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REVIEW ARTICLE

Human Metapneumovirus: Another respiratory virus of concern for Public Health

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ABSTRACT

Human Metapneumovirus (HMPV) was first identified in 2001 and is a significant respiratory pathogen affecting children under the age of five, the elderly, and immunocompromised individuals. An outbreak of HMPV was reported in Beijing, China, in December 2024, with subsequent cases identified in multiple countries, including India. Globally, HMPV accounts for 3-10% of respiratory infections, with severe cases such as bronchiolitis and pneumonia predominantly occurring in high-risk populations. Despite localized clusters in January 2025, Indian health authorities have not reported a significant surge in cases, indicating a need for further surveillance. RT-PCR remains the gold standard for detection, while treatment is mainly supportive, with emerging antiviral and monoclonal antibody therapies showing promise in research. Despite its low mortality rate, HMPV poses challenges for resource-limited settings. This review highlights the critical need for comprehensive epidemiological research, accelerated vaccine development, and increased public awareness to address HMPV's impact in India effectively.

Keywords: Human Metapneumovirus, Respiratory Virus , Outbreak

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INTRODUCTION

The recent outbreak of Human Metapneumovirus (HMPV) was first reported in Beijing, China, in December 2024. Following its identification, the virus has been detected in several countries, including India, South Korea, Japan, the United States, Canada, the United Kingdom, and Australia, indicating its potential for widespread transmission. Although there is currently no evidence to suggest an imminent pandemic, the global health community must remain vigilant. Understanding the virology, epidemiology, and clinical impact of HMPV is crucial for tracking its spread, managing infections effectively, and implementing preventive measures.

HMPV was first isolated in 2001 from the nasopharyngeal samples collected from Dutch newborns suffering from upper respiratory tract infections (URTI). Since then, it has emerged as a major respiratory pathogen that causes upper and lower respiratory tract infections, with a pronounced impact on children, elderly and immunocompromised populations (1). It is an enveloped, single-stranded ribonucleic acid (RNA) virus classified under the order *Mononegavirales*, family *Paramyxoviridae*, and subfamily *Pneumoviridae*. Measuring 150–200 nanometers with a genome size of approximately 13 kilobases, HMPV shares structural and functional similarities with the respiratory syncytial virus (RSV), a pathogen from the same family that causes similar clinical symptoms (2)

Globally, HMPV is estimated to cause 3–10% of respiratory infections, particularly in children, the elderly, and immunocompromised individuals. Its clinical symptoms range from mild respiratory illness to bronchiolitis and pneumonia. HMPV is reported as the second leading causative agent of hospitalization due to respiratory illness in young children under 5 years of age after RSV (3)In India, as of January 2025, since a month after the outbreak in China, several confirmed cases of HMPV have been documented, impacting both infants and the elderly. Despite its global significance, the epidemiology and clinical characteristics of HMPV in the Indian context remain underexplored. This review provides an

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overview of HMPV infections in India and its implications for clinical and public health management.

Pathophysiology

HMPV) has a negative-sense RNA genome encoding nine structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), matrix-2 protein (M2), short hydrophobic (SH) viroporin, glycoprotein (G), and RNA-dependent RNA polymerase (L), organized in a 3′-5′ orientation (Figure 1). The F and G proteins mediate viral attachment and fusion to facilitate entry into respiratory epithelial cells (4).The SH protein acts as a viroporin, regulating membrane permeability, and is also thought to modulate fusion protein function during infection (5).The G protein plays a critical role as a virulence factor, inhibiting immune responses by targeting Retinoic acid-inducible gene I (RIG-I), a key intracellular viral RNA sensor (6).while the SH protein is implicated in the inhibition of the NF-kB pathway. The M2 gene contains two overlapping open reading frames, M2-1 and M2-2, both expressed during infection. M2-2 acts as an IFN antagonist, blocking RIG-I–dependent signaling with the mitochondrial antiviral signaling (MAVS) protein to prevent the production of type I interferons and inflammatory cytokines (7) The M2-1 protein is a phosphorylated zinc-binding protein that plays a regulatory role in RNA synthesis (8)

