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Review Article

Exploring Pathogenesis, Clinical Manifestations, and Management of Human Metapneumovirus Infection

Gaurao Damre[1,*], Snehal Sathe[1], Dhanashree Shinde[1], Vaibhav V Bhone[1], Pooja R Patil[2]

[1]Department of Pharmacy Practice, Pravara Rural College of Pharmacy, Pravaranagar, Maharashtra, INDIA.
[2]Department of Pharmacology, Pravara Rural College of Pharmacy, Pravaranagar, Maharashtra, INDIA.

ABSTRACT

Human Metapneumovirus (HMPV), identified in 2001, is an emerging respiratory virus. Within the Pneumoviridae family, genus Metapneumovirus. This RNA virus is now recognised as a substantial cause of both upper along lower Respiratory Tract Infections (RTIs), affecting individuals belonging to all ages. While this virus may impact healthy adults, the most vulnerable populations include young children, infants, elderly adults, as well as immunocompromised individuals. Pathophysiology of HMPV involves its entry into respiratory epithelial cells, facilitated by viral Fusion (F), attachment (G) proteins. After entering the host cell, HMPV replicates in the cytoplasm, leading to the production of new virions that further propagate the infection. Both innate along adaptive components are essential to the complicated immune response to HMPV. Innate immunity, including pattern recognition receptors and natural killer cells, provides the first line of defence, while the adaptive immune response, consisting of T cells, antibodies, and B cells, is responsible for clearing the virus and offering long-term immunity. However, in severe cases, immune responses may contribute to lung injury, airway remodelling, and fibrosis, especially in individuals with pre-existing conditions or those experiencing prolonged infections. Clinically, HMPV infection varies from mild symptoms like cough, fever, as well as sore throat to more severe manifestations, for example, pneumonia, bronchiolitis, and respiratory failure. Supportive care, which includes hydration, is the main emphasis of management and rest, though antiviral treatments, for example, intravenous immunoglobulin, ribavirin, along with monoclonal antibodies, may be considered in severe cases.

Keywords: Fusion Protein (Human Metapneumovirus) HMPV, Immunoglobulins, RNA Interference, Respiratory syncytial virus, Ribavirin.

Correspondence:
Dr. Gaurao Damre
Department of Pharmacy Practice,
Pravara Rural College of Pharmacy,
Pravaranagar, Maharashtra, INDIA.
Email: gauraodamre@gmail.com

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INTRODUCTION

HMPV initially distinguished itself from other common respiratory viruses when it was discovered in respiratory secretions of twenty-eight young children in the Netherlands in the year 2001 by Bernadette G. van den Hoogen and associates (Kahn, 2003; Schuster and Williams, 2014). Since then, HMPV has emerged as a major contributor to the upper and lower RITs in people of all ages. Specifically, infants account for 5-7% of HMPV infections.

Transmission of HMPV occurs similarly to other common cold viruses, mainly through infectious respiratory particles spread through the air from an infected person to others. This can happen when someone is near a sick individual or shares a confined space with them. Additionally, the virus can enter the body through coming into touch with contaminated surfaces, like doorknobs, then by touching eyes, nose, or mouth (Schildgen *et al.*, 2011). HMPV is an RNA virus, closely connected to avian pneumovirus, and is classified within the family Pneumoviridae and genus Metapneumovirus. A negative-stranded, enveloped, non-segmented virus is this (Amarasinghe *et al.*, 2018; Pan *et al.*, 2020).

Its almost 13 kb genome has eight genes that code for 9 distinct proteins, that is, Matrix protein (M), Fusion protein (F), Large polymerase protein (L), Phosphoprotein (P), Glycoprotein (G), Nucleoprotein (N), Small Hydrophobic (SH) protein, along with matrix-2 proteins (M2-1 and M2-2) (Ye *et al.*, 2023; Pan *et al.*, 2020). HMPV strains are categorised into 4 genotypes (A1, A2, B1, and B2) and 6 lineages (A1, A2a, A2b, A2c, B1, and B2) as per the genetic characteristics of F and G genes (Decool *et al.*, 2021; Yi *et al.*, 2019). ARTIs (Acute respiratory tract infections), for example, those resulting from HMPV, are responsible for significant morbidity and mortality worldwide (Pan *et al.*, 2020).

