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Review Article

Human Metapneumovirus: An Emerging Respiratory Pathogen

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ABSTRACT

A surge in cases of acute respiratory infections with human metapneumovirus (hMPV) in January 2025 has become a serious global health concern. The hMPV spread from an infected person to others through secretions from coughing and sneezing, close personal contact, such as touching or shaking hands, touching objects or surfaces that have the viruses on them then touching the mouth, nose, or eyes. The infections were usually mild, affecting infants, elderly or immunocompromised, and common in winter and early spring. Early symptoms included runny nose, cough, and sore throat. Good hygiene practices, such as regular hand washing and avoiding close contact with infected individuals are important in prevention. There are many myths and misconceptions about hMPV infections. This review dives deep into the outbreak and discusses about the human metapneumovirus, and its transmission, clinical features, diagnosis, treatment and preventive measures, and attempts to dispel myths and create awareness among the public and healthcare providers.

Keywords: Human metapneumovirus, COVID-19, Outbreak, Respiratory infections.

INTRODUCTION

Human metapneumovirus (HMPV) is a significant pathogen responsible for respiratory tract infections across all age groups, including children, adults, older individuals, and those with weakened immune systems. It is initially classified under the *Paramyxoviridae* family, and was reassigned in 2016 to the *Pneumoviridae* family. The virus is genetically categorized

into two main groups, A and B, which are further divided into sublineages A1, A2, B1, and B2, showing variations from year to year [1].

It was first identified in 2001 in the Netherlands during attempts to isolate viral pathogens from respiratory specimens using monkey kidney cell lines. The discovery was made in samples obtained from 28 epidemiologically unrelated pediatric patients presenting with respiratory illness [2].

The cytopathic changes induced by the newly identified virus were initially comparable to those caused by respiratory syncytial virus (RSV). However, nucleotide sequencing revealed a closer genetic relationship with avian metapneumovirus (aMPV). Human metapneumovirus (HMPV) is believed to have originated from a zoonotic transmission event involving an avian reservoir host, as it shares a common evolutionary ancestor with avian metapneumovirus subtype C (AMPV-C). Phylogenetic analyses using Bayesian models suggest that this cross-species spillover likely occurred around 200 years ago, leading to the establishment of HMPV as a human pathogen [3]. Following its discovery, the International Committee on Taxonomy of Viruses (ICTV) classified the virus within the subfamily *Pneumovirinae* of the *Paramyxoviridae* family, where aMPV was the only recognized member of the genus. Accordingly, the novel pathogen was provisionally designated as human metapneumovirus (hMPV). In 2016, this classification was revised, and both hMPV and aMPV were reassigned to the genus *Metapneumovirus* within the family *Pneumoviridae* under the order *Mononegavirales* [4,5].

A recent systematic review and meta-analysis of hMPV-associated acute respiratory infections in older adults estimated that in 2019, the virus accounted for approximately 473,000 hospital admissions globally among individuals aged 65 and over. Notably, about 185,000 of those hospitalizations occurred in high-income settings, while 288,000 occurred in low- and middle-income countries, underscoring the disproportionate impact of hMPV in resource-limited regions [6]. With this background this review is undertaken to discuss about the human metapneumovirus, its transmission, clinical features, diagnosis, treatment and preventive measures, and attempts to dispel myths and create awareness among the public and healthcare providers.

Etiology

Human metapneumovirus (hMPV) is a spherical, enveloped, with an average diameter of about 209 nanometers. Its genome is composed of a single-stranded, non-segmented, negative-sense RNA molecule approximately 13.3 kilobases in length (Fig 1). The hMPV genome encodes nine structural proteins arranged in the following order: 3′-N-P-M-F-M2 (-1/-2)-SH-G-L-5′. Each of these proteins plays a distinct role in viral replication and pathogenesis. The nucleoprotein (N), with an approximate molecular weight of 43.5 kDa, functions to encapsidate the viral single-stranded RNA genome, thereby ensuring its protection and stability through specific RNA-binding activity. The phosphoprotein (P), with a molecular weight of approximately 32.4 kDa, serves as an essential cofactor for the viral polymerase (L protein). It plays a critical role in stabilizing the polymerase complex and facilitating efficient transcription and replication of the viral genome through its

interaction with the RNA-bound nucleoprotein (N) [7].

