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HUMAN METAPNEUMOVIRUS: EMERGING THREAT IN RESPIRATORY TRACT INFECTIONS

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Abstract

Human Metapneumovirus (HMPV), first identified in 2001, is now recognized as a major viral pathogen responsible for acute respiratory tract infections (ARTIs) globally, particularly affecting infants, the elderly, and immunocompromised individuals. Belonging to the Paramyxoviridae family, HMPV shares structural and clinical similarities with Respiratory Syncytial Virus (RSV), presenting with symptoms ranging from mild upper respiratory tract infections to severe bronchiolitis and pneumonia. Despite its significant clinical burden, no specific antiviral therapy or approved vaccine exists for HMPV, and management is largely supportive. The virus circulates seasonally, peaking in late winter and early spring, with co-infections further complicating diagnosis and treatment. Molecular diagnostics such as RT-PCR are the gold standard for HMPV detection, offering high sensitivity and specificity. Current research focuses on monoclonal antibodies and vaccine development using platforms like mRNA and recombinant protein technology. However, challenges such as immune evasion, genetic variability, underreporting, and limited surveillance systems hinder effective control. Preventive strategies—including infection control practices, early detection, and public health awareness—are crucial in managing outbreaks. Future directions include the development of novel therapeutics, integrated global surveillance, and large-scale vaccine trials. This review consolidates current knowledge on the epidemiology, virology, clinical manifestations, diagnostics, treatment, and prevention of HMPV, emphasizing its growing significance in global respiratory health.

Keywords: Human Metapneumovirus, respiratory infections, molecular diagnostics, vaccine development, monoclonal antibodies, antiviral research.

Introduction

Human Metapneumovirus (HMPV) is an enveloped, negative-sense, single-stranded RNA virus that belongs to the *Pneumovirinae* subfamily within the *Paramyxoviridae* family. Since its discovery in 2001 by Dutch scientists in children with respiratory infections, HMPV has been recognized as a significant pathogen responsible for a wide range of respiratory illnesses. Genetically and clinically, HMPV bears close resemblance to Respiratory Syncytial Virus (RSV), and together they represent major causes of bronchiolitis and pneumonia, particularly in young children and elderly individuals [1,2]. The virus primarily targets the respiratory epithelium, triggering both upper and lower respiratory tract infections. These infections range from mild cold-like symptoms to severe bronchiolitis and pneumonia requiring hospitalization. Importantly, HMPV can affect all age groups but poses the highest risk to infants, immunocompromised individuals, and the elderly [3,4]. Several studies have documented its association with hospital admissions, intensive care needs, and, in rare cases, mortality. Its global circulation and seasonal outbreaks, often peaking during late winter and spring, contribute to its increasing clinical relevance [5].

Although HMPV was officially identified only in 2001, retrospective serological studies have shown that the virus had been circulating globally for at least 50 years prior to its discovery. The first isolation occurred in the Netherlands when unidentified viral agents were found in respiratory samples from children [6]. Genetic analysis placed HMPV within the *Paramyxoviridae* family, closely aligned with avian metapneumovirus, suggesting zoonotic origins followed by adaptation to human hosts. HMPV is now categorized under the *Metapneumovirus* genus. Based on genetic variability, it is classified into two main genetic lineages (A and B), each further subdivided into sublineages (A1, A2, B1, and B2). These lineages show antigenic diversity but limited cross-neutralization, which may have implications for vaccine development and epidemiological tracking. Despite its relatively recent recognition, HMPV is now accepted as a globally endemic virus [7-9].

Human Metapneumovirus has emerged as a prominent viral pathogen in the etiology of acute respiratory tract infections (ARTIs), ranking among the top causes of hospitalization in pediatric populations. It accounts for 5–15% of all respiratory infections in children, with similar disease burdens reported in elderly and immunocompromised adults. The clinical spectrum of HMPV infection overlaps with other common respiratory viruses like influenza and RSV, often complicating diagnosis and management. The burden of disease is especially pronounced in low- and middle-income countries where surveillance is limited, and respiratory infections remain a leading cause of pediatric mortality. Despite its growing significance, no specific antiviral therapies or approved vaccines exist for HMPV, underscoring the urgent need for targeted interventions. [10,11] Its ability to co-circulate with other viruses and cause reinfections due to incomplete immunity further emphasizes its public health relevance. Understanding the molecular biology, transmission patterns, and immune responses to HMPV is vital for developing effective diagnostics, therapeutics, and vaccines to mitigate its impact on global health [12].

