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Human Metapneumovirus (HMPV): A Comprehensive Review on Epidemiology, Pathogenesis, and Therapeutic Strategies

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Abstract

Human metapneumovirus (HMPV), a respiratory pathogen first identified in 2001, has gained attention due to its role in seasonal outbreaks of respiratory illnesses, particularly in vulnerable populations. Belonging to the Pneumoviridae family, HMPV shares similarities with respiratory syncytial virus (RSV) in its clinical presentation, causing symptoms include mild colds to severe bronchiolitis and pneumonia. This review explores the genetic structure, pathogenesis, immune response, and epidemiology of HMPV, highlighting its transmission mechanisms, diagnosis methods, and treatment challenges. Although primarily affecting adolescent children, aged people, and immunocompromised individuals, HMPV lacks specific antiviral treatments or vaccines, with current management relying on supportive care. Comparative analysis with COVID-19 underscores both shared and distinct characteristics, emphasizing HMPV's seasonal nature and limited global impact compared to the SARS-CoV-2 pandemic. In India, HMPV poses a potential public health challenge, particularly during co-circulation with other respiratory pathogens. Strengthened surveillance, public health measures, and healthcare readiness are essential to mitigate the virus's impact and manage potential outbreaks effectively.

Keywords*:* Human metapneumovirus, respiratory illnesses, Pneumoviridae family, pathogenesis, immune response, genetic structure, seasonal outbreaks, epidemiology, healthcare readiness, public health.

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1. Introduction

The year 2025 began with a global concern over human metapneumovirus (HMPV), especially due to a rise in respiratory illnesses among children in China [1]. Six years after the discovery of COVID-19 in 2019, HMPV has become a significant focus [2]. HMPV, which is a member of the family Pneumoviridae and the order Mononegavirales, includes two species: human metapneumovirus and avian metapneumovirus. This family also hosts respiratory syncytial viruses (RSV) [3]. Avian metapneumovirus (AMPV) and Human metapneumovirus (HMPV) are RNA viruses from the Pneumoviridae family, which includes respiratory syncytial virus (RSV) and belongs to the order Mononegavirales [3,4]. AMPV was identified in South African turkeys in 1978 and is believed to spread primarily through wild migrating birds [5]. It can infect ducks, chickens, and turkeys worldwide, causing significant economic losses due to severe respiratory infections and reproductive issues. While the fatality rate is low and variable, the morbidity rate can be as high as 100% [6].

There are four subgroups of AMPV based on the genetic diversity of its attachment (G) protein [7]:

- Subtype A was first isolated in South Africa [8].
- Subtype B has been found in several European countries [8].
- Subtype C was detected in the United States in 1996 [8].
- Subtype D was discovered in France in 2000 [9].

Moreover, scientists found a mutated form HMPV which was missing the usual G protein that could infect African green monkeys effectively. This finding led to the conclusion that the F protein can independently perform both the attachment to host cells and the fusion process in a living organism. [10]. Researchers in the Netherlands discovered Human metapneumovirus (HMPV) in 2001 by examining stored samples from children with respiratory illnesses. They used techniques like electron microscopy and RT-PCR. Unlike similar viruses, HMPV caused changes in monkey kidney cells but didn't attach to red blood cells. Its genetic makeup is very similar to a bird virus (avian metapneumovirus serotype C), yet HMPV replicates well in monkeys but not in birds [3]. Interestingly, antibodies against HMPV were found in humans from the 1950s [11]. Studies from Canada and the US also found HMPV in samples from the 1970s to early 2000s [12,13,14]. These findings suggest HMPV has been around unnoticed for many years. Researchers in the Netherlands discovered Human metapneumovirus (HMPV) in 2001 by examining stored samples from children with respiratory illnesses. They used techniques like electron microscopy and RT-PCR. Unlike similar viruses, HMPV caused changes in monkey kidney cells but didn't attach to red blood cells. Its genetic makeup is very similar to a bird virus (avian metapneumovirus serotype C), yet HMPV replicates well in monkeys but not in birds [3]. Interestingly, antibodies against HMPV were found in humans from the 1950s [11]. Studies from Canada and the US also found HMPV in samples from the 1970s to early 2000s [12,13,14]. These findings suggest HMPV has been around unnoticed for many years. Similar to that of *Computer Physics Communications*. It should be emphasized, however, that the final appearance of your paper in print and in electronic media will very likely *vary to some extent* from the presentation achieved in this Word® document.

2. Genetic Structure and Organization

Human metapneumovirus (HMPV) is an RNA virus which has single-stranded genetic material and consists of a single chain of RNA nucleotides. It is classified as "negative-sense," meaning that its RNA sequence is complementary to the messenger RNA (mRNA) required for the virus to produce proteins. Additionally, being "non-segmented" signifies that the viral genome is a single, continuous strand of RNA, rather than being split into multiple segments. The entire genome is roughly 13,000 nucleotides long [15]. The HMPV genome carries genetic information for nine different proteins, encoded by eight genes. These proteins include: Structural proteins: - Matrix protein (M): Responsible for shaping the virus particle. - Fusion protein (F): Allows the virus to enter host cells by merging its membrane with that of the host cell. - Nucleoprotein (N): Encapsulates and safeguards the viral RNA

genome. - Glycoprotein (G): Assists the virus in attaching to host cells. Non-structural proteins: - Phosphoprotein (P): Crucial for the replication and transcription of viral RNA. - Small hydrophobic (SH) protein: Contributes to viral replication and may disrupt the host immune response. - Matrix-2 proteins (M2-1 and M2-2): Potentially play a role in viral assembly and release. - Large (L) polymerase protein functions as the enzyme that replicates the viral RNA genome. [16]. The N, L, and P proteins combine to produce the viral replication complex, much like in other paramyxoviruses [15]. The fusion (F) and attachment (G) proteins are two key hMPV surface glycoproteins that have played essential roles in viral replication and host immune response and have been extensively used for studying hMPV genetic diversity [17,18].Phylogenetic analysis of the F and G genes reveals two distinct genetic lineages within Human Metapneumovirus (hMPV): Group A and Group B. These major groups are further subdivided into six distinct genotypes: A1, A2a, A2b, A2c, B1, and B2. [19]. The genetic evolution and transmission of HMPV play a crucial role in epidemic control; however, they have not been extensively investigated to date [16]. Upon further research and studies, co-prevalence of other sub lineages or sub genotype has been documented frequently, but the comprehensive association between disease severity and HMPV genotype is still undefined [17].

The genetic diversity observed in Human Metapneumoviruses (HMPVs) is likely driven by evolutionary forces such as mutation and recombination, as seen in other RNA viruses. These forces, potentially acting together or sequentially, can influence the accumulation of genetic changes. These changes may arise spontaneously or as a response to the host's immune system, ultimately shaping the evolutionary trajectory of HMPVs [20]. The virion of HMPV is enveloped and displays three surface glycoproteins: the small hydrophobic protein (SH), the attachment protein (G), and the fusion protein (F)arranges everything for you in a user-friendly way.

3. Pathogenesis and Immune Response

After the discovery of the virus in 2001[16], researchers found out that human metapneumovirus is most closely related to respiratory syncytial virus (RSV)[20,21,22] which also effects humans. The observed symptoms of the virus can vary from mild to severe bronchiolitis, and in some cases, pneumonia, mirroring the clinical presentation of Respiratory Syncytial Virus (RSV) [22]. Multiple studies have established HMPV as a significant cause of severe respiratory illnesses, typically ranking second or third behind other major respiratory pathogens in children. While adolescent child, the aged, and individuals with enfeebled immune systems or any fundamental health conditions are at more risk of severe disease, HMPV can infect people of all ages [23]. Human Metapneumovirus (HMPV) produces a small hydrophobic (SH) protein, which is likely embedded in the viral membrane. The initiation of HMPV infection requires specific receptors on the surface of host cells to be engaged. This important step is typically aided by viral attachment proteins and is succeeded by membrane fusion. In this phase, the viral envelope fuses with the membrane of the host cell. This critical event is driven by the viral F protein. [24]. The G protein is a type II transmembrane protein that can interact to cellular glycosaminoglycans (GAGs). The G protein is a type II transmembrane protein that can bind to the cellular glycosaminoglycans (GAGs) located in the membranes of the cells, enhancing the virus's attachment to the cell and playing a part in the infection capability of hMPV [25]. The first few studies suggested that hmpv can affect airway epithelium which in turn results in more mucus generation, necrosis, neutrophilic response. Even the virus can cause extensive tissue damage so that it results in local haemorrhage [22].

HMPV utilizes several proteins to evade the host's innate immune response, particularly interferon (IFN) signalling. These viral proteins can disrupt the host's immune surveillance mechanisms and interfere with the proper activation of adaptive immunity. As a result, HMPV can effectively replicate and spread within the respiratory tract. This viral evasion leads to immune-mediated lung damage, similar to that caused by Respiratory Syncytial Virus (RSV). Moreover, these immune evasion strategies may contribute to the development of weak long-term immunity and the likelihood of repeated infections [26].

The innate immune response plays a crucial role in controlling HMPV infection.Pattern recognition receptors (PRRs) on host cells identify viral components during viral entrance, which causes cytokines and chemokines to be released. By attracting immune cells to the infection site and triggering antiviral systems, these signaling molecules start an inflammatory response. [27,29]

The chemokines IL-8 (CXCL8) and CCL5 (RANTES) are secreted when lung epithelial cells infected with hMPV. Although both cytokines can reach their maximum output at 48 hours post-infection, IL-8 can be found as early as 6 hours post-infection, whereas CCL5 can be seen after 12 hours post-infection. Significant IL-8 secretion has been linked to bronchiolitis brought on by hMPV infection, and it is linked to the recruitment of neutrophils to the infection site [28,29,30]. Both the recruitment of neutrophils and eosinophils, as well as the escalation of asthmatic symptoms in the lungs, have been linked to CCL5 release.Neutrophils accounted for the largest proportion of the immune cells assessed in the lung infiltrate, peaking and declining during the duration of infection, according to a study conducted in hMPV-infected mice. The high concentration of neutrophils in BAL and bronchial and alveolar histology samples is associated with lung diseases such interstitial pneumonitis and alveolitis [25,31].

During the acute phase infection, macrophage population gets really higher along with dendritic cells among the other immune cells. Alveolar macrophages (AMs) can facilitate the spread of hMPV infection. This may involve a mechanism where infected macrophages disseminate the virus, leading to subsequent infection of airway epithelial cells [31]. HMPV infection can influence the migration of dendritic cells (DCs) from the lungs to lymph nodes. Furthermore, HMPV infection can disrupt the effective presentation of antigens by pulmonary DCs to T-cells, potentially impairing the development of a robust T-cell response. This impaired T-cell response may contribute to the observed lack of long-lasting immunity and the susceptibility to recurrent hMPV infections [32]. Dendritic cells also serve as a connection between innate and adaptive immunity aactivating lymphocytes, the major participants in the adaptive response, so that they can successfully combat the viral infection [33].

The adaptive immune response against HMPV is characterized by both specificity and a broad range of effector mechanisms. This response is critically dependent on interactions with the innate immune system [34]. Existing evidence suggests that the SH and G glycoproteins play crucial roles in HMPV immune evasion, particularly by suppressing type-I interferon-mediated antiviral responses. Additionally, the precise mechanisms by which HMPV modulates the activity of intracellular Toll-like receptors (TLRs) in the context of viral and intracellular pathogen recognition remain to be fully elucidated. Notably, commonly used animal models for HMPV infection, including hamsters, mice, and non-human primates, exhibit varying degrees of susceptibility to viral infection [35].

4. HMPV diagnosis and detection methods

Human metapneumovirus (HMPV) can usually be identified applying nucleic acid amplification techniques like RT-PCR, which are extremely successful [36,37]. Several commercial multiplex molecular tests detect HMPV [38]. Viral cultures and serological tests have lower sensitivity, making them less trustworthy [38,39]. The late identification of HMPV is due to the difficulties in growing the virus in cell cultures. For effective replication in vitro, HMPV needs the addition of exogenous trypsin. Although it can infect various cell lines, it shows considerable cytotoxic effects on tertiary monkey kidney and LLC-MK2 (rhesus kidney) cells[39]. While there are currently not commercially available immunochromatographic assays, a direct immunofluorescent-antibody (IFA) test, which uses labelled antibodies to detect specific viral antigens in patient samples, can be useful for diagnosing HMPV infections during outbreaks. Detection methods for HMPV antigens, such as enzyme immunoassays (EIA) and enzyme-linked immunosorbent assays (ELISA), are seldom used [40].

5. Treatment and management

There are no licensed antiviral drugs for HMPV, therefore treatment consists primarily on supportive care. Ribavirin and immunoglobulin have been investigated as potential therapies. Ribavirin is a nucleoside that has been demonstrated in lab trials to be effective against RNA viruses, including HMPV [40] and proved certain benefits in mice [41]. Generic intravenous immunoglobulin (IVIG) has been shown to have neutralising activity against HMPV, implying

that it can help to reduce the virus's symptoms [42]. Despite anecdotal reports of ribavirin with IVIG use in people, there are no controlled research studies or governmental recommendations advising their use [43].

6. Comparative analysis between HMPV and COVID-19

COVID-19 is caused by the SARS-CoV-2 virus, identified as a new coronavirus at the end of 2019.SARS-CoV-2 is part of the Coronaviridae family, distinct from the virus that causes HMPV belongs to family Paramyxoviridae [44, 45]. HMPV is primarily transferred via respiratory droplets produced during coughing, sneezing, or talking. It can also spread by contact with contaminated surfaces, unlike COVID-19 is primarily transmitted through respiratory droplets, aerosols, and close contact. While contaminated surfaces (fomites) can play a role, airborne transmission is a major element in Covid-19 [13,45]. HMPV typically circulates over the winter and early spring months, resulting in seasonal epidemics. In contrast, COVID-19 has produced a global pandemic with ongoing outbreaks since its appearance in late 2019, and the proliferation of variants has influenced the disease's epidemiology [13,46]. COVID-19 has a more variable incubation period than HMPV, particularly with emerging SARS-CoV-2 variants, with most cases exhibiting symptoms around 4 to 5 days after exposure. Asymptomatic cases are common, and some people may experience a delayed onset of symptoms, especially in severe disease [13, 47, 48, 49].

7. Prevention and control

Control methods such as appropriate hand hygiene and cough etiquette are the primary means of preventing the transmission of hMPV. Limiting exposure in settings where hMPV could be transmitted, such as day care centres, is also critical [50]. These precautions, which were rigidly enforced throughout the pandemic, are thought to have led to a reduction in other infections. It is also speculated that COVID-19's extensive distribution aided in the prevention of additional viral infections [51].

8. Conclusion:

After reviewing all these facts and cases, it is clear that the Human Metapneumovirus (HMPV) outbreak in China in 2025 is now a matter of global concern, both HMPV and COVID-19 have similar respiratory symptoms, transmission mechanisms, and impact on vulnerable populations. However, they differ in terms of genetic makeup, epidemiology, and global response. COVID-19 has had a far-reaching impact due to its widespread distribution, increased rates of disease and mortality, and the rapid development of vaccinations and treatments. HMPV remains significant, but it is less damaging on a worldwide level. Human Metapneumovirus (HMPV) can cause a variety of respiratory diseases, from mild to severe. It has the potential to spread rapidly across India, particularly through international travel and seasonal outbreaks during the cooler months. HMPV, while less well-known than other respiratory viruses, has the potential to have a large impact on young children, particularly infants and toddlers, who are at risk for serious illnesses such as bronchiolitis and pneumonia. Furthermore, the elderly and those with compromised immune systems, such as those suffering from diabetes, heart disease, or cancer, are more likely to develop serious sickness.

The impact of HMPV in India will be strongly reliant on the healthcare system, which could put hospitals under strain if the virus co-circulates with other respiratory illnesses such as influenza, RSV, or COVID 19. There is no specific vaccination or antiviral treatment for HMPV, so supportive care is the major therapeutic option. Strengthening surveillance systems, raising hygiene awareness, and improving healthcare readiness are critical for managing possible epidemics.

HMPV is expected to spread globally by the mid of 2025, especially to India due to its high population rate, where it poses a substantial public health risk. This respiratory virus primarily affects vulnerable people, such as young children and the elderly, putting a pressure on India's healthcare system due to its high population density and movement. To counteract the spread, India should prioritise preventive measures. Strengthening monitoring and early detection systems is critical for timely epidemic detection and containment. Public awareness efforts that emphasise appropriate cleanliness, mask use, and

avoiding contact with infected people can help prevent transmission. Furthermore, vaccine and antiviral research is critical, and increasing flu vaccination rates can help reduce the danger of co-infections. Implementing travel limits and border screening can help limit the virus's spread from high-risk locations, while healthcare facilities must be ready to handle an influx of cases. Community-based interventions, such as promoting healthy living habits, are also important in reducing infections.

In the final analysis, with integrated efforts in monitoring, education regarding public health, research, and healthcare readiness, India may effectively manage the development of HMPV, limiting its impact and protecting public health.

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Table 1: Functional overview of HMPV genes and proteins

Gene	Protein	Length of Amino Acid	Role
F	Fusion Protein	539	Helps in virus-cell binding and membrane fusion
G	Attachment glycoprotein	229-236	Adheres to cellular glycosaminoglycans (GAGs)
L	Large polymerase protein	2005	Catalytic activity for viral propagation
M	Matrix Protein	254	Helps with the assembly and budding of viruses
M2	M2-1 protein	187	RNS transcription processivity factor
	M2-2 protein	71	Regulates RNA transcription/replication
N	Nucleoprotein	394	RNA genome encapsidation
P	Phosphoprotein	294	Polymerase co-factor
SH	Small hydrophobic protein	177–183	Possible viroporin or innate immune inhibition

Table 2: Comparative overview of HMPV and COVID-19

Aspect	HMPV	COVID-19
Discovery Year	2001	2019
Virus Family	Paramyxoviridae	Coronaviridae
Transmission	Respiratory droplets, contaminated surfaces	Respiratory droplets, aerosols, contaminated surfaces
Incubation Period	3-6 days	2-14 days with most symptoms around 4-5 days
Seasonality	Winter and early spring	Year-round
Symptoms	Cold-like symptoms,	Respiratory symptoms, loss of taste and smell, systemic effects

	bronchiolitis, pneumonia	
Duration of Illness	Few days to weeks	Weeks to months, risk of long-COVID
Severity	Generally mild, severe in high-risk groups	Ranges from mild to severe, more systemic
Vaccines	None	Available and effective
Treatment	Supportive care	Vaccines, antivirals, respiratory support
Significance	Seasonal outbreaks	Global pandemic

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