The matrix protein (M) is a key structural component of hMPV, playing a pivotal role in viral assembly and the release of progeny virions via budding from the host cell membrane. It contains a high-affinity calcium-binding site and constitutes the major protein component of the viral particle, providing structural integrity and coordinating interactions between the nucleocapsid and the viral envelope [7]. The gene encoding the M2 protein contains two distinct open reading frames (ORFs), which give rise to the M2-1 and M2-2 proteins. These proteins, with molecular weights of approximately 21.2 kDa and 8.1 kDa respectively, are critical for regulating viral replication. M2-1 functions as a transcriptional processivity factor that enhances RNA polymerase activity, while M2-2 modulates the balance between transcription and replication and contributes to the regulation of host immune responses during infection [7].

The fusion protein (F), with an approximate molecular weight of 58.4 kDa, is critical for mediating viral entry. It facilitates the initial attachment of hMPV to host cell receptors and drives the subsequent fusion of the viral envelope with the host cell membrane, enabling delivery of the viral genome into the cytoplasm [8]. The small hydrophobic (SH) protein, with an approximate molecular weight of 20.9 kDa, plays a multifunctional role in hMPV pathogenesis. It contributes to immune evasion by suppressing the host interferon (IFN)-mediated antiviral response and also functions as a viroporin, forming ion channels that may facilitate viral replication and enhance cytopathic effects [9].

The glycoprotein (G), with an approximate molecular weight of 25.7 kDa, mediates viral attachment by binding to cellular glycosaminoglycans on the host cell surface. This interaction enhances the efficiency of viral entry and contributes to the establishment of infection [7].

In addition to its role in viral attachment, the G protein has been shown to interfere with the host's type I interferon (IFN-1) response, thereby contributing to immune evasion. It also promotes airway inflammation by facilitating neutrophil recruitment through the upregulation of several chemotactic mediators, including CXCL2, CCL3, CCL4, IL-17, and tumor necrosis factor-alpha (TNF-α) [10]. The large polymerase protein (L), with an approximate molecular weight of 230.6 kDa, is the central enzymatic component of hMPV replication. It possesses zinc-binding domains and exhibits multiple catalytic functions, including RNA-dependent RNA polymerase, capping, and methyltransferase activities. In coordination with essential cofactors such as the P and M2 proteins, the L protein drives transcription and replication of the viral genome [7,8].

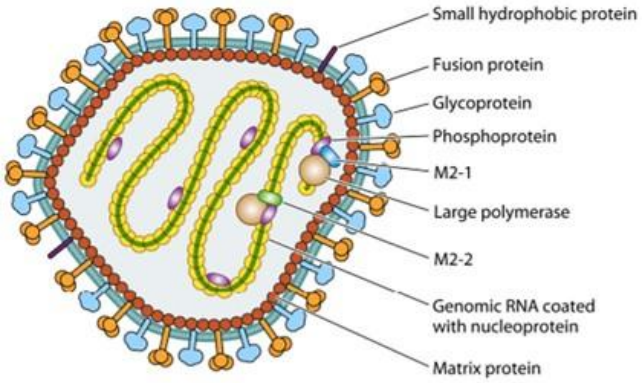

Fig 1: The structure of human metapneumovirus [3]

Genotype variations

The G protein of hMPV shows substantial nucleotide variability, which contributes to the genetic diversity observed across these genotypes. Specifically, nucleotide conservation in the G gene ranges from approximately 45% to 53% among genotypes, while amino acid conservation varies between 22% and 27% [7,11,12].

Human metapneumovirus (hMPV) is classified into two main genotypes, A and B, each of which is further divided into two subgroups: A1 and A2 for genotype A, and B1 and B2 for genotype B. Notably, subgroup A2 is further subdivided into three lineages: A2a, A2b, and A2c (Fig 2). Globally, the A2b sub-lineage of genotype A2 has been the most prevalent for several years. Interestingly, A2b strains often harbor a duplication region of 111 or 180 nucleotides in the G gene. Although hMPV infection is generally associated with severe illness in children, emerging evidence suggests that the A2c genotype may more frequently cause disease in younger adults than in children. In India, circulating hMPV lineages include B1, B2, A2b, and A2c, reflecting the global genetic diversity of the virus [7,11,12].

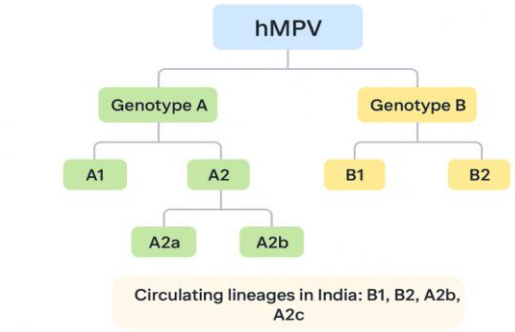

Fig 2: Circulating hMPV lineages in India [12]