Virology and Pathogenesis

Human Metapneumovirus (HMPV) is a member of the *Paramyxoviridae* family, *Pneumovirinae* subfamily, and *Metapneumovirus* genus. It shares close phylogenetic and structural similarities with Respiratory Syncytial Virus (RSV), especially in terms of genome organization and infection profile. HMPV is a negative-sense, single-stranded RNA virus with a genome approximately 13 kilobases in length, encapsidated by the nucleoprotein (N) and enclosed in a lipid envelope [13].

Genetic Structure and Viral Proteins

The HMPV genome encodes eight genes that translate into nine proteins, arranged in the order: 3'-N–P–M–F–M2–SH–G–L-5'. These include [14]:

- **Nucleoprotein (N):** Encapsidates the viral RNA genome.
- **Phosphoprotein (P):** Functions as a cofactor for the viral polymerase.
- **Matrix protein (M):** Involved in virus assembly and budding.
- **Fusion protein (F):** Facilitates viral entry by mediating membrane fusion.
- **M2 gene:** Produces two proteins (M2-1 and M2-2) involved in transcription regulation.
- **Small hydrophobic protein (SH):** Its role is not fully understood but may aid in immune evasion.
- **Glycoprotein (G):** Involved in virus attachment to host cells.
- **Large protein (L):** Encodes the RNA-dependent RNA polymerase.

Mechanism of Infection and Replication

HMPV initiates infection by attaching to the epithelial cells of the respiratory tract using the G protein. The F protein facilitates membrane fusion, allowing the viral RNA to enter the cytoplasm. The virus replicates entirely in the cytoplasm using its RNA-dependent RNA polymerase (L protein), producing both genomic and subgenomic RNAs. Viral assembly occurs at the plasma membrane, followed by budding and release of infectious virions [15].

Immune Evasion and Host Response

HMPV has evolved several strategies to evade host immunity. The SH, G, and M2 proteins interfere with interferon signaling and innate immune activation. The virus dampens the production of type I interferons, limiting early antiviral responses. Despite inducing robust inflammation, HMPV often leads to incomplete protective immunity, allowing reinfections to occur throughout life. The host immune response includes both innate components—like neutrophils and macrophages—and adaptive responses, particularly cytotoxic T-cells and neutralizing antibodies, though these are often short-lived [16].

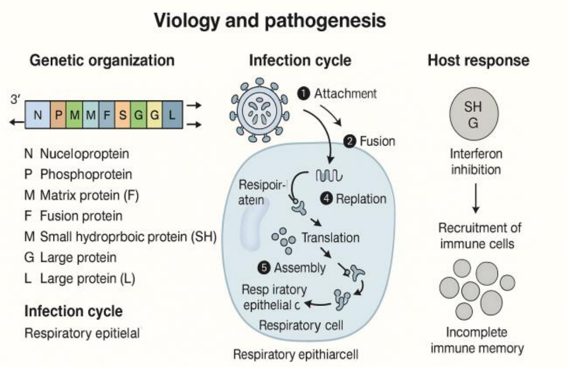

Fig.1: Virology and Pathogenesis of HMPV

Epidemiology

Human Metapneumovirus (HMPV) is globally recognized as a significant etiological agent of acute respiratory tract infections, especially in vulnerable populations such as infants, older adults, and immunocompromised individuals. Since its identification in 2001, epidemiological surveillance has confirmed its widespread distribution across all continents. HMPV exhibits clear seasonal trends, with peak incidences typically occurring during late winter and early spring, paralleling the circulation of other respiratory viruses such as respiratory syncytial virus (RSV) and influenza. Studies suggest that nearly all children are exposed to HMPV by the age of five, with reinfections commonly observed in later life due to waning immunity. The virus is frequently associated with co-infections, particularly with RSV, influenza viruses, adenoviruses, and human rhinoviruses, which can exacerbate disease severity and complicate diagnosis. Hospital-based reports have highlighted that HMPV contributes significantly to pediatric hospitalizations due to bronchiolitis and pneumonia, while also posing a substantial burden on the elderly and individuals with underlying chronic illnesses. These findings underscore the necessity of improved surveillance systems, molecular diagnostics, and targeted preventive strategies, especially during seasonal peaks and in high-risk groups [17]

