REVIEW ARTICLE

Current Therapeutic Approaches for Human Metapneumovirus Infections: Challenges and Opportunities

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Abstract

Human metapneumovirus (hMPV) is a widely spread respiratory virus that mainly infects infants, older adults, and immunocompromised individuals with mild-to-severe respiratory disease. This review discusses the transmission, clinical presentations, current treatment methods, and diagnostic challenges associated with the hMPV. Due to the overlapping of symptoms with other respiratory viruses, such as respiratory syncytial virus and influenza, hMPV is frequently misdiagnosed, which adds to the difficulties of managing the disease. To date, no antiviral drugs or vaccines have been licensed for the treatment of hMPV, and supportive therapy remains the standard of care. Recent studies have focused on emerging therapeutic strategies, including nucleoside analogs, fusion inhibitors, monoclonal antibodies, and RNA interference-based treatments. Vaccine approaches, such as subunit protein vaccines, virus-like particles, and live attenuated vaccines, are also widely practical. The article also focuses on persistent challenges surrounding current treatments, including diagnostic constraints, immune evasion, and the need for enhanced surveillance to monitor viral evolution. Progress in molecular diagnostics and immunotherapy holds promise for future advances in hMPV control, underscoring the importance of ongoing research and global preparedness.

Key words: Challenges, human metapneumovirus, progress, prospects, treatment

INTRODUCTION

Human metapneumovirus (hMPV), often abbreviated as hMPV, is a pathogen that generally causes upper and lower respiratory illness and affects infants, geriatric patients, and the immunocompromised population. It generally causes symptoms similar to those of a common cold and cough.[1] In some cases, it shows symptoms of asthmatic flare-ups. This infection is most common in the winter and spring seasons. hMPV is part of the family Pneumoviridae, and the virus was first isolated in 2001; however, serologic data indicate that this infection has been affecting patients for decades.[2] The virus has affected patients worldwide and has been a significant contributor to respiratory illnesses globally. It is primarily a communicable disease that spreads through respiratory droplets and with direct and indirect contact with the infected patient or contaminated surfaces. The symptoms can range from a mild runny nose, sore throat, cough, fever, body pain, to extreme pneumonia and asthma flare-ups.[3] The virus can also cause serious diseases such as bronchiolitis, bronchitis, and pneumonia, leading to respiratory insufficiency in some patients. Even though it is clinically significant, to date, there has been no approved antiviral

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treatment or vaccine for hMPV, and thus, disease management is complex and needs supportive care measures.[4] Although it is clinically relevant, hMPV remains an underdiagnosed respiratory pathogen and is often misdiagnosed as other viral infections, such as influenza, respiratory syncytial virus (RSV), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to symptom overlap. In addition, the lack of widely available rapid tests makes it challenging to perform timely diagnoses and interventions, hence risking underreporting. Recent diagnostic protocols are based on polymerase chain reaction (PCR) assays and serology, which are extremely sensitive but not always readily available in every resource-constrained setting. In the absence of specific antiviral treatments, symptomatic therapy takes on the priority role, with oxygenation, hydration, and bronchodilators being the most crucial treatment interventions for severe disease.

This review focuses on the latest treatment approaches for hMPV infections, ranging from antiviral advances to immunotherapy and palliative care. It also addresses today's treatment challenges, identifies areas for further research, and outlines potential areas of progress in the future, including the development of a vaccine and new antiviral agents.[5] These are all worthwhile avenues to pursue to improve clinical outcomes and reduce the global burden of hMPV infection.

TRANSMISSION AND CLINICAL MANIFESTATIONS

hMPV, a single-stranded RNA virus belonging to the Pneumoviridae family, is a significant cause of acute respiratory infections in individuals of all ages, with severe disease primarily affecting young children, older adults, and individuals with immunocompromising conditions.[6] Initially discovered in the Netherlands in 2001, hMPV clinically resembles RSV and generally circulates in late winter and early spring.[7] Transmission occurs through respiratory droplets, direct contact with an infected person, and contaminated surfaces, with an incubation period of approximately 3–6 days. Infected patients can experience mild symptoms, such as nasal congestion, cough, sore throat, fever, and headache, or, in a severe form, lead to bronchiolitis, pneumonia, or an exacerbation of chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease. The diagnosis of the disease is based on PCR assays and rapid antigen testing on nasopharyngeal specimens. Other imaging modalities, such as chest X-rays or computed tomography scans, can be employed in cases of severe respiratory distress.[8] Due to its clinical cross-reactivity with other respiratory viruses, co-infection with influenza, RSV, or SARS-CoV-2 may complicate the diagnosis and treatment of patients. No direct antiviral therapy is currently available for hMPV, and management is supportive only, including hydration, antipyretics such as acetaminophen or ibuprofen, and oxygen supplementation in more severe presentations. Patients hospitalized due to respiratory failure can be supported with mechanical ventilation.[9]

DIAGNOSIS AND TESTS OF HMPV

The clinical presentation is the primary basis for diagnosing hMPV, but laboratory work is necessary to rule out the condition with certainty. Because hMPV mimics the symptoms of other respiratory viruses, such as influenza and RSV, accurate identification is vital for effective patient management. Some standard diagnostic tests include PCR, enzyme-linked immunosorbent assay (ELISA), and viral culture.[10] Of these, reverse transcription-PCR (RT-PCR) is the reference method because of its high specificity and sensitivity. With this, RNA of hMPV is detected in respiratory specimens such as nasopharyngeal swabs, aspirates, or bronchoalveolar lavage fluid. Serology, for example, ELISA, is used to identify hMPV-specific antibodies; however, its use is not helpful in acute infections for the simple reason that time is needed for an immune response to occur.[11] Paired sera obtained at the acute and convalescent stages can be tested to determine seroconversion; however, this practice is more applicable to epidemiologic investigations than to clinical rapid diagnosis. Immunofluorescence tests and direct fluorescent antibody testing may be used, but they have lower sensitivity than RT-PCR. In addition, viral culture remains a traditional diagnostic procedure; however, hMPV exhibits slow growth in cell culture and typically necessitates secondary confirmation methods, making it less desirable for everyday use.[12] The clinical presentation is the cornerstone of hMPV diagnosis; however, laboratory examination is necessary for verification. Since hMPV has a similar presentation to other respiratory viruses, including influenza and RSV, accurate differentiation is essential for effective patient management. The most frequent diagnostic tests are ELISA, PCR, and viral culture. Of these, RT-PCR is the preferred one due to its specificity and sensitivity. RT-PCR detects hMPV RNA in respiratory specimens such as nasopharyngeal swabs, aspirates, or bronchoalveolar lavage fluid.[13]

Figure 1 demonstrates a pathway illustrating how macrophages detect and respond to hMPV infection.

