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# Human Metapneumovirus: A Comprehensive Review of Insights and Advances

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**ABSTRACT**

Human Metapneumovirus (HMPV) is a respiratory virus belonging to the Paramyxoviridae family and is closely related to the respiratory syncytial virus (RSV). It was first identified in 2001 and is a leading cause of respiratory infections across all age groups, particularly in children, older adults, and immunocompromised individuals.

In vitro investigations involving HMPV have predominantly utilized monolayers of undifferentiated epithelial cells. Conversely, in vivo research conducted on cynomolgus macaques and cotton rats has identified ciliated epithelial cells as the primary targets of HMPV infection; however, such findings cannot be effectively examined within monolayer systems. In this study, we developed a bronchial culture model derived from organoids, which facilitates physiologically relevant research on HMPV [1]. The inoculation of various prototype HMPV viruses and recent clinical isolates resulted in notable differences in replication rates among the HMPV strains. The extensive replication of HMPV within this model led to damage to the ciliary layer, including the loss of cilia at later stages following infection [2]. These cytopathic effects were consistent with those documented in prior in vivo studies involving cynomolgus macaques. Furthermore, the evaluation of innate immune responses in three different donors following HMPV and RSV inoculation underscored the necessity of including multiple donors to address donor-dependent variability. In summary, these findings suggest that the organoid-derived bronchial cell culture model closely mirrors in vivo observations, making it a suitable and reliable platform for future HMPV research [3].

**Keywords:** Human metapneumovirus, Genotype, Diagnosis methods, Epidemiological characteristics

## Introduction

The human metapneumovirus (HMPV) was first identified in the Netherlands in 2001 and belongs to the Pneumoviridae family. Infections caused by HMPV can affect individuals across all age groups; however, children under five years, the elderly, and those with compromised immune systems are particularly vulnerable to severe manifestations of the disease. HMPV is classified into two genotypes, A and B, which were originally divided into four sublineages: A1, A2, B1, and B2. Notably, the A1 sublineage has not been detected since 2006, while the other sublineages have persisted and evolved, leading to the identification of new sublineages. Recently, there have been reports of viruses exhibiting a duplication in the attachment gene (G) of either 111 or 180 nucleotides, all of which fall under the newly established lineage A2.2.2.

Previous experimental studies involving cynomolgus macaques infected with HMPV NL/1/00 (A1) revealed that the virus induced lesions throughout the respiratory system, primarily targeting ciliated epithelial cells. Similarly, research conducted on cotton rats indicated the presence of viral antigens predominantly on the apical surface of epithelial cells within the respiratory tract [4]. Despite these observations, in vitro investigations of HMPV have largely been conducted using monolayer undifferentiated cells, which typically exhibit a basal cell-like phenotype, presenting challenges in the study of respiratory virus infections. A limited number of studies have explored HMPV replication in three-dimensional primary epithelial models, often with only moderate success due to restricted viral replication.

In this research, we developed a differentiated primary cell culture model to investigate HMPV infection. Stem cells were isolated from adult bronchial tissue and expanded into undifferentiated organoids. Following this, differentiation was achieved at the air-liquid interface (ALI), resulting in cultures that included ciliated, club, and goblet cells [5].

## Current scenario

Human Metapneumovirus (hMPV) is a respiratory pathogen that generally results in mild to moderate respiratory ailments, including cough, fever, and nasal congestion. Nevertheless, it has the potential to cause more serious health issues, such as bronchitis or pneumonia, particularly in vulnerable populations such as young children, the elderly, and those with compromised immune systems.

- Recent Developments:

- China: In December 2024, a notable rise in hMPV cases was reported in China, especially among children under the age of 14. The Chinese Center for Disease Control and Prevention indicated that hMPV represented 6.2% of positive tests for respiratory illnesses during this timeframe. Despite this increase, the World Health Organization (WHO) affirmed that these figures remain within the anticipated range for the winter season.

- Global Perspective: Other nations, including Malaysia, Italy, and Ukraine, have also documented cases of hMPV. Health authorities stress that hMPV is a recognized virus with seasonal trends and currently does not represent a significant global health risk.

