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# Chandipura Vesiculovirus: Clinical Manifestation, Neuroinvasion and Public Health Interventions

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## ABSTRACT

Chandipura virus (CHPV), a vesiculovirus in the Rhabdoviridae family, has emerged as a critical pathogen responsible for severe encephalitis outbreaks in rural India, predominantly affecting children. This review examines the current understanding of CHPV's epidemiology, clinical features, pathogenesis, and available diagnostic and treatment strategies. CHPV, transmitted primarily through phlebotomine sandflies, can cause rapid progression from febrile illness to severe neurological symptoms and death, with a high case fatality rate. Despite advancements in diagnostic methods like real-time PCR and improved serological assays, no specific antiviral treatments are available. Research into vaccines and antiviral therapies is ongoing, showing promising results but requiring further validation. Effective prevention relies heavily on vector control, public awareness, and improved sanitation. The importance of this review lies in its comprehensive synthesis of current knowledge and its emphasis on the urgent need for enhanced surveillance, early detection, and preventive measures. By highlighting gaps in current understanding and outlining potential research directions, this review underscores the critical need for continued efforts to mitigate CHPV's impact on public health.

***Keywords:*** Chandipura vesiculovirus, outbreak, encephalitis, neuroinvasion

## INTRODUCTION

Chandipura virus ( CHPV), a vesiculovirus of the Rhabdoviridae family, has emerged as a significant human pathogen that causes outbreaks of encephalitis in India [1]. CHPV is responsible for outbreaks in rural areas in India. It primarily affects children causing influenza-like illnesses such as fever, headache, and acute encephalitis, which can quickly escalate to seizures, coma, and potentially death. Although it is not contagious, the virus's capacity to induce severe neurological symptoms demands swift detection and treatment to avoid fatal outcomes[2]. It is transmitted through vectors like mosquitoes, ticks, and sandflies. The diagnosis of this can be done using real-time PCR. The virus has a negative sense RNA genome encoding 5 proteins: N, P, M, G, and L. The P protein plays a vital role in the virus's life cycle while the M protein is lethal. Currently, there are no specific treatments available. Symptomatic and supportive care is given to patients that include interventions to reduce the symptoms and brain edema. However, vaccinations are available for prevention. A vero cell-based vaccine acts as a preventive vaccine. Prevention methods like vector control, immunity, good nutrition, hygiene measures, and public awareness are essential[3,4].

CHPV induces neuronal death via the Fast-mediated extrinsic apoptotic pathway, activating caspase-8 and -3. The virus displays genetic diversity, forming distinct clades in India and West Africa, with the potential for future human spillover due to codon usage adaptation. CHPV primarily impacts children aged 2-16 years, with a high case fatality rate of 55-75%. In India, CHPV has become increasingly prevalent in cases of acute encephalitis syndrome (AES) since 2000, even surpassing the Japanese encephalitis virus in some regions. CHPV came into prominence in 2003 due to an outbreak in southern India, where approximately 350 children developed acute encephalitis, resulting in around 200 deaths [5]. The first reported case of CHPV in Bihar, India, occurred in 2016, indicating its expanding geographical reach and underscoring the need for enhanced surveillance and diagnostic efforts[6,7].

This review aims to provide complete and updated information based on the most recent research. This also underlines the importance of prevention and usage of public health strategies to help spread the virus and also emphasizes the importance of early detection of this to prevent complications and to create a better prognosis and overall quality of life for the patient.

**Host - Virus interaction**

CHPV was first isolated in India in 1965 in the state of Maharashtra from patients with febrile illness [1,5]. The virus has a bullet-shaped structure, 150-165 nm long and 50-65 nm wide as studied by transmission electron microscopy. Recent studies have proposed the carrier of the virus to be the female phlebotomine sandfly. CHPV displays genetic diversity, forming distinct clades in India and West Africa, with the potential for future human spillover due to codon usage adaptation [5,8,9].

Phylogenetically distinct from its prototype Vesiculovirus, vesicular stomatitis virus (VSV), but closely related to Isfahan virus (ISFV). CHPV does not induce distinct stress granules (SGs) but causes condensation and recruitment of stress granule proteins into inclusion bodies (IBs). These IBs show different dynamics compared to SGs and are involved in viral replication [5]. SGs are formed during cellular stress and act as a s defense mechanism by storing mRNA and arresting translation to conserve energy. CHPV infection recruits SG proteins like TIA-1 and PKR into Ibs by bypassing the conventional SG formation and promoting viral replication. PKR and TIA-1 are the identified pro-viral factors in CHPV infection and virus replication[5,10–12]. CHPV forms replication factories or inclusion bodies in the host cell cytoplasm which are crucial for its replication and understanding the formation and function of these inclusion bodies could be key in developing precise antiviral therapeutics against CHPV [5,13].

