

O'nyong-nyong Virus Infection: Virology, Transmission Dynamics, Pathogenesis, and Public Health Implications

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ABSTRACT

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O'nyong-nyong virus (ONNV) is a mosquito-borne alphavirus of the *Togaviridae* family, known for causing febrile illness and severe polyarthralgia in humans. The virus has drawn scientific and public health attention due to its potential for widespread outbreaks in sub-Saharan Africa. ONNV is an enveloped, spherical virus measuring about 65–70 nm in diameter. Its genome is a single-stranded, positive-sense RNA of approximately 11.8 kilobases, encoding two major open reading frames (ORFs) responsible for structural (Capsid, E1, E2, E3, and 6K) and non-structural (nsP1–nsP4) polyproteins, which play vital roles in replication and assembly. Transmission occurs primarily through the bites of *Anopheles funestus* and *Anopheles gambiae* mosquitoes, with an incubation period of 7–10 days. Infection begins when ONNV enters host cells via receptor-mediated endocytosis, followed by uncoating and replication of viral RNA. Newly formed virions are released through budding, leading to systemic dissemination. The virus initially infects skin-resident immune cells before spreading to joints and muscles, inducing inflammatory responses responsible for fever, joint pain, and lymphadenopathy—its hallmark symptoms. ONNV infections are largely confined to East and Central Africa, notably in Uganda, Kenya, and Tanzania, particularly in rural communities where vector density is high. All age groups are susceptible, though adults experience more pronounced arthralgia, and those with outdoor occupations are at increased risk. Diagnosis involves viral isolation, serological assays, molecular detection, and immunofluorescence tests. Currently, no specific antiviral therapy or vaccine exists for ONNV. Prevention relies on mosquito control measures, personal protection, and surveillance in endemic regions to mitigate transmission and disease burden.

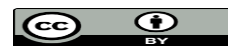
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O'nyong-nyong virus, Alphavirus, Mosquito-borne infection, Arthralgia, Vector control

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1. Introduction

In the annals of infectious diseases, few viruses have generated both scientific intrigue and public health concerns quite like the O'nyong-nyong virus (ONNV). Named after the Lugbara word meaning "weakening of the joints," ONNV is a mosquito-borne alphavirus of the family *Togaviridae*, known for its capacity to cause febrile illness and debilitating polyarthralgia (Powers et al., 2001). Although it is not as widely recognized as other arboviruses like dengue or chikungunya, ONNV has had a significant epidemiological impact in parts of sub-Saharan Africa, where it has caused large-scale outbreaks with substantial socio-economic repercussions (Williams et al., 2015).

ONNV is primarily transmitted through the bites of infected *Anopheles* mosquitoes, particularly *Anopheles funestus* and *Anopheles gambiae*—species that are also major vectors of malaria and are widespread across Africa (Lanciotti et al., 1998). This unusual mode of transmission (as most arboviruses are vectored by *Aedes* mosquitoes) complicates control efforts, especially in regions where *Anopheles* mosquitoes are ubiquitous and vector control infrastructure is limited. Infected individuals typically present with a constellation of clinical features including high fever, maculopapular rash, lymphadenopathy, and marked joint pain. The arthralgia, often symmetric and involving large joints, can persist for several weeks and is a distinguishing feature of ONNV infection (Posey et al., 2005).

Historically, several ONNV outbreaks have been recorded. The most prominent occurred between 1959 and 1962, affecting over two million people across East Africa (Kariuki Njenga et al., 2008). More recent outbreaks, such as the one in 1996 in northern Uganda, reaffirm the virus's capacity for re-emergence under favorable conditions (Lutwama et al., 1999). ONNV has also been reported in Kenya, Tanzania, and the Democratic Republic of the Congo, confirming its endemic presence in the region. The public health burden of ONNV outbreaks extends beyond immediate morbidity; economic productivity often declines sharply due to incapacitation of the workforce, and overstretched health systems struggle to meet the surge in demand for care (Powers and Logue, 2007).