EPIDEMIOLOGY AND GLOBAL BURDEN

hMPV is a worldwide-distributed respiratory virus recognized on all continents. Its circulation in temperate climates is most notable in late winter to spring, usually coinciding with or succeeding the season's peak of RSV. hMPV, however, is observed throughout the year in most areas, with a reduced prevalence in late spring, summer, and autumn. Genomic sequencing and phylogenetic analysis define hMPV into two large genotypes, A and B, that are further subdivided into distinct groups.[14] These distinctions hold irrespective of the gene – N, M, F, G, or L – that is examined. Although the genomic structure of both genotypes is the same, there are extensive nucleotide polymorphisms, especially in the G and SH proteins. The G gene, similar to RSV, exhibits

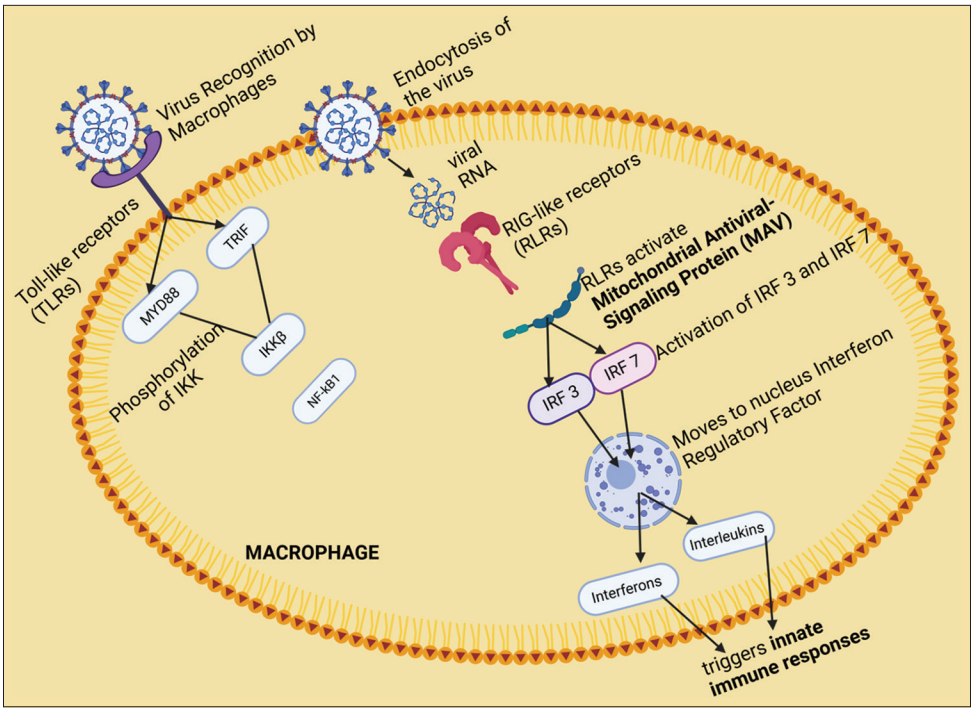

Figure 1: Pathway illustrating how macrophages detect and respond to human metapneumovirus infection

substantial strain-to-strain variability, resulting in amino acid substitutions, frame-retaining insertions, and alternative transcriptional termination codons.[15] The G protein's extracellular domain shows the highest variability, with only 32–37% amino acid identity between the A and B genotypes, paralleling the differences observed in RSV subgroups.

The hMPV epidemiology is dynamic and complex, in contrast to the predictable global dissemination pattern of influenza viruses. Outbreaks of hMPV tend to be regional, with each population having unique strains per year. Phylogenetic characterization has revealed that strains from various locations, including the Netherlands, Australia, Canada, and the United States, share overlapping genetic profiles, despite being isolated in different years.[16] Analysis of the F gene sequences from isolates in Australia (2001), France (2000, 2002), Canada (1999–2002), Israel (2002), and the Netherlands (2001) suggests a high degree of genetic relatedness, with minimal polymorphisms. Both genotypes A and B, along with their respective subgroups, co-circulate within the same year, and studies from St. Louis, Missouri, demonstrate that the predominant genotype can switch from 1 year to the next.[17] Despite these genetic shifts, no significant difference in illness severity has been observed between genotypes.

In 2004, a genetically unique variant of hMPV was isolated in a 6.5-year-old child with acute asthma exacerbation. This strain, detectable only by N gene-specific primers, showed genetic divergence from the four recognized hMPV lineages, and a possibility of a new genotype exists. Additional sequencing analyses will be required to ascertain its classification, and if it is being circulated extensively, diagnostic genomic amplification protocols may need to be modified. Recent research also suggests that hMPV Genotype A may be more genetically heterogeneous than ever anticipated, and there is a need for continued surveillance and genomic studies.[18] Since the virus exhibits genetic heterogeneity, seasonal fluctuations, and regional epidemic behavior, it is crucial to continue genomic investigations to monitor hMPV evolution, refine diagnostic strategies, and achieve adequate disease control.

Table 1 summarizes the common differences between hMPV-infected common cold, viral flu (influenza), and normal common cold.