**Epidemiology**

CHPV was discovered during a dengue/chikungunya outbreak investigation in Nagpur district, Maharashtra, India, in 1965. The virus was first isolated from Phlebotomine sandflies in Aurangabad district, Maharashtra, between 1967 and 1969 [14]. There were no significant human cases reported initially for two decades after its discovery. Later was linked to the death of an 11-year-old child in the state of Chattisgarh in India due to CHPV-induced encephalopathy. In the early 2000s, CHPV caused explosive outbreaks in Maharashtra and Andhra Pradesh, killing over 300 children with a case fatality rate (CFR) exceeding 50%. A similar outbreak in the State of Gujarat. Reported a CFR exceeding 75% [8,15]. Despite no major outbreaks since 2004, sporadic cases have been reported in the Warangal district of Andhra Pradesh (now Telangana) and Vidarbha region of Maharashtra [14,16,17]. Certain seroprevalence studies conducted on samples collected since 1955 revealed the presence of neutralizing antibodies to CHPV in both humans and animals. Seroprevalence is the percentage of people in a population who

have proteins called antibodies in their blood that show they have been exposed to a virus or other infectious agent.[18] The epicenter of CHPV activity has primarily been in Central India, including parts of Gujarat, Madhya Pradesh, Andhra Pradesh, and Maharashtra. Other regions like Bihar, Telangana, and Kerela also reported some cases. CHPV has been isolated from a hedgehog in Nigeria and sandflies in Senegal, indicating its presence in West Africa since 1975 [19–21]. Antibodies to CHPV have been detected in monkeys in Sri Lanka, suggesting the virus's broader geographic spread. The virus's activity is mostly concentrated in rural and semi-rural areas, where vector control and healthcare access may be limited. The presence of CHPV or related viruses in various regions of India and West Africa, along with evidence of antibodies in different species, suggests the potential for broader geographic spread and public health risk [8,14,22].

## Clinical Features and early manifestations

Clinical features of CHPV infection include high-grade fever, vomiting, altered sensorium, diarrhea, Neurological dysfunction, and meningeal irritation progression to coma, even leading to death within 48 hours of hospitalization [9,14,23]. While initially considered an orphan virus, CHPV has been associated with sporadic cases of fever, arthralgia, and Reye's syndrome as well as epidemic encephalitis [24]. Previous outbreaks have shown us a wide spectrum of clinical manifestations and some common ones as well which initially started from febrile illness and later evolved to give more fatal manifestations like encephalitis. In some cases during the Gujarat outbreak, vesicular eruptions were observed, which developed into hyperpigmentation upon healing. Some patients had palpable liver enlargement and elevated levels of liver enzymes, such as alanine aminotransferase and aspartate aminotransferase. In children infected with CHPV, higher levels of interleukin (IL)-2, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)α were detected compared to the control population. Other outbreaks showed similar presentations but with variable fatality rates. In some outbreaks, the fatality rate was found to be lower [14,23,25,26]. The above-mentioned clinical presentations and early manifestations of CHPV are illustrated in figure 1.

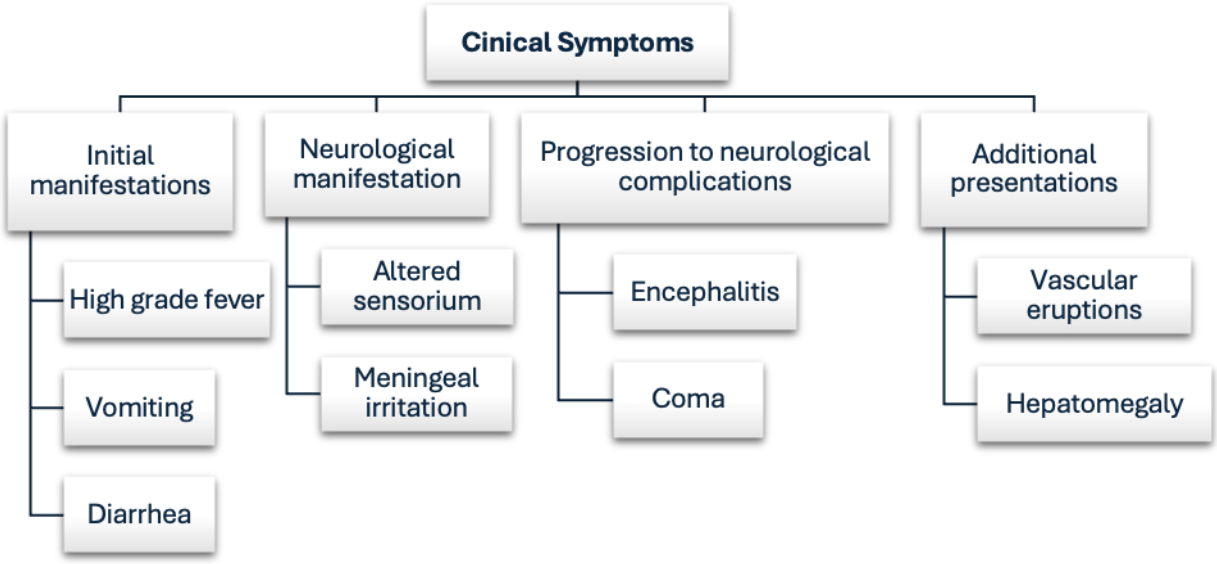


**Figure 1. Clinical presentations of CHPV**

**Disease pathogenesis and neuroinvasion**

CHPV's neuropathogenesis is well-documented, but its exact CNS entry route and triggers for neuronal death are unclear. CHPV can enter the central nervous system through various mechanisms including neuronal retrograde transport and by disrupting the blood-brain barrier [27,28]. CHPV infection triggers cellular stress and production of reactive oxygen species (ROS) and neuronal death. The innate immune response especially Toll-like receptor 4 (TLR4) is crucial in CHPV pathogenesis. The TLR4 activation results in the production of proinflammatory cytokines and nitric oxide, contributing to the disease progression [27,29].

Neuroinvasion is the ability of the virus to enter the central nervous system or peripheral nervous system [30]. Most probably, CHPV primarily invades the CNS through the hematogenous route. After being introduced into the bloodstream, CHPV infects immune cells such as monocytes, macrophages, dendritic cells, and Langerhans cells. These cells transport the virus to other target cells, including epithelial and endothelial cells. Increased permeability of the blood-brain barrier (BBB), a common feature in neurotropic viral infections, facilitates the virus's entry into the CNS. Once through the BBB, infected monocytes differentiate into macrophages and dendritic cells, which produce nitric oxide (NO) and tumor necrosis factor (TNF), contributing to neuroinflammation. CHPV may spread among neuronal populations through synaptic pathways. Despite its significance as a cause of pediatric viral encephalitis in India, the precise mechanism by which CHPV enters the CNS remains uncertain. It is proposed that high-titer viremia allows the virus to infect immune cells, evade host immune surveillance, and traverse the BBB [28,31–33].

**Diagnosis**

Due to the swift progression from initial symptoms to severe illness, serological methods are often inadequate for diagnosis. Instead, CHPV is detected in cerebrospinal fluid (CSF) and sera from patients during the acute phase using a one-step RT-PCR assay, which can identify virus levels as low as 10-100 plaque-forming units per milliliter. This real-time RT-PCR method demonstrates a reliable linear relationship across a broad range of viral RNA concentrations, with perfect specificity when tested against RNA from other viruses or healthy individuals [23].

For serological detection, traditional methods have faced challenges due to polyclonal antibodies interfering with specificity. To address this, CHPV-specific IgM capture ELISA has been enhanced by substituting polyclonal antibodies with monoclonal antibodies, improving the assay's sensitivity and specificity. Additionally, the plaque reduction neutralization test (PRNT), while considered the gold standard for detecting neutralizing antibodies, is labor-intensive and subjective. An alternative to PRNT is the recently developed micro-neutralization ELISA (MN ELISA), which provides quicker results and measures neutralizing antibodies through optical density readouts. This method offers a more efficient option for serological surveillance and vaccine research [19,34].

CHPV typically enters the central nervous system (CNS) via the hematogenous route, infecting immune cells such as monocytes, macrophages, and dendritic cells. These cells then transport the virus to other target cells, including epithelial and endothelial cells. Increased permeability of the blood-brain barrier (BBB) allows CHPV to cross into the CNS. Once there, infected monocytes differentiate into macrophages and dendritic cells, producing inflammatory mediators like nitric oxide (NO) and tumor necrosis factor (TNF), which contribute to neuroinflammation. The virus spreads among neurons through synaptic pathways after entering the CNS, resulting in severe neurological symptoms.

