TABLE 4: Classification of influenza viruses.

Types	Subtypes
Influenza A (infects wide range of animals and birds)	• Avian (can infect humans) • H5N1 • H7N3 • H7N7 • H7N9 • H9N2 • H10N8 • Swine (can infect humans) • H1N1 • H1N2 • H3N2
Influenza B (mainly affects humans)	
Influenza C (infects humans and pigs)	
Influenza D (infects cattle)	

Clinical features: Rare cases of encephalitis and cerebellitis in children have been reported

Nidovirus

Nidovirus includes several families of large RNA viruses, arranged from the longest to the shortest genome as *Coronaviridae, Roniviridae, Mesoniviridae*, and *Arteriviridae* **(Table 5)**.

- *Coronaviruses* are large, roughly spherical particles with unique surface projections. They usually cause mild upper respiratory tract illnesses in humans. However, three coronaviruses have caused more serious disease in people: (1) SARS-CoV, which emerged in November 2002 and causes SARS; (2) Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), which emerged in 2012 and causes MERS; and (3) SARS-CoV-2, which emerged in 2019 and causes coronavirus disease 2019 (COVID-19). Though a few suspected cases of SARS were reported from India, none of them were confirmed, and in the official declaration by the government (as reported on May 2, 2003), India was declared by the World Health Organization (WHO) as a "SARS free" country. Absence of HLA B*46 in Indian population could be the reason of protection from SARS (2003) epidemic. Coronaviruses are known to undergo genetic recombination which may lead to new genotypes and outbreaks. The possibility of the re-emergence of SARS and other novel viruses from animals or laboratories was always there. Due to this came a pandemic of SARS-CoV-2.

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TABLE 5: Classification of nidovirales.

Order	Family	Subfamily	Genus	Species
Nidovirales	*Coronaviridae*	*Torovirinae*	• *Torovirus* • *Bafinivirus*	
		Coronavirinae	*Alpha*	• *HcoV-229E* • *HcoV-NL63*
			Beta	• *HcoV-OC43* • *HcoV-HKU1* • *SARS-CoV* • *MERS-CoV* • *SARS-CoV-2*
			• *Gamma* • *Delta*	
	Arteriviridae			
	Mesoniviridae			
	Roniviridae			

- *SARS-CoV-2* is a novel coronavirus.[3,8] The lack of awareness in hospital infection control and international air travel facilitated the rapid globalization of this agent. The findings that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host emphasize the importance of wildlife and biosecurity in farms and wet markets, which can serve as the source and amplification centers for emerging infections.

  Epidemiology: The first cases of COVID-19 in India were reported on January 30, 2020, in Kerala, among three Indian medical students who had returned from Wuhan, the epicenter of the pandemic. Lockdowns were announced in the country on March 25. Infection rates started to drop from mid-September to below 15,000 in January 2021. A second wave beginning in March 2021 was much more devastating than the first, with shortages of vaccines, hospital beds, oxygen cylinders, and other medical supplies in parts of the country. On April 30, 2021, it became the first country to report over 400,000 new cases in a 24-hour period.

  Clinical features: The presentation of SARS-CoV-2 infection, a neuroinvasive virus, may range from an asymptomatic state to a critical illness, including high fever, dyspnea, myalgias, fatigue, and delirium. Common presenting neurologic symptoms are headaches and meningismus. In the first year of the pandemic, many intensive care unit (ICU)-hospitalized SARS-CoV-2–positive patients developed encephalopathy and had high CSF SARS-CoV-2 antibody titers. It was also associated with CNS and systemic inflammation ("cytokine storm"). Acute neurologic symptoms, such as encephalopathy, encephalitis, parainfectious ADEM, large vessel strokes, cranial neuropathies, myelitis, and postinfection GBS, were noticed throughout the pandemics. Autoimmune complications were ADEM and acute necrotizing myelitis (ANM). Long-term sequelae (long COVID), including cognitive impairment, are well established.

Picorna Viruses

Picorna viruses from the family Picornaviridae are small, nonenveloped, positive-strand RNA viruses. These viruses include poliovirus, coxsackievirus, enterovirus 71 and rhinovirus, cardioviruses (encephalomyocarditis virus), parechovirus, and hepatitis A virus **(Table 6)**.

Enterovirus

Enterovirus, a genus within the family Picornaviridae, comprise enteroviruses, coxsackieviruses, rhinoviruses, polioviruses, and echoviruses.

- *Poliovirus* has three poliovirus serotypes, numbered 1, 2, and 3. Poliomyelitis is an exclusive human disease transmitted via the fecal–oral route.