Despite its impact, ONNV remains understudied compared to other arboviruses. Limited funding, diagnostic challenges, and overlap in clinical presentation with chikungunya and dengue contribute to its relative neglect (Weaver and Reisen, 2010). However, advances in molecular diagnostics and genomic surveillance have recently improved the identification and understanding of ONNV, shedding light on its evolution, transmission dynamics, and potential reservoirs (Simon et al., 2019).

Prevention strategies largely rely on vector control, given the absence of specific antiviral therapies or vaccines. These include the use of insecticide-treated bed nets, indoor residual spraying, and environmental management to eliminate

mosquito breeding habitats. Public health initiatives also emphasize early detection and outbreak response to mitigate transmission (WHO, 2018). However, these measures must be reinforced by community education, improved surveillance systems, and increased investment in ONNV-specific research.

1.1 History of O'nyong-nyong virus

O'nyong-nyong virus (ONNV) is an arthropod-borne virus (arbovirus) belonging to the genus *Alphavirus* in the family *Togaviridae*. It was first identified during a large epidemic in East Africa between 1959 and 1962, affecting over two million people across Uganda, Kenya, Tanzania, Zaire (now the Democratic Republic of Congo), Malawi, and Mozambique (Williams et al., 2015; Lutwama et al., 1999). The virus name comes from the Acholi word "o'nyong-nyong," meaning "weakening of the joints," a reference to one of its hallmark symptoms—debilitating polyarthritis.

ONNV was the first alphavirus shown to be transmitted by *Anopheles* mosquitoes (*An. gambiae* and *An. funestus*), differing from other alphaviruses like chikungunya, which are spread by *Aedes* mosquitoes (Lanciotti et al., 1998). After decades of relative dormancy, a significant resurgence occurred in Uganda in 1996–1997, with thousands of cases reported and confirmed serologically and virologically (Lutwama et al., 1999).

Phylogenetic studies have shown that ONNV is closely related to the chikungunya virus, and its periodic re-emergence in East Africa has raised concerns about its potential for future outbreaks in endemic regions (Powers et al., 2001).

1.2 Classification of O'nyong nyong Virus

O'nyong-nyong virus (ONNV) is a mosquito-borne virus classified under the following taxonomic hierarchy:

- **Domain:** Riboviria
- **Realm:** Riboviria
- **Kingdom:** Orthornavirae
- **Phylum:** Kitrinoviricota
- **Class:** Alsuviricetes
- **Order:** Martellivirales
- **Family:** *Togaviridae*
- **Genus:** *Alphavirus*
- **Species:** *O'nyong-nyong virus*

ONNV is closely related to other alphaviruses such as Chikungunya virus (CHIKV) and Semliki Forest virus (SFV), sharing genomic and structural similarities. It is an enveloped virus with a single-stranded, positive-sense RNA genome of approximately 11.8 kb. Among alphaviruses, ONNV is unique in being transmitted primarily by *Anopheles* mosquitoes rather than *Aedes* species (Powers et al., 2001; Lanciotti et al., 1998).

2. Structure and Genome organization of O'nyong nyong Virus

O'nyong-nyong virus (ONNV) is an enveloped, spherical virus (Fig. 1) belonging to the *Alphavirus* genus in the family

Togaviridae. Its structure and genome organization (Fig. 2) are typical of alphaviruses, sharing many characteristics with related viruses such as Chikungunya virus (CHIKV) and Semliki Forest virus (SFV).

2.0.1 Virion Structure

- **Shape and Size:** The virion is approximately **65–70 nm in diameter**, with a nearly spherical morphology and icosahedral symmetry (T=4).
- **Envelope:** ONNV is surrounded by a lipid envelope derived from the host cell membrane. Embedded in this envelope are **glycoprotein spikes** formed by **E1 and E2 envelope proteins**, which mediate host cell attachment and entry.
- **Capsid:** Beneath the envelope lies the **nucleocapsid core**, composed of **capsid proteins (C)** arranged around the viral RNA genome. The capsid has icosahedral symmetry and encapsidates the viral RNA, providing protection and structural integrity.