HMPV replicates by synthesizing positive-sense mRNA, which is translated into viral proteins. These proteins bind the negative-sense RNA, forming a ribonucleoprotein (RNP) complex that replicates the negative-sense RNA into positive-sense RNA, generating many copies of the viral genome for new virions (9)HMPV infection primarily affects the lower respiratory tract, causing inflammation, sloughing, and necrosis of bronchiolar epithelium, resembling the pathogenesis of hRSV (4). Notably, HMPV RNA can persist within infected respiratory cells for extended periods after the initial infection (10). Studies have shown RNA persistence in lung cells for up to two months (11). However, it is important to distinguish between this prolonged RNA persistence and active viral shedding. The detection of viral RNA does not necessarily indicate ongoing viral replication or infectivity. In fact, the median duration of HMPV shedding, defined as the presence of infectious virus, is typically much shorter, around 5 days (IQR 3.5-10.0) in young children (12)

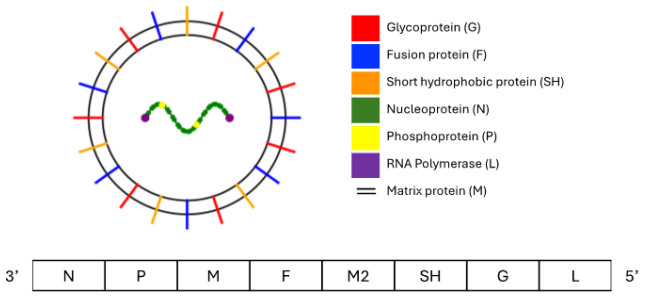

Figure 1: Schematic representation of hMPV viral proteins

Furthermore, studies have demonstrated that neither HMPV RNA nor infectious virus can be detected in extrapulmonary tissues such as serum, spleen, kidneys, heart, trachea, or brain (11). This suggests that HMPV infection remains localized to the respiratory tract. The virus spreads similarly to COVID-19, via respiratory droplets from coughing, sneezing, and contact with contaminated surfaces.

Clinical symptoms of HMPV infection include cold-like symptoms, fever lasting up to 10-days, nasal congestion, sore throat, cough, tachypnea, dyspnea, hypoxia, and breathing difficulties, especially in infants, the elderly, and immunocompromised individuals. Various studies in humans have documented sloughed epithelial cells, syncytia, diffused alveolar damages, cytoplasmic eosinophilic inclusions and development of hyaline membranes. Otitis media affects approximately 50% of newborns with HMPV infection, and the virus can cause severe complications in vulnerable populations, such as pneumonia, bronchiolitis, and acute respiratory distress, which may require hospitalization. The severity of infection correlates with high viral titers, and the virus suppresses the host immune response, leading to delayed viral clearance and a low development of neutralizing antibodies (13,14). Reoccurrence of infection in infants is frequent due inadequate production of antibody or infection by a new (14). In young adults, re-infection typically results in milder symptoms, however, elderly patients may experience severe symptoms, including pneumonitis. Moreover, HMPV infections are associated with asthma exacerbations in both children and adults and can worsen in patients with chronic obstructive pulmonary disease (COPD). There are also reports linking HMPV infection in children to central nervous system disorders, including febrile seizures and severe encephalitis (15)

Epidemiology

HMPV outbreaks are seasonal, and it has been isolated from each continent. The winters and early spring spanning from December to April are the most conducive for its outbreak (16). Serological investigations indicate that HMPV infection is universal by age of five and is responsible for significant respiratory diseases (13; 17). Pediatric studies report HMPV as the second most frequent cause of lower respiratory tract infection in children after HRSV. In 2018, among children younger than 5 years globally, there were an estimated 14·2 million HMPV-associated acute LRI cases (18)

Globally, about 20% of paediatric respiratory tract infections have been linked to HMPV. According to serologic studies, in between 90% to 100 % of children have been infected with HMPV by the time they are 5 to 10 years (14) The median age at which HMPV infection first appears is around 12 months. Interestingly, a study conducted in Switzerland highlighted an off-season resurgence of HMPV cases following the relaxation of COVID-19 restrictions, with an increase in the average age of patients. The 2021/2022 season recorded the highest case numbers in 11 years, accompanied by an unusual off-seasonal pattern. This was followed by another season of relatively higher case numbers in 2022/2023 (19) Limited viral

circulation during the early COVID-19 pandemic resulted in older ages at initial HMPV infection, leading to an increase in the average age of hospitalized children.((19) The current global increase in cases during the 2024/2025 season may be continuing this trend.