- Current Situation in India:

As of January 2025, India has reported confirmed cases of hMPV. The Union Health Secretary has urged states to enhance surveillance for influenza-like illnesses and severe acute respiratory infections. The public is advised to adopt preventive measures such as frequent handwashing and maintaining proper respiratory hygiene. Health officials have reassured that there is no cause for alarm, as the rise in respiratory illnesses is typical for the winter season, and India is adequately prepared for any potential increase in cases.

- Preventive Measures:

- Hygiene Practices: Regular handwashing with soap and water, covering the mouth and nose when coughing or sneezing, and avoiding close contact with infected individuals are effective strategies to mitigate the spread of hMPV.

- Medical Attention: Individuals experiencing severe respiratory symptoms are encouraged to seek medical assistance without delay.

At present, there is no specific antiviral treatment or vaccine available for hMPV. Management primarily focuses on supportive care to alleviate symptoms [6][8].

## Characteristics of Human Metapneumovirus (hMPV)

Human metapneumovirus (hMPV) is an important respiratory pathogen characterized by several key features:

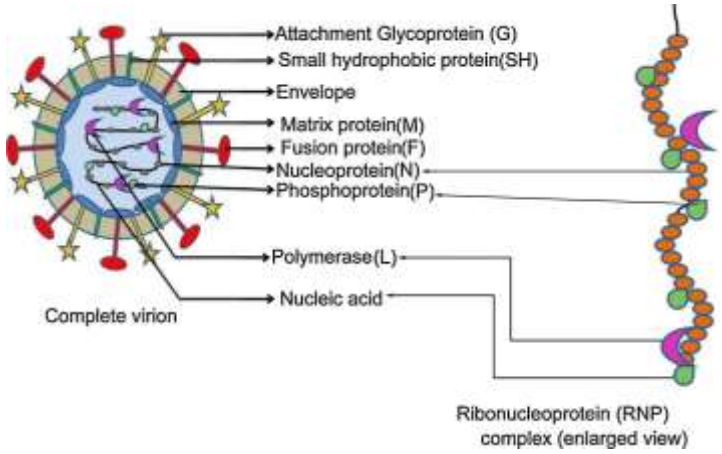
1. Virus Family: hMPV is classified within the Pneumoviridae family, exhibiting similarities to respiratory syncytial virus (RSV).
2. Structure: It is an enveloped virus with a single-stranded RNA genome.
3. Transmission: The virus is transmitted via respiratory droplets, direct contact with infected persons, or through contaminated surfaces.
4. Symptoms: hMPV can lead to a range of respiratory illnesses, from mild cold-like symptoms to more severe conditions such as bronchiolitis, pneumonia, and exacerbations of asthma.
5. Seasonality: The virus is generally more common in late winter and early spring, with outbreaks following seasonal trends similar to other respiratory viruses.
6. Target Groups: It predominantly impacts young children, the elderly, and individuals with compromised immune systems or pre-existing respiratory conditions.
7. Diagnosis: Accurate identification is achieved through laboratory tests, including PCR, antigen detection, or viral culture.
8. Treatment: There is no specific antiviral treatment available; management focuses on alleviating symptoms and providing supportive care.
9. Prevention: Implementing good hygiene practices and minimizing close contact with infected individuals are crucial for curbing transmission[10][11].

## Molecular Virology

The hMPV virion exhibits a pleomorphic structure, with dimensions ranging from 150 nm to 600 nm. Its genomic orientation is akin to that of other members within the Paramyxoviridae family (refer to Figure 1). The genome organization of hMPV bears a close resemblance to that of avian pneumovirus (MPV), particularly type C. Notably, the genomes of hMPV and hRSV show significant similarities, with some distinctions in the gene order and the absence of non-structural genes in the hMPV genome (see Figure 2). In the case of hRSV, two non-structural proteins, N51 and NS2, have been recognized as effective multifunctional antagonists of the interferon (IFN) signaling pathways. The lack of these proteins in hMPV may account for the observed differences in the host innate immune response during infections caused by hRSV and MPV. The MPV genome consists of negative-sense