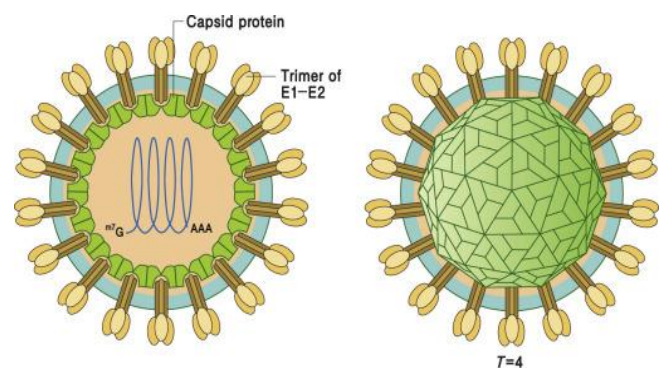


Figure 1: Structure of O'nyong nyong virus
 Source: Power and Logue, (2007)

2.0.2 Genome Organization

- **Type:** Single-stranded, positive-sense RNA (+ssRNA)
- **Size:** Approximately **11.8 kilobases**
- **Genome Features:**
 - The genome is capped at the 5' end and polyadenylated at the 3' end, allowing it to function directly as mRNA.
 - It encodes two major open reading frames (ORFs):
 - **Non-structural polyprotein:** Translated from the genomic RNA, includes proteins **nsP1, nsP2, nsP3, and nsP4**, which are involved in viral RNA replication and transcription.
 - **Structural polyprotein:** Translated from a subgenomic RNA, encodes **capsid (C), E3, E2, 6K, and E1** proteins. These proteins are involved in virion assembly, envelope formation, and host cell entry.

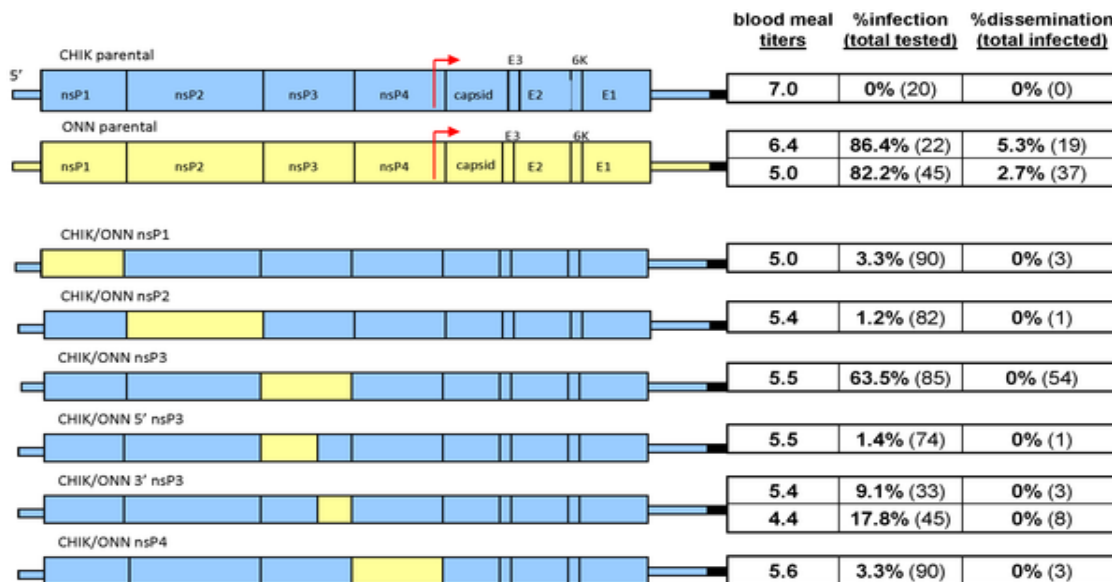


Figure 2: Genomic Organization of O'nyong nyong virus
 Source: Power and Logue, (2007)

Table 1: Key Structural Proteins and Functions

Protein	Function
Capsid (C)	Packages the viral RNA genome and forms the nucleocapsid. Also involved in virion assembly.
E1	Facilitates fusion of the viral envelope with the host cell membrane during entry.
E2	Mediates host cell receptor binding and is a major antigenic determinant.
E3	Plays a role in the proper folding and processing of E2 during virion assembly.
6K	Involved in virion budding and membrane permeability.
nsP1–nsP4	Non-structural proteins that form the replicase complex for viral RNA synthesis.