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METHODOLOGY

A comprehensive literature search was conducted to identify relevant studies on Human Metapneumovirus (HMPV). Databases including PubMed, Web of Science and Google Scholar were searched for articles. Search terms used alone or in combination included Human metapneumovirus, HMPV, Respiratory tract infections, pathogenesis, epidemiology, diagnosis, treatment and vaccine development.

Inclusion and Exclusion criteria

Studies were included if they:

- Addressed epidemiology, pathogenesis, immune response, clinical features, and diagnosis, management, or prevention of HMPV.
- Included original research articles, systematic reviews, narrative reviews and clinical studies.
- Were published in English.

Studies were excluded if they:

- Were conference abstracts, editorials, or letters without primary data.
- Study Selection and Data Extraction

Titles and abstracts of retrieved articles were screened for relevance. Full-text articles were reviewed when necessary. Key information was extracted, including study design, population characteristics, virological findings, clinical manifestations, diagnostic methods, treatment approaches, and outcomes. Data were qualitatively synthesised to provide an integrated overview of current knowledge.

Epidemiology

HMPV spreads globally, especially causing infections during the winter. According to various studies, the peak incidence of HMPV infections takes place in the winter season, with increased frequency of hospitalisations during these periods (Hoogen *et al.*, 2001a, 2001b). HMPV affects both children and adults, but it is particularly common in young children under 5years old. Studies have documented that up to 15-20% of children with respiratory illnesses are infected with hMPV (Takeuchi and Lin, 2002). HMPV has worldwide incidence. It has been reported in several continents, including Asia, North America, Europe, along Australia. This virus is commonly detected in both developing as well as developed nations (Burrows *et al.*, 2002; Nissen *et al.*, 2002). In a few geographical regions, A considerable percentage of Lower Respiratory Tract Infections (LRTIs) in children admitted to hospitals are caused by HMPV (Jartti *et al.*, 2002). The most severe outcomes of HMPV infection occur in young children, elderly adults, and those with serious health issues, particularly immunocompromised individuals (Boivin *et al.*, 2003; Hamelin *et al.*, 2006; Wyde *et al.*, 2003).

Pathophysiology

HMPV is a negative-sense, single-stranded RNA virus that is closely connected with RSV and a member of the *Paramyxoviridae* family (Hoogen *et al.*, 2001b). In all age groups, but especially in infants, elderly individuals, along with immunocompromised patients, it is a leading cause of RTIs (Boivin *et al.*, 2007a). HMPV infection causes a spectrum of respiratory illnesses, varying from mild URTIs (upper respiratory tract infections) to severe LRTIs, including bronchiolitis and pneumonia (Kahn, 2003). The pathophysiology of HMPV infection involves viral replication in the respiratory epithelium, immune system activation, and inflammation, leading to airway obstruction and lung injury.

Viral Entry and Replication

The respiratory tract's epithelial cells are primarily infected by HMPV. The entry is facilitated by two types of glycoproteins. F (Fusion) proteins facilitate the membrane of the virus to fuse with that of the host cell (Verma *et al.*, 2025). G (Attachment) proteins execute the role of viral attachment, but are not essential for infection (Cox *et al.*, 2012). The virus binds to heparan sulfate proteoglycans and uses host receptors such as integrins to enter the cell (Akhras *et al.*, 2010). Upon entry, HMPV proliferates in the cytoplasm with the help of RNA-dependent RNA polymerase (Cox *et al.*, 2012). This leads to the development of new virions that infect other neighbouring cells.

Response of immunity to HMPV infection

First-line immune defence means activation of innate immunity. TLRs (Toll-like receptors), predominantly TLR3 and TLR7, identify viral RNA as well as start the immune response (Del Valle-Mendoza *et al.*, 2019). RIG-I and MDA5 are sensors that identify RNA of viruses and activate Interferon Regulatory Factors (IRFs), then production of interferon I and III (Del Valle-Mendoza *et al.*, 2019). HMPV infection triggers the release of proinflammatory cytokines (IL-1β, TNF-α, IL-6) along with Chemokines (CCL5, CCL2), leading to immune cells to the infection site (Guerrero-Plata *et al.*, 2005). Natural Killer (NK) Cells play a role in recognizing infected cells and inducing apoptosis (Derdowski *et al.*, 2008).