Despite the progress in diagnostic techniques, the precise mechanism of CHPV entry into the CNS remains unclear. High-titer viremia likely facilitates viral entry into the brain, where the virus can evade immune surveillance and replicate within immune cells, subsequently crossing the BBB and causing rapid onset of encephalitis. The combination of advanced molecular and serological diagnostic tools has significantly improved the detection and management of CHPV infections, providing better tools for early diagnosis and understanding of its pathogenesis [8,23,35,36].

**Current treatment strategies**

Currently, there's no specific treatment for Chandipura virus (CHPV), so management mainly revolves around symptomatic care. Medications like aspirin and NSAIDs, including ibuprofen and ketoprofen, are avoided due to their potential adverse effects. There's also no vaccine available for phlebotomus-borne viruses, and no specific antiviral agents are effective against CNS infections from these viruses [3,37]. Treatment focuses on managing complications such as seizures, hyponatremia, and elevated intracranial pressure. Research into antiviral therapies shows promise: Ribavirin has an in vitro IC50 of 89.84 μM against CHPV, while favipiravir has an EC50 of 92.26 μM in Vero cells and has demonstrated 100% survival in mice at a dosage of 300 mg/kg/day [23,38,39]. A SCID mouse model has supported favipiravir's effectiveness in improving survival and reducing viral loads, though more clinical trials are needed before it can be used in humans. Additionally, targeting specific cytokines like TNF might reduce disease severity, and early administration of mannitol can be life-saving by reducing brain swelling. RNA interference (RNAi) targeting the P and M genes of CHPV has shown promise, with P gene siRNA protecting mice from severe encephalitis. Preventative measures focus on controlling vector populations in high-risk areas and using personal protective strategies, such as insect repellents and treated bednets, to help manage and reduce the impact of CHPV infections [3,40,41].

**Prevention and public health strategies for outbreak control**

Since no treatment is available foe this disease to date, a strong and effective prevention plan has to be used. Prevention and other public health interventions like vaccinations and vector control are very crucial in curbing the spread of this virus and also preventing the complications of the disease.

Studies have shown two promising vaccines that have been developed to combat the Chandipura virus (CHPV). The recombinant vaccine, utilizing the G gene expressed in a baculovirus system, showed high immunogenicity in mice with 90% seroconversion and robust cell-mediated and humoral responses. Combined with a DPT vaccine, it yielded even higher antibody levels. Meanwhile, a killed virus vaccine using beta-propiolactone inactivation demonstrated 100% seroconversion and protection in mice. However, these vaccines are subjected to further studies and confirmation of their efficacy in disease prevention as well as their safety [14,42,43]. Many animal-based studies are being conducted to develop specific antiviral treatments for CHPV. These drugs aim to target P and M proteins due to their importance in the life cycle of the virus [23].

Control of phlebotomine sandflies, the vector responsible for transmission of CHPV is very important in terms of prevention. They are seen to transmit the virus by transovarial and venereal routes. Usage of insecticides could help bring down their population significantly. Control of the vector in endemic areas can be challenging. This is because this sandfly breeds in damp places like construction sites where they grow in crevices of stone used for construction where insecticide spraying is generally not possible. In rural setup, cow dung smearing on the floor and walls of the houses gives them a ground to grow and feed on [23,36,44].

## CONCLUSION

Chandipura virus (CHPV) presents a significant health challenge, especially in rural regions of India, where it causes severe outbreaks of encephalitis, predominantly affecting children. The rapid escalation from initial febrile symptoms to severe neurological complications underscores the urgency for early diagnosis and intervention. While specific antiviral treatments are still not available, advancements in diagnostic techniques, such as real-time PCR and enhanced serological assays, have improved early detection and surveillance capabilities. The development of promising vaccines and ongoing research into antiviral therapies offer hope for future prevention and treatment. CHPV's pathogenesis involves complex interactions with host cells, including the formation of inclusion bodies and the activation of apoptotic pathways leading to neuronal death. Its genetic diversity and the presence of distinct clades in India and West Africa highlight the need for continuous monitoring and research to address potential public health risks and prevent future outbreaks. Effective preventive measures are essential, including robust vector control programs, improved sanitation, and increased public awareness to manage and reduce the incidence of CHPV infections. Strengthening healthcare infrastructure and access in endemic areas is crucial for improving early detection, and patient management, and ultimately reducing the morbidity and mortality associated with CHPV. While CHPV poses a substantial health threat, ongoing research and public health strategies provide a pathway to enhance prevention, diagnosis, and treatment. A concerted effort towards improved surveillance, effective vaccination, and comprehensive vector control will be vital in combating this emerging viral threat and protecting public health.

### *Declaration by Authors*

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