CURRENT TREATMENT FOR HMPV

At present, there is no specific treatment for hMPV. There are only management steps that can be taken to treat hMPV, which primarily focus on steps taken to provide symptomatic treatment for the management of hMPV, especially in high-risk populations. These steps include treatments such as oxygen therapy for individuals in respiratory distress, hydration, and antipyretics such as ibuprofen or acetaminophen to lower fever.[26,27] In extreme situations, mechanical ventilation or critical care support could be required, especially for hospitalized patients who have hypoxia or respiratory failure.

NUCLEOSIDE ANALOGS AS ANTIVIRAL AGENTS

Nucleoside analogs are an emerging method for treating viral diseases, such as hMPV. Nucleoside analogs can mimic the

Table 1: Common differences between hMPV infection, influenza (viral flu), and the common cold

Feature	hMPV-infected common cold	Viral flu (influenza)	Normal common cold
Causative virus	Human metapneumovirus (hMPV), a *Paramyxoviridae* family virus	Influenza virus (Orthomyxoviridae family)	Rhinoviruses and other respiratory viruses[19]
Primary affected groups	Mostly young children, older people, and immunocompromised individuals	Affects all age groups, but is severe in infants, older people, and those with chronic conditions	Mainly affects children but can infect adults[20]
Incubation period	3–6 days	1–4 days	1–3 days
Mode of transmission	Respiratory droplets, direct contact with contaminated surfaces	Spreads through respiratory droplets and contaminated surfaces	Airborne droplets and direct contact with infected individuals
Common symptoms	Runny nose, nasal congestion, persistent cough (sometimes wheezing), fever (moderate-to-high), and shortness of breath (severe cases)	High fever (100–104°F), chills, dry cough, severe body aches and fatigue, sore throat[20]	Sneezing, sore throat, mild cough, nasal congestion, low-grade fever (sometimes)[20]
Fever intensity	Mild-to-moderate can be absent in some cases	High fever (often>102°F) lasting 3–4 days	Mild, rarely above 102°F (38.9°C)
Cough characteristics	Persistent, often severe, may be wet or wheezing	Severe, dry, and hacking[21]	Mild and dry
Symptom progression	Gradual onset, but can lead to severe respiratory distress	Sudden onset with severe symptoms	Gradual onset with mild respiratory symptoms
Duration of illness	Typically lasts 7–14 days, longer in severe cases	5–14 days, severe fatigue can last weeks	Resolves within 7–10 days
Possible complications	Can cause bronchiolitis, pneumonia, and respiratory failure	Can lead to pneumonia, bronchitis, myocarditis, or organ failure in severe cases	Rare, usually clears up without complications
Seasonal occurrence	Most common in late winter and early spring	Peaks in winter, highly seasonal	Year-round, peaks in fall and spring
Pathophysiology	Infects the lower respiratory tract, causing inflammation and mucus buildup	Inflames the respiratory tract and can spread to the lungs, causing viral pneumonia[22]	Infects the upper respiratory tract, causing mild irritation
Immune response	Stronger immune activation can lead to lung tissue damage	Strong immune activation, leading to cytokine storm in severe cases	Mild immune activation, leading to localized inflammation[23]
Laboratory findings	Elevated inflammatory markers, viral RNA detectable through PCR	Leukopenia, elevated inflammatory markers, positive influenza antigen test	Laboratory tests are rarely needed
Diagnosis	PCR, viral culture, or antigen-based assays	PCR, rapid influenza diagnostic tests (RIDTs)	Clinical diagnosis based on symptoms
Chest X-ray/imaging findings	May show lung infiltrates, hyperinflation in severe cases	Can show patchy lung opacities in viral pneumonia cases	Normal or mild inflammation in the nasal passages
Treatment approaches	Supportive care: Hydration, oxygen therapy, bronchodilators if needed	Antiviral medications (oseltamivir, zanamivir) for severe cases, symptomatic care[24]	Symptomatic relief using OTC medications, hydration, and rest
Management for high-risk groups	Close monitoring is necessary for infants, older adults, and individuals with compromised immune systems.	High-risk individuals (elderly, pregnant, immunocompromised) may require hospitalization.	No special monitoring needed
Severity of illness	Can range from mild to severe, particularly in vulnerable populations	Moderate to severe can be life-threatening in high-risk groups	Generally mild and self-limiting

(Contd...)

Table 1: *(Continued)*

Feature	hMPV-infected common cold	Viral flu (influenza)	Normal common cold
Impact on breathing	Can cause shortness of breath, wheezing, and respiratory distress	Can cause severe respiratory distress and ARDS in severe cases[25]	Rarely affects breathing significantly
Hospitalization need	May require hospitalization in severe cases	Common in high-risk patients, particularly the elderly and those with chronic illnesses	Rarely needed
Vaccine availability	No licensed vaccine yet, research ongoing	The annual flu vaccine is available and recommended for high-risk groups	No vaccine, some immunity from prior exposure
Preventive measures	Hygiene (hand washing, mask-wearing, avoiding exposure), extra care for high-risk individuals	Annual vaccination, hygiene, and avoiding crowded places during flu season[25]	Good hygiene, avoiding infected individuals

natural nucleoside and interfere with the virus's replication process, further inhibiting its reproduction. Nucleoside analog s incorporate themselves into the RNA or DNA strands and disrupt the synthesis of normal nucleic acid, which may result in premature termination of the viral genome or mutation in the viral replication process.[28] Henceforth, nucleoside analogs act against hMPV, which relies on RNA-dependent RNA polymerases for its replication cycle, thereby impairing its replication process.