Replication

The virus initially attaches to airway epithelial cells (AECs) through interactions between its glycoproteins and heparansulfate on the cell surface, followed by the fusion protein (F protein) engaging an integrin on AECs, a critical step that promotes membrane fusion and allows viral genetic material to enter the host cell. Once inside, the viral RNA-dependent RNA polymerase converts the negative-sense RNA genome into monocistronic positive-sense messenger RNA (mRNA), which is then translated into viral proteins. The newly synthesized glycoproteins are transported via the Golgi apparatus to the cell membrane, where they accumulate in preparation for virion assembly. When viral protein levels reach a sufficient threshold, the polymerase replicates the genome into positive-sense RNA, which serves as a template for producing new negative-sense genomic RNA. Finally, the matrix (M) protein orchestrates the assembly of viral particles, which are released from the host cell through budding from the membrane (Fig 3) [13].

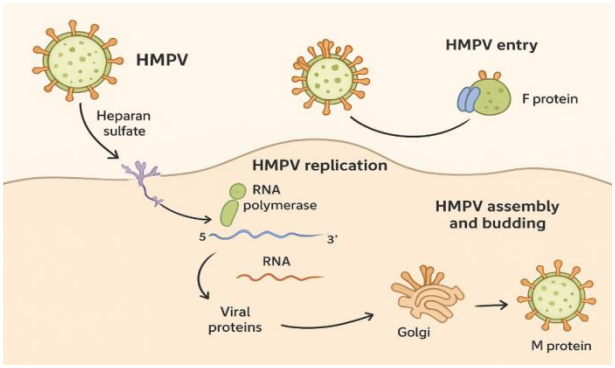

Fig 3: The replication of human metapneumovirus [13]

Epidemiology

Human metapneumovirus (hMPV) infections have been documented worldwide, with cases reported across all continents, highlighting its

global distribution, with infection rates showing seasonal peaks, particularly during the winter months. Respiratory tract infections, including those caused by hMPV, are increasingly recognized as a major cause of global morbidity and mortality. Human metapneumovirus predominantly circulates in temperate regions during late winter and spring. However, several studies have also reported infections occurring in summer and early autumn [14].

geographic differences. Similarly, human metapneumovirus has been implicated in approximately 15% of community-acquired pneumonia cases that require hospitalization, affecting both children under five as well as older pediatric age groups (Fig 1) [15].

According to a study by Walsh *et al*., human metapneumovirus infection is also prevalent in adults, although it frequently remains asymptomatic. Across four consecutive