Adaptive Immune Response

This response is crucial for long-term immunity, involving CD4+ T cells help in B-cell activation along with cytokine production (Biacchesi *et al.*, 2004). CD8+ T cells, utilising perforin and granzyme pathways it directly attacks the infected cells, contribute to viral clearance, but also lung inflammation (Williams *et al.*, 2004). Neutralising antibodies (IgG and IgA) help prevent reinfection but are often short-lived, leading to recurrence of infection (Piñana *et al.*, 2024).

Inflammatory Response and Lung Injury

HMPV infection generates an inflammatory response, which can contribute to the pathology of lung infection**.** Infiltration of macrophage and neutrophil cells leads to tissue damage and increased mucus production, contributing to the obstruction of airways (Piñana *et al.*, 2024). Reactive oxygen species, responsible for oxidative stress (Cheemarla and Guerrero-Plata, 2015). Viral replication leads to cell death, disrupting the epithelial barrier and predisposing the lungs to secondary bacterial infections (Brynes *et al.*, 2024). In chronic and severe cases, inflammation can lead to fibrosis, impairing lung function (Scott *et al.*, 2024).

The severity of HMPV infection varies and depends on several host factors, immune factors, age, as well as comorbid conditions, which include COPD (Chronic Obstructive Pulmonary Disease) or asthma. HMPV infection is also connected with exacerbations of asthma along with COPD, likely due to excessive immune activation and airway remodelling (Scott *et al.*, 2024).

Clinical Features

All age groups are susceptible to HMPV infections, although young children, the elderly, and those with immunocompromised conditions are most susceptible (Hoogen *et al.*, 2001a). Mild URTIs to serious LRTIs that include pneumonia along with bronchiolitis are among the clinical manifestations (Manoha *et al.*, 2007). Some common symptoms are fever, sore throat, and runny nose (Kneyber *et al.*, 1996; Sarasini *et al.*, 2006). In chronic patients, infection may lead to breathlessness, respiratory distress (Williams *et al.*, 2004). Other symptoms include fatigue, aches and diarrhoea (Kotaniemi-Syrjänen *et al.*, 2003). Severe cases require early hospitalisation.

Diagnosis

RT-PCR (Reverse transcription polymerase chain reaction) is a Gold standard test that detects HMPV RNA with high sensitivity and specificity rapidly and is widely used in clinical settings. Viral Culture involves isolating hMPV in LLC-MK2 or Vero cells, but it is slow and less sensitive (Boivin *et al.*, 2007b). Serology (ELISA - Enzyme-Linked Immunosorbent Assay) detects IgM or IgG antibodies against hMPV, useful for epidemiological studies (Boivin *et al.*, 2007b; Ebihara *et al.*, 2003).

Management

Goals of Management

The management goals for Human Metapneumovirus (HMPV) infections focus on symptom relief, supportive care, and preventing complications (Boivin *et al.*, 2007b). Treatment includes antipyretics, hydration, and humidified air to ease symptoms (Nair *et al.*, 2013). Oxygen therapy, along with mechanical ventilation, might be needed in severe cases. Preventing complications like bacterial superinfection and respiratory distress is crucial, especially in high-risk groups. Infection control measures, for example, hand hygiene, isolation, help reduce transmission (Nascimento-Carvalho, 2020).

Nonpharmacologic Management

Ensuring adequate fluid intake is essential to prevent dehydration and help loosen mucus, which can improve breathing and promote recovery (Chiotos *et al.*, 2020). Adequate sleep and rest are necessary for immune function. During illness, more energy is required by the body to fight against infection, and rest helps in immune recovery (Xia *et al.*, 2020). Using a humidifier or cool mist vaporiser can help soothe irritated airways and relieve nasal congestion and cough. Moist air helps keep the respiratory tract moist and may reduce coughing (Byber *et al.*, 2021). Elevating the head while sleeping can help reduce the discomfort of nasal congestion and coughing. For patients with breathing difficulties, elevating the head of the bed may facilitate easier breathing and improve sleep quality (Bhandari *et al.*, 2022). Patients with viral infection should avoid exposure to smoke, dust, and other environmental irritants that may lead to exacerbation of symptoms (Laghari *et al.*, 2023). Saline drops can help alleviate nasal congestion and clear mucus from the nasal passages, improving airflow and comfort during HMPV infections (Wang *et al.*, 2009).