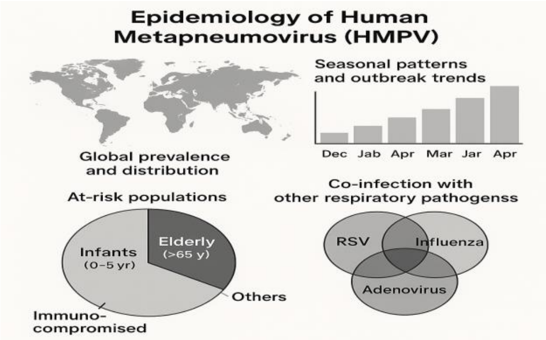

Fig.2: Epidemiology of Human Metapneumovirus

Clinical Manifestations

Human Metapneumovirus (HMPV) causes a spectrum of respiratory symptoms ranging from mild upper respiratory tract infections (URTI) to severe lower respiratory tract infections (LRTI), including bronchiolitis and pneumonia. Common symptoms include cough, nasal congestion, rhinorrhea, fever, and wheezing. HMPV closely resembles Respiratory Syncytial Virus (RSV) in clinical presentation but can be distinguished by subtle epidemiological and immunological differences. Severity varies with age and underlying health status; young children, older adults, and immunocompromised individuals are at higher risk for severe outcomes. Complications may include acute respiratory distress, secondary bacterial infections, and, in rare cases, hospitalization or mortality. Understanding these manifestations is essential for timely diagnosis and management [18,19].

Diagnostic Methods

Timely and accurate diagnosis of HMPV is crucial due to its overlapping symptoms with other respiratory pathogens. Molecular diagnostic tools like reverse transcription polymerase chain reaction (RT-PCR) and quantitative PCR (qPCR) are the gold standards due to their high sensitivity and specificity. Serological tests help in retrospective or epidemiological studies by detecting HMPV-specific antibodies. Rapid antigen detection kits provide point-of-care options but have limited sensitivity. Differential diagnosis with RSV, influenza, adenovirus, and parainfluenza is essential to avoid misdiagnosis and guide appropriate management strategies [20-22].

Table 1: Comparison of Clinical Features – HMPV vs RSV

Feature	HMPV	RSV
Common Symptoms	Cough, fever, rhinorrhea	Cough, wheezing, nasal flaring
Peak Incidence	Late winter to early spring	Late fall to early spring
Age Groups Affected	Infants, elderly, immunocompromised	Primarily infants <2 years
Severity	Moderate to severe in high-risk groups	Often severe in infants
Associated Complications	Bronchiolitis, pneumonia	Bronchiolitis, apnea

Table 2: Diagnostic Tools for HMPV

Method	Principle	Advantages	Limitations
RT-PCR/qPCR	Detects viral RNA	High sensitivity/specificity	Requires lab setup
Serology (ELISA, IFA)	Detects antibodies	Useful in surveillance studies	Delayed response (post-infection)
Rapid Antigen Tests	Detects viral proteins	Point-of-care use	Lower sensitivity
Viral Culture	Virus isolation in cell lines	Confirmatory method	Time-consuming

Current Treatment Strategies

Despite its clinical significance, there is currently no approved antiviral therapy specifically targeting Human Metapneumovirus (HMPV). Consequently, treatment remains primarily supportive and symptomatic. Most cases, especially those involving immunocompetent adults and older children, are self-limiting and managed in outpatient settings. Supportive care typically includes hydration, antipyretics, and decongestants to alleviate symptoms such as fever, cough, and nasal congestion.[23,24]

In severe cases, particularly among infants, elderly individuals, or immunocompromised patients, hospitalization may be required. Oxygen therapy is the cornerstone of inpatient management for patients experiencing hypoxia or respiratory distress. In rare cases, mechanical ventilation may be necessary for individuals with acute respiratory failure due to bronchiolitis or pneumonia caused by HMPV.The lack of virus-specific treatments remains a major clinical challenge. Although ribavirin-a broad-spectrum antiviral-has shown some efficacy against HMPV in *in vitro* and animal studies, its use in humans is limited due to toxicity concerns and lack of strong clinical evidence. Immunoglobulin therapy has been explored in immunocompromised hosts with mixed results [25, 26].

Recent research has focused on the development of monoclonal antibodies (mAbs) and fusion inhibitors that target viral surface proteins such as the F (fusion) protein. Notably, mAb-based therapies similar to Palivizumab (used for RSV) are under investigation, offering promise for high-risk groups. Additionally, small interfering RNAs (siRNAs) and host-directed therapies are being explored in preclinical models. The advancement of these antiviral candidates requires extensive clinical trials to validate safety and efficacy. Until then, early diagnosis and risk stratification remain essential to guide effective supportive interventions and reduce morbidity and mortality associated with HMPV infections [27].