One such example of nucleoside analogs is ribavirin, which has been extensively studied for the treatment of RSV infections. Ribavirin achieves its antiviral action by inducing lethal mutagenesis in viral genomes and interfering with viral RNA polymerase function.[29] A further nucleoside analog under investigation is lumicitabine (ALS-8176), a prodrug that is metabolized to ALS-8112, which has shown activity against RSV and potential against hMPV.[30] Lumicitabine acts through mechanisms similar to those of ribavirin, directly inhibiting viral RNA polymerases and interfering with replication. In addition, molnupiravir has been of interest because it exhibits broad-spectrum antiviral activity against numerous RNA viruses. Its active metabolite, NHC-5′-triphosphate, competes with the natural nucleotides for incorporation into the viral RNA and causes mutations that inhibit viral replication.[31,32] Despite the promise of nucleoside analogs, their clinical use for hMPV treatment is still an open area of investigation.

FUSION INHIBITORS

The viral fusion protein is a class I transmembrane protein that aids in the initial stages of virus-cell fusion.[33] Henceforth, hMPV F protein serves as a promising target for antiviral interventions, including fusion inhibitors. The F protein of hMPV is present as trimers on the surface of the viral membrane. It comprises two essential heptad repeats (HR) domains, HR-1 and HR-2, which engage each other to facilitate membrane fusion.[34] Synthetic peptides corresponding to HR domains of other paramyxoviral fusion proteins, including HIV, RSV, and measles virus, have shown the capacity to block viral fusion by competing with their natural counterparts.[35] In the same way, HR-1 sequences of the F protein of hMPV have been made synthetically and have been found to inhibit hMPV infectivity *in vitro* by blocking virus-cell fusion. The suggested mechanism is that synthetic HR-1 peptides either trap the native HR-2 domain or insert into the trimeric bundle, replacing the native HR-1.

Research testing both HR-1 and HR-2 synthetic peptides has shown highly active antiviral properties against all four hMPV subtypes *in vitro*, and one HR-1 peptide also offers significant protection from hMPV challenge in BALB/c mice.[36] Furthermore, research by Marquez-Escobar et al created a gene that codes for an antiviral peptide modeled on HR-1. With the aid of the tobacco plant, a peptide for inhibiting hMPV was developed.[37] In another study, Deffrasnes *et al.* isolated several peptides from the heptad repeat regions of hMPV F protein and determined their capacity to diminish viral morbidity and mortality.[38] Among them, the HRA2 peptide displayed high antiviral activity, substantially decreasing lung viral load, pulmonary inflammation, airway obstruction, and levels of pro-inflammatory cytokine/chemokines in treated BALB/c mice. Furthermore, specific research has proven that peptide-based inhibitors, as well as small-molecule fusion inhibitors, are another promising field of study. JNJ-5371867, a RSV fusion inhibitor, has shown efficacy by binding to the viral F protein in its pre-fusion state, inhibiting viral entry.[39] Due to the structural similarity between RSV and hMPV, finding small-molecule fusion inhibitors that target the hMPV F protein is a crucial area of research.

INTERFERING RNAS

RNA interference (RNAi) is an essential post-transcriptional silencing of genes in eukaryotic cells that is Dicer-mediated

and produces double-stranded RNA to yield small interfering RNAs (siRNAs).[40] The siRNAs are channeled into the RNA-induced silencing complex, and the result is sequence-specific mRNA destruction and repression of protein synthesis. Researchers also identified effective siRNAs with hMPV-targeting specificity, such as siRNA45 and siRNA60, which particularly targeted nucleoprotein (N) and phosphoprotein (P) mRNAs at subnanomolar IC50 values.[41] The dicer-substrate siRNAs to hMPV genes demonstrated inhibition of viral replication *in vitro* and partial activity in mice. However, siRNAs to glycoprotein (G) mRNA did not impact viral replication. Follow-up studies confirmed that 2′-O-methyl-modified siRNAs against conserved hMPV nucleocapsid mRNA could partially inhibit viral replication with no off-target or cytokine-mediated inhibition.[42] The findings suggest the potential for RNAi-based therapy against hMPV, but with a need for optimization in clinical applications.

MONOCLONAL ANTIBODIES

Monoclonal antibodies targeting conserved viral immunogenic protein epitopes have shown significant potential in providing protection or reducing the severity of disease in infected individuals. The utility of palivizumab, a RSV prophylactic monoclonal antibody, has been proven in high-risk populations.[43] Similarly, the hMPV fusion (F) protein, which is both highly conserved and immunogenic across various viral subtypes, presents a promising target for antibody therapy.[44,45] Recently, it has been demonstrated that 54G10, a human monoclonal antibody targeting the conserved epitope of the hMPV F protein, exhibits high neutralizing activity, effectively reducing viral titers in the lungs and nasal aspirates of infected, permissive mouse models.[46] Its prophylactic and therapeutic activity was as potent as palivizumab in nasal aspirates but superior in decreasing viral load in lung homogenates.[47] Previously, Fab DS7, an antibody fragment from a recombinant human monoclonal antibody raised using phage display technology, has been shown to significantly curb the development of hMPV in the lungs of cotton rats.[48] Previous work by Ulbrandt *et al.* resulted in the development of a panel of monoclonal antibodies against the F protein of hMPV in animal models, of which MAb 338 and MAb 234 had broad neutralizing activity against all four subtypes of hMPV.[49] It was further emphasised that further humanization and improvement of antibiotics would make them more effective for treating hMPV. In 2005, Ma *et al.* also generated two monoclonal antibodies from mice, 1G3 and 9B10, which demonstrated potent neutralization in hMPV-infected cells.[50] These results suggest that monoclonal antibodies can be a promising treatment modality for hMPV.

SUBUNIT PROTEINS AS A VACCINE STRATEGY

Fusion (F) proteins are significant immunogenic antigens of paramyxoviruses, such as hMPV. These type I transmembrane glycoproteins are initially presented as precursor proteins (F0), which are cleaved by host proteases to yield two subunits, F1 and F2, connected through disulfide bridges.[51] Due to the structural and functional analogy between hMPV F protein and the RSV F protein, several groups have suggested the construction of subunit vaccines based on the hMPV F protein to provide protective immunity.