single-stranded RNA and encompasses eight genes that encode nine proteins. The arrangement of the genes in the genome, from the 3' to the 5' end, is as follows: N-P-M-F-M2-5H-G-L. The proteins include the nucleoprotein (N protein), phosphoprotein (P protein), matrix protein (M protein), fusion glycoprotein (F protein), putative transcription factor (M2-1 protein), RNA synthesis regulatory factor (M2-2 protein), small hydrophobic glycoprotein (SH protein), attachment glycoprotein (G protein), and viral polymerase (L protein). The RNA core is encased by the M protein and enveloped in a lipid membrane, which features three surface glycoproteins (F, SH, and G) that form spikes measuring approximately 13-17 nm. The core nucleic acids are associated with the proteins IP, N, L, M2-1, and M2-2, forming a nucleocapsid with a diameter of 17 mm. Utilizing the G and F proteins, hMPV binds to and fuses with heparan sulfate receptors located on the cell surface.Following the fusion process, the viral nucleocapsid enters the host cell's cytoplasm and replicates. The newly created viral genome combines with the P, N, L, and M2 proteins, then proceeds to the host cell membrane. The virion exits the cell, presenting the F, SH, and G proteins on the membrane's exterior. The P protein serves as a co-factor that stabilizes the L protein, facilitating the assembly of the virus ribonucleoprotein (RNP) complex during viral replication. The M protein is essential for virus assembly and budding as it interacts with the RNP complex. The N protein encases the viral genome, shielding it from nuclease action. Aside from controlling viral transcription and replication, the M2-2 protein significantly contributes to virulence by reducing the host's innate immune response. Similar to other members of the Paramyxoviridae family, hMPV disrupts the host's innate immune system through particular mechanisms. The virus undermines cellular responses by modulating pattern recognition receptors, such as toll-like receptors and retinoic acid-inducible gene-like receptors, as well as other signaling molecules. Infection disrupts dendritic cell function and diminishes antigen-specific T cell activation. Consequently, the elimination of the virus is not fully achieved, resulting in a higher likelihood of re-infection.

Members of the two genotypes exhibit significantly lower amino acid and nucleotide similarity (nucleotide 84-86%, amino acid 94-97%) compared to members of the same subgroup (Al and A2, or B1 and B2) within a single genotype (nucleotide 94-96%, amino acid 97-99%) as determined by the F gene sequence. When comparing the subgroups (A1, A2, B1, and B2), it is observed that the N gene shows the highest conservation levels at both nucleotide and amino acid levels (91.2% and 98.4%, respectively), whereas the & gene exhibits the lowest conservation (79% and 59.2%, respectively.




## Epidemiology

Human metapneumovirus (HMPV) is a respiratory pathogen that predominantly impacts young children, the elderly, and individuals with compromised immune systems. The epidemiological characteristics of HMPV encompass several important aspects:

1. Seasonality: HMPV infections generally manifest in seasonal outbreaks, with peak occurrences noted during the fall and winter months in temperate climates, while in tropical areas, infections can take place throughout the year.

2. Transmission: The primary modes of transmission for the virus include respiratory droplets, direct contact with infected bodily fluids, and interaction with contaminated surfaces.

3. Age Group: Although HMPV can affect individuals of all ages, it is particularly prevalent among infants and young children. Severe manifestations of the disease are more common in very young children, the elderly, and those with pre-existing health issues such as chronic respiratory conditions, cardiovascular diseases, or weakened immune systems.

4. Global Distribution: HMPV is present globally, with its prevalence varying by region. It is recognized as a significant cause of respiratory infections, often presenting symptoms akin to those caused by other respiratory viruses, including respiratory syncytial virus (RSV) and influenza.

5. Symptoms: The infection can lead to a spectrum of respiratory symptoms, ranging from mild cold-like signs to severe conditions such as pneumonia and bronchiolitis. In severe instances, hospitalization may be required, particularly among at-risk groups.

6. Diagnosis: The diagnosis of HMPV is usually established through methods such as PCR testing, viral culture, or immunofluorescence assays, which detect the virus in respiratory specimens.

7. Co-infection: HMPV frequently co-occurs with other respiratory viruses, including RSV, influenza, and rhinovirus, which can complicate both diagnosis and treatment strategies.

The epidemiological profile of HMPV underscores the necessity for ongoing surveillance and public health initiatives aimed at mitigating its effects, particularly among vulnerable populations.

- Several risk factors elevate the probability of experiencing severe disease or complications resulting from human metapneumovirus (HMPV) infection. These factors include:

1. Age:

- Infants and young children are particularly susceptible to severe respiratory manifestations, such as bronchiolitis and pneumonia.