HMPV typically has a low mortality rate, with most individuals recovering within a few weeks. Severe cases are more common in vulnerable populations, but mortalities are significantly less frequent compared to other respiratory infections like Influenza and COVID-19 (20; 21). In small cohort studies involving immunocompromised adult patients with cancer or those undergoing transplantation, mortality rates associated with HMPV have ranged from 10% to 80% (21,22). Risk factors linked to higher mortality include steroid therapy, oxygen requirements exceeding 2 liters, mechanical ventilation, and the use of bone marrow as a cell source in transplantation cases (21). Additionally, bacterial coinfections were identified in approximately 73% of patients with HMPV, emphasizing the importance of thorough microbiological screening and consideration of antibiotic treatment (22).

In children, the presence of complex chronic conditions has been shown to significantly increase the risk of mortality from HMPV compared to children without such conditions (23). Globally, a study conducted in 2018 revealed that 58% of hospital admissions for HMPV were in infants under 12 months, while 64% of in-hospital deaths occurred in infants younger than 6 months. Alarmingly, 79% of these fatalities took place in low-income and lower-middle-income countries, highlighting significant disparities in outcomes (24)

Countries with limited resources, such as India, face heightened vulnerability to such diseases. Therefore, there is an urgent need for improved statistical research, preventive strategies, and epidemiological studies to better understand and address the burden of HMPV. Within the scope of this mini-review, the focus is on HMPV cases reported in India previously and during the 2024/2025 outbreak.

Cases in India

While Human Metapneumovirus (HMPV) has likely been present in India for several years, its detection has been historically limited by a lack of widespread testing and specific awareness. Cases are sporadic and could often be misdiagnosed as other respiratory infections. However, recent advancements in diagnostic capabilities and increased surveillance efforts have facilitated the identification of more cases. The Indian Council of Medical Research (ICMR) and the Integrated Disease Surveillance Programme (IDSP) are central to establishing a more robust surveillance system.

More recently, following the outbreak in China in December 2024, several confirmed cases of HMPV gained public attention in India in January 2025. India reported two confirmed cases in the southern city of Bengaluru: A 3-month-old female and an 8-month-old male, both hospitalized with bronchopneumonia, tested positive for HMPV (25). Following this, cases were noted in cities like Ahmedabad, Chennai, and Salem, indicating geographically diverse spread; these were primarily based on initial press releases and news reports (26,27,28)Times of India, 10 Jan 2025; Business Standard, 7 Jan 2025; Livemint, 15 Jan 2025) (Figure 2). A study conducted in Pondicherry highlighted a prevalence rate of approximately 2.5% for HMPV among children under five years old presenting with acute respiratory infections (ARIs), mirroring global prevalence data (29).

In response to these cases, the Indian government has intensified surveillance efforts. The Indian Council of Medical Research (ICMR) is closely monitoring HMPV circulation throughout the year. The health authorities in Karnataka, Gujarat and Delhi have advised the healthcare bodies for surveillance and testing of HMPV. While the situation is being closely watched, health authorities emphasize that there is no cause for alarm. As per the Press Information Bureau (PIB) report, India is well equipped and prepared to manage any potential rise in respiratory infections (30).

Research suggests that HMPV infections typically peak during winter and spring globally(31). In India, the rainy season may also contribute to increased prevalence due to favorable environmental conditions for viral transmission (32). Given our recent battle with COVID-19, similar preventive measures should be followed for HMPV, including proper hygiene and respiratory etiquette.

Diagnostic Methods

The detection and diagnosis of HMPV have significantly improved with advancements in molecular and immunological techniques. Currently, Nucleic Acid Amplification Tests

Figure 2: Cities that reported HMPV cases in the first 10 days of January 2025, following the outbreak in China. No previous international travel history suggests a local transmission.

(NAATs), particularly Reverse Transcription-Polymerase Chain Reaction (RT-PCR), serve as the gold standard for HMPV detection (33) RT-PCR offers high sensitivity and specificity, with real-time RT-PCR providing rapid results and the ability to quantify viral load. These molecular methods can often detect multiple respiratory pathogens simultaneously, enhancing their diagnostic utility. Sample collection typically involves upper respiratory tract specimens such as nasopharyngeal swabs, nasal washes, or aspirates.