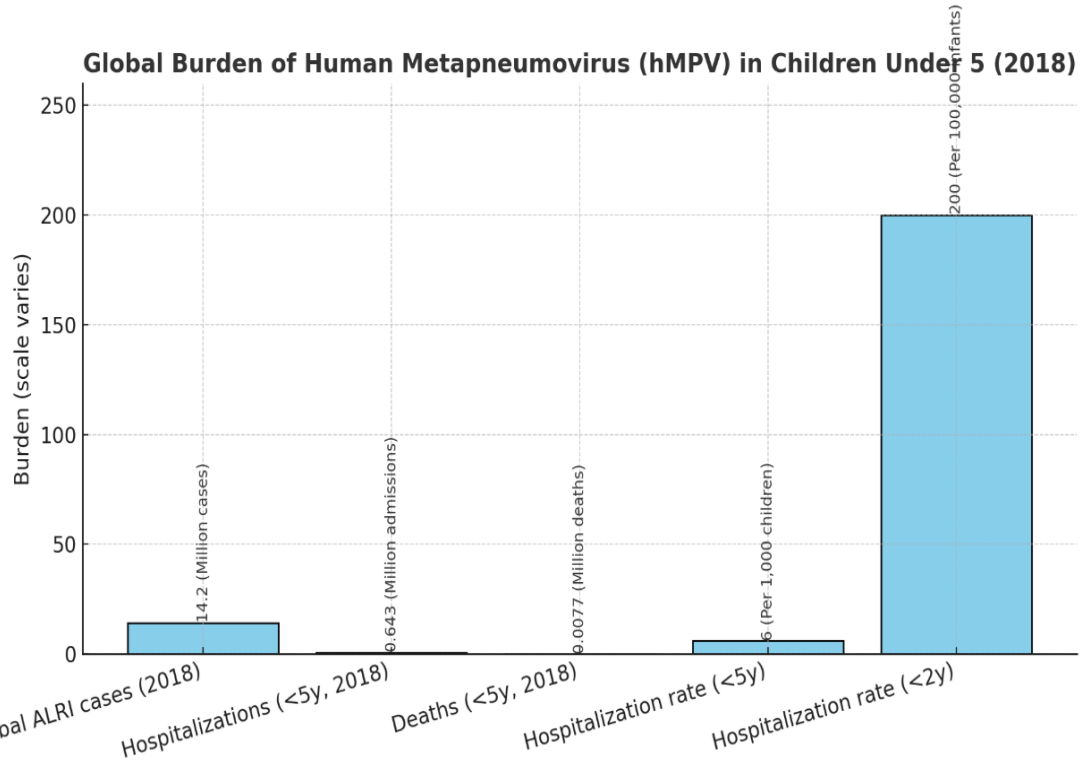

Fig 1: Graphical presentation of the global burden of hMPV in children under five (2018). The chart shows worldwide cases, hospitalizations, deaths, and hospitalization rates, with units clarified for easy comparison [14].

Human metapneumovirus (hMPV) is recognized as a major etiological agent of respiratory tract infections and is responsible for nearly 10% of acute hospitalizations among pediatric patients under five years of age. Among children under five, they represent the second leading cause of death worldwide, irrespective of regional or

winter seasons, the prevalence of hMPV infection in the adult population was reported to range between 3% and 7.1%. These findings are comparable to the annual average infection rate of respiratory syncytial virus (RSV), estimated at 5.5%, but exceed the average annual infection rate of influenza, which is reported to be around 2.4%. The

hospitalization rate for hMPV-associated respiratory tract infections in adults aged 50 years and older is estimated at 4.5%, compared with 6.1% for RSV and 6.5% for influenza A virus infections in the same age group [16].

Primary infection with human metapneumovirus generally occurs within the first six months of life, after which reinfections are common and may persist throughout life. Immunity following natural infection is only partial and short-lived. Although the initial infection induces both humoral and cellular immune responses, neutralizing antibody levels tend to wane over time, predisposing individuals to recurrent infections. Maternal antibodies transferred transplacental or via breast milk provide some degree of early protection in infants, but this is often insufficient to prevent primary infection. In older children and adults, reinfections are usually less severe due to the presence of immunological memory; however, the elderly and immunocompromised individuals remain vulnerable to clinically significant disease [14].

Mechanisms of transmission

Human metapneumovirus (hMPV) is transmitted primarily through respiratory droplets and aerosols released by infected individuals during close contact with infected individuals or by direct contact with infected individuals. Most children are exposed to HMPV by the age of five, and reinfections are common throughout life [17]. Importantly, asymptomatic individuals can also contribute to the spread of hMPV, with studies reporting a transmission rate of approximately 4.1% from asymptomatic carriers [18].

Community transmission of hMPV

Human metapneumovirus (hMPV) is primarily spread through respiratory droplets released during speaking, coughing, or sneezing. Environments such as schools, day care centres, and households act as key hubs for transmission due to close and frequent interactions among individuals [19].

Hospital transmission of hMPV

In hospital settings, procedures that generate aerosols—known as aerosol-generating procedures (AGPs), such as suctioning, bronchoscopy, and intubation significantly increase the risk of hMPV transmission. While direct evidence of fomite-based transmission in clinical settings is limited, there is considerable indirect evidence. Contaminated hospital surfaces including medical instruments, doorknobs, and bed rails have been shown to harbor viable hMPV, posing a risk for indirect transmission [19].

Pathogenesis and clinical manifestations

The incubation period generally ranges from 3 to 5 days, although it may vary among individuals. After entry, the virus initially infects the nasopharyngeal mucosa and subsequently spreads throughout the respiratory tract, targeting host epithelial cells. The host immune response, involving the activation of monocytes and lymphocytes, contributes to viral clearance but also triggers pulmonary inflammation, which underlies the clinical manifestations of infection [20].

Following initial replication in the nasopharyngeal mucosa, the virus rapidly disseminates throughout the respiratory tract. The hMPV genome encodes eight genes that direct the synthesis of nine proteins essential for viral infectivity. Among these, the attachment glycoprotein (G) facilitates

viral binding to host cells, while the fusion protein (F) mediates transmembrane fusion through interactions with host cell integrins, enabling viral entry. Once inside the nucleocapsid is released into the cytoplasm where replication and transcription occur. Viral infection triggers the secretion of pro-inflammatory cytokines and chemokines, including IL-6, IFN-α, TNF-α, IL-2, and macrophage inflammatory proteins, which contribute to peribronchiolar and perivascular infiltration. The subsequent recruitment of monocytes and lymphocytes into the airway epithelium drives pulmonary inflammation, ultimately manifesting clinically as cough, mucus hypersecretion, fever, and dyspnea [2,17,20].

