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Human Metapneumovirus: A Comprehensive Review of Etiology and Pathogenesis

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KEYWORDS

HMPV, Pathogenesis, Virology, History, Outbreak..

ABSTRACT:

Objective: This review examines Human Metapneumovirus (HMPV) virology, genetic diversity, pathophysiology, and immune evasion mechanisms. Furthermore, it assesses the clinical consequences, current treatment choices, and preventive strategies, including vaccine research.

Study Design: This study uses a narrative literature review to summarize known research on Human Metapneumovirus (HMPV). It examines data from peer-reviewed publications to get insight into the virus's virology, pathogenesis, clinical impact, and therapeutic advances.

Methods: We undertook a comprehensive examination of peer-reviewed articles to collect data on HMPV virology, host interactions, and clinical outcomes. Several databases were searched for research articles on HMPV's epidemiology, molecular features, immunological response, and treatment approaches.

Results: HMPV is a leading cause of respiratory infections, especially in children, the elderly, and immunocompromised patients. It employs immune evasion strategies such as interferon response suppression and immunological signaling manipulation. Genetic variation, particularly in the F and G proteins, influences reinfection and disease severity. While supportive care remains the mainstay of treatment, antiviral agents such as ribavirin and monoclonal antibodies are being investigated. Vaccine creation is difficult due to antigenic variety, but emerging techniques, such as mRNA and subunit vaccines, hold promise.

Conclusions: HMPV is a global public health concern, requiring additional study on virus-host interactions, diagnostic tools, and targeted therapies. Advances in molecular virology and immunology will be critical in creating viable vaccines and treatments to reduce the HMPV-related illness load.

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1. Introduction

1.1 Overview of human Metapneumovirus (HMPV)

Human Metapneumovirus (HMPV) is a single-stranded, negative-sense RNA virus of the Pneumoviridae family, especially the Metapneumovirus genus (1). It was first discovered in 2001 and is now recognized as a leading cause of acute respiratory infections (ARIs) in humans, affecting people of all ages but especially young children, the elderly and immunocompromised individuals. The clinical manifestations of HMPV infection vary from moderate upper respiratory symptoms to severe lower respiratory tract disease, including bronchiolitis and pneumonia (2).

1.2. Historical Background and Discovery

HMPV was discovered relatively recently, despite its extensive history in humans. It was initially identified from respiratory specimens from children in the Netherlands who presented with unexplained ARIs, and its discovery marked a step forward in understanding the viral etiologies of respiratory diseases. Phylogenetic investigations demonstrated that HMPV has a tight evolutionary relationship with avian Metapneumovirus (AMPV), implying zoonotic origins (3, 13). Later research traced HMPV back decades, showing serological evidence of its prevalence in human populations as early as 1958 as shown in table 1(4).

Table: 1 Discovery, Phylogenetic studies and Global Epidemiology Studies with their detail

Year	Event	Details	References
2001	Discovery	HMPV was isolated from respiratory specimens in Dutch children with unexplained ARIs.	2
2003	Phylogenetic studies	Relationship with AMPV established, supporting zoonotic origins.	3
2004	Global epidemiology studies	HMPV identified in respiratory outbreaks across multiple continents.	9

1.3 Importance of studying HMPV and its pathogenesis

Human Metapneumovirus is a major global health problem due to its frequency, particularly in pediatric populations. According to studies, nearly all children are exposed to HMPV by the age of five, with reinfection occurring throughout life (5). Despite its clinical significance, we still don't know much about its molecular virology, immune evasion methods, and long-term effects on respiratory health (6).

Understanding the pathogenesis of HMPV is crucial for developing targeted treatments and vaccines. Its capacity to decrease innate immune responses, notably interferon signaling, tests the host's defense mechanisms (7). Furthermore, co-infections with other respiratory pathogens worsen illness severity, emphasizing the importance of precise diagnosis and treatment approaches (8).