Pharmacologic Treatment for HMPV

Ribavirin

A nucleoside is a Ribavirin analogue that inhibits the synthesis of viral RNA (Kitanovski *et al.*, 2013; Wyde *et al.*, 2003). It has been used to treat viral infections, for example, HMPV, along with RSV, by interfering with the replication of these viruses (Gross and Bryson, 2015). Inhaled Ribavirin is given for severe respiratory infections in hospital settings (Avery *et al.*, 2020).

Intravenous Immunoglobulin (IVIG)

IVIG is a preparation of pooled human plasma that contains a broad spectrum of antibodies, which may help neutralise viral infections (Brunetti *et al.*, 2009). It is particularly useful in immunocompromised patients, especially beneficial in the pediatric population or those unable to mount an adequate immune response (Scheuerman *et al.*, 2016).

Monoclonal Antibodies

It has been demonstrated that monoclonal antibodies that target the HMPV fusion protein efficiently neutralise the virus and prevent it from entering host cells (Williams *et al.*, 2007).

Prophylactic (Preventive): May be considered for high-risk populations, such as those suffering from underlying respiratory conditions or weakened immune systems, to prevent infection. Research has identified monoclonal antibodies that neutralise HMPV and other paramyxoviruses (Shafagati and Williams, 2018; Williams *et al.*, 2007).

Fusion Inhibitors

Fusion inhibitors block the viral fusion protein, preventing the virus from merging with host cell membrane and entering the cell (Contreras *et al.*, 2021). Used to block viral replication as well as prevent the virus from spreading within the respiratory system. A highly effective fusion inhibitor has been identified in research studies, showing strong antiviral effects against HMPV (Deffrasnes *et al.*, 2008).

RNA Interference

DsiRNA (Dicer-substrate siRNA) or siRNA (Small interfering RNA) target the viral mRNA and inhibits the translation of proteins, such as the nucleocapsid protein, thus preventing viral replication (Darniot *et al.*, 2012). Currently, siRNA is being investigated in clinical and preclinical studies for its potential to treat hMPV by blocking key stages of the viral life cycle (Nitschinsk *et al.*, 2018; Preston *et al.*, 2012).

New small molecule inhibitors targeting the fusion mechanism and replication are preclinical investigation. This molecule blocks the viral membrane fusion and RNA synthesis.

Subunit Vaccine

Several subunit vaccines are designed for HMPV viral infection. To modulate immunity and address safety concerns, some formulations are available, including purified protein fragments, virus-like particles, and lipid nanoparticles. IVX-A12is a bivalent subunit vaccine with HMPV and RSV preF-trimers formulated with two virus-like particles (Tariq *et al.*, 2022).

CONCLUSION

A substantial and underrecognized respiratory pathogen is HMPV that predominantly affects infants, the elderly, along immunocompromised individuals. With its seasonal variations and ability to cause both URTIs and LRTIs, which include pneumonia, bronchiolitis, along with exacerbation of asthma, HMPV contributes substantially to global respiratory disease burden. Despite its widespread prevalence, many aspects of its pathogenesis, immune response, and long-term health consequences remain incompletely understood, necessitating further research to develop effective therapeutic and preventive strategies. The virus's ability to infect the respiratory epithelium and provoke a strong immune response leads to inflammation, airway obstruction, and, in severe cases, long-term pulmonary complications, particularly in high-risk populations. Given its ability to cause a spectrum of disease severity, timely diagnosis and appropriate clinical management are critical in reducing morbidity and mortality.