Clinically, the virus is associated with both upper and lower respiratory tract infections, with lower tract involvement being more prevalent. The clinical presentation of human metapneumovirus (hMPV) infection generally begins as a mild upper respiratory tract illness, characterized by symptoms such as fever, malaise, and occasionally vomiting. In more severe cases, the infection may progress to wheezing, pneumonia, croup, or bronchiolitis or acute asthma exacerbations, or chronic obstructive pulmonary disease (COPD) (Table 1). Less common manifestations that have been reported include conjunctivitis, otitis media, diarrhea, rash, seizures, and abnormalities in liver function tests [20].

Role of co-infections and comorbidities

Human metapneumovirus can co-infect with various respiratory pathogens, including respiratory syncytial virus (RSV), bocavirus, rhinovirus, enterovirus, parainfluenza virus, coronaviruses, and influenza viruses (A and B). In addition, hMPV has been shown to co-occur with bacterial pathogens such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. These co-infections, particularly with bacteria like *Streptococcus pneumoniae* or *Staphylococcus aureus*, can complicate clinical outcomes by causing secondary bacterial pneumonia or sepsis. Notably, over half of secondary infections affect the lower respiratory tract, often developing alongside the primary viral infection [21].

Co-infections generally worsen the clinical course of hMPV, especially when occurring with RSV, influenza, or bacterial pathogens. For instance, hMPV-RSV co-infections can lead to serious lower respiratory tract

Table 1: Clinical manifestation of hMPV infection in children and adults [20]

Category	Mild / self-limiting illness	Severe / hospitalized Cases
Pediatric population	Coryza (runny nose), cough, low-grade fever, sore throat. Symptoms often resolve within days	Bronchiolitis, pneumonia, wheezing, hypoxia. Prolonged fever (up to 10 days)
Adult population	Similar to children: cough, rhinorrhea, mild fever. Often self-limiting, may remain asymptomatic in some cases	Pneumonia, bronchitis, exacerbation of chronic conditions (COPD, asthma, hypoxia. Hospitalization more likely in elderly or immunocompromised patients

complications, increased inflammation, and airway damage, frequently resulting in ICU admission, particularly among children under one year, who are highly susceptible [22].

Co-infections with influenza while less frequent, can intensify respiratory symptoms and increase the risk of complications such as acute respiratory distress syndrome (ARDS). The elderly and immunocompromised individuals, including patients with HIV or cancer, are prone to prolonged and severe infections, often complicated by secondary bacterial or fungal infections. Metabolic disorders such as diabetes and obesity impair immune responses, delay viral clearance, and aggravate clinical outcomes, whereas neurological disorders increase the risk of respiratory complications, including aspiration pneumonia [23].

hMPV during COVID-19

During the COVID-19 pandemic, hMPV circulation was initially reduced due to public health interventions such as masking, social distancing, and lockdowns. However, as these measures were relaxed, hMPV activity resurged, often overlapping with COVID-19 cases, which posed diagnostic and management challenges. Unlike SARS-CoV-2, hMPV primarily affects young children and high-risk populations, causing seasonal outbreaks rather than sustained global transmission. Human metapneumovirus infections predominantly occur during winter and spring, similar to respiratory syncytial virus (RSV) and influenza. In contrast, COVID-19, caused by SARS-CoV-2, can spread year-round due to evolving viral variants and changes in population immunity [24].

Diagnosis

Reverse transcription polymerase chain reaction (RT-PCR) is the primary method for detecting human metapneumovirus. Real-time RT-PCR, commonly used for identifying various respiratory pathogens, is also effective for hMPV detection. For rapid and accurate diagnosis of hMPV infections, a combination of imunofuorescence assays and direct fluorescent antibody methods is used as the first-line of diagnosis, followed by RT-PCR on the negative samples [25].

In vitro, hMPV replication is restricted to a limited number of cell lines that require trypsin for optimal growth, resulting in suboptimal propagation under standard cell culture conditions. Various cell lines, such as vero cells, HEp-2 cells, Hep G2 cells, 293 cells, and LLC-MK2 cells have been used for the growth and isolation of hMPV. In cell cultures, hMPV has a slow growth rate, with late cytopathic effects varying from the rounding of cells and their detachment from the culture matrix to small syncytium formation. For this reason, the detection of hMPV antigen using anti-hMPV antibody in direct fluorescence or ELISA-based assays is widely used along with cell culture methods [26].

Recent advances in diagnostic tools have greatly enhanced HMPV surveillance. Multiplex PCR enable simultaneous detection of HMPV and co-circulating respiratory viruses, such as RSV, influenza, parainfluenza, and rhinovirus. Rapid and accurate testing improves patient triage and informs isolation protocols, helping to reduce hospital-acquired infections. Additionally, these technologies facilitate real time epidemiological monitoring, allowing health authorities to track dominant pathogens during outbreaks and implement targeted public health interventions [27].

