Review Article

A REVIEW ON CHANDIPURA VIRUS: OUTBREAKS AND EMERGING INFECTIOUS DISEASE FOR CHILDREN IN INDIA

ABSTRACT:

Chandipura virus, also known as Chandipura vesicular virus is a rare and poorly understood virus belonging to the family Rhabdoviridae. The virus mostly affects children and is known to cause very painful and sometimes fatal brain inflammation. Chandipura disease is a disease caused by infected sandflies. The symptoms include sudden onset of fever, brain changes and seizures, often leading to encephalitis. The rapid growth and high mortality of Chandipura disease establish a major public health problem. Diagnosing Chandipura virus infection in children involves a combination of clinical assessment and laboratory tests. Diagnostic confirmation relies on laboratory tests such as polymerase chain reaction (PCR) to detect viral RNA, and serological assays to identify specific antibodies against the virus. In some cases, viral isolation from blood or cerebrospinal fluid may be performed. Treatment for Chandipura virus infection is primarily supportive, as there are no specific antiviral therapies available. This includes fever management with antipyretics, ensuring adequate hydration, and providing supportive care for neurological symptoms such as seizures or encephalitis. In severe cases, hospitalization may be required for close monitoring and advanced supportive measures. Preventative measures, such as reducing sandfly exposure through the use of insect repellent and protective clothing, are crucial in endemic areas to reduce the risk of infection. Public health programs should focus on promoting environmental control measures to reduce sandfly populations, such as proper waste management and eliminating standing water.

KEY WORDS: Children; Virus; Encephalitis; Sand fly; Fever; Region

Fig 1- graphical abstract

INTRODUCTION:

In recently, chandipura virus has emerged as an encephalitis virus and has been associated with many outbreaks in many parts of India. Children under the age of 15 are most susceptible to infection. CHPV is emerging as a major encephalitis-causing virus in the Indian subcontinent. Serious disease caused by this virus has been reported in many parts of India.

Chandipura virus, also known as Chandipura vesicular virus is a rare and poorly understood virus belonging to the family Rhabdoviridae. The virus mostly affects children and is known to cause very painful and sometimes fatal brain inflammation.

This virus was first discovered in 1965 by the National Institute of Virology, ICMR-Pune in the village of Chandipura in Nagpur district of Maharashtra, India. This virus has been associated with several outbreaks of unexplained encephalitis in Central India.

Between June and August 2003, 329 children were affected and 183 died in the Indian states of Andhra Pradesh and Maharashtra. In 2004, an unprecedented number of child cases and deaths were recorded in the state of Gujarat [19-21].

Chandipura disease is a disease caused by infected sandflies. It has occurred a lot, especially in children. The symptoms include sudden onset of fever, brain changes and seizures, often leading to encephalitis. The rapid growth and high mortality of Chandipura disease poses a major public health problem.

OUTBREAK OF INFECTION:

Chandipura virus outbreaks are concerning because of their capability to motive distinct essential ailments, in particular in children and immunocompromised people. The virus is thought to motive neurological complications together with seizures and coma, posing challenges for treatment and manage. A month for the purpose that outbreak of Chandipura Acute Viral Encephalitis (CHPV) in Gujarat, the state has noted 137 patients with suspected CHPV, amongst whom fifty-one have tested positive result for the virus and also observed cases of Viral Encephalitis spreading to 24 of the 33 districts of the Gujrat, with deaths of 56 kids being recorded. Teams from the National Institute of Virology in Pune and the National Centre for Disease Control stayed put in the state "Conducting studies" to ascertain the nature and spread of the virus. While six sufferers of viral encephalitis are from Rajasthan, where children have died, four are from Madhya Pradesh, which has suggested one death. One case has been recorded in Maharashtra. Health Minister J P Nadda informed the Rajya Sabha, fifty-three presented occurrences of Chandipura virus, 61 cases have been detected in Gujarat and three have been detected in Rajasthan.

In a written reaction to a question, Nadda said that of those fifty-three occurrences of Chandipura virus, 19 persons have died and all deaths have been mentioned from Gujarat. In the meantime, the ultra-modern bulletin from the Gujarat authorities released, the quantity of Chandipura virus cases have reached upto 64. Between early June and 15 August 2024, the Ministry of Health and Family Welfare of the Government of India reported 245 cases of AES including 82 deaths (CFR 33%). A total of 43 districts in India are currently reporting AES cases. Cases are sporadically present across various districts as in previous outbreaks. Notably, there is a rise in CHPV outbreaks every four to five years in Gujarat state.

CHANDIPURA VIRUS VECTORS AND ITS TRANSMISSION:

The CHPV infection is primarily caused by the biting of the following:

- Sandflies
- Mosquitoes
- Ticks

The Chandipura virus (CHPV) is an arthropod-borne virus that belongs to the family Rhabdoviridae and the genus Vesiculovirus. CHPV has a distinctive bullet-shaped morphology, which is characteristic of the Rhabdoviridae family. This shape is similar to a bullet or a rod with rounded ends. The virus is approximately 150-200 nanometers in length and about 50-70 nanometers in diameter.

CHPV is an enveloped virus, meaning it has an outer lipid bilayer derived from the host cell membrane. This envelope is acquired as the virus buds from the host cell. Embedded in the lipid bilayer are glycoproteins (GP),

which are essential for the virus's ability to attach to and enter host cells. These glycoproteins play a crucial role in the virus's infectivity and are the main target for the host's immune response.
Inside the envelope, CHPV has a helical nucleocapsid. This consists of a single-stranded RNA (ssRNA) genome that is tightly coiled around nucleoproteins (N) to form a helical structure. The genome of CHPV is a single-stranded RNA of negative polarity. This means that the RNA cannot be directly translated into proteins and must be converted into a positive-sense RNA by an RNA-dependent RNA polymerase (RdRp) before it can be translated. It has Structural Proteins-Nucleoprotein (N), Matrix Protein (M), Glycoprotein (G) and Non-Structural Proteins-RNA Polymerase (L), Phosphoprotein (P).

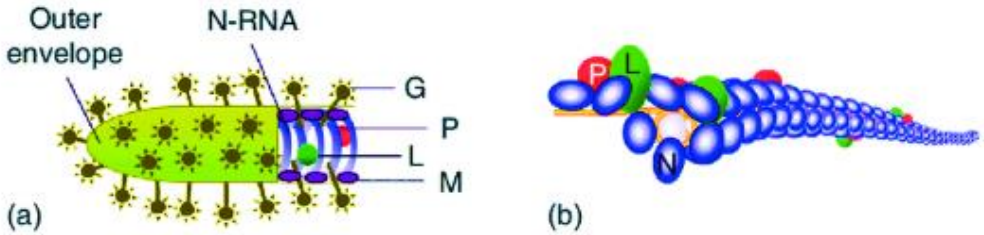

Fig 2- (a) schematic presentation of bullet shaped Chandipura virus with glycoprotein G protruding out of the viral envelope. (b) A proposed view of Chandipura virus genome RNA encapsidated with Nucleocapsid protein. Nucleocapsid protein binds to viral RNA to enclose it in a disc like structure.

Near residence, the authority found the presence of sandflies – the primary vector believed to be of CHPV transmission, particularly species of the genus Phlebotomus (Phlebotomus papatasi, Phlebotomus argentipes or Sergentomyia spp.). These tiny, blood-sucking insects are prevalent in tropical and subtropical regions. "Sandflies are known to be the main vectors for this virus. t is transmitted by sandflies and mosquitoes, including Aedes aegypti, which is also a vector for dengue. The virus resides in the salivary glands of these insects and can be transmitted to humans. Most of the cases are from north Gujarat, where the dry temperature is favorable for the breeding of sandflies. They are found in cracks of walls where they breed and lay their eggs and in mud houses," Dr. Pradeip Umarigar, health officer, Surat Municipal Corporation, told HT (Hindustan times).

Pathogenesis of Infection

The pathogenesis of Chandipura virus (CHPV) involves several key stages, from entry into the host to replication and the resultant clinical disease. Here's a detailed overview of how CHPV causes disease:

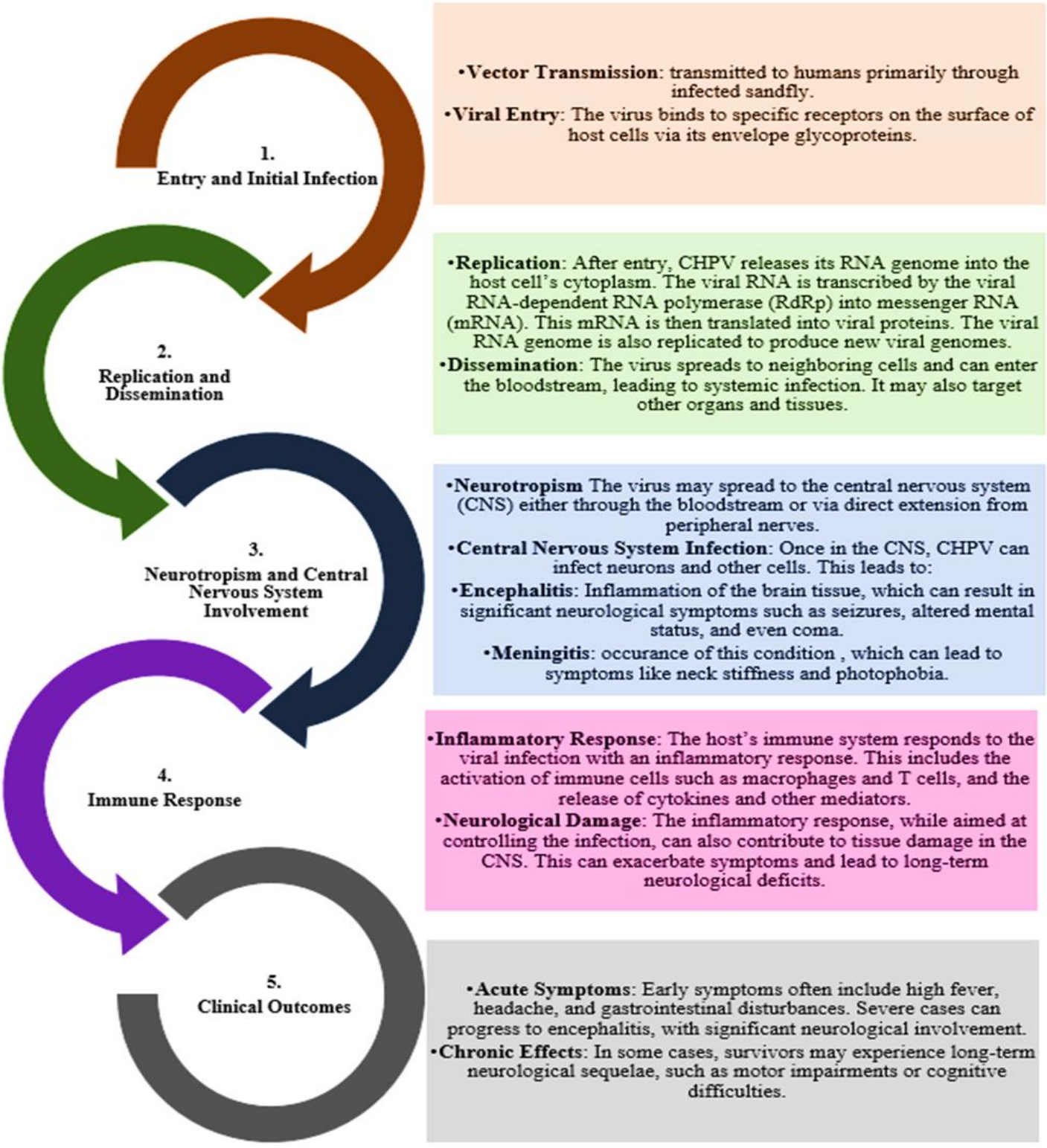

Fig 3- Pathogenesis and Clinical progression of Chandipura virus (CHPV)

CLINICAL FEATURES AND SYMPTOMS:

Chandipura virus (CHPV) infection can manifest with a range of clinical features and symptoms, often affecting the central nervous system. Here's a detailed overview of the clinical presentation of CHPV infection:

1. **Incubation Period**
   - Typical Duration: The incubation period for CHPV is generally between 2 to 14 days after exposure to the virus through mosquito bites.
2. **Initial Symptoms**
   - Fever: One of the earliest symptoms is a high fever, which can be sudden and may last for several days.
   - Headache: Severe headaches are common and can be quite debilitating.
   - Body Aches: General body aches and malaise are also frequently reported.
3. **Neurological Symptoms**
   - Seizures: Neurological involvement can lead to seizures, which are a significant clinical feature of severe CHPV infection.
   - Altered Mental Status: Patients may experience confusion, drowsiness, or agitation. In severe cases, there may be loss of consciousness or coma.
   - Meningeal Signs: Symptoms such as neck stiffness and photophobia (sensitivity to light) can indicate meningitis.
4. **Gastrointestinal Symptoms**
   - Nausea and Vomiting: These can occur alongside other symptoms, especially in the initial stages of the illness.
5. **Other Symptoms**
   - Rash: Some patients may develop a rash, although this is less common.
   - Weakness: Generalized weakness or paralysis can occur in severe cases.
6. **Severe Manifestations**
   - Encephalitis: In severe cases, CHPV infection can lead to encephalitis, which is an inflammation of the brain. This can result in significant neurological impairment and is associated with a higher risk of complications or death.
   - Severe Neurological Damage: Long-term neurological sequelae may occur, such as motor deficits or cognitive impairments, especially in severe or untreated cases.

DIAGNOSIS OF CHANDIPURA VIRUS (CHPV) INFECTION:

Clinical Diagnosis:

- Symptoms Review: Clinical diagnosis often starts with a review of symptoms, particularly in regions where CHPV is known to be endemic. Key symptoms include high fever, headache, nausea, vomiting, seizures, and neurological signs such as altered mental status.
- Neurological Symptoms: In severe cases, signs of encephalitis or meningitis, such as neck stiffness and photophobia, may be present.

Laboratory Diagnosis:

- Serology: Detection of specific antibodies (IgM and IgG) against CHPV in the blood can confirm infection. IgM antibodies are typically detectable in the early stages, while IgG indicates a past infection.
- Polymerase Chain Reaction (PCR): PCR tests can detect CHPV RNA in blood, cerebrospinal fluid (CSF), or tissue samples. This method is highly sensitive and specific for confirming the presence of the virus.
- Cerebrospinal Fluid (CSF) Analysis: In cases of suspected encephalitis or meningitis, CSF analysis may show elevated protein levels, normal glucose levels, and an increased white blood cell count. PCR can be performed on CSF for more precise diagnosis.

- Virus Isolation: Although less commonly used due to the need for specialized facilities, virus isolation from clinical samples can confirm the presence of CHPV.

Imaging Studies:

- Neuroimaging: Techniques such as MRI or CT scans can be used to assess the extent of neurological damage and to rule out other causes of neurological symptoms.

Practicality of Diagnosis in Endemic Areas

There are several diagnostic techniques available for **Chandipura Virus (CHPV),** their practicality in endemic and rural areas of India is significantly limited by factors such as:

- **Lack of Healthcare Infrastructure**: Advanced diagnostic techniques (e.g., PCR, virus isolation, and neuroimaging) require specialized equipment and trained personnel, which are often absent in rural or resource-limited settings.
- **Cost Constraints**: Techniques like PCR, CSF analysis, and virus isolation are expensive, and their costs may not be feasible for widespread use in rural areas where healthcare resources are scarce.
- **Delay in Diagnosis**: The need for sample transportation, the unavailability of immediate testing, and the complex procedures involved lead to delays in diagnosis, which could result in worsened patient outcomes due to the viral nature of the infection.
- **Expertise Gaps**: Limited expertise in handling and interpreting results from advanced diagnostics (e.g., PCR or CSF analysis) further hampers the effective management of CHPV outbreaks in rural areas.

TREATMENT OF CHANDIPURA VIRUS (CHPV) INFECTION:

Supportive Care:

- Hydration and Nutrition: Ensuring adequate fluid intake and nutrition is essential to support the patient's overall health.
- Antipyretics: Medications like acetaminophen or ibuprofen can help manage fever and provide symptomatic relief.
- Seizure Management: Antiepileptic drugs may be used to control seizures, especially in patients with severe neurological symptoms.
- Monitoring: Close monitoring in a hospital setting may be required for severe cases, particularly for managing neurological symptoms and complications.

Experimental Treatments:

- Antiviral Agents: There are no specific antiviral treatments approved for CHPV. Research into antiviral drugs and therapeutic approaches is ongoing.
- Clinical Trials: Patients may be eligible for experimental treatments or clinical trials, which should be considered under the guidance of healthcare professionals.

PREVENTION OF CHANDIPURA VIRUS (CHPV) INFECTION:

1. Vector Control:

- Eliminate Breeding Sites: Reducing mosquito populations by eliminating standing water in containers, tires, and other potential breeding sites.
- Use of Insecticides: Applying insecticides to control mosquito larvae and adult mosquitoes in areas where CHPV is known to be active.
- Environmental Management: Improving sanitation and waste management to reduce mosquito breeding habitats.

2. Personal Protection:

- Insect Repellents: Using repellents containing DEET, picaridin, or other effective ingredients on exposed skin and clothing.
- Protective Clothing: Wearing long-sleeved shirts and long pants, especially during peak mosquito activity periods (dawn and dusk).
- Mosquito Nets: Sleeping under mosquito nets, particularly in endemic areas, to prevent mosquito bites.

3. Community Education:

- Awareness Programs: Educating communities about the risks of CHPV and the importance of mosquito bite prevention can help reduce transmission.
- Health Campaigns: Public health campaigns can inform people about preventive measures and symptoms of CHPV infection.

4. Surveillance and Monitoring:

- Monitoring Mosquito Populations: Regular monitoring of mosquito populations and CHPV activity can help in early detection and control of outbreaks.
- Early Detection: Surveillance systems can aid in the early identification of CHPV cases and prompt public health responses.

Some effective Vector Control Programme related to Chandipura virus

Chandipura virus (CHPV) is a mosquito-borne virus primarily transmitted by Rhipicephalus mosquitoes and is a significant cause of encephalitis in certain regions, particularly in India. Vector control is a critical component of managing the spread of CHPV, as the virus primarily spreads through mosquitoes.

1. Integrated Vector Management in Andhra Pradesh (India)

Andhra Pradesh has been a focal point for Chandipura virus outbreaks, with several reports of encephalitis cases attributed to CHPV. The state implemented an Integrated Vector Management (IVM) program as part of broader efforts to control the transmission of arboviral diseases, including Chandipura virus.

Insecticide-treated bed nets (ITNs): Mass distribution of ITNs was carried out in affected districts to reduce the exposure of people to mosquito bites, particularly at night when the mosquitoes are most active.

Indoor Residual Spraying (IRS): Houses in high-risk areas were sprayed with insecticides, especially during the peak transmission seasons.

Larval source management: The authorities focused on eliminating potential mosquito breeding sites by clearing stagnant water sources like ponds, ditches, and containers where mosquitoes lay eggs.

Surveillance and Early Detection: Surveillance of both mosquito populations and suspected human cases of encephalitis (often CHPV-related) was ramped up. This helped to detect outbreaks early and deploy control measures more effectively.

2. Vector Control in Maharashtra (India)

Maharashtra has faced multiple outbreaks of Chandipura virus, and as a result, several vector control programs were initiated to curb the spread of the virus.

Community Engagement and Education: Public health campaigns were launched to educate people about the importance of eliminating standing water around their homes. Educational materials and training sessions were provided to local communities on how to reduce mosquito breeding sites.

Larvicidal Application: In areas with significant mosquito breeding grounds, **larvicides** like *Bacillus thuringiensis israelensis* (Bti) were applied to water sources to kill larvae before they could mature into adult mosquitoes.

Environmental Management: The municipal corporations in affected areas carried out a series of environmental interventions, such as desilting ponds and removing debris from water bodies to prevent mosquito breeding.

3. Chhattisgarh: Targeted Vector Control and Surveillance

Chhattisgarh has been another region where Chandipura virus has caused significant encephalitis outbreaks. In response, the state implemented a focused vector control program designed to reduce mosquito populations and monitor potential outbreaks of CHPV.

Environmental Control: A major focus was on controlling mosquito breeding grounds, particularly in rural areas where water storage containers and puddles serve as breeding sites. Community-led clean-up campaigns were promoted to eliminate stagnant water.

Use of Insecticides: Indoor and outdoor insecticide spraying was carried out using **pyrethroid-based insecticides**, with an emphasis on areas where mosquito larvae were abundant.

Surveillance: Active surveillance systems were set up to monitor both mosquito populations and suspected cases of **viral encephalitis**. This allowed health officials to track potential CHPV outbreaks and respond quickly with vector control measures.

4. Bihar and Uttar Pradesh: Cross-border Vector Control Cooperation

Bihar and Uttar Pradesh have experienced outbreaks of CHPV, and due to the interconnected nature of vector transmission in border areas, these states have collaborated on regional vector control efforts.

Cross-border collaboration: The two states have shared surveillance data and coordinated their efforts to implement vector control measures at the regional level. This included joint campaigns to reduce mosquito breeding sites and the distribution of insecticide-treated bed nets in high-risk areas.

Public Health Education: Mass awareness campaigns were conducted in villages to inform the public about CHPV and the importance of reducing mosquito exposure. Local health workers played a significant role in disseminating knowledge and encouraging people to use insect repellent and sleep under nets.

Vector Control Teams: Special teams were set up in high-risk districts to conduct thorough inspections of water bodies, clear potential breeding sites, and carry out spraying operations.

5. Delhi: Urban Vector Control Program

Delhi, with its high population density and rapid urbanization, has been at risk of various mosquito-borne diseases, including Chandipura virus. The Delhi Health Department initiated a focused vector control program to address this risk, targeting mosquitoes that could spread CHPV.

Anti-mosquito campaigns: Intensive mosquito control campaigns were launched during the monsoon season, including the application of **insecticides** in areas with reported mosquito infestations.

Larvicidal interventions: Local health authorities distributed **larvicides** to households and water bodies where mosquitoes were likely to breed.

CHALLENGES WITH CHANDIPURA VIRUS IN INDIA

Chandipura virus is a significant concern in India due to its impact on public health. This virus, which belongs to the vesiculo virus genus in the Rhabdoviridae family, primarily affects children and can cause severe neurological complications. It poses significant challenges in India, particularly in the states of Maharashtra, Gujarat, and Madhya Pradesh.

some of the primary challenges related to CHPV and the potential international collaboration and solutions:

1. Limited Awareness and Research on CHPV

- **Challenge**: In many regions of India, CHPV remains a poorly understood virus due to limited research funding and a lack of awareness among healthcare providers. This leads to misdiagnosis or delayed diagnosis, hampering timely treatment.
- **Underlying Causes**: Lack of sufficient research funding, underreporting of cases, and limited medical expertise in rural or underserved areas contribute to this issue.
- **Recommendation**:
    - **Increase funding for research**: The Indian government and international partners can collaborate to increase funding for research on CHPV's epidemiology, clinical manifestations, and treatment options.
    - **Public health education campaigns**: Both national and international organizations (such as WHO) can aid in spreading awareness regarding CHPV's symptoms, prevention, and early diagnosis.
    - **International collaborations for research**: Encourage international partnerships between Indian research institutions and global scientific bodies to improve understanding and develop vaccines or therapies.
- **Potential Benefit of Global Partnerships**:
    - **Global research collaboration** can accelerate the discovery of diagnostic tools, treatments, and vaccines.
    - **Knowledge exchange** from countries with experience in controlling similar vector-borne diseases could be critical in reducing the spread of CHPV.

2. Inadequate Diagnostic Infrastructure

- **Challenge**: Diagnostic capabilities for CHPV are limited, especially in rural areas. The virus often goes undetected or misdiagnosed as other more common diseases, delaying proper treatment.
- **Underlying Causes**: Insufficient healthcare infrastructure, limited availability of specialized diagnostic tests, and lack of trained personnel in rural or remote areas.
- **Recommendation**:
    - **Improve diagnostic infrastructure**: The government, in collaboration with international health organizations, can establish diagnostic facilities and train healthcare providers to recognize symptoms of CHPV.
    - **Mobile diagnostic units**: Implement mobile health units to reach remote areas and provide timely testing and diagnosis.
    - **Collaborate with global health organizations**: Tap into international knowledge and technologies to develop low-cost, rapid diagnostic tests for CHPV.
- **Potential Benefit of Global Partnerships**:
    - **Cross-border information exchange** can help bring in innovative diagnostic technologies developed in other parts of the world.
    - **Global organizations like WHO** can play a role in harmonizing diagnostic protocols and providing funding for infrastructure development.

3. Vector Control Challenges

- **Challenge**: CHPV is primarily transmitted by sandflies, and vector control is difficult due to environmental factors, limited resources, and gaps in vector management strategies.
- **Underlying Causes**: Poor sanitation, lack of mosquito control programs, and inadequate vector monitoring.
- **Recommendation**:
    - **Comprehensive vector control programs**: Launch national and regional vector control initiatives with better monitoring systems, environmental sanitation efforts, and the use of insecticides.
    - **Community-based programs**: Engage local communities in vector control practices, such as eliminating breeding grounds and using repellents.
    - **Research into novel vector control strategies**: Collaborate internationally on finding innovative, eco-friendly ways to control sandfly populations.
- **Potential Benefit of Global Partnerships**:
    - **Global collaboration on vector control**: Countries with experience in vector-borne disease control (e.g., WHO, CDC) can share their best practices, technologies, and strategies to address CHPV transmission.
    - **International research partnerships** can lead to new tools and methods for vector control.

4. Limited Public Health Surveillance and Reporting

- **Challenge**: Surveillance systems for monitoring outbreaks of CHPV are often fragmented, with underreporting of cases, especially in rural or hard-to-reach areas.
- **Underlying Causes**: Lack of efficient surveillance networks, insufficient funding for public health infrastructure, and cultural or logistical barriers to reporting.
- **Recommendation**:
    - **Strengthen surveillance systems**: Establish more robust, real-time surveillance systems with mobile technology for better reporting of suspected cases.
    - **Collaborative monitoring with global agencies**: Establish a partnership with international health organizations to set up surveillance networks and ensure reporting.

- **Potential Benefit of Global Partnerships**:
    - **International surveillance collaboration** can help ensure that outbreaks are detected early, preventing widespread transmission.
    - **Data sharing** across countries can lead to better forecasting, early warnings, and coordinated responses.

5. Insufficient Healthcare Access and Capacity

- **Challenge**: Many affected regions, particularly rural and remote areas in India, lack adequate healthcare facilities, limiting access to treatment for CHPV-infected individuals.
- **Underlying Causes**: A shortage of medical infrastructure, lack of qualified healthcare personnel, and transportation barriers in rural areas.
- **Recommendation**:
    - **Enhance healthcare access**: Increase the number of healthcare centers in rural areas and improve the healthcare workforce through training programs.
    - **Telemedicine and mobile health**: Leverage telemedicine and mobile health technologies to provide remote consultation and support to rural communities.
- **Potential Benefit of Global Partnerships**:
    - **International healthcare partnerships** can improve healthcare access through funding and technical support.
    - **Telemedicine collaborations** with global tech firms and healthcare systems can bring expert care to underserved regions.

DISCUSSION

Chandipura Virus presents an urgent public health challenge in India, particularly for children, with significant morbidity and mortality. While progress has been made in understanding the virus's epidemiology, transmission, and clinical impact, critical gaps remain, particularly in areas like diagnostics, treatment, vaccine development, and vector control. The synthesis of findings across different domains highlights the need for a more integrated, multidisciplinary approach to challenge CHPV effectively.

Future research should prioritize developing rapid diagnostic tests, targeted antiviral therapies, and an effective vaccine. In parallel, efforts should be made to enhance public health surveillance, improve vector control strategies, and better understand the environmental factors that contribute to CHPV outbreaks. International collaboration, both in terms of research and resource-sharing, will be essential in accelerating progress in all of these areas.

CONCLUSSION

CHPV remains a significant public health concern, especially in regions where it is endemic, particularly in the states of Gujarat, Maharashtra, and Madhya Pradesh. The virus primarily affects children, causing severe neurological complications such as encephalitis, seizures, and coma, with a high case fatality rate. Its transmission, primarily through sandflies and mosquitoes, is exacerbated by environmental factors conducive to the breeding of these vectors, such as dry and warm climates. Despite its known association with periodic outbreaks, the virus remains poorly understood, and there is no specific vaccine or antiviral treatment available, making prevention efforts reliant on vector control and public awareness.

The outbreaks of CHPV have highlighted several key challenges, including difficulties in early diagnosis due to non-specific symptoms, inadequate surveillance systems, and the lack of sufficient healthcare infrastructure in

affected areas. The absence of a vaccine compounds the difficulties in controlling the virus, and the high mortality rate underscores the urgency for effective intervention strategies. Furthermore, while there have been efforts to monitor and control the spread of the virus, the lack of coordinated, widespread surveillance hinders timely responses.

Public education plays a critical role in managing CHPV outbreaks, emphasizing the importance of vector control measures, early detection, and symptomatic management. There is an urgent need for more research to better understand the virus's pathogenesis, transmission dynamics, and potential treatments. Improving healthcare infrastructure, enhancing surveillance, and fostering community engagement are essential steps toward controlling the spread of Chandipura virus and mitigating its impact on public health in India.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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