Other traditional methods include viral culture, which might be used for viral strain characterization and antiviral susceptibility testing (34). Immunological methods such as Direct Immunofluorescence Assay (DFA) and Enzyme Immunoassay (EIA) offer rapid detection of viral antigens or antibodies but are generally less sensitive than molecular methods like RT-PCR.

Emerging technologies are expanding the diagnostic landscape for HMPV. Microarray-based assays allow for the simultaneous detection of multiple pathogens, proving useful in epidemiological studies. Mass spectrometry is emerging as a potential method for rapid virus identification and high-throughput screening.

While RT-PCR remains the preferred diagnostic method, the choice may depend on factors such as clinical presentation, available resources, and specific clinical or research requirements. In recent years, there has been a growing interest in Point-of-Care Testing (POCT) for respiratory tract infection (35). Rapid antigen tests are available for HMPV detection, offering quicker results compared to RT-PCR, although they are generally less sensitive. These tests can be particularly useful in settings where quick decision-making is crucial, such as emergency departments or outpatient clinics.

In resource-limited settings like rural India, the feasibility of low-cost diagnostics is a significant consideration. While molecular tests like RT-PCR offer high sensitivity and specificity, they may not be widely available in primary care settings due to cost and infrastructure requirements. In such scenarios, rapid antigen tests or other POCT methods could play a crucial role in HMPV diagnosis, despite their lower sensitivity compared to RT-PCR (35)

Recent advancements have led to the development of more accessible molecular testing methods. For instance, isothermal amplification techniques like Loop-mediated Isothermal Amplification (LAMP) offer a promising alternative for HMPV detection in resource-limited settings (36)"itemDat a":{"id":511,"type":"article-journal","abstract":"Background and Objectives: The coronavirus disease (COVID-19. These methods require less sophisticated equipment and can provide results in a shorter time compared to traditional RT-PCR.

Another innovative approach is the combination of Recombinase-aided Amplification (RAA) with CRISPR-Cas12a systems. This method has shown potential for rapid HMPV detection with high sensitivity, completing the test within 30 minutes (37). Such advancements could make molecular testing more feasible in primary care settings, even in resource-constrained areas.

Despite these developments, the availability of molecular tests in primary care settings remains limited in many parts of the world. Efforts are ongoing to develop and validate more affordable and user-friendly diagnostic tools for HMPV, which could significantly improve detection capabilities across various healthcare settings, including those in rural and underserved areas.

Treatment Options

To date, there is no antiviral therapy to treat HMPV infection. Symptoms are managed by supportive measures, including rest and hydration. Treatment mainly focuses on clearing the virus and reducing respiratory inflammation. Corticosteroids can be provided to ease the symptoms. In severe cases, mechanical ventilation and oxygen therapy are used to manage the symptoms.

However, emerging therapeutic approaches show promise. Broad-spectrum antiviral agent like Ribavirin along with intravenous immunoglobulin shows potential efficacy against HMPV infection (38,39). It's important to note that while ribavirin and IVIG have shown promise in some cases, their efficacy for HMPV treatment is not conclusively proven, and they are not officially approved for this indication (40)

Table 1: Ongoing research studies on various treatment options for HMPV

Treatment Option	*Mechanism of Action*	*Phase of Research*
Ribavirin	Broad-spectrum antiviral with immunomodulatory effects	In vitro and animal studies(45)
54G10	Broadly neutralizing human monoclonal antibody	In vivo (46)
RSV-199	Engages with HRSV and HMPV F proteins	Early development (47)
MAb 338	Monoclonal antibody targeting hMPV fusion protein	Animal models (48)
Human Fab DS7	Fully human monoclonal antibody fragment against severe HMPV infection	In vitro and in vivo (49)
MPV467	Monoclonal antibody against HMPV	In vivo (50)
Probenecid	Inhibits HMPV replication	In vitro and in vivo (51)
Fusion Inhibitors	Peptides targeting HMPV fusion protein domains	Preclinical (43)
RNA Interference (RNAi)	siRNA molecules targeting the HMPV replication complex	In vitro (42)
Other compounds: Sulfated sialyl (NMSO3) & Heparin	Antiviral activity	In vitro (45)

Since HMPV has phylogenetic similarity with HRSV, monoclonal antibodies used againt HRSV have been potential targets against HMPV as well. Some mAB have shown promising results in mouse, rat and hamster models (41). Table 1 provides a comprehensive summary of these ongoing studies, detailing the various treatment options, their mechanisms of action, and the current phase of research for each.