Treatment and management

No specific antiviral treatment or vaccine is available. Currently, management is limited to supportive care, which may include oxygen therapy, administration of antipyretic and anti-inflammatory agents, and intravenous fluid administration when necessary. Most patients with hMPV recover fully. Although ribavirin has potential against hMPV, its high cost and adverse effects, particularly

Table 2: Comparison of COVID-19 and hMPV infections [24]

Feature	hMPV	COVID-19 (SARS-CoV-2)
Severity	Ranges from mild to severe; severe cases are mostly observed in infants, the elderly, and immunocompromised individuals. Mortality is rare.	Ranges from mild to critical; can cause severe illness or death even in previously healthy individuals.
Mortality rate	Generally low, primarily associated with pre-existing conditions and advanced age.	Higher, especially in early pandemic phases; varies by vaccine coverage, variant type, and healthcare capacity.
Hospitalization	Less frequent; mainly affects young children and older adults.	More frequent across all age groups, contributing to a substantial global healthcare burden.
Transmission	Spread via respiratory or oral droplets, close contact, and contaminated surfaces.	Spread via droplets, aerosols, and contaminated surfaces; airborne transmission plays a larger role compared to hMPV.
Infectiousness	Moderate transmissibility.	Highly transmissible; varies by variant (e.g., Delta, Omicron).
Seasonality	Peaks in winter and early spring.	Initially showed no clear seasonality; waves often correlate with colder months.
Common symptoms	Fever, cough, nasal congestion, sore throat, wheezing, and difficulty breathing.	Fever, fatigue, sore throat, headache, loss of taste or smell (especially in earlier strains).
Severe complications	Bronchiolitis, pneumonia, and respiratory failure in high-risk groups.	Severe pneumonia, acute respiratory distress syndrome (ARDS), thromboembolic events, and multi-organ failure.
Unique symptoms	Wheezing and bronchiolitis are more typical in children.	Loss of taste and smell (early variants), broader systemic involvement.
Acute illness duration	Typically resolves within 1–2 weeks in healthy individuals.	Recovery varies; can last weeks or months, with some experiencing long COVID symptoms.
Chronic complications	Rare post-viral sequelae.	Long-term cardiovascular, respiratory, neurological, and fatigue-related complications reported.
Reinfection	Reinfections can occur; immunity is partial and temporary.	Reinfections are common; severity depends on prior immunity and circulating variants.

hemolyticanemia, limit its widespread use [28]. Another promising candidate, $NMSO_3$, is a modified lipid molecule containing sialic acid and sulfate groups, has been shown to inhibit hMPV replication, prevent syncytia formation, and block cell-to-cell viral spread in culture [29].

Monoclonal antibodies such as mAb234 and mAb338 murine antibodies), MPE8 (human monoclonal antibodies) targeting the hMPV F protein have shown significant promise in preclinical studies [30]. Deffrasnes et al. [28] had identified two potent siRNAs (siRNA45 against N gene and siRNA60 against P gene) and demonstrated their efficacy against the strains of all four subgroups of hMPV [31].

Prevention

Since there is no specific antiviral treatment, prevention is a key to control hMPV spread. It is recommended to follow basic standard preventive measures precautions to prevent the spread of infection [1,23].

Preventing human metapneumovirus (HMPV) infection follows similar principles to other respiratory illnesses. Effective measures include wearing a mask in crowded or poorly ventilated areas, improving indoor ventilation when possible, practicing regular and thorough hand hygiene with soap and water or an alcohol-based hand rub, and avoiding touching the eyes, nose, or mouth without first cleaning hands. Maintaining a healthy immune system through a balanced diet, regular exercise, and sufficient sleep can also help reduce susceptibility to infection [23,32].

For individuals who are ill, preventing transmission to others involves staying home when symptomatic, covering the nose and mouth with a tissue or bent elbow when coughing or sneezing, wearing a mask around others, ensuring good ventilation in shared spaces, and regularly cleaning hands and disinfecting frequently touched surfaces [23,32].

Vaccine development

Currently, no vaccine is licensed for hMPV, though research into vaccine development is ongoing. Preclinical studies have explored multiple vaccine candidates against human metapneumovirus, showing promising results, although no human trials have been conducted to date. Vaccines targeting T-cell epitopes appear to mitigate the immune modulation caused by hMPV, resulting in reduced cytokine production following infection. Chimeric vaccines tested in African green monkeys and hamsters elicited neutralizing antibody responses and conferred protection against disease [33].