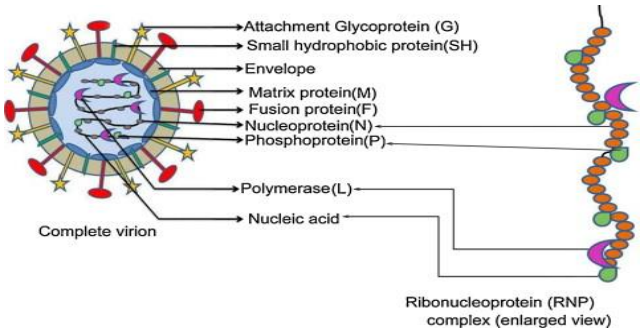

Figure: 1 Structure of Human Meta Pneumovirus

Figure: 1 A schematic representation of the human Metapneumovirus particle and ribonucleoprotein (RNP) complex.

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Virology of human Metapneumovirus (HMPV)

2.1. Classification & Phylogeny

Human Metapneumovirus (HMPV) is a negative-sense, single-stranded RNA virus from the Pneumoviridae family, genus Metapneumovirus. It is closely linked to the respiratory syncytial virus (RSV) in the same family, having structural and functional similarities (1, 10).

2.2. Gene Diversity and Subgroups

HMPV is genetically classified into two major lineages, A and B, which are further separated into four subgroups: A1, A2, B1, and B2 as shown in table 2. Variations in the glycoprotein (G) and fusion (F) genes serve as the basis for lineage differentiation. These subgroups have diverse geographic distributions and antigenic variants, which influence epidemiological trends and illness severity (11, 12).

Table: 2 Lineages, Subgroup, and their Key feather

Lineage	Subgroup	Key Features	References
Lineage A	A1, A2	More prevalent in pediatric cases; associated with severe respiratory infections.	11
Lineage B	B1, B2	Shows antigenic differences from Lineage A; milder symptoms reported.	12

2.3. Genome Structure and Organization

HMPV has a non-segmented, negative-sense RNA genome of about 13 kilobases in length. The genome encodes nine proteins: structural, non-structural, and regulatory proteins as shown an table 3 (13).

Table: 3 HMPV Key Genes and Their Functions

Gene	Protein	Function	References
N	Nucleoprotein	Encapsidates the viral genome, protecting RNA.	10
F	Fusion protein	Mediates membrane fusion for viral entry and syncytia formation.	26
G	Glycoprotein	Facilitates attachment to host cells.	23
SH	Small hydrophobic protein	Role in immune evasion and apoptosis inhibition.	41

1.3. Viral Life Cycle

2.3.1. Entry and Attachment to host cells.

The G protein allows HMPV to connect to host epithelial cells, while the F protein promotes membrane fusion. The interaction of these proteins with host receptors, such as heparan sulfate, is critical for viral entry (14).

2.3.2. Replication and Transcription Mechanisms

The viral polymerase complex, which consists of L and P proteins, initiates replication and transcription. The RNA genome is converted into monocistronic mRNAs, which are then translated into viral proteins (15).

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2.3.3. Assembly and Release of Virions

Following replication, newly produced nucleocapsids assemble on the host cell membrane. Virion budding occurs when the M protein interacts with the host's lipid bilayer, releasing infectious particles (16).

2.4. Evolutionary insights

2.4.1. Genetic drift and antigenic variations

HMPV exhibits genetic drift, resulting in antigenic changes largely in the G protein. These modifications enable the virus to elude host immunity, resulting in reinfections (17).

2.4.2. Comparative Analysis with RSV

HMPV and RSV have structural similarities, including genomic organization and host immune evasion tactics. However, HMPV has a lower replication rate and less severe immunopathology (18).

3. Pathogenesis of the Human Metapneumovirus

3.1 Host Tropism and Cellular Targeting

HMPV predominantly infects epithelial cells in the upper and lower respiratory tracts. The F protein is essential for viral fusion with host cell membranes, which allows entry and initiates infection. This tropism contributes to the virus's relationship with respiratory diseases (19).