Experiments have shown that an hMPV F protein, produced in soluble form without a transmembrane domain, could elicit potent neutralizing antibodies and confer excellent protection against the challenge virus in the cotton rat models.[52] Although the present vaccine regimen successfully decreased viral loads within the lower respiratory tract, its impact in the upper respiratory tract was weaker but still substantial. Interestingly, the immunized animals failed to produce skewed TH2 responses or enhanced alveolitis and eosinophilic infiltrates, which are characteristic of formalin-inactivated RSV (FI-RSV) vaccines. This suggests the safety promise of F subunit-based vaccines.[53]

Follow-up investigations in Syrian golden hamsters have explored the immunogenicity of F subunit vaccines with various adjuvants, which successfully triggered a protective antibody response against both homologous and heterologous hMPV subgroup infections.[54] The matrix (M) protein of hMPV has been identified as another crucial immunomodulatory element, capable of triggering dendritic cell maturation and cytokine induction. BALB/c mice studies demonstrated that co-administration of the F subunit and alum adjuvant of M protein reduced pulmonary viral titers following challenge with hMPV compared to immunization with the F subunit alone. It suggests that the addition of M protein can enhance vaccine efficacy by influencing the cellular immune response, specifically by modulating the TH1/TH2 cytokine ratio.[55]

In primate models, a subunit vaccine of the hMPV F protein induced robust neutralizing antibody titers; however, the titers dropped sharply over weeks, highlighting a significant challenge in the generation of long-term and effective hMPV vaccines. Further studies are needed to optimize formulations, adjuvants, and delivery systems to achieve long-term immunity.[56] Subunit vaccines against the hMPV F protein remain an option despite these difficulties, providing a potential route to safe and effective immunization against hMPV infection.

VIRUS-LIKE PARTICLES (VLPS) AS A VACCINATION STRATEGY FOR HMPV

VLPs have emerged as a new vaccine platform, showing considerable promise for a range of viral infections, including hMPV. VLPs are composed of VLPs created by viral structural proteins, but they stand alone, free of genetic content, making them non-replicative and non-infectious.[57] Their molecular identity with indigenous viruses enables them to present viral antigens in a repetitive and ordered manner, effectively stimulating intense immune responses, primarily through B cell activation. VLP-based vaccines are beneficial in human papillomavirus immunization and have been shown to induce both humoral and cellular immunity.[58] In addition, adjuvants can be incorporated into VLPs to enhance their immunogenicity.

VLP vaccine candidates have also been tested against RSV, a close relative of hMPV, with positive outcomes. VLP-produced RSV-F and RSV-G were investigated with improved antibody responses and significant viral load reductions in animal models.[59] VLPs secreting the prefusion conformation of the F protein, in particular, induced stronger titers of neutralizing antibodies than VLPs secreting the postfusion conformation.[36] The results suggest that the same strategy would be beneficial in the context of hMPV vaccine development, as the F protein is a key factor in viral entry and a primary target for neutralizing antibodies.

For hMPV, VLPs displaying the fusion (F) and glycoprotein (G) proteins (F/G-VLPs) or the F protein alone (F-VLPs) have been tested in animal models. Immunization of mice with these VLPs has been found to induce neutralizing antibodies. In contrast, mice immunized with G-VLPs alone did not, further supporting the idea that the G protein plays little role in protective immunity.[36] Furthermore, F-VLPs alone elicited a comparable extent of neutralizing antibody response to that induced by F/G-VLPs, further highlighting the central role played by the F protein in vaccine construction.

F and matrix (M) protein, including VLP-based vaccines, have also been found to elicit strong neutralizing antibody responses when used in conjunction with adjuvants.[60] Immunization using these VLPs provided complete protection against infection by hMPV in the lungs of mice and strongly inhibited viral replication within nasal tissues. In addition, VLP vaccination appeared to induce CD8+ T cell responses, which may contribute to long-term immunity. However, the degree of T cell contribution to protection is yet to be entirely determined.[61]

In general, VLP-based vaccines represent a promising direction in the hMPV immunization approach. This type of vaccine elicits potent immune responses with no risk of viral replication. Furthermore, the incorporation of adjuvants and structural optimization could further enhance its potential as an appealing option for replacing traditional vaccines.[62] More studies are necessary to optimize these preparations and their efficiency in human clinical trials.

LIVE ATTENUATED VIRUSES AS A VACCINATION STRATEGY

Live attenuated viruses are weakened virus particles intended to provide protective immunity while closely simulating a natural infection. Both humoral and cellular immune responses are elicited by these vaccines, providing long-term immunity without the need for booster injections. However, one of the main drawbacks of live attenuated viral vaccines is the assurance that the virus will not revert into virulent form and will remain attenuated.[63] These vaccines are hazardous for immunosuppressed patients.

For hMPV, several live-attenuated vaccine candidates have been developed using various approaches. One of these is cold-passaging temperature-sensitive hMPV strains, which induce multiple mutations along the viral genome, reducing viral replication in animal model respiratory tracts while still eliciting strong immune responses.[64] One such approach is the use of reverse genetics to eliminate specific viral genes, such as SH, G, or M2-2, thereby achieving varying levels of attenuation.[65] Disruption of the G and SH genes has been shown in research to reduce viral replication considerably and induce protective immunity in animal models. Similarly, replacement of the M2-1 gene by modifying the zinc-binding motif or mutagenesis of the S-adenosylmethionine binding site of the L protein has resulted in highly attenuated viruses that might induce superior neutralizing antibody responses.[66]

Recombinant live attenuated hMPV vaccines have also been further improved by replacing viral proteins with homologous virus proteins, such as avian metapneumovirus (MPV), which has been reported to suppress viral replication in healthy adults significantly. Further, modifications of the fusion (F) protein, e.g., removal of N-linked carbohydrates, have also demonstrated protective immunity against homologous and heterologous hMPV strains. Recent research has clarified the function of M2-2 protein-based vaccine candidates, which, in addition to stimulating cellular immunity via cytotoxic T lymphocyte (CTL) epitopes, also regulate host innate immunity by modulating immune-related microRNA expression.[67]

Although promising in early preclinical studies, further validation through human clinical trials is needed to establish the safety and efficacy of such vaccine candidates. Notably, no increased disease has been established after immunization with live attenuated hMPV vaccines using animal model-based models, a key concern in vaccine design. Through additional research, live attenuated vaccines can be a beneficial and safe measure in preventing hMPV infection, especially in vulnerable populations such as children and the elderly.