Subunit vaccines based on the soluble hMPV fusion (F) protein elicited neutralizing antibody responses and exhibited high levels of protection against viral challenge in cotton rats. Additionally, virus-like particle (VLP) vaccines displaying both F and G proteins induced strong humoral responses in mice across several hMPV strains. Live attenuated vaccines, particularly those developed using reverse genetics, remain a promising approach. Recombinant hMPVs with deletions in SH, G, or M2–2 genes retained immunogenicity, and modifications to the glycosylation site of the F protein produced strains that provided full protection against homologous virus and partial protection against heterologous strains [34].

Overall, the integration of vaccine development, antiviral therapies, monoclonal antibodies, and novel approaches such as RNAi highlights the multi-faceted strategies

being explored to prevent and treat hMPV. These preclinical findings provide a foundation for future clinical studies aimed at controlling this significant respiratory pathogen [35].

CONCLUSION

Human metapneumovirus is an important respiratory pathogen with significant global health implications. Its complex transmission, influenced by environmental and host factors, disproportionately affects vulnerable populations, including young children, the elderly, and immunocompromised individuals. The clinical similarity of hMPV to other respiratory viruses, particularly respiratory syncytial virus (RSV) and influenza, coupled with the absence of specific antiviral therapies and licensed vaccines, presents considerable challenges for healthcare providers. The resurgence of hMPV infections following the relaxation of COVID-19 restrictions underscores the urgent need for effective surveillance and containment strategies.

Future efforts to improve hMPV management should prioritize the development of antiviral therapeutics targeting key viral proteins, especially the fusion (F) protein, and vaccines capable of providing broad protection across diverse genotypes. Research should focus on elucidating the immune responses that govern hMPV infection, designing antivirals that interfere with viral replication, and creating vaccines that confer cross-protection, particularly for immunocompromised individuals and young children, who experience prolonged viral shedding and more severe disease.

Equally important is the implementation of rapid, affordable diagnostic tools suitable for resource-limited settings, alongside comprehensive surveillance networks to monitor viral evolution and outbreak patterns. International collaboration will be critical in addressing these challenges, ultimately reducing the global burden of hMPV and enhancing preparedness for future emerging respiratory infections.

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REFERENCES

1. Vinci A, Lee PJ, Krilov LR. Human Metapneumovirus infection. Pediatr Rev 2018 Dec;39(12):623-624.
2. Uche IK, Guerrero-Plata A. Interferon-mediated response to human Metapneumovirus infection. Viruses 2018 Sep 18;10(9):505.
3. Wen SC, Williams JV. New Approaches for immunization and therapy against human Metapneumovirus. Clin Vaccine Immunol 2015 Aug;22(8):858-66.
4. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis 2014 Aug;25:45-52.
5. Schuster JE, Williams JV. Human Metapneumovirus. Microbiol Spectr 2014 Oct;2(5).
6. Kulkarni D, Cong B, Ranjini MJK, Balchandani G, Chen S, Liang J, et al. The global burden of human metapneumovirus-associated acute respiratory infections in older adults: a systematic review and meta-analysis. Lancet Healthy Longev 2025 Feb;6(2):100679.
7. van den Hoogen BG, Bestebroer TM, Osterhaus AD, Fouchier RA. Analysis of the genomic sequence of a human metapneumovirus. Virology 2002;295:119-132.