3.2 Immune Evasion Mechanisms

The virus adopts a variety of tactics to avoid human immunity. It lowers innate immune responses by decreasing type I interferon production and altering cytokine networks. The SH protein has been linked to reduced apoptosis and immunological detection (20).

3.3. Host Immune Response.

3.3.1. Innate Immunity: Early infection activates TLRs and NK cells, contributing to innate immunity. TLRs identify viral RNA and activate downstream signaling pathways that promote antiviral responses (21).
3.3.2. Adaptive Immunity: Both B-cells and T-cells play important roles in eliminating infections. Neutralizing antibodies target the F and G proteins, whereas CD8+ T-cells drive lethal responses against infected cells (22).

3.4 Factors influencing disease severity

3.4.1. Host age: Severe consequences are more prevalent in newborns and the elderly because to immature or decreasing immunity (9).

3.4.2. Comorbidities: Underlying problems, such as asthma or immunosuppression, enhance illness severity (23).

3.4.3. Co-Infections: Concurrent infections with RSV or other pathogens can have a synergistic effect, affecting clinical results (24).

3.4.4. Viral load and genetic variants: Higher viral loads and alterations in the F and G genomes have been associated to higher virulence (25).

4. Clinical implications of HMPV pathogenesis.

4.1. The severity of the disease ranges from asymptomatic to severe respiratory illness

Human Metapneumovirus (HMPV) infections can be asymptomatic or cause severe respiratory disease. Mild instances frequently present with common cold-like symptoms such as cough, nasal congestion, and fever. Severe cases, particularly in vulnerable groups such as young infants, the elderly, and immunocompromised people, can result in bronchiolitis, pneumonia, and acute respiratory distress syndrome (ARDS) (9, 26) . Mortality rates are higher in hospitalized patients with severe disease, particularly those with underlying comorbidities (27) As shown in Figure 1, a significant proportion of HMPV cases are mild to moderate.

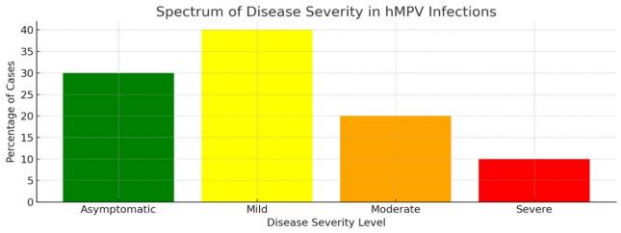

Figure 1: Spectrum of Disease Severity in HMPV Infections

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4.2. Differences in Pediatric and Adult Populations

4.2.1. Pediatric population

HMPV is the most common cause of acute lower respiratory tract infections (ALRTIs) among children under the age of five, accounting for a considerable portion of global morbidity and mortality. Infants and toddlers are more vulnerable because of their underdeveloped immune systems and lack of previous exposure to the virus. Common symptoms include bronchiolitis, croup, and wheezing (28).

4.2.2. Adult population

In adults, HMPV causes milder respiratory symptoms that resemble upper respiratory tract infections. However, elderly people and those with chronic conditions like COPD or heart failure may have severe exacerbations that necessitate hospitalization (29, 30).

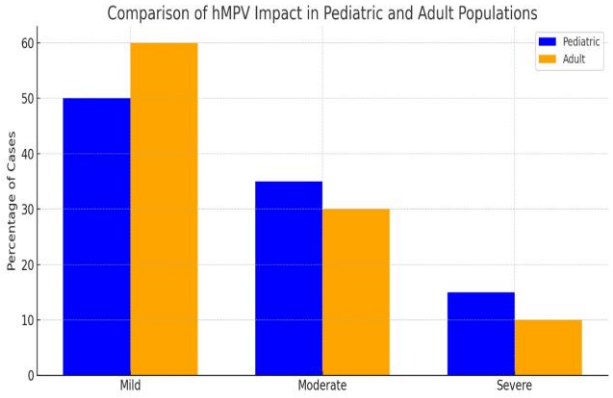

Figure 2: Age-Specific Differences in HMPV Infections: Comparative analysis of disease presentation in pediatric and adult populations, emphasizing differences in severity and immune response.

