Human Metapneumovirus: An Emerging Challenge for Public Health

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Abstract:

Human metapneumovirus (hMPV) is a negative-sense single-stranded RNA virus, discovered in 2001, that belongs to the Paramyxoviridae family. This respiratory pathogen causes acute infections in individuals of all ages, being potentially severe in children, the elderly, and immunocompromised individuals. The epidemiology of hMPV shows seasonal prevalence, distributed globally, often coexisting with other respiratory viruses. The pathogenesis of hMPV involves the infection of epithelial cells in the lower respiratory tract, leading to symptoms ranging from mild colds to severe bronchiolitis and pneumonia. Clinical manifestations include fever, cough, wheezing, and dyspnea. Diagnosis is made using methods such as polymerase chain reaction (PCR) and rapid antigen tests. As for treatment, there is no specific antiviral; symptoms are managed with respiratory support and fluids. Prevention relies on hygiene measures, such as handwashing and avoiding close contact with infected individuals, with no vaccines currently available.

Keywords: Human metapneumovirus, virus, respiratory infection

Introduction

Human metapneumovirus (hMPV) is an emerging respiratory virus that has gained increasing relevance since its identification in 2001. It belongs to the *Paramyxoviridae* family and is a significant etiological agent of acute respiratory infections, particularly in vulnerable populations such as children under five years of age, older adults, and immunocompromised individuals. hMPV infections present with a clinical picture that can be indistinguishable from other respiratory viral infections, especially respiratory syncytial virus (RSV) and influenza, posing challenges for both timely diagnosis and therapeutic management. In severe cases, hMPV can lead to complications such as bronchiolitis and pneumonia, which are associated with a substantial burden of morbidity.

Transmission occurs mainly through contact with respiratory secretions, highlighting the importance of implementing preventive measures in both community and hospital settings. Despite its impact on public health, hMPV has historically been less studied compared with other highly prevalent respiratory viruses. Its capacity to generate seasonal outbreaks and its association with severe clinical presentations, particularly in the context of coinfection, underscore the need for greater scientific attention. The absence of vaccines or specific antiviral treatments makes hMPV an emerging challenge that requires strengthening epidemiological surveillance, molecular diagnostics, and preventive strategies.

Biological, Epidemiological, and Clinical Aspects of Human Metapneumovirus

Discovery and Historical Evolution

Human metapneumovirus (hMPV) is a negative-sense, single-stranded RNA virus belonging to the *Paramyxoviridae* family. It was first identified in 2001 in the Netherlands, although retrospective studies suggest that it has been circulating in the human population since the 1950s. Its close phylogenetic relationship with avian metapneumoviruses supports a zoonotic origin, with evidence of more than 50 years of circulation in humans (1).

Taxonomy

- **Domain:** *Riboviria*
- **Kingdom:** *Orthornavirae*
- **Phylum:** *Negarnaviricota*
- **Class:** *Monjiviricetes*
- **Order:** *Mononegavirales*
- **Family:** *Pneumoviridae*
- **Genus:** *Metapneumovirus*

Genetic Characterization and Lineages

Within the genus *Metapneumovirus*, four hMPV lineages have been identified: A1, A2, B1, and B2. Lineage A1 is widely distributed and has been associated with respiratory infections in both children and adults, with a tendency to cause more severe disease, especially in vulnerable populations such as the elderly and immunocompromised. Lineage A2 shows greater genetic variability, which may enhance its ability to evade immune responses. Lineage B1 has been detected in sporadic outbreaks and is generally linked to milder disease. In contrast, lineage B2 has emerged more recently and may be associated with increased clinical severity, possibly due to distinctive genetic characteristics compared with other lineages.

Prevalence and Global Distribution

The prevalence of hMPV is significant worldwide, particularly among vulnerable groups such as children and older adults. It is recognized as one of the leading causes of acute respiratory infections (ARI), with detection rates varying according to population and clinical setting.

In children, hMPV infection is particularly relevant, as most have been exposed to the virus by the age of five. It is considered the second most frequent cause of lower respiratory tract infections in pediatrics, after RSV. Studies report that hMPV accounts for 7% to 19% of all ARI cases in hospitalized and outpatient children, with clinical manifestations ranging from mild illness to severe pneumonia (2–4).

In adults, detection rates are approximately 3%, although this figure likely underestimates the true burden, particularly in older adults and immunocompromised patients, who are at greater risk of severe disease, hospitalization, and even death. In these populations, presentations may range from mild respiratory symptoms to severe respiratory distress requiring hospital care (5).

hMPV has a global distribution and has been isolated on all continents. Its circulation follows a seasonal pattern, with higher incidence during colder months, likely related to environmental factors that favor transmission, such as low temperatures and increased time spent indoors. Despite its impact, it remains underdiagnosed in clinical practice, partly because diagnostic priorities are often given to other well-known respiratory viruses such as RSV or influenza (4,5).

Risk Factors

Age-related vulnerability

Children under five years of age are particularly susceptible to hMPV due to the immaturity of their immune systems. It is estimated that most children have had at least one hMPV infection by the age of five, with infants under six months being especially vulnerable because of their limited capacity to mount effective immune responses against respiratory pathogens (6).

In older adults, particularly those over 65 years, immunosenescence—the age-related decline in immune function—contributes to an increased susceptibility to severe infections, including those caused by hMPV. This phenomenon raises the risk of respiratory complications and hospitalization (7).

Preexisting health conditions

Chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular disease represent important risk factors for severe hMPV infection (8).

Immunocompromised patients, such as those undergoing cancer treatment, transplant recipients, or people living with HIV, are at substantially higher risk of severe illness, complications such as pneumonia or acute respiratory distress syndrome (ARDS), and poor outcomes (7).

Genomic Structure and Viral Proteins

hMPV possesses a negative-sense, single-stranded RNA genome of approximately 13.3 kb in length. This genome is encapsidated by nucleoproteins and organized in a layout that encodes nine essential proteins.

Unlike other viruses in the Pneumoviridae family, hMPV lacks the nonstructural proteins NS1 and NS2, which implies differences in its immune evasion mechanisms. The 3′ and 5′ ends of the genome contain complementary sequences that are critical for viral replication and transcription (10,11).

Three major surface proteins are expressed on the viral envelope:

F (fusion protein): Crucial for viral entry into host cells through membrane fusion. It is the main target for vaccine and antiviral development.

G (attachment protein): Facilitates binding to cellular receptors, including heparan sulfates and chemokines.

SH (small hydrophobic protein): Its function is not fully defined, though it appears to participate in immune evasion and viral persistence.

The F protein is synthesized as an inactive precursor (F0) that requires proteolytic cleavage to become active, yielding two subunits, F1 and F2, which are essential for virus-cell fusion. This process involves the formation of a stable six-helix bundle (6HB), necessary to bring viral and cellular membranes together and enable viral genome entry (12–18).

Replication Mechanism

hMPV replication occurs in the cytoplasm of infected cells, where inclusion bodies (IBs) form and act as specialized platforms for genome transcription and replication. This mechanism, shared with other *Mononegavirales* viruses, ensures efficient replication by concentrating viral proteins and genomic RNA in the same site (10).

Whole-genome sequencing studies have revealed high genetic diversity among circulating strains, with notable variability in the gene encoding the

G protein, which may have implications for host immune responses and epidemiological surveillance (19,20).

Pathogenesis and Interaction with the Immune System

hMPV primarily infects epithelial cells of the lower respiratory tract, triggering an inflammatory response that can range from mild to severe, depending on the host's immune status.

Key immune evasion mechanisms include:

- The G glycoprotein, which inhibits innate immune signaling, reducing immune cell activation and facilitating viral persistence (21).
- Modulation of type I interferon responses, which alters immune activity by suppressing proinflammatory cytokines such as IL-1β while increasing others such as IL-6 and TNF-α, potentially contributing to excessive inflammation (22).
- CD8+ T-cell dysfunction, through upregulation of the inhibitory receptor PD-1, which compromises adaptive immunity and facilitates reinfection or viral persistence (23,25).

hMPV infection can induce a skewed Th2-type immune response, predisposing to chronic inflammation and exacerbation of respiratory diseases, particularly in individuals with asthma or altered immunity (24).

Clinical Manifestations

The clinical presentation of hMPV varies according to age and immune status:

Children: Cough, rhinorrhea, wheezing, fever, and dyspnea predominate. Severe cases present as bronchiolitis and pneumonia, especially in infants aged 6 to 12 months. hMPV is estimated to account for 5–7% of pediatric hospitalizations due to respiratory infections (26–28).

Adults: Symptoms include cough, fever, nasal congestion, dyspnea, and sore throat. Patients with chronic conditions may develop bronchitis, pneumonia, or exacerbations of underlying disease (2,6,27).

Older adults: Cough, fever, and wheezing are common, but complications such as pneumonia and bronchospasm occur more frequently. Hospitalization rates are significantly higher in this group due to greater clinical severity (2,26,29).

Diagnostic Methods

The diagnosis of hMPV is primarily based on molecular techniques:

- Real-time RT-PCR: The reference method due to its high sensitivity and specificity, allowing detection and quantification of viral RNA.
- Duplex RT-PCR: Enables differentiation between subgroups A and B.
- RT-RPA combined with CRISPR/Cas12a: A rapid and highly sensitive method capable of detecting a single copy per microliter in under 30 minutes (30).
- Whole-genome sequencing: Using platforms such as MinION (Oxford Nanopore), it enables genetic characterization and epidemiological surveillance of circulating variants.
- Viral culture: Of limited use in clinical practice due to low sensitivity and the requirement of several days to obtain results.
- Systemic Complications
- Bacterial coinfections: observed in up to 29% of cases, with healthcare-associated infections in 43.7% and mortality rates of up to 37.5% among older adults and immunosuppressed patients (34,35).
- Acute kidney injury: Reported in 18.7% of patients, reflecting the virus's capacity to induce systemic damage beyond the respiratory tract (7).

Symptomatic Treatment and Supportive Care

Currently, no specific antiviral therapy has been approved for hMPV. Management is primarily symptomatic and supportive, and includes:

- Fever control with antipyretics.
- Adequate hydration.
- Oxygen therapy in cases of respiratory failure.
- Non-invasive or invasive ventilation in severe cases.
- Monitoring and management of complications, particularly in patients with comorbidities or immunosuppression (33).

Immunization and Vaccine Development

- At present, no licensed vaccine is available against hMPV.
- Vaccines under development:
  - A bivalent mRNA-based candidate targeting the F protein of both hMPV and human parainfluenza virus type 3 (hPIV3).
  - Induces neutralizing antibodies against hMPV-A, hMPV-B, and hPIV3 strains.
  - The F protein is the main antigenic target due to its essential role in viral fusion (38).

Preventive Measures

- General measures: Hand hygiene, mask use during outbreaks, respiratory etiquette, and surface disinfection.
- Isolation of symptomatic patients: Avoiding contact with vulnerable populations.
- Immune system strengthening: Balanced diet, adequate rest, and regular physical activity as complementary measures.

Conclusion

Human metapneumovirus (hMPV) has established itself as a relevant etiological agent of acute respiratory infections worldwide, particularly in pediatric populations, older adults, and immunocompromised individuals. Its ability to produce clinical syndromes indistinguishable from other respiratory viral infections, such as respiratory syncytial virus or influenza, poses challenges for both timely diagnosis and the implementation of appropriate therapeutic strategies.

Although significant progress has been made over the past two decades in understanding its biology, pathogenesis, and epidemiological profile, important limitations remain in terms of therapeutic and preventive tools. The current absence of an effective vaccine and specific antiviral agents underscores the urgent need to strengthen research efforts focused on developing immunoprophylactic strategies and targeted antiviral therapies.

In this context, it is imperative to reinforce epidemiological surveillance strategies, particularly in regions with a high burden of respiratory diseases, and to promote the sustained implementation of non-pharmacological preventive measures, such as respiratory hygiene, patient isolation, and surface disinfection.

Recent outbreaks and accumulating evidence reaffirm that, in a global health scenario still shaped by the consequences of the SARS-CoV-2 pandemic, the impact of other emerging respiratory pathogens such as hMPV should not be underestimated. Vigilance, understanding, and control of this virus are essential to mitigating its burden on healthcare systems and reducing associated morbidity and mortality, particularly among the most vulnerable groups.

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