Beyond monoclonal antibodies, other innovative approaches like RNA interference (42) and fusion inhibitors (43) are being investigated. These emerging therapies represent a diverse range of approaches to combating HMPV infection. While many have shown promise in preclinical studies using mouse, rat, and hamster models, further research and clinical trials are necessary to establish their safety and efficacy in humans.

Currently, there is no vaccine available for HMPV, but research is ongoing to develop effective immunization strategies. Recent advancements, such as an AI-guided engineered vaccine based on a closed prefusion trimer of the HMPV fusion protein (44), have shown promise in preclinical studies, offering hope for future preventive measures.

Challenges in HMPV Management in India

Despite significant progress in understanding Human Metapneumovirus, several critical gaps in our knowledge and management still exist. HMPV is not widely recognized among healthcare providers in India. This lack of awareness can lead to underdiagnosis, as symptoms may be mistaken for other respiratory infections. Improving education and training for medical professionals is crucial to address this issue.

Moreover, epidemiological studies and surveys assessing the burden of the virus in India is lacking. Comprehensive data on its prevalence, seasonal trends, and regional variations are critical to understanding the virus's impact and guiding public health strategies. Current surveillance systems may require expansion to capture detailed information on HMPV-related hospitalizations, mortality, and high-risk groups.

Furthermore, research into the socio-economic and healthcare burdens caused by HMPV in low-resource settings, like rural India, is limited. Understanding these dynamics is vital for developing targeted interventions, including the formulation of public health policies and cost-effective diagnostic tools. Without addressing these gaps, the full extent of HMPV's impact on India's healthcare system remains underestimated.

The development of an effective vaccine against HMPV is a high priority for the scientific community. India's involvement in global vaccine development efforts, alongside its robust pharmaceutical industry, could accelerate access to HMPV vaccines once they are approved.

As India reports its first confirmed cases of HMPV, the existing gaps in knowledge and treatment options become increasingly evident, underscoring the importance of continued research and development in this field. The Indian government is taking steps to tackle these issues. Efforts are underway to enhance surveillance systems, increase testing capacity, and raise awareness among healthcare providers. These initiatives aim to improve HMPV management and preparedness across the country.

CONCLUSION

While HMPV presents challenges to India's public health system, the country's experience in managing respiratory infections positions it well to address this emerging concern. However, effectively combating HMPV requires a multifaceted approach that extends beyond national borders.

Continued investment in research, diagnostics, and public awareness will be crucial in mitigating HMPV's potential impact. India must prioritize the development of rapid, point-of-care testing solutions to enhance early detection capabilities, particularly in resource-limited settings(52). Strengthening surveillance systems and expanding diagnostic facilities, especially in rural areas, is essential for timely responses to outbreaks (53).

To advance our understanding of HMPV and develop effective interventions, there is an urgent need for interdisciplinary research. This should encompass virology, immunology, epidemiology, and clinical medicine to address critical knowledge gaps (54)"itemData":{"id":495,"type":"article-journal","abstract":"Human Metapneumovirus (hMPV. Priority areas include vaccine development, with a focus on live attenuated and subunit vaccines, as well as novel antiviral therapies and immunomodulatory approaches.

Public-private partnerships (PPPs) have proven successful in addressing other health challenges in India, such as malaria control(55). Similar models could be adapted for HMPV management, leveraging the expertise and resources of both sectors to enhance surveillance, improve diagnostics, and develop innovative treatment strategies.

Global cooperation is paramount in addressing HMPV effectively. The global burden study highlights that low- and middle-income countries (LMICs), including India, face significant challenges due to limited surveillance data on HMPV-associated hospitalizations among older adults (56) This underscores the need for enhanced research and resource allocation to better understand the virus's impact on vulnerable populations. Sharing data, exchanging research insights, and establishing international monitoring systems are crucial for preventing and controlling future outbreaks (53).

By adopting a systematic, collaborative, and global approach, India can not only effectively navigate the challenges posed by HMPV but also contribute significantly to the worldwide scientific understanding of this pathogen. This concerted effort will be essential in protecting public health both nationally and internationally, potentially preventing future epidemics and improving respiratory health outcomes globally.

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