- Elderly adults, especially those aged 65 and older, face a heightened risk of severe outcomes, including hospitalization and mortality.

2. Immunocompromised individuals:

- Those with compromised immune systems, including patients undergoing chemotherapy, organ transplant recipients, and individuals living with HIV/AIDS, are at an increased risk for severe infections and extended illness.

3. Chronic respiratory conditions:

- Individuals suffering from pre-existing lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis, are more likely to experience severe symptoms due to HMPV infection.

4. Congenital heart disease:

- Both children and adults with heart conditions, particularly those with congenital or chronic heart diseases, are at a greater risk of complications from respiratory infections like HMPV.

5. Premature birth:

- Infants born prematurely possess underdeveloped immune and respiratory systems, rendering them more susceptible to serious HMPV infections.

6. Crowded or institutional settings:

- Residing in environments such as daycare centers, hospitals, long-term care facilities, or nursing homes can heighten the risk of HMPV transmission due to close interactions with infected individuals.

7. Co-infection with other respiratory pathogens:

- The presence of co-infections with other viruses (such as respiratory syncytial virus [RSV], influenza, or rhinovirus) or bacteria can intensify the severity of HMPV-related illness.

8. Environmental factors:

- Exposure to environmental pollutants, tobacco smoke, or allergens may worsen respiratory symptoms and amplify the severity of infection, particularly among vulnerable populations [12][14][15].

## Pathogenesis

The pathogenesis of Human Metapneumovirus (HMPV) is characterized by the virus's capacity to infect and replicate within the respiratory tract, resulting in a spectrum of clinical presentations, ranging from mild upper respiratory symptoms to severe lower respiratory illnesses. The following is a comprehensive overview of its pathogenesis:

1. Viral Entry and Infection:

Initial Infection: HMPV primarily gains entry into the body through the respiratory tract. It attaches to host cell receptors utilizing viral surface proteins, notably the fusion (F) protein and attachment (G) protein. These proteins facilitate the virus's adherence to and penetration of respiratory epithelial cells.

Target Cells: The virus predominantly targets epithelial cells that line both the upper and lower respiratory tract, including the nasal mucosa, trachea, bronchi, and bronchioles.

2. Replication:

Upon entering the host cell, HMPV releases its RNA genome, which is utilized to synthesize viral proteins and generate new viral particles. This replication occurs within the cytoplasm of the infected cells, resulting in the production of viral progeny.

The replication process inflicts direct damage on the epithelial cells of the respiratory system, leading to cell death and the shedding of infected cells.

3. Immune Response:

Innate Immune Response: The innate immune system of the body identifies the viral infection through pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), which detect viral RNA. This recognition prompts the release of pro-inflammatory cytokines and interferons, initiating an immune response aimed at controlling the infection.

Adaptive Immune Response: Both cell-mediated immunity (via T-cells) and humoral immunity (via B-cells and antibodies) play significant roles in the immune response. T-cells assist in eliminating infected cells, while antibodies generated against the virus can neutralize viral particles. Nevertheless, HMPV has the ability to evade complete immune clearance in certain individuals, particularly those with compromised immune systems, resulting in prolonged or more severe infections.

4. Inflammation and Tissue Damage:

The viral infection induces inflammation within the respiratory tract, particularly affecting the bronchi and bronchioles. The immune response activates the release of inflammatory mediators, including cytokines and chemokines, which result in airway edema, increased mucus production, and bronchoconstriction.

In more severe instances, this inflammation may escalate to bronchiolitis, pneumonia, and lung consolidation, thereby exacerbating respiratory distress.

5. Clinical Manifestations:

The pathogenesis of HMPV presents clinically as a spectrum of respiratory symptoms. In mild instances, individuals may exhibit nasal congestion, cough, and fever. However, in more severe cases, particularly among young children, elderly adults, or those with compromised immune systems, HMPV can lead to significant lower respiratory tract infections, including bronchiolitis, pneumonia, and exacerbations of pre-existing pulmonary conditions such as asthma or chronic obstructive pulmonary disease (COPD).

6. Potential Complications:

Secondary bacterial infections: The impairment of the respiratory epithelial lining and the suppression of the immune system during HMPV infection can heighten the risk of secondary bacterial infections, complicating the clinical progression.