Source: Powers and Logue, (2007)

2.1 Transmission of O'nyong-nyong Virus

O'nyong-nyong virus (ONNV) is primarily transmitted to humans through the **bite of infected *Anopheles* mosquitoes**, specifically *Anopheles funestus* and *Anopheles gambiae*, which are also vectors for malaria. This mosquito-borne route makes ONNV unique among alphaviruses, as *Aedes* species are the primary vectors. Transmission is typically **anthroponotic**, meaning that humans are the main reservoir during outbreaks, without the need for an animal host.

The transmission cycle involves:

- Infection of Mosquitoes:** When a female *Anopheles* mosquito bites a viremic human (someone with ONNV in their bloodstream), it ingests the virus along with the blood meal. The virus then infects the mosquito's midgut and replicates.
- Extrinsic Incubation Period:** After replication in the mosquito, the virus disseminates to the salivary glands. This takes several days (typically 7–10 days), after which the mosquito becomes capable of transmitting ONNV.
- Transmission to Humans:** Once infectious, the mosquito can transmit ONNV to other humans

through subsequent bites. The virus is introduced into the skin and bloodstream during feeding.

- Human-to-Mosquito-to-Human Cycle:** During epidemics, the virus circulates in a continuous loop between humans and mosquito vectors, leading to widespread transmission.

2.2 Factors Influencing Transmission

- **Mosquito abundance** in endemic regions.
- **Rainy seasons**, which increase mosquito breeding.
- **Lack of mosquito control measures**, such as insecticide-treated bed nets or indoor spraying.
- **Close human population density**, which facilitates rapid spread during outbreaks.

2.3 Viral replication

The replication of O'nyong-nyong virus (ONNV), an *Alphavirus* in the *Togaviridae* family, occurs entirely in the cytoplasm of the host cell. The process is divided into several well-defined stages:

1. Attachment and Entry

ONNV begins infection by attaching to specific receptors on the host cell surface via its envelope glycoprotein E2. After attachment, the virus enters the host cell through clathrin-mediated endocytosis. Once inside the endosome, the acidic environment induces a conformational change in the E1 protein, which facilitates fusion between the viral envelope and the endosomal membrane. This releases the viral nucleocapsid into the cytoplasm (Strauss and Strauss, 1994; Weaver and Barrett, 2004; Ihekumere *et al.*, 2025a).

2. Uncoating and Translation of Non-Structural Proteins

The nucleocapsid disassembles to release the positive-sense single-stranded RNA genome into the cytoplasm. The host ribosomes translate the 5' two-thirds of the viral genome into a non-structural polyprotein. This polyprotein is cleaved into four non-structural proteins (nsP1 to nsP4), which form the viral RNA replication complex (Powers *et al.*, 2001; Ihekumere *et al.*, 2025b).

3. Genome Replication

The replication complex synthesizes a complementary negative-sense RNA strand using the positive-sense genomic RNA as a template. This negative strand serves as the template for producing more positive-sense genomic RNA and a subgenomic RNA, which is required for the synthesis of structural proteins (Powers, 2018; Iheukwumere *et al.*, 2025c).

4. Translation of Structural Proteins

The subgenomic RNA (26S RNA) is translated into a structural polyprotein that includes the capsid protein (C), envelope glycoproteins (E3, E2, 6K, and E1), and is processed via the endoplasmic reticulum and Golgi apparatus. The capsid protein self-cleaves and assembles around newly synthesized genomic RNA to form the nucleocapsid (Strauss and Strauss, 1994; Iheukwumere *et al.*, 2025d).

5. Assembly and Maturation

The envelope glycoproteins E1 and E2 are incorporated into the host cell plasma membrane. The nucleocapsid migrates to the plasma membrane, where budding occurs. During this process, the virus acquires its envelope, and E1/E2 proteins are embedded, forming mature virions (Weaver and Barrett, 2004; Iheukwumere *et al.*, 2025e).

6. Release

Mature virions are released from the host cell by budding. The released ONNV particles are now capable of infecting adjacent cells or being taken up by mosquito vectors, continuing the transmission cycle (Powers, 2018; Iheukwumere *et al.*, 2025f).