EPITOPE-BASED VACCINE

Epitope-based vaccines are one of the most targeted and focused methods of immunization, aiding in the activation of the host's adaptive immune response against viral diseases. In comparison with conventional vaccines, epitope-based vaccines target a small and highly defined segment of the viral protein, which activates both cellular and humoral immune reactions. Several researchers have noted that epitopes, such as hMPV N, G, M2-2, and SH protein CTL epitopes, have been shown to trigger strong immune responses.[68] Peptide vaccines expressing these CTL epitopes have been shown to generate effector and memory CTL responses, and to induce the production of Th1-type cytokines like interferon-gamma and interleukin-12 (IL-12).[69] These cytokines are responsible for antiviral immunity by improving the T-cell response, downregulating Th2-type cytokines (IL-10, IL-4) to suppress overactive inflammation.

One promising approach in vaccine design is through multi-epitope peptides (MEPs), which incorporate several B cell, CTL, and T helper (Th) cell epitopes.[69,70] A recent report proved that an MEP specific for hMPV, grown in bacteria and adjuvanted, could effectively elicit both cell-mediated immunity and neutralizing antibodies in BALB/c mice and that serum taken from immunized mice could efficiently neutralize infection with hMPV in vitro. Epitope-based vaccines offer high specificity, low toxicity, and broad-spectrum protection by targeting conserved viral epitopes, making them a promising candidate for protecting high-risk populations, such as infants and immunocompromised individuals. But more clinical trials are required to establish their long-term efficacy in humans. Table 2 summarizes current therapeutics for hMPV.

CHALLENGES IN TREATMENT AND MANAGEMENT OF HMPV

hMPV is a newly discovered respiratory pathogen that is notoriously difficult to treat and manage as a result of a number of factors, most notably the unavailability of approved antivirals and vaccines, diagnostic insufficiencies, and drug resistance and immune evasion problems.

Unavailability of approved antivirals and vaccines

Even with the identification of hMPV as a serious cause of respiratory illness, especially among high-risk groups like young children, elderly, and immunocompromised patients, there are no FDA-approved antiviral medications or vaccines available to target this virus. Supportive care is the mainstay in the management of hMPV infections, and this involves hydration, oxygen, and symptomatic treatment with over-the-counter agents.[71]

Research has also delved into promising antiviral approaches, identifying the viral fusion protein as an attractive drug development target. So far, improvements have been glacial, and only a few candidates have undergone preclinical investigations. The lack of efficacious antiviral treatments makes severe cases difficult to manage in a clinical setting, with hospitalized and intensive care treatment being required.[72]

Diagnostic limitations

Diagnosis of hMPV infection is usually impaired by the unavailability of quick and specific diagnostic tests. Conventional tests like viral culture are slow and might not be practicable in acute clinical environments. Although molecular diagnostic methods have enhanced the precision of pathogen identification, they are not used universally or consistently in all medical centers. This restriction can result in delays in proper management and treatment choices, especially among high-risk individuals, where intervention is critical in a timely manner.[73]

In addition, the clinical course of hMPV may simulate other respiratory viruses such as influenza and RSV, making it even more challenging to diagnose. Consequently, the majority of the cases might go undetected or misdiagnosed and thus receive ineffective treatment strategies.[74]

Drug resistance and immune evasion

Another major challenge to controlling hMPV is the possibility of drug resistance and immune evasion. As with most viral pathogens, there is a threat that hMPV may become resistant to any antiviral drugs that could be developed in the future. This is further compounded by the fact that the virus can evade host immune responses through multiple mechanisms.[75]

For example, research has indicated that hMPV is able to change its antigenic characteristics, which makes it challenging for the immune system to develop an effective response. This immune evasion not only makes treatment more challenging but also highlights the need for continued surveillance and research on vaccine development.[76]

Co-infections and disease severity

hMPV frequently occurs as a co-infection with other respiratory viruses, including RSV, influenza viruses, or bacteria. Such co-infections may aggravate disease severity and complicate clinical management. Research has shown that patients with hMPV co-infections develop more severe illness, prolonged hospitalization, and higher risks of complications than those with solitary hMPV infections. Identification of the effects of each pathogen in a case of co-infection is the biggest challenge that