Long-term respiratory sequelae: Some research indicates that severe HMPV infections may lead to long-term respiratory complications, particularly in children, manifesting as wheezing and asthma-like symptoms.

7. Host Factors:

Various host factors, such as age, immune status, and pre-existing respiratory conditions, play a significant role in determining the severity of the infection. Young children, elderly individuals, and those with chronic respiratory diseases or weakened immune systems are at an elevated risk for experiencing severe disease.

In conclusion, the pathogenesis of HMPV encompasses the entry of the virus into respiratory epithelial cells, subsequent replication, activation of the immune response, and the resulting inflammation. These processes collectively lead to the distinctive respiratory symptoms and possible complications associated with the infection. The capacity of HMPV to circumvent immune responses and induce varying levels of damage to the respiratory tract accounts for the diverse range of disease severity seen in those affected [17][19].

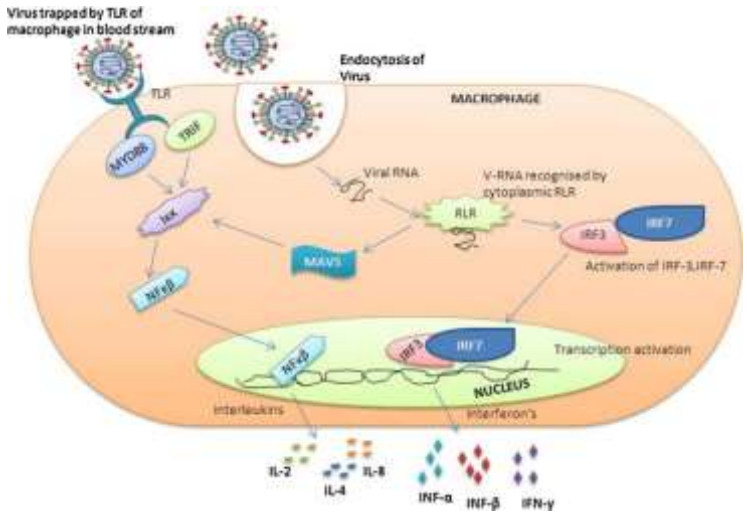
## Diagnosis

Prompt identification of HMPV infection is essential for effective outbreak control and patient care. The conserved amino acid sequences of the F protein in HMPV and RSV have limited the development of serological tests for HMPV-specific antibodies. As a result, various molecular diagnostic methods have been developed, including RT-PCR, RT-qPCR, and RT-LAMP, for detecting HMPV [20].

RT-PCR

Over the last few decades, RT-PCR tests have been extensively utilized for the molecular detection of viruses, such as HMPV. Typically, the genomic areas with significant sequence similarity to HMPV, like the F and N genes, are utilized as molecular indicators for creating RT-PCR techniques, and these specific areas can be applied for genotype examination. Li et al. created a multiplex RT-PCR method using the GenomeLab Gene Expression Profiler genetic analysis system (GeXP) for the quick and sensitive identification of sixteen pathogens related to ARTIs (including HMPV), with a detection limit of 1000 copies per reaction for each virus when all viral targets were included in the reaction.

Typically, RT-PCR tests for detecting pathogens show reduced sensitivity relative to RT-qPCR techniques, which also require sophisticated equipment . Consequently, RT-PCR techniques have seen reduced use for clinical detection of HMPV in recent years [22].




RT-qPCR

RT-qPCR is a highly sensitive and accurate technology for detecting viral nucleic acids, often preferred over traditional RT-PCR due to its lower contamination risk. A TaqMan-based RT-qPCR method by Lu et al. (2008) achieved a detection limit of 10 copies/μL, identifying 19.62% of

clinical samples as positive for HMPV, compared to 13.92% with conventional RT-PCR. Sugimoto et al. developed a duplex RT-qPCR assay that can differentiate HMPV A and B subgroups with a sensitivity of less than 10 copies per reaction.

To address multiple viral infections causing acute respiratory tract infections (ARTIs), multiplex RT-qPCR assays have been created. You et al. established a triple TaqMan-based method detecting HMPV, RSV, and GAPDH, with a detection limit of 100 copies per reaction. Feng et al. developed a multiplex one-tube nested RT-qPCR assay that distinguishes RSV, human rhinovirus (HRV), and HMPV, achieving a sensitivity of 5 copies per reaction for all three.

Recently, digital microfluidic (DMF) technology has been applied to pathogen diagnostics. Huang et al. created an RT-qPCR platform using DMF for simultaneous detection of eleven respiratory pathogens, with off-chip and on-chip sensitivities of ≤ 150 and ≤ 120 copies per reaction, respectively [24].

Nucleic acid isothermal amplification techniques

LAMP:

The LAMP technology, developed by a Japanese research team in 2000, stands as one of the most prevalent isothermal methods utilized in pathogen diagnostics. Song et al. employed the online LAMP primer design tool, Primer-Explorer V4, to create four pairs of primers targeting the M genes, thereby establishing two RT-LAMP reactions aimed at detecting and distinguishing between HMPV genotypes A and B. The limit of detection (LOD) for the method developed for HMPV genotypes A and B was determined to be 4.33 copies/μl and 3.53 copies/μl, respectively, demonstrating a sensitivity that is tenfold greater than that of traditional RT-PCR techniques. In a similar vein, Wang et al. designed three pairs of primers targeting the N gene for HMPV detection, achieving a sensitivity of 10 copies/μl, which also surpassed that of the RT-PCR method.

In summary, LAMP is conducted in an isothermal environment (approximately 65°C) and exhibits high amplification efficiency without the need for complex thermal cycling equipment. Additionally, the LAMP method offers enhanced specificity due to the inclusion of two or three pairs of primers in the reaction system, which also contributes to improved amplification efficiency. Furthermore, the results obtained from the LAMP method can be visually assessed, thereby streamlining the detection process.

Recombinase-aided amplification (RAA):

RAA is a recently developed thermostatic amplification technique characterized by its ease of operation, minimal equipment requirements, and high amplification efficiency, making it widely applicable in the field diagnosis of various pathogens. Jiao et al. utilized the conserved region of the HMPV N gene to design primers for the RT-RAA method, achieving a limit of detection of 100 copies/μl, which is significantly lower than that of the commercial RT-qPCR method.

Additionally, the RT-RAA reaction was conducted at 39°C for 15 minutes, requiring less time than the RT-qPCR method.

CRISPR-Cas 120

Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins (Cas) have found extensive applications in the field of gene editing. Based on the genetic characteristics of the Cas gene in prokaryotes, Cas protein families are categorized into three distinct types. Notably, the CRISPR-Cas12a system is recognized as a potent tool for the in vitro detection of nucleic acids. Furthermore, the sensitivity and reliability of the CRISPR-Cas12a detection system can be significantly enhanced when integrated with reverse transcription and isothermal amplification technologies, such as loop-mediated isothermal amplification (LAMP), recombinase-assisted amplification (RAA), and recombinase polymerase amplification (RPA).

Additionally, the results from the CRISPR-Cas12a detection can be visually observed when paired with lateral flow (LF) methods, making this technology suitable for use in point-of-need settings, including airports and customs facilities. Qian et al. successfully developed a technique for detecting HMPV RNA by integrating RT-RPA with the CRISPR-Cas12a system. In summary, the HMPV N gene was amplified using RT-RPA, and the resulting products were detected through CTISPR-Cas12a in conjunction with LF. Overall, the RT-RPA combined with the Cas12a-based LF assay can be completed in under 30 minutes, achieving a limit of detection (LOD) of less than 700 copies/ml. Moreover, the RT-RPA-Cas12a-1.F method demonstrated a 96.4% detection agreement with the quantitative RT-PCR assay, suggesting its potential as an alternative diagnostic tool for HMPV that does not require specialized equipment [26].

## Conclusions

Human metapneumovirus (hMPV) is a relatively newly identified virus, and it appears to pose a similar level of risk as human respiratory syncytial virus (hRSV) regarding morbidity and mortality. As a significant respiratory pathogen, it is crucial to comprehend the pathogenesis of hMPV and the molecular factors that contribute to severe disease in order to enhance treatment options and to facilitate the development of an effective vaccine against hMPV. Recent research utilizing animal models of hMPV infection and reverse genetics techniques has provided valuable insights into the pathogenesis of hMPV and has enabled the assessment of live vaccine candidates. It is now imperative to commence clinical trials to evaluate the various treatment modalities available for hMPV infection.

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