  Epidemiology: The oldest reference to polio is approximately 3,000 years ago. In India, compared to 150,000 cases in 1995, the cases in 2003 were only 134 and India was declared polio free on March 27, 2014. The reemergence of poliovirus was caused by circulating vaccine-derived poliovirus and gaps in immunization. In 2024, 280 vaccine-associated poliovirus infections were reported.[8-10]

  Clinical features: Poliovirus enters the oropharynx and multiplies locally in the tonsils, lymph nodes of the neck, and Peyer patches of the small intestine.

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TABLE 6: Classification of enterovirus.

Family	Genus	Species	Genotype
Picornaviridae	*Enterovirus*	*Enterovirus A*	Enterovirus A71
		Enterovirus B	Coxsackievirus B3
		Enterovirus C	Poliovirus
		Enterovirus D	Enterovirus D68
		Rhinovirus A	Rhinovirus A2
		Rhinovirus B	Rhinovirus B14
		Rhinovirus C	Rhinovirus C15
		5 animal enterovirus species	
	Parechovirus	• *Parechovirus A* • *Parechovirus B*	Human parechovirus 1-16
	Hepatovirus	Hepatitis A virus	
	Aphthovirus	• Foot and mouth disease virus • Equine rhinitis A virus	
	Cardiovirus	• Encephalomyocarditis virus • Theilovirus	Saffold virus
	24 other genera		

The incubation period ranges from 2 to 35 days. The majority of exposed patients (around 95%) is asymptomatic. The ratio of asymptomatic to paralytic cases ranges from 50:1 to 1,000:1.

Abortive poliomyelitis is a mild infection seen in 4–8% of cases. Initially, patients present with gastroenteritis and influenza-like illness which subside within 1 week. Aseptic meningitis (1% of cases) presents with severe neck pain which follows a brief flu-like illness. Paralytic poliomyelitis (<1% of patients) presents with asymmetrical flaccid paralysis. The three forms are spinal poliomyelitis, bulbar poliomyelitis, and a combination of spinal and bulbar poliomyelitis (bulbospinal). Post-polio syndrome presents with progressive muscular weakness, fatigue, and skeletal deformities.

Investigations: Polymerase chain reaction (PCR) from samples of stool, throat swabs, blood, or cerebrospinal fluid. A 4-fold rise in the antibody titer is essential for confirmation of the infection.

- *Enterovirus A71 (EV-A71) and Enterovirus D68 (EV-D68)* transmission is by the fecal–oral route in EV-A71 and by the respiratory route in EV-D68.

Epidemiology: Since its discovery in 1969, large worldwide outbreaks of EV-A71 associated hand, foot, and mouth disease (HFMD) and CNS complications have occurred, particularly in Southeast Asia, China, and Australia. While EV-D68 outbreaks and sporadic cases are reported globally, a single case has been reported from India.[5,8,9]

Clinical features: EV-A71 and EV-D68 infections primarily affect children under 5 years of age. HFMD presents with fever, rashes, or vesicles in the perioral areas, hands, feet, and buttocks. CNS complications (<1%) are aseptic meningitis, acute flaccid paralysis, and encephalomyelitis with brainstem involvement. EV-A71 encephalitis presents with tremor, myoclonus, ataxia, and ocular motor dysfunction. EV-D68 is also associated with acute myelitis.

Parechovirus

Parechovirus (PeV)[7] is reported worldwide with a higher incidence in Europe, China, United States, and Cameroon.

Clinical presentation: Human parechovirus (HPeV) is transmitted by the fecal–oral route causing mild gastrointestinal and respiratory illness. Encephalitis, meningitis, flaccid paralysis, and Reye's syndrome are reported.

Cyclovirus

Cyclovirus[7] belonging to the Circovirdae family is a nonenveloped DNA virus. These viruses have been associated primarily with disease in animals, including birds and pigs.

Epidemiology: It has been reported in Africa, commonly in Malawi, with no reported cases in India.[8-10]

Clinical presentation: Mild febrile illness and AFP are diagnosed by molecular assay.

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CONCLUSION

Rapid globalization, immunocompromised state, and environmental factors have significantly increased the spread of neurotropic viruses leading to their emergence and reemergence. These viruses are associated with significant morbidity and mortality and cause significant burden on healthcare services. Viral neuroinfections are underdiagnosed. Adequate clinical and diagnostic measures, development of antiviral drugs and vaccines, adequate vector control, and improving healthcare infrastructure to handle and quarantine affected patients should be prioritized by healthcare policy makers.

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