ARBOVIRAL DISEASES

Arboviral diseases are caused by a diverse group of arthropod-borne viruses that may be spread to humans through the bite of an infected arthropod, predominantly mosquitoes and ticks.[1]

ARBOVIRUSES

- There are **≈600 recognized arboviruses worldwide**, of which approximately 150 are known to cause disease in humans.[2]
- Most diseases caused by arboviruses are **zoonoses** that can occasionally cause infections in humans. Although most cases are asymptomatic, some may be severe and even fatal.[3]
- **Global warming** has had direct effects on the spread of the two most important vectors: **mosquitoes and ticks**.[4] The speed and extent of actual pathogen(s) changes are unpredictable, and many arboviruses co-exist within the same geographic area.[5]
- Many of the symptoms of an arboviral infection are **unspecific**, and may be confused with illnesses such as malaria, typhoid, and bacterial meningitis.[6]
- **Vulnerable populations** in tropical and sub-tropical regions are typically most exposed, and many are threatened by the circulation of multiple arboviruses.[7] Although the presence of arboviruses remains predominantly (sub)tropical, more temperate regions are also now experiencing increased exposure.

AR-BO-VIRUS = ARthropod-BOrne VIRUS[8]

600 arboviruses identified; **3 main families**

Togaviridae	*Bunyaviridae*	*Flaviviridae*
Chikungunya virus (CHIKV)	Rift Valley fever virus (RVFV)	Yellow fever virus (YFV)
O'nyong-nyong virus (ONNV)	Crimean Congo Hemorrhagic fever virus (CCHFV)	Dengue virus (DENV)
Ross River virus (RRV)	Sandfly fever virus (SFV)	Zika virus (ZIKV)
Mayaro virus (MV)		Japanese encephalitis virus (JEV)
		West Nile virus (WNV)
		Tick-borne encephalitis virus (TBEV)

EPIDEMIOLOGY AND BURDEN[9]

- Arboviruses are present worldwide with some viruses showing restricted geographical distribution.
- Worldwide, the **most prevalent human arboviral diseases** per year are[2]:
  - Dengue (96 million cases)
  - Chikungunya (693,000 cases)
  - Yellow fever (130,000 cases)
  - Japanese encephalitis (42,500 cases)
  - West Nile fever (2,588 cases)
  - Zika (500,000 cases during epidemic)
- The global burden of arbovirus-related diseases is significant, with up to **700,000 deaths annually**.[10]

Global distribution of a number of important arboviruses[9]

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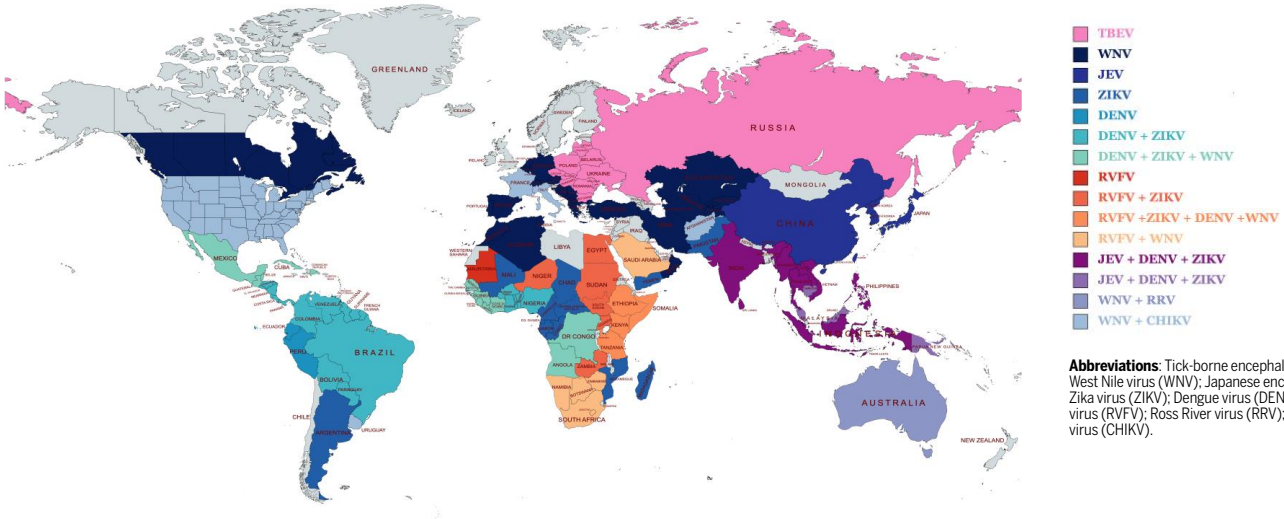

Abbreviations: Tick-borne encephalitis virus (TBEV); West Nile virus (WNV); Japanese encephalitis virus (JEV); Zika virus (ZIKV); Dengue virus (DENV); Rift Valley fever virus (RVFV); Ross River virus (RRV); and Chikungunya virus (CHIKV).

Impact of climate change

Transmission of arboviruses requires **ideal environmental conditions** for both the vector and the virus.
Modeling studies have demonstrated the correlation between climate and arboviral diseases, and the potential expansion of both vectors and arboviruses into areas that are currently unsuitable for arbovirus transmission. For example, modeling experiments based on the most extreme climate scenarios indicate the potential for autochthonous dengue transmission during the UK's summer by 2100.[11]

The frequency and scale of arthropod-borne virus outbreaks, especially those transmitted by *Aedes* mosquitoes, are on the rise worldwide due to the **interaction of ecological, economic, and social factors**. These factors include rapid urbanization, migration patterns, climate fluctuations, poverty levels, and inadequate water and sanitation systems.[7]

TRANSMISSION

- Arthropod-borne viruses (or arboviruses) survive in nature by **transmission from infected to susceptible hosts** by certain species of mosquitoes, ticks, sandflies or biting midges.[12]
- Following ingestion of a blood meal from an infected host, viruses multiply within the tissues of the arthropod. They are then passed on to humans or other vertebrates during insect biting.
- Multiple factors influence the transmission of arthropod pathogens, including genetics, evolution, nutrition, hosts and climate.[13]
- **Four distinct transmission cycles** can be observed for arboviruses.[12]

Four different transmission cycles[12]

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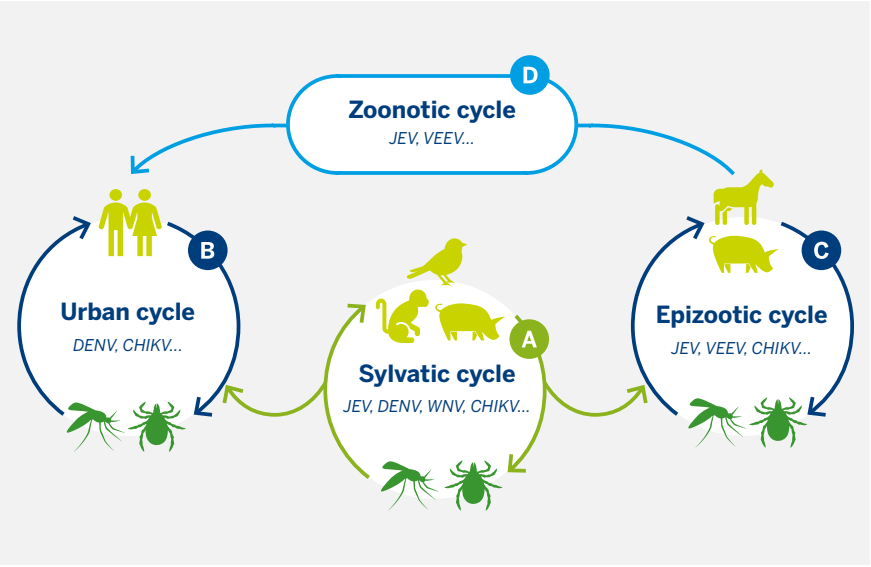


A Sylvatic cycle
when viruses are transmitted and maintained in their natural hosts such as in birds or in nonhuman primates.

B Urban cycles
when spillover occurs and immunologically naive human populations get infected. Humans are usually dead-end hosts for these arboviruses. However, many arboviral infections (e.g., CHIKV and DENV infections) can be transmitted from infected humans to uninfected humans through mosquito or tick vectors.

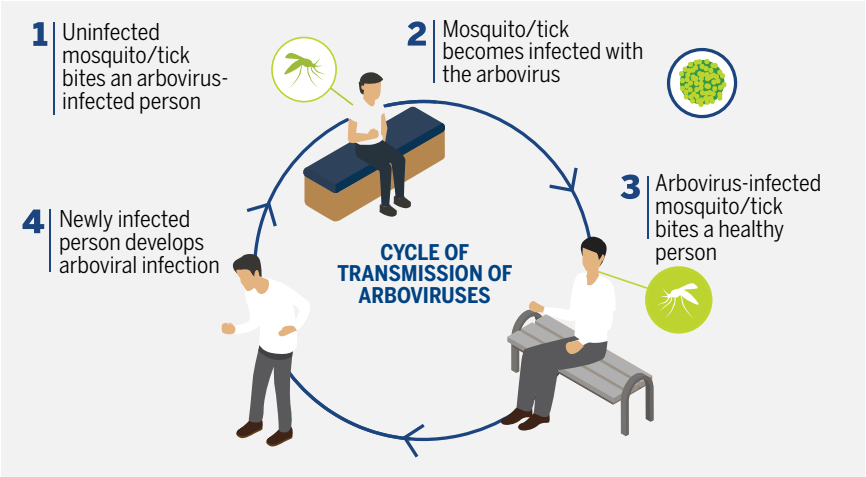
C Epizootic cycles
when pathogenic arboviruses (e.g., VEEV and JEV) infect domestic animals, such as pigs (JEV) and horses (VEEV).

D Zoonotic cycle
when handlers of arbovirus-infected animals get infected by the arboviruses through direct contact with the infected animals or through vectors that were infected upon feeding on these infected animals.

Abbreviations: Chikungunya virus (CHIKV); Dengue virus (DENV); Japanese encephalitis virus (JEV); Venezuelan equine encephalitis virus (VEEV).

Urban cycle of arbovirus transmission

Source: bioMérieux infographic

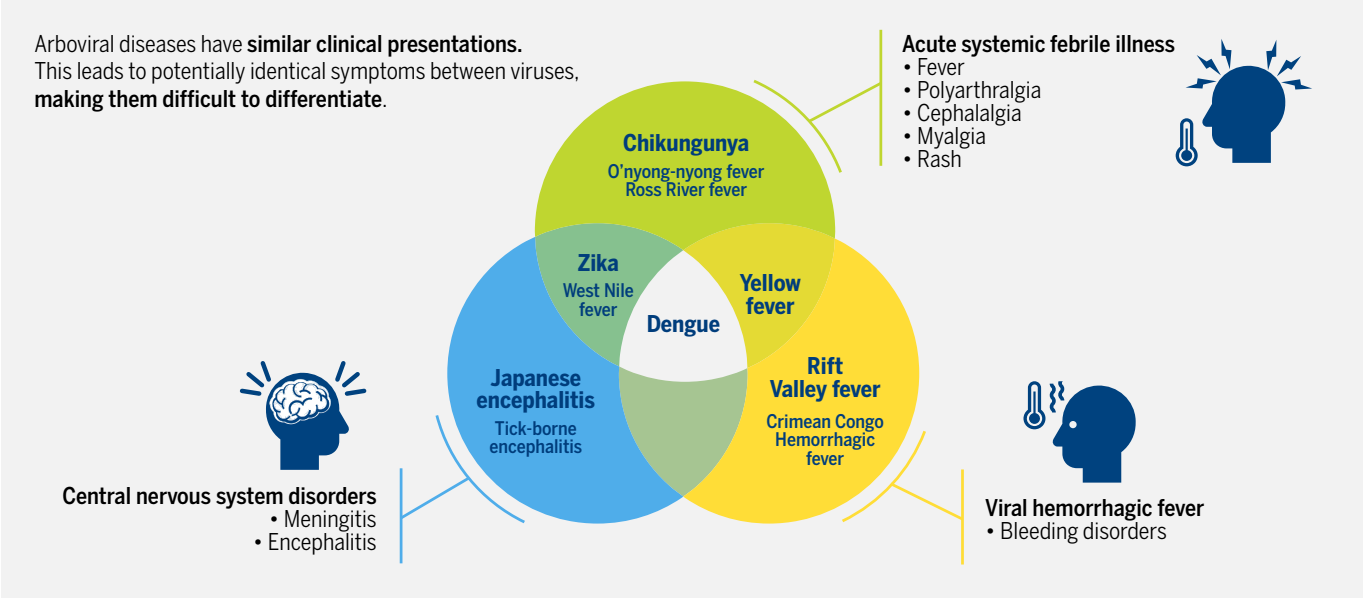


CLINICAL PRESENTATION

- Most arboviral infections are **asymptomatic** and resolve on their own, but the range of diseases is extensive, with some cases leading to severe debilitation or even death[6], for example:
  - **Dengue hemorrhagic fever**: shock, internal bleeding, organ failure and death[14]
  - **Chronic chikungunya disease**: severe joint pain rand loss of autonomy[15]
  - **Maternofetal transmission of Zika virus**: malformations, including microcephaly, in around 5% of infants[16]
- Arboviral diseases are categorized into **four main syndromes**: fever, polyarthralgia, encephalitis, hemorrhagic fever.[14]
- A single virus may be associated with more than one syndrome.
- Symptoms can manifest between **3 to 14 days** after exposure.

Clinical presentation of arboviral diseases[17-19]

Adapted from Eckerle I, *et al. Clin Microbiol Infect*. 2018;24:240-245; Ali A, *et al. Asian Pac. J Trop Med*. 2017;10(4):321-331; Beltrán-Silva SL, *et al. Rev Med Hosp Gen Méx*..2018;81(3):146-153



DIAGNOSTIC APPROACH

- A **differential diagnostic approach** is essential, since many arboviral infections manifest with similar clinical symptoms, and may co-exist with other tropical infections (malaria, scrub typhus...).
- The ability to accurately diagnose an arbovirus infection is critical to:
  - **Implement prevention measures**: mosquito control, mandatory reporting...
  - **Help prevent severe cases**, through the identification of individuals at risk of complications.
- Diagnosis of the infecting arbovirus or another pathogen may assist in determining and managing:
  - Prognosis (e.g. West Nile fever)
  - Complications (e.g. Zika)
  - Treatment (e.g. malaria, bacteria)
  - Follow-up (e.g. dengue)[9]
- Diagnostic tests are also essential for **epidemiological surveillance** of pathogens to detect clusters, predict outbreaks, early epidemics or pandemics, assess the need for vaccination and implement preventive measures in high-risk areas (e.g. vector control, public health measures).
- **Syndromic molecular testing** for simultaneous detection of several arboviruses can quickly and accurately identify pathogens in patients with unexplained tropical fever, supporting **optimized patient management**, including antimicrobial intervention, clinical outcomes, and public health. These tests are intended for both endemic and non-endemic regions, encompassing travelers and military personnel.
- However, many arboviruses are found in resource-limited settings that, in some cases, have inadequate infrastructure for diagnostic testing, emphasizing the importance of **inexpensive, rapid and sensitive point-of-care (POC) tests** that can be used for field deployment.[9]

LABORATORY CONFIRMATION

- Several laboratory methods are available to confirm diagnosis:
  - **Direct methods** such as virus isolation, or nucleic acid amplification tests, which detect the virus in the blood: e.g., NS1 antigen test (dengue), quantitative reverse transcriptase PCR (RT-qPCR) or sequencing (less common);
  - **Indirect methods** such as serological testing, which detect the host immune response to infection: enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA) and neutralization assays;
  - **Rapid point-of-care (POC) tests.**
- Specific and sensitive diagnostic tests for arboviral infections that are easy-to-use, affordable, and suitable for low- and middle-income countries are essential for patient management in endemic regions.

Most common direct and indirect diagnostic tests for differential diagnosis of arboviral infections[20]

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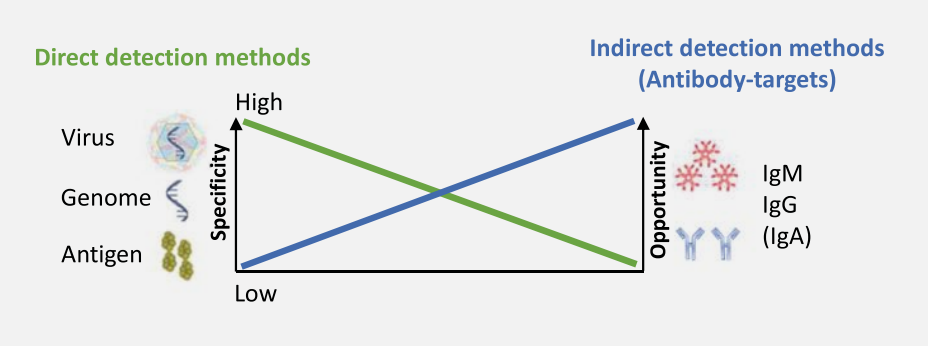

- Diagnosis of arboviral infections can be performed in various ways (direct and indirect detection methods).
- During the acute/viremic phase, viral RNA or antigen (Ag) can be detected.
- Unlike antibody (Ab) detection, viral RNA detection offers high specificity, though testing opportunities are limited due to the brief duration of the acute phase.
- If the acute phase is missed, diagnosis relies on the detection of IgM, IgG, or both, in convalescent serum.

An Example of Time Windows of Viremia, Antigenemia, and Antibody Responses against Arboviral Infections (for dengue infection)

Timeline of humoral immune response and biomarker appearance during primary and secondary dengue infection[20]

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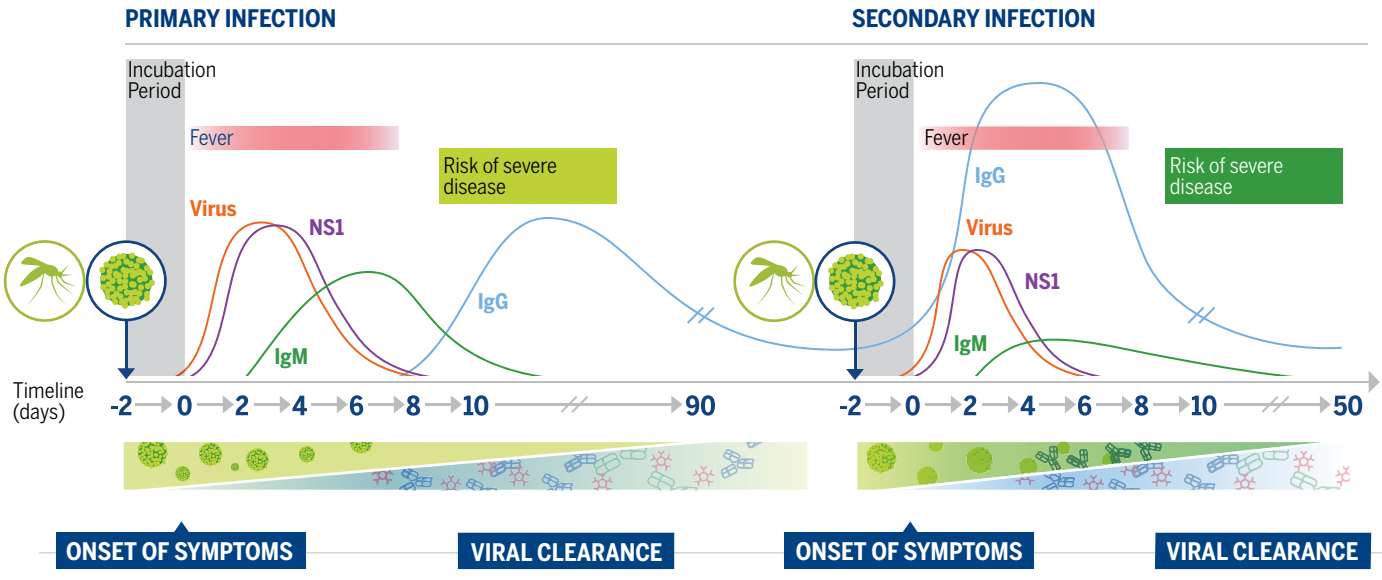

TREATMENT

- The management of arboviral diseases typically involves **supportive care to alleviate symptoms** such as fever, headache, rash, and joint pain. However, there are no specific antiviral treatments for most arbovirus infections, making prevention through vector control strategies crucial.[21]
- In cases where severe symptoms or complications arise, **hospitalization** may be required for close monitoring and intensive supportive care, including intravenous fluids and pain management.[22]
- Research is on-going into antiviral drugs and vaccines targeting specific arboviruses, in order to **improve treatment options** and help **prevent outbreaks** of these diseases in susceptible populations.

PREVENTION AND CONTROL

- According to experts, arboviral diseases will remain a **public health emergency of international concern (PHEIC)** for the next two decades.[20]
- Public health measures such as **surveillance, early detection, and community education** all play a vital role in controlling the spread of arboviral infections and reducing their impact on public health.[23]
- In addition, **novel approaches** such as gene-edited mosquitoes via CRISPR/Cas9 and enveloped Virus-Like Particle (eVLP) vaccines could significantly contribute to global public health initiatives to combat arboviral diseases, reducing transmission rates and associated morbidity and mortality.[24]
- The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the **first vaccine, Ixchiq**, to prevent disease caused by the chikungunya virus.[25] The vaccine is intended for individuals aged 18 to 64 living in regions where the chikungunya virus is endemic.[26]
- **Two vaccines against dengue** have also been approved by the FDA, EMA and the Pan-American Health Organization (PAHO).[27, 28]

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