4.3. Long-Term Effects of Severe Infections

4.3.1. Chronic Respiratory Morbidity: Severe bronchiolitis caused by HMPV in early childhood has been associated to an increased risk of recurrent wheeze and asthma later in life as shown an figure 3 (9, 31).

4.3.2. Immunological Impacts: Persistent inflammation and immunological dysregulation after severe infections may predispose people to subsequent infections (32).

4.3.3. Functional impairments: Hospitalized patients with HMPV-induced pneumonia may have longer recovery times, poorer lung function, and a lower quality of life (33).

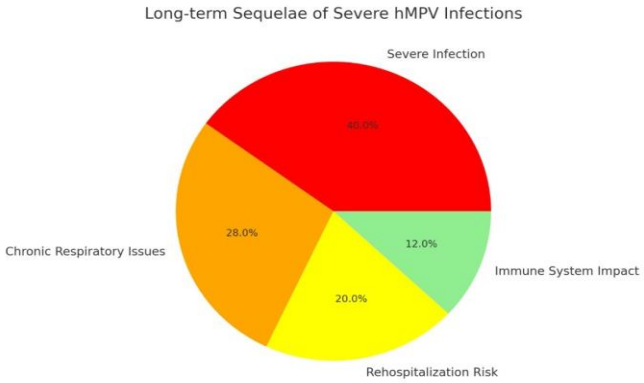

Figure 3: Long-Term Sequelae of Severe HMPV Infections: Diagram highlighting potential long-term impacts of severe HMPV infections, including chronic respiratory conditions and immune system alterations.

5. Therapeutic and Preventive Strategies

5.1. Current Treatment Options

5.1.1. Ribavirin: A broad-spectrum antiviral that inhibits HMPV replication in vitro by interfering with RNA synthesis, although clinical application is limited due to toxicity (34).

5.1.2. Fusion Inhibitors: Preclinical investigations have revealed that experimental compounds targeting the F protein can impede viral entrance (17, 35).

5.1.3. RNA interference (RNAi): Small interfering RNA (siRNA) has been shown to effectively silence HMPV genes and reduce viral load in experimental models (36).

5.2. Role of Immunomodulators and Supportive Care

5.2.1. Corticosteroids: Corticosteroids are used to treat severe inflammation, their usage is contentious since they may inhibit antiviral immunity (37).

5.2.2. Supportive Care: Oxygen therapy, hydration, and mechanical ventilation are essential for treating acute respiratory distress. Bronchodilators may alleviate symptoms in some circumstances as shown an table 4 (38).

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Table 4: Comparison of Disease Manifestations in Pediatric and Adult Populations

Parameter	Pediatric Patients	Adult Patients	References
Common Symptoms	Wheezing, bronchiolitis, and apnea.	Fever, cough, shortness of breath.	(9, 41)
Disease Severity	Often severe in young infants.	Milder except in immunocompromised.	(29)
Hospitalization Rates	Higher due to immature immune response.	Lower unless comorbidities are present.	(17)
Complications	Pneumonia, otitis media.	Secondary bacterial infections.	(22)

5.3. Vaccination Efforts

5.3.1. Challenges in Vaccine Development

5.3.1.1. Antigenic Diversity: HMPV is divided into four subgroups (A1, A2, B1, B2), making creating widely protective vaccines problematic (39).

5.3.1.2. Immune evasiveness: The virus can affect innate immune responses, making vaccinations ineffective (40).

5.3.1.3. Population Specific Needs: Shi et al, suggest that vaccine methods should be tailored to the unique immune responses of pediatric and geriatric populations to associated illnesses (41).

5.3.2. Updates on Clinical Trials and Potential Candidates

5.3.2.1. Live-Attenuated Vaccines: