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HUMAN METAPNEUMOVIRUS: A RISING THREAT IN ACUTE RESPIRATORY INFECTIONS AND ADVANCES IN DIAGNOSTIC AND PREVENTIVE STRATEGIES

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ABSTRACT

Human metapneumovirus (hMPV) is a key contributor to acute respiratory infections (ARIs), particularly in young children, the elderly, and individuals with weakened immune systems. Since its discovery in 2001, this negative-sense RNA virus has been recognized for its seasonal transmission, often coinciding with other respiratory pathogens. Severe cases are more likely to occur in patients with underlying health conditions or at a very young age. Treatment options are primarily supportive, although potential antivirals such as ribavirin and fusion inhibitors are being explored. Advances in molecular diagnostics such as RT-PCR have enhanced the ability to detect hMPV and distinguish it from coinfections. Promising vaccine candidates are currently under investigation, including subunit vaccines, virus-like particles, and live attenuated strains. However, challenges, such as antigenic diversity and incomplete immunity from natural infections, remain barriers to vaccine development. Continued research on hMPV's pathogenesis, immune evasion strategies, and vaccine development is essential to reduce the global health burden, especially in high-risk groups.

KEYWORDS: Human metapneumovirus (hMPV), Acute respiratory infections (ARIs), Respiratory pathogens, Molecular diagnostics, Vaccine development.

INTRODUCTION

Acute respiratory tract infections (ARIs) are among the leading causes of morbidity and mortality worldwide, particularly in children under the age of five years.[1] Recent global estimates suggest that ARIs contribute to over five million hospitalizations annually, with a significant burden in low- and middle-income countries, underscoring the

urgent need for improved prevention and treatment strategies.[2] In 2000, ARIs accounted for approximately 20% of all deaths in this age group, with the majority of fatalities occurring in sub-Saharan Africa and Southern Asia.[3] While the incidence rates of ARIs are comparable in developed and developing countries, mortality rates are disproportionately higher in low-income regions due to limited access to healthcare.[4] Although several well-established viral pathogens, such as the human respiratory syncytial virus (RSV), parainfluenza virus, influenza virus, coronavirus, and rhinovirus, are known to cause ARIs, a significant number of respiratory infections, estimated to range between 20% and 40%, remain unknown.[5,6]

Human metapneumovirus (hMPV), first discovered in the Netherlands in 2001 by using molecular and serological techniques, has emerged as a key contributor to ARIs, particularly in children.[7,8] Retrospective studies have shown that hMPV has been circulating since at least 1967.[9] Belonging to the Metapneumovirus genus within the Pneumoviridae family, hMPV is a negative-stranded RNA virus with two main genotypes (A and B) and is further divided into subgroups.[10] Approximately 95% of children are infected with hMPV by the age of five years, and the virus can continue to cause reinfections throughout life.[11] Despite advances in the understanding of its molecular biology and epidemiology, there is still no reliable vaccine to prevent hMPV infection, highlighting the need for further research into its pathogenesis and immune evasion mechanisms.[12] Notably, efforts to develop vaccines are ongoing, although challenges such as antigenic variability and the lack of robust immunity following natural infection remain significant hurdles.

The Virus

Human metapneumovirus (hMPV) is a lipid-enveloped, single-stranded, negative-sense RNA virus belonging to the Pneumoviridae family under the genus Metapneumovirus.[13] It is transmitted via respiratory droplets, and severe infections are linked to risk factors such as premature birth, immunocompromised status, and chronic pulmonary, neurological, or cardiac conditions.[14] hMPV have a spherical structure (150–200 nm in diameter) and are divided into two major subgroups (A1, A2, B1, and B2) based on genetic variations. Subgroup A shows greater genetic diversity than Subgroup B.[15]

The hMPV virion is pleomorphic, ranging in size from 150 to 600 nm, and contains a negative-sense single-stranded RNA genome organized as N–P–M–F–M2–SH–G–L, which encodes nine proteins.[16] The nucleocapsid, made up of the N, P, L, and M2 proteins, is surrounded by the matrix (M) protein and enveloped in a lipid bilayer containing surface glycoproteins, including F, SH, and G.[14,16] The F protein facilitates fusion with the host cell membrane, the G protein plays a key role in viral attachment, and the SH protein is thought to modulate host immune responses.[17] The F and G proteins facilitate viral attachment and fusion with heparan sulfate receptors on host cells, enabling viral entry, replication, and budding. These proteins are also potential targets for therapeutic intervention because of their critical role in the viral life cycle.[18]

The M protein plays a key role in assembly and budding, whereas N protects the viral genome from nuclease degradation.[19] Additionally, the M2 protein regulates replication and suppresses the host innate immunity, contributing to the ability of the virus to evade detection.[19,20]

hMPV is classified into two major genotypes, A and B, which are further subdivided into subgroups (A1, A2, B1, and B2).[10] Genomic analyses revealed that nucleotide and amino acid similarities were higher within subgroups than

between genotypes, with the N gene being the most conserved and the G gene the least conserved.[10,17] The virus uses various mechanisms to evade the host immune response, including interference with pattern recognition receptors such as toll-like receptors and RIG-I-like receptors, as well as suppression of dendritic cell activity and T-cell activation.[21] These immune evasion strategies result in incomplete viral clearance and increased likelihood of reinfection.[21,22] Understanding the structure, genomic diversity, and immune evasion tactics of hMPV is crucial for developing effective vaccines and targeted therapies.

Epidemiology and Transmission

Human Metapneumovirus (hMPV) is a globally distributed respiratory pathogen that was first identified in the Netherlands in 2001, although retrospective studies trace its circulation back to 1958.[7,8] hMPV primarily affects children under two years of age and immunocompromised individuals, with seroprevalence studies indicating that 90–100% of children are infected by the age of 5–10 years.[11] The virus is transmitted through respiratory droplets, direct contact with infected secretions, and contaminated surfaces, with outbreaks typically occurring during the winter and spring.[14]

Crowded environments, such as schools, day care centers, and healthcare settings, facilitate transmission, leading to significant morbidity.[23] While adults usually experience mild symptoms, severe complications are more common in infants, the elderly, and those with underlying chronic conditions or weakened immunity such as pneumonia, bronchiolitis, or acute respiratory failure.[23,24] hMPV's seasonal distribution shows peak infection periods between January and March in the northern hemisphere and June to July in the southern hemisphere.[25] This seasonal trend is thought to be influenced by climate-related factors such as temperature and humidity, which may affect viral stability and human susceptibility to infections.

Studies have indicated that the hMPV infection season often overlaps with that of other respiratory viruses such as RSV and influenza.[26] The incubation period for hMPV varies among individuals, typically lasting 3days.[27] In animal models, peak viral titers were observed between days 4 and 5.[28] Re-infection with hMPV can occur throughout adulthood due to insufficient immunity from prior infections or exposure to different viral genotypes.[14] The virus often co-circulates in genotypes A and B during peak respiratory virus seasons, and frequent re-infections with different genotypes have been observed.[27]

In 2018, an estimated 142 lakh cases of hMPV-associated acute lower respiratory infections occurred in children worldwide, emphasizing their significant impact on pediatric health.[2] In India, the prevalence of hMPV in children with ARIs varies by region.[29] Rates were reported in Chennai (4%), Pondicherry (5%), and Vellore (12.7%).[30] Risk factors for severe hMPV infection include premature birth, young age, chronic pulmonary conditions, and underlying heart or neurological disorders. Infected children are more likely to require supplemental oxygen, have longer stays in intensive care units (ICU), and undergo chest radiography.[31] Approximately 40% of hospitalized children with hMPV have pre-existing high-risk conditions such as asthma or chronic lung disease.[32] The hospitalisation rate was significantly higher in children under six months of age than in those aged six months to five years.[33] hMPV infections in adults are typically mild, but in the elderly or those with chronic respiratory diseases such as COPD, more severe complications can arise, including dyspnea.[34]

The virus is often reported to be co-infected with other respiratory pathogens such as RSV, bocavirus, rhinovirus, influenza, and parainfluenza viruses.[35] In some cases, co-infection with bacteria such as Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae has been observed.[36] However, the impact of co-infection on the severity of hMPV infections remains unclear, with some studies suggesting that co-infection may increase the likelihood of ICU admission and prolonged hospital stays, while others find no such correlation.[37] Despite the significant role of the virus in respiratory infections, particularly in vulnerable populations, no vaccine is available, highlighting the need for continued research into preventive and therapeutic strategies.

Pathogenesis

hMPV persists in the host owing to a delayed immune response, with minimal and late activation of cytotoxic T lymphocytes, leading to impaired virus clearance.[38] It interferes with superantigen-induced T-cell activation by infecting dendritic cells, restricting the proliferation of CD4+ T cells, and impairing long-term immunity.[39] Compared to other respiratory viruses such as RSV and influenza, hMPV is less effective in inducing cytokines such as IL-12, TNF-α, IL-6, IL-1β, IL-8, and IL-10. hMPV infection induces pulmonary inflammation with increased levels of pro-inflammatory molecules, such as IL-2, IL-8, IL-4, IFN-α, macrophage inflammatory protein-1α, and monocyte chemotactic proteins, leading to perivascular and peribronchiolar infiltration and alveolar damage.[38] While the role of toll-like receptor signalling in hMPV pathogenesis is not fully understood, studies in MyD88-deficient mice have shown reduced pulmonary inflammation, suggesting the importance of this pathway.[39] Evidence of systemic infection is limited but includes the detection of hMPV in the middle ear fluid and brain tissue of patients with encephalitis.[27] Clinically, hMPV causes a range of respiratory illnesses ranging from mild cold-like symptoms to severe respiratory distress, such as bronchiolitis and pneumonia, particularly in vulnerable populations, such as young children, the elderly, and immunocompromised individuals.[27] Risk factors for more severe disease include age, underlying respiratory conditions, such as asthma and COPD, and immunocompromised status.[11] Early identification and intervention are crucial for managing hMPV infections and preventing complications, emphasizing the need for continued research to better understand the impact of the virus and develop effective interventions.

Clinical Manifestations of hMPV

Human metapneumovirus (hMPV) presents with a broad range of respiratory symptoms, ranging from mild upper respiratory tract infections (URTI) to severe lower respiratory tract infections (LRTI). The virus has an incubation period of **5–6** days, with common symptoms, including nasal congestion, cough, sore throat, fever, and general discomfort. Severe infections can cause bronchiolitis, pneumonia, wheezing, and respiratory distress, particularly in infants, older adults, and immunocompromised patients.[14,27,34]

Potential complications include respiratory failure, secondary bacterial infections, and worsening of preexisting lung diseases. Given its clinical similarity to RSV, influenza, and other respiratory viruses, accurate diagnosis is essential. Early recognition of hMPV is vital for timely intervention, particularly in high-risk groups, to minimize complications and improve outcomes.[15,28,35]

Diagnosis and Laboratory Testing

Accurate diagnosis of hMPV infection requires a combination of clinical evaluation and laboratory testing techniques to effectively identify the virus and differentiate it from other respiratory pathogens.[41] Commonly used diagnostic methods include the polymerase chain reaction (PCR), which detects viral RNA, and serological tests, which identify

antibodies against hMPV.[11] These tests not only confirm the presence of the virus but also help assess the stage of infection, guiding the selection of appropriate therapeutic measures. Furthermore, differentiating hMPV from other respiratory pathogens is crucial for implementing effective public health strategies, enabling tailored treatment and improving patient outcomes.[42] Several cell lines, including Vero, HEp-2, Hep G2, and LLC-MK2 cells, have been used for hMPV growth and isolation.[43] A recent study identified the human Chang conjunctiva cell line (clone 1-5C4) and the feline kidney CRFK cell line as the most suitable for hMPV propagation.[44] However, hMPV has a slow growth rate in cell culture, with cytopathic effects such as cell rounding, detachment, and syncytium formation, making it less efficient for diagnostic purposes.[41,44] As a result, antigen detection methods using anti-hMPV antibodies in direct fluorescence or ELISA-based assays are often employed alongside cell culture.[31] The sensitivity and specificity of cell culture detection were reported to be 68% and 99%, respectively, compared with real-time RT-PCR detection.[41] Although cell culture is rarely used for hMPV diagnosis, molecular methods, such as RT-PCR and real-time RT-PCR, have become the standard. Multiplex PCR (mRT-PCR) assays have been developed to detect a broader range of respiratory viruses with increased sensitivity and speed, with 100% sensitivity and 96% specificity compared to 54.6% sensitivity and 100% specificity of traditional RT-PCR. mRT-PCR also enables the detection of co-infections, even with low viral loads that may not be detectable through cell culture or immunostaining. However, routine diagnostic RT-PCR tests for hMPV are not widely available in clinical laboratories. For rapid and accurate diagnosis, immunofluorescence assays and direct fluorescent antibody methods are used as the first-line tests, followed by RT-PCR for negative samples.[27] In the future, the availability of shell vial centrifugation cultures and hMPV monoclonal antibodies will significantly enhance the speed and accuracy of hMPV diagnosis in the clinical setting.[45]

Current Treatment and Prevention Strategies

Current treatment and prevention strategies for human metapneumovirus (hMPV) primarily focus on supportive care, vaccination efforts, and the exploration of antiviral therapies that target specific viral mechanisms.[40] Recent advancements have emphasized the importance of early diagnosis and intervention to improve patient outcomes, facilitate timely therapeutic measures, and implement effective vaccination strategies, particularly for at-risk populations.[41] These strategies aim to enhance the immune response against hMPV, thereby reducing the severity of symptoms and preventing hospitalization among vulnerable groups. Currently, the available treatments for hMPV infection are mainly supportive; however, some reports suggest the potential use of ribavirin, immunoglobulin, fusion inhibitors, and small interfering ribonucleic acids in the treatment and control of infection.[27] Various vaccine candidates have been tested in rodent and non-human primate models, yielding promising results, although none have been tested in human volunteers.[27,41] Challenges exist in vaccine development, as a heat-inactivated viral vaccine was found to enhance lung disease in mice.[42] T-cell epitope vaccines have shown promise in reducing immunomodulation caused by hMPV, and animals immunized with cytotoxic T lymphocyte epitope vaccines produced fewer cytokines compared to non-immunized mice.[43] Additionally, chimeric vaccines tested in hamsters and African green monkeys have been shown to induce neutralizing antibody production and provide immunity against wild-type hMPV challenges.[42] Subunit vaccines using hMPV fusion proteins have also demonstrated cross-protective immunity in hamsters. Several hMPV F-subunit vaccines have provided strong protection in rodents, hamsters, and nonhuman primates.[44] A recent study showed that hMPV virus-like particles (VLPs), which mimic the viral surface properties of both subgroups A and B, induced a strong humoral immune response in mice, suggesting the potential use of a broad-spectrum vaccine.[45] However, further research is needed to develop an effective vaccine against all hMPV subgroups. The development of plasmid-based reverse genetics systems has significantly advanced the efforts to create live

vaccines. Recombinant hMPVs with deletions in genes such as SH, G, or M2-2 have been evaluated for viral replication levels, showing that these gene deletions do not affect the immunogenicity or antigenicity of the virus.[27] A live attenuated vaccine strain, created by modifying the glycosylation site of the F protein, provided complete protection against homologous viral challenges and partial protection against heterologous challenges even 56 days after inoculation.[44] These findings highlight the need for more in-depth research on the molecular pathogenesis of hMPV in order to develop an effective vaccine.

CONCLUSION

Human Metapneumovirus (hMPV) is a major respiratory pathogen, especially for vulnerable populations like young children, the elderly, and immunocompromised individuals. Currently, there are no effective vaccines or widely approved antiviral treatment. Management relies on supportive care; however, research on vaccines and antiviral therapies, including subunit vaccines and virus-like particles, shows promise in animal models. Early diagnosis using molecular techniques such as RT-PCR is crucial. Despite these challenges, ongoing research on hMPV pathogenesis and vaccine development is essential to address its global health impact, and clinical trials are needed to evaluate potential treatments.

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