Table 2: Summary of current therapeutics for human metapneumovirus

Therapeutic/Vaccine Strategy	Mechanism of action	Current status	Challenges	Opportunities for improvement	References
Nucleoside Analogues (Ribavirin, Lumicitabine, Molnupiravir)	Mimic natural nucleosides, become incorporated into viral RNA, and induce mutations that block replication	Under investigation	Possible toxicity, few clinical trials for hMPV	Synthesis of safer analogues with greater specificity	[28,29]
Fusion Inhibitors (HR-peptides, JNJ-5371867)	Inhibit the viral F protein, blocking virus fusion with host cells	Preclinical studies	Delivery issues, viral resistance	Small-molecule fusion inhibitors of conserved fusion domains	[34-36]
Interfering RNAs (siRNA Therapy)	Suppresses viral genes by targeting hMPV RNA, blocking viral protein synthesis	Experimental phase	Delivery system constraints, stability problems	Nanoparticle-based RNA delivery for improved specificity	[42]
Monoclonal Antibodies (54G10, DS7, Mab 338, 1G3, 9B10)	Bind to hMPV surface proteins (primarily, F protein) to neutralize the virus and prevent entry into host cells	Preclinical studies	Low production cost, ease of access	Mass production of humanized monoclonal antibodies	[45]
Subunit Vaccines (Fusion (F) Protein-based)	Utilize purified F protein to stimulate an immune response and generate protective antibodies	Preclinical animal studies	Limited long-term immunity seen	Optimization of adjuvants for extended immune response	[52]
Virus-Like Particles (VLPs)	Mimic the virus structurally without genetic material, stimulating a strong immune response	Limited animal studies[58]	Expensive production, poor scalability	Improved adjuvants can be made for improved immunogenicity	[58]
Live Attenuated Vaccines	Contain weakened hMPV strains that replicate at low levels and therefore provide long-lasting immunity.	Experimental phase[63]	Risk of reversion to virulence and acting negatively on the patient's health, safety concerns for immunocompromised patients, and the elderly	Genetic modifications can be done for stable attenuation and better protection	[64]
Epitope-Based Vaccines (Multi-epitope peptides)	Use small viral protein segments (epitopes) to stimulate targeted immune responses.	Promising preclinical research	Requires optimization for a broad immune response	Experts develop individual vaccination methods by enhancing essential protein sequences from viruses using epitope engineering	[70]
Supportive care (oxygen therapy, hydration, antipyretics)	Symptomatic treatment	Standard care is used for severe patients	The treatment fails to eliminate the virus infection while providing only supportive care for symptoms.	Enhanced critical care strategies	[4,5]

Table 3: Recent patents from the last decade on advanced therapeutics for the treatment of human metapneumovirus (hMPV)

Title of patent	Patent No.	Inventors	Publication year	Brief abstract	References
Compositions containing molecular iodine and methods against acute respiratory infection	KR20250016360A	Daehwang Kim	2025	Researchers developed an iodine-based spray for the prevention and treatment of respiratory infections, rhinitis, and nasal congestion through spraying or inhalation.	[78]
Compositions, methods, and kits to detect metapneumovirus, adenovirus, and/or rhinovirus nucleic acids	AU2024266774A1	Pamela DOUGLASS Amber HILLIUS Daniel Kolk Mehrdad R. Majlessi Ankur Shah	2024	The inventors formulated several compositions along with multiple kits that utilize oligomers for detecting metapneumovirus, adenovirus, and rhinovirus through uniplex or multiplex amplification.	[79]
DNA therapeutic encoding an antibody or antigen-binding fragment	AU2024264716A1	Hong Jiang	2024	Scientists designed non-viral DNA vectors in lipid vesicles to facilitate therapeutic protein expression. These vectors can be administered systemically or locally to treat various infections, cancers, and inflammatory diseases.	[80]
A nucleic acid composition, kit, and detection method for simultaneously and rapidly detecting 16 respiratory pathogens	CN119162388A	Zou Lilong, Li Zhencui, Li Baisheng, Guo Qianqiang, Zhang Chang, Chen Weishan, Sun Jiangshan, Wu Chunyang	2024	Researchers developed a multiplex PCR-based nucleic acid kit that enabled the rapid, cost-effective, and simultaneous detection of 16 different respiratory pathogens.	[81]
Method for quantitatively analyzing target material	US20240418710A1	Jun Kyu ChoiGyeong Woo KANG	2024	The inventors introduced a biochip-based quantitative analysis method that used multi-frame imaging to accurately quantify target substances and significantly improve resolution.	[82]
A kit for detecting respiratory viruses and its application	CN118547117A	Lu Mengmeng, Chen Jiangpo, Fat Tieliang Wang, Wenxuan Wang, Yongkai Ma, Mengmeng Liu Kangyong	2024	The researchers designed a respiratory virus detection kit that simultaneously detects up to 14 different viruses with high sensitivity, with efficient processing and batch detection.	[83]
Combination hMPV/RSV RNA vaccines	US20240366748A1	Giuseppe CiaramellaSunny Himansu	2024	This research presented ribonucleic acid (RNA) vaccines and combination vaccines, along with the processes for using them and the compositions that contain these vaccines.	[84]
hMPV viral vector-based vaccines	US20240415952A1	Yvonne ChanSukanya Sasmal Antonia Stuebler Michael Kishko Sophia Mundle Linong Zhang Josh Di Napoli Judith Alamares-Sapuay Natalie ANOSOVA Sudha	2024	The researchers developed a hMPV vaccine that includes an hMPV F protein antigen and a method for inducing an immune response through vaccination.	[85]

(Contd...)

Table 3: *(Continued)*

Title of patent	Patent No.	Inventors	Publication year	Brief abstract	References
		CHIVUKULA Hillary Danz Tod STRUGNELL Rachel Groppo Peter Collins Ursula Buchholz Shirin Munir Bibha DAHAL			
Combination respiratory mRNA vaccines	WO2024231565A1	Nicholas Keith CLARK Emilie DANVE-CHERY Joshua DINAPOLI Michael KISHKO Bachra Rokbi Christopher SLADE Timothy John TIBBITTS William Warren Linong Zhang	2024	Researchers investigated mRNA formulations encoding F protein antigens from RSV, hMPV, and PIV3 to induce immune responses against hMPV viruses.	[86]
Antibody neutralizing human respiratory syncytial virus (RSV)	US20240247052A1	Kalpit A. VoraKara S. Cox Aimin Tang Zhifeng Chen Daniel Di Stefano Lan Zhang Hua-Poo Su	2024	The researchers generated high-neutralizing monoclonal antibodies against RSV and hMPV, including encoding nucleic acids for diagnostic, preventive, and therapeutic applications, particularly for infants and the elderly.	[87]
Antibodies to human pneumoviruses and methods of use thereof	WO2024173657A2	James E. Crowe, Jr.	2024	This research presented antibodies that neutralized RSV and hMPV.	[88]
hMPV whole genome enrichment kit for sequencing analysis	CN117646088A	Tian Gu, Du Lian, Wang Lei, Zhang Zhiqiang	2024	Scientists developed a 29-primer set that facilitated high-coverage whole-genome sequencing of hMPV, achieving ≥99% coverage at ≥1000×depth.	[89]
Respiratory virus nucleic acid vaccines	US20230381301A1	Giuseppe Ciaramella, Sunny Himansu	2023	This patent reports RNA-based vaccines that express the F proteins of hMPV and hPIV3, offering potential immunity against these respiratory viruses.	[90]
hMPV mRNA vaccine composition	US20220378904A1	Lori Panther, Christine Shaw, Igor Smolenov, Michael Watson, Tal Zaks	2022	This patent reports an mRNA-based vaccine that utilizes lipid nanoparticles to trigger immune responses against the hMPV and hPIV3 fusion glycoproteins.	[91]
Antibody neutralizing human RSV.	US11981726B2	Kalpit A. Vora, Kara S. Cox, Aimin Tang, Zhifeng Chen, Daniel DiStefano, Lan Zhang, Hua-Poo Su	2023	In this patent, researchers developed high-titer anti-RSV monoclonal antibodies for passive immunization, along with corresponding nucleic acids for diagnostic, preventive, and therapeutic applications.	[92]