3. Pathogenesis

The pathogenesis of O'nyong-nyong virus (ONNV), a mosquito-borne *Alphavirus*, involves both direct viral effects and host immune responses, resulting in the hallmark clinical features such as fever, polyarthritis, and lymphadenopathy. After being transmitted via the bite of an infected *Anopheles* mosquito, ONNV begins its replication in dermal dendritic cells and fibroblasts at the inoculation site.

1. Viral Entry and Local Replication

Following entry into the skin via mosquito bite, ONNV infects resident dendritic cells, fibroblasts, and macrophages. These infected cells support initial viral replication and contribute to the release of progeny virions into the local tissue, initiating a proinflammatory environment (Weaver and Reisen, 2010; Iheukwumere *et al.*, 2024a).

2. Dissemination and Viremia

Once replication is established locally, the virus enters the bloodstream, causing a systemic viremia. This enables the virus to disseminate to secondary sites including joints, lymph nodes, skin, and muscle tissues. Viremia typically coincides with the onset of fever and other systemic symptoms (Powers, 2018; Iheukwumere *et al.*, 2024b).

3. Immune Response and Inflammation

The host's innate immune system responds rapidly to ONNV infection through pattern recognition receptors (PRRs), such as Toll-like receptors and RIG-I-like receptors. This induces the production of type I interferons and proinflammatory

cytokines (e.g., TNF- α , IL-6, IFN- γ), which help control viral replication but also contribute to tissue damage and symptom severity (Suhrieb, 2019; Iheukwumere *et al.*, 2024c).

4. Tissue Damage and Clinical Symptoms

ONNV has a strong tropism for musculoskeletal tissues. The virus replicates in synovial and muscle tissues, triggering inflammation that leads to intense arthralgia (joint pain) and myalgia (muscle pain). Lymphadenopathy results from infection and immune activation in lymphoid tissues. These symptoms can persist for weeks due to sustained immune-mediated inflammation, even after viral clearance (LaBeaud *et al.*, 2011; Iheukwumere *et al.*, 2024d).

5. Resolution and Recovery

In most immunocompetent individuals, ONNV infection is self-limiting. The adaptive immune system, particularly the development of virus-specific neutralizing antibodies and cytotoxic T-cell responses, plays a vital role in viral clearance and recovery. Long-term complications are rare, but persistent joint pain may occur in some cases (Powers *et al.*, 2001; Iheukwumere *et al.*, 2024e).

3.1 Clinical manifestations

O'nyong-nyong virus (ONNV) infection, an arthropod-borne disease caused by an *Alphavirus*, presents with a constellation of clinical features that are often sudden in onset and mimic those of other febrile viral illnesses, especially chikungunya.

Common Signs (observable by a clinician)

- **Fever:** Elevated body temperature, often $>38.5^{\circ}\text{C}$ (101.3°F)
- **Maculopapular Rash:** Non-itchy rash typically appearing on the face, trunk, and limbs
- **Lymphadenopathy:** Enlarged lymph nodes, especially cervical and inguinal
- **Joint Swelling:** Inflammation of joints, usually symmetrical
- **Conjunctival Injection:** Redness of the eyes without discharge
- **Fatigue or Lethargy:** Noticeable weakness or reduced responsiveness
- **Muscle Tenderness:** Especially in the limbs
- **Gait Abnormalities:** Due to severe joint pain

Common Symptoms (reported by patient)

- **Polyarthralgia:** Severe joint pain in knees, wrists, ankles, fingers, and toes
- **Headache:** Often frontal or generalized
- **Myalgia:** Generalized body and muscle aches
- **Fatigue:** Persistent tiredness and weakness
- **Nausea and Vomiting:** Occasionally reported
- **Photophobia:** Sensitivity to light in some patients
- **Malaise:** General discomfort or uneasiness

Duration and Course

- The febrile and rash phases usually last **3–7 days**
- **Arthralgia and fatigue** can persist for **weeks**, occasionally longer in older adults

Distinguishing Features

- ONNV is differentiated from similar alphavirus infections (like chikungunya) by its **vector (Anopheles mosquitoes)** and occasional **widespread outbreaks** in East and Central Africa.

3.2 Distribution of O'nyong nyong virus

Geographic Distribution

O'nyong-nyong virus (ONNV) is geographically confined to **sub-Saharan Africa**, where it has caused several documented outbreaks since its discovery in the 1950s. The virus is particularly prevalent in **East and Central Africa**, with major epidemics reported in **Uganda, Kenya, Tanzania**, and the **Democratic Republic of the Congo**. The first and most significant outbreak occurred between **1959 and 1962**, affecting over 2 million people across **Uganda, Kenya, and Tanzania** (Williams and Woodall, 1961). Subsequent outbreaks have been reported in Uganda (1996) and more recently in Kenya and other parts of East Africa (LaBeaud et al., 2015).

ONNV activity is often associated with areas where its vector mosquitoes (*Anopheles funestus* and *Anopheles gambiae*) are abundant. These mosquitoes thrive in regions with high humidity and standing water, particularly during and after rainy seasons, which contribute to periodic outbreaks. There is limited evidence of ONNV circulation in West African countries such as Nigeria and Senegal, primarily based on serological surveys, but no large-scale outbreaks have been reported from these regions. Similarly, ONNV is rarely detected in Southern Africa, and no cases have been documented outside the African continent, confirming its endemic status in Africa.

Demographic Distribution

The O'nyong-nyong virus affects individuals of all age groups and genders, although some demographic trends have been noted:

- **Age:** Both children and adults can contract the virus. However, adults often report more prolonged joint pain (arthralgia), which is one of the virus's hallmark symptoms. In contrast, children may experience milder or less persistent symptoms.
- **Sex:** There is no known sex-based susceptibility, and infection rates appear similar among males and females during outbreaks.
- **Occupation and Lifestyle:** Individuals who are frequently outdoors or live near mosquito breeding sites are at a higher risk. These include:
 - Farmers and agricultural workers
 - Fishermen
 - People living in rural areas or near stagnant water
- **Urban vs Rural Settings:** ONNV transmission is more common in rural and peri-urban environments, where *Anopheles* mosquitoes are more likely to breed and vector control is often inadequate.

The virus disproportionately affects economically disadvantaged populations, particularly in rural areas with limited access to healthcare, mosquito control, and public health infrastructure. This demographic vulnerability further exacerbates the impact of ONNV outbreaks on affected communities.

4. Laboratory Diagnosis

The laboratory diagnosis of O'nyong-nyong virus (ONNV) infection is essential for confirming clinical cases, especially during outbreaks, and for distinguishing it from other arboviral infections with similar symptoms, such as

chikungunya and dengue fever. Diagnosis typically relies on a combination of virological, serological, and molecular methods.

1. Virus Isolation

Isolation of ONNV from patient blood samples or mosquito vectors remains a definitive diagnostic method. The virus can be cultured in several mammalian cell lines, such as **Vero cells** or **C6/36 mosquito cells**. Cytopathic effects (CPE) are observed within a few days, confirming viral presence (Lanciotti et al., 1997). However, virus isolation requires specialized biosafety facilities and is time-consuming, limiting its use in routine diagnostics (Iheukwumere et al., 2024f).

2. Serological Tests

Serological assays detect antibodies generated in response to ONNV infection, particularly **IgM** and **IgG** antibodies:

- **Enzyme-Linked Immunosorbent Assay (ELISA):** ELISA is widely used to detect anti-ONNV IgM antibodies during the acute phase of infection, indicating recent exposure. IgG detection is useful for epidemiological surveys and determining past infection (Mackenstedt et al., 1990; Iheukwumere et al., 2025g).
- **Hemagglutination Inhibition (HI) Test:** This test can detect antibodies but may cross-react with other alphaviruses, limiting specificity (Williams et al., 1965).
- **Plaque Reduction Neutralization Test (PRNT):** Considered the gold standard for serological confirmation, PRNT measures virus-specific neutralizing antibodies, distinguishing ONNV from closely related viruses (Powers et al., 2001).