Currently, supportive care provides the fundamental aspect of treatment, with oxygen therapy, hydration, and respiratory support playing vital roles in managing severe cases. Although antiviral agents such as ribavirin, monoclonal antibodies, and fusion inhibitors, subunit vaccines, show promise, their clinical efficacy and widespread availability remain limited. The absence of a targeted antiviral therapy or approved vaccine underscores the urgent need for further advancements in HMPV research. Understanding the molecular mechanisms governing viral entry, replication, immune evasion, and host-pathogen interactions is essential for developing novel therapeutic approaches and vaccines.

FUTURE DIRECTIONS

Research should be centralised on the molecular structure and mechanism of HMPV entry, replication mechanism, immune evasion, and host immune response activations to facilitate the development of targeted antiviral therapies. Vaccine development remains a critical priority, with various strategies being explored, including live-attenuated, protein-based, and vector-based vaccines. These approaches aim to elicit a robust and durable immune response, particularly in high-risk populations. However, challenges such as ensuring vaccine safety, optimising immunogenicity, and addressing potential cross-protection with related respiratory viruses must be carefully considered. Given the increasing incidence of HMPV infections and their contribution to respiratory-related hospitalisations, continued epidemiological surveillance is essential to track viral evolution, transmission dynamics, and emerging variants.

As the global impact of HMPV continues to grow, a comprehensive approach involving improved diagnostic tools, effective antiviral treatments, as well as the safe and efficacious vaccine development will be crucial in mitigating its health burden. Further interdisciplinary collaboration among researchers, clinicians, along public health experts will be essential in advancing our understanding of HMPV pathogenesis and enhancing prevention, along with treatment strategies. In conclusion, although considerable advancements have been achieved in acknowledging the clinical significance of HMPV, ongoing research endeavours are essential for creating focused therapies that will ultimately diminish the morbidity and death associated with this crucial respiratory infection.

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ABBREVIATIONS

HMPV: Human Metapneumovirus; **RTI:** Respiratory tract infections; **URTI:** Upper respiratory tract infections; **LRTI:** Lower respiratory tract infections; **ARTI:** Acute respiratory tract infections; **RSV:** Respiratory syncytial virus; **RNA:** Ribonucleic acid; **F Protein:** Fusion protein; **G Protein:** Attachment

glycoprotein; **M Protein:** Matrix protein; **L Protein:** Large polymerase protein; **P Protein:** Phosphoprotein; **N Protein:** Nucleoprotein; **SH Protein:** Small hydrophobic protein; **M2-1/M2-2:** Matrix 2 proteins; **TLRs:** Toll-like receptors; **RIG-I:** Retinoic acid-inducible gene I; **MDA5:** Melanoma differentiation-associated protein 5; **IRF:** Interferon regulatory factor; **NK cells:** Natural killer cells; **IL:** Interleukin; **TNF-α:** Tumor Necrosis Factor Alpha; **CCL:** C-C motif chemokine ligand; **IgG:** Immunoglobulin G; **IgA:** Immunoglobulin A; **IVIG:** Intravenous immunoglobulin; **RT-PCR:** Reverse transcription polymerase chain reaction; **ELISA:** Enzyme-linked immunosorbent assay; **COPD:** Chronic obstructive pulmonary disease; **siRNA:** Small interfering RNA; **DsiRNA:** Dicer-substrate small interfering RNA; **ROS:** Reactive oxygen species.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTIONS

Dr Gaurao S. Damre: Conceptualise the review and data strategy. **Ms Snehal Sathe:** Conducted literature review, Drafting of Manuscript. **Ms Dhanashree Shinde:** Drafting of Manuscript. Ms **Pooja R Patil:** Critical review of manuscript.

SUMMARY

Human metapneumovirus is an infection that causes respiratory tract infections globally, contributing to morbidity across all age groups, specifically among infants and in immunocompromised populations. This review focuses on current evidence on the virological characteristics, epidemiology, transmission, pathophysiologic pathways, and immune response pathways, clinical spectrum of HMPV infection. Although much is known about HMPV biology, its clinical management is still mainly supportive because no approved antiviral treatment or vaccine is available. Emerging therapeutic approaches, including monoclonal antibodies, fusion inhibitors. RNA-based strategies and subunit vaccine platforms- demonstrate promise but require further clinical validation. Continued research focused on molecular mechanism, improved diagnostics, targeted therapeutics

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