8. Schowalter RM, Smith SE, Dutch RE. Characterization of human metapneumovirus F protein-promoted membrane fusion: critical roles for proteolytic processing and low pH. J Virol 2006;80:10931-10941.
9. Masante C, El Najjar F, Chang A, Jones A, Moncman CL, Dutch RE. The human metapneumovirus small hydrophobic protein has properties consistent with those of a viroporin and can modulate viral fusogenic activity. J Virol 2014;88:6423-6433.
10. Bao X, Liu T, Shan Y, Li K, Garofalo RP, Casola A. Human metapneumovirus glycoprotein G inhibits innate immune responses. PLoS Patho 2008;4(5):e1000077.
11. Banerjee S, Sullender WM, Choudekar A, et al. Detection and genetic diversity of human metapneumovirus in hospitalized children with acute respiratory infections in India. J Med Virol 2011;83:1799-1810.
12. Parida P, Sudheesh N, Sanjay ER, Jagadesh A, Marate S, Govindakaranavar A. The emergence of human metapneumovirus G gene duplication in hospitalized patients with respiratory tract infection, India, 2016-2018. Mol Biol Rep 2023;50:1109-1116.
13. Cox RG, Mainou BA, Johnson M, Hastings AK, Schuster JE, Dermody TS, Williams JV. Human metapneumovirus is capable of entering cells by fusion with endosomal membranes. PLoS Pathog 2015;11(12):e1005303.
14. Edwards KM, Zhu Y, Griffin MR, et al. Burden of human metapneumovirus infection in young children. N Engl J Med 2013;368:633-643.
15. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835-845.
16. Walsh EE, Peterson DR, Falsey AR. Human metapneumovirus infections in adults: another piece of the puzzle. Arch Intern Med 2008;168:2489-2496.
17. Freymuth F, Vabret A, Legrand L, Dina J, Gouarin S, Cuvillon-Nimal D, Brouard J. Human metapneumovirus. Pathol Biol (Paris) 2009;57(2):133-41.
18. Bruno R, Marsico S, Minini C, Apostoli P, Fiorentini S, Caruso A. Human metapneumovirus infection in a cohort of young asymptomatic subjects. New Microbiol 2009;32:297–301.
19. Mohammadi, K., Faramarzi, S., Yaribash, S. et al. Human metapneumovirus (hMPV) in 2025: emerging trends and insights from community and hospital-based respiratory panel analyses-a comprehensive review. Virol J 2025;22:150.
20. Howard LM, Edwards KM, Zhu Y, et al. Clinical features of human metapneumovirus infection in ambulatory children aged 5-13 years. J Pediatric Infect Dis Soc 2018;7:165-168.
21. Shehu MT, Pascual A, Kapinos P, El Khoury MY. Mortality and morbidity of human metapneumovirus infection in the Pre-COVID-19 era: the value of the Charlson comorbidity index on outcome prediction. Cureus 2024;16(1):e52321.
22. De Paulis M, Gilio AE, Ferraro AA, Ferronato AE, do Sacramento PR, Botosso VF, et al. Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. J Pediatr (Rio J) 2011;87:307-13.
23. World Health Organization (WHO). COVID-19 Weekly Epidemiological Update 2023.
24. Zheng S, et al. Epidemiology of human metapneumovirus infections during the COVID-19 pandemic, Spain. Emerg Infect 2023;29(4):850-852.
25. Jokela P, Piiparinen H, Luiro K, Lappalainen M. Detection of hMPV and RSV by duplex real time PCR assay in comparison with DFA. Clin Microbiol Infect 2012;16:1568-1573.
26. Isaeva EI, Kozulina IS, Podcherniaeva RI, Grinkevich OM. Reproduction of the metapneumovirus in different cell lines. Vopr Virusol 201;57:19-23
27. Litwin CM, Bosley JG. Seasonality and prevalence of respiratory pathogens detected by multiplex PCR at a tertiary care medical centre. Arch Virol 2014;159(1):65-72.
28. Kumar P, Srivastava M. Prophylactic and therapeutic approaches for human metapneumovirus. Virus Disease. 2018;29(4):434-444.
29. Wyde PR, Moylett EH, Chetty SN, Jewell A, Bowlin TL, Piedra PA. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by $NMSO_3$ in tissue culture assays. Antiviral Res 2004;63:51-59.
30. Schuster JE, Cox RG, Hastings AK, Boyd KL, Wadia J, Chen Z, et al. A broadly neutralizing human monoclonal antibody exhibits *in vivo* efficacy against both human metapneumovirus and respiratory syncytial virus. J Infect Dis 2015;211(2):216:25.
31. Deffrasnes C, Hamelin ME, Prince GA, Boivin G. Identification and evaluation of highly effective fusion inhibitor for human metapneumovirus.

Antimicrob Agents Chemother 2008;52(1):279-287.

32. Schildgen V, van den Hoogen B, Fouchier R, Tripp RA, Alvarez R, Manoha C, Williams J, Schildgen O. Human Metapneumovirus: lessons learned over the first decade. Clin Microbiol Rev 2011;24(4):734-54.
33. Hamelin ME, Couture C, Sackett MK, Boivin G. Enhanced lung disease and Th2 response following human metapneumovirus infection in mice immunized with the inactivated virus. J Gen Virol 2007;88(12):3391-3400.
34. Iacchesi S, Skiadopoulos MH, Yang L, Lamirande EW, Tran KC, Murphy BR, Collins PL, Buchholz UJ. Recombinant human Metapneumovirus lacking the small hydrophobic SH and/or attachment G glycoprotein: deletion of G yields a promising vaccine candidate. J Virol. 2004;78(23):12877-87.
35. Alvarez R, Elbashir S, Borland T, et al. RNA interference-mediated silencing of the respiratory syncytial virus nucleocapsid defines a potent antiviral strategy. Antimicrob Agents Chemother 2009;53:3952-3962.