(Contd...)

Table 3: *(Continued)*

Title of patent	Patent No.	Inventors	Publication year	Brief abstract	References
Immunogenic antigen identification from a pathogen and correlation to clinical efficacy	US11931408B2	Ann Marie Leen, Pailbel Aguayo-Hiraldo, Ifigeneia Tzannou, Juan F. Vera Valdes	2022	In this patent, researchers developed a method to detect immunogenic pathogen antigens and match T cell properties with clinical efficacy through mathematical modeling.	[93]
Recombinant hMPV f proteins and their use	WO2021222639A2	Peter Kwong, Guillaume Stewart-Jones, Jason Gorman, Li OU, TongqingZhou, Baoshan Zhang, Wing-Pui Kong, Yaroslav TSYBOVSKY, John Mascola, Peter Collins, Ursula Buchholz	2021	In this patent, researchers designed stabilized hMPV F ectodomain trimers and nucleic acids to provoke immune responses and contribute to the prevention and treatment of hMPV infection.	[94]
Anti-RSV antibodies and methods for their production and use	JP2020503844A	Laura M. Walker, Laura M. Walker	2020	In this patent, researchers identified and produced neutralizing anti-RSV antibodies that target RSV subtype A and RSV subtype B, while also developing methodologies for their isolation, preparation, and use.	[95]
Pharmaceutical composition for reducing the symptoms and disease of the respiratory infection caused by hMPV, which comprises at least one agent that neutralises the function of the TSLP and/or TSLPR and/or OX40L and/or CD177 molecules, and a pharmaceutically acceptable excipient, and the use thereof	AU2016402264B2	Susan Marcela Bueno Ramirez, Alexis Mikes Kalergis Parra, Margarita Kam-Lem LAY REMOLCOI	2018	In this reported pharmaceutical formulation, monoclonal antibodies targeting TSLP, TSLPR, OX40L, and CD177 were used, which attenuate symptoms associated with hMPV infection.	[96]
Treatment of hMPV	WO2016200916A1	Ronald D. Moss	2016	In this patent, researchers developed sialidase-anchoring inhibitors that interfere with virus entry into target cells, effectively preventing hMPV infection.	[97]

clinicians face and influences treatment policy, which might lead to an undesirable outcome. Interaction between hMPV and other pathogens must also be understood with respect to the mechanisms causing increased severity of the disease.[76]

Narrow knowledge regarding sequelae aute

While hMPV has been defined as an agent of acute respiratory illness, hMPV sequelae on the long-term outcome of the illness remain narrow to fully know. Recent findings, however, provide indications that hMPV may have long-term sequelae manifested in terms of asthma exacerbation and bronchiolitis obliterans mainly among young children. Further studies are, however, required to completely define the possible long-term sequelae of hMPV infection and their effect on respiratory health. Longitudinal research is necessary to monitor the health status of those who have undergone hMPV infection and determine risk factors for the development of chronic respiratory morbidity. This information will guide the design of early interventions and prevention of long-term respiratory morbidity related to hMPV.[77]

There has been much advancement in the treatment of hMPV, and Table 3 summarizes the latest patents in the last decade regarding advanced therapeutics in treatment of hMPV

CONCLUSION AND FUTURE SCOPE

The worldwide public health importance of hMPV remains substantial because it primarily affects three vulnerable populations, including infants and elderly people, along with immunocompromised patients. Scientific understanding of hMPV epidemiology and transmission mechanisms, and pathogenic processes has not led to any licensed antiviral medications or vaccine solutions. The only available management today involves supportive care, revealing an urgent requirement to develop targeted therapeutic interventions according to research findings. The current studies on nucleoside analogs, monoclonal antibodies, fusion inhibitors, and RNAi hold promising pathways for the creation of effective treatments. Studies aim to establish long-term immunity through three different vaccine strategies, including subunit proteins along with VLPs and live attenuated viruses. The application of diagnosis and treatment remains challenging due to misdiagnosis errors from respiratory virus symptom similarities and limited testing access, and viral immune system escape behavior. Attaining solutions through these barriers stands essential for both improved clinical results and reduced global impact from infections with hMPV. Research on hMPV should advance toward developing affordable diagnostic methods alongside treatments that can be easily accessible worldwide.

The development of epitope-based and VLP vaccines stands out as a promising approach toward sustainable immunity protection that produces minimal adverse events. The development of targeted therapies will depend on intensified studies into antiviral drug candidates alongside their clinical efficiency assessments. Early detection and virus mutation tracking through molecular virology methods, together with artificial intelligence predictive models, lead to optimized treatment plans. Knowing how hMPV affects long-term respiratory health conditions will help in designing a prevention framework. Virologists, along with immunologists and pharmaceutical scientists, need to collaborate using interdisciplinary techniques to break current obstacles that stand in the way of developing hMPV-specific interventions.

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