Preventive Approaches

Given the absence of approved antiviral therapies and vaccines for Human Metapneumovirus (HMPV), preventive strategies remain pivotal in controlling its spread. Infection control measures are the frontline approach and include rigorous hand hygiene, respiratory etiquette, isolation of symptomatic individuals, and environmental disinfection-especially in healthcare and long-term care settings where vulnerable populations reside. The development of a preventive vaccine is an area of active investigation. Several platforms-including live-attenuated vaccines, recombinant subunit vaccines, virus-like particles (VLPs), and mRNA-based approaches-are under preclinical or early-phase clinical evaluation. However, vaccine development is complicated by the need for broad immunogenicity, safety across age groups (especially infants), and the genetic diversity of HMPV strains [28].

Monoclonal antibodies (mAbs) targeting the HMPV F (fusion) protein are also progressing through preclinical and early clinical stages. These biologics, modeled after successful agents like Palivizumab for RSV, offer a promising prophylactic option for high-risk infants and immunocompromised patients. However, their high production cost and delivery challenges limit widespread application at present. Public health recommendations emphasize early diagnosis, improved surveillance, and education of caregivers and healthcare workers to recognize and isolate cases, thereby minimizing outbreaks-particularly in neonatal ICUs, pediatric wards, and nursing homes [29,30].

Challenges and Knowledge Gaps

Despite growing awareness, significant challenges and knowledge gaps hinder comprehensive management of HMPV. Early detection remains difficult due to the nonspecific clinical presentation and symptom overlap with RSV, influenza, and other respiratory pathogens. Many cases go unrecognized or are misclassified, leading to underreporting and gaps in epidemiological data. Another major challenge is the limited global surveillance infrastructure, especially in low- and middle-income countries. This impairs the understanding of HMPV's burden and transmission dynamics. Additionally, the virus exhibits genetic variability, including mutations in surface glycoproteins, which may affect host immune recognition and complicate vaccine development [31, 32].

There is also a lack of longitudinal studies to assess the long-term impact of HMPV on respiratory health, particularly in children with recurrent infections. Moreover, there are no validated animal models that completely mimic human HMPV pathogenesis, limiting preclinical testing of therapeutics and vaccines [33,34].

Future Directions

Future strategies should focus on the development of effective vaccines using novel platforms such as mRNA technology and recombinant protein expression, which have shown success in COVID-19 vaccine development. These platforms may enable rapid design and production of strain-specific or broadly protective vaccines.

Simultaneously, the identification of novel therapeutic targets within the viral replication machinery or host interaction pathways could pave the way for small-molecule antiviral development. Integration of omics technologies (genomics, proteomics, and transcriptomics) will be crucial to map host-pathogen interactions and discover biomarkers for early diagnosis and prognosis.

An integrated global surveillance network is also needed to track seasonal patterns, strain variations, and outbreak potential of HMPV. International collaboration can support real-time data sharing and outbreak preparedness. Finally, public health strategies should include educational campaigns, routine diagnostics, and healthcare worker training to minimize transmission and improve clinical outcomes, especially in high-risk populations.

Conclusion

Human Metapneumovirus (HMPV) is a globally circulating respiratory virus with significant clinical implications for vulnerable populations such as infants, the elderly, and immunocompromised individuals. Despite its similarity to RSV in clinical presentation, HMPV often remains underdiagnosed due to nonspecific symptoms and inadequate surveillance infrastructure, particularly in developing nations. Current treatment remains supportive, as there are no targeted antiviral therapies or licensed vaccines available. However, advances in molecular diagnostics have improved the accuracy and speed of detection. Ongoing efforts in vaccine development—especially using mRNA and recombinant protein platforms—and the emergence of monoclonal antibody therapies offer hope for future preventive strategies. Nonetheless, challenges such as viral genetic variability, limited longitudinal data, and a lack of effective animal models hinder progress. Strengthening global surveillance systems, fostering research collaborations, and promoting public awareness are crucial for minimizing the impact of HMPV infections. With a comprehensive and proactive approach, it is possible to reduce morbidity and mortality linked to this emerging viral pathogen.

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Conflict of Interest

Authors are declared that no conflict of interest.

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Author Contributions

Kaseena Naga Visalakshi , Himasri Puppala and Chelsy Grace Rajanala ,contributed to data collection, literature review, and writing of the manuscript. A. Suneetha assisted in content structuring and critical revisions. Patibandla Jahnavi conceptualized, supervised, and approved the final manuscript.

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