3. Molecular Techniques

Molecular methods provide rapid and sensitive diagnosis, particularly during the early stages of infection:

- **Reverse Transcriptase Polymerase Chain Reaction (RT-PCR):** RT-PCR assays targeting specific ONNV genomic sequences enable detection of viral RNA in patient serum or plasma during the viremic phase (Griffin et al., 2005; Iheukwumere et al., 2025h). Real-time RT-PCR enhances sensitivity and allows quantification of viral load.
- **Sequencing and Phylogenetic Analysis:** Sequencing of PCR products helps characterize viral strains, track outbreaks, and understand epidemiology (Wacharapluesadee et al., 2015; Iheukwumere et al., 2025i).

4. Immunofluorescence Assay (IFA)

IFA uses virus-infected cells as antigens to detect antibodies in patient sera. It is a useful confirmatory test but requires fluorescence microscopy and skilled personnel (Iheukwumere et al., 2025j).

4.1 Treatment of O'nyong nyong virus

Currently, there is no specific antiviral treatment or vaccine available for O'nyong-nyong virus (ONNV) infection. Management of the disease is primarily **supportive and**

symptomatic, focusing on relieving symptoms such as fever, joint pain, and inflammation. Common treatments include:

- **Analgesics and antipyretics:** Medications like acetaminophen (paracetamol) or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are used to reduce fever and alleviate joint and muscle pain (Staples and Fischer, 2014).
- **Rest and hydration:** Patients are advised to rest adequately and maintain good hydration to support recovery.
- **Avoidance of aspirin:** Aspirin is generally avoided to reduce the risk of hemorrhagic complications, especially in cases where co-infection with other arboviruses like dengue cannot be ruled out.

Because ONNV causes symptoms similar to other alphavirus infections like chikungunya, treatment protocols are often adapted from those diseases.

4.2 Prevention

Prevention of **O'nyong-nyong virus (ONNV)** focuses on reducing mosquito exposure and controlling vector populations, as there is currently no licensed vaccine or specific antiviral treatment available. The primary mosquito vectors—**Anopheles funestus** and **Anopheles gambiae**—are also major malaria vectors, so prevention strategies often overlap with those for malaria control.

Key Prevention Strategies:

1. Vector Control:

Insecticide-treated bed nets (ITNs): Widely recommended to prevent night-time mosquito bites, particularly in endemic areas (WHO, 2017).

Indoor residual spraying (IRS): Application of long-lasting insecticides on walls and ceilings to kill resting mosquitoes.

Larval source management: Eliminating standing water where mosquitoes breed, such as in containers, puddles, and drains.

2. Personal Protection Measures:

Wearing long-sleeved clothing and trousers to reduce skin exposure.

Using mosquito repellents containing **DEET**, **picaridin**, or **IR3535** on exposed skin.

Ensuring proper housing infrastructure, such as screened windows and doors, to reduce indoor mosquito entry.

3. Community-Based Interventions:

Public health education to raise awareness about ONNV and mosquito-borne illnesses.

Community engagement in vector control initiatives, including environmental clean-up and source reduction.

4. Surveillance and Early Warning Systems:

Strengthening disease surveillance to detect ONNV outbreaks early and respond quickly.

Vector surveillance to monitor *Anopheles* mosquito populations and insecticide resistance.

5. Travel Precautions:

Travelers to endemic regions in East and Central Africa should be advised on preventive measures, including mosquito protection and awareness of disease symptoms.

5. Conclusion

O'nyong-nyong virus (ONNV), an arthropod-borne alphavirus primarily transmitted by *Anopheles* mosquitoes, remains a significant but under-recognized public health concern in East and Central Africa. Characterized by febrile illness, debilitating joint pain, rash, and lymphadenopathy, ONNV outbreaks can lead to substantial socioeconomic impacts due to widespread morbidity and loss of productivity in affected communities. Although typically non-fatal, the virus's ability to cause large-scale epidemics highlights the need for ongoing vigilance. The absence of a specific antiviral treatment or vaccine emphasizes the critical importance of vector control, public health education, and improved surveillance systems to prevent future outbreaks. With climate change and globalization influencing vector ecology and disease spread, sustained investment in research and preparedness is essential to mitigate the threat posed by ONNV and other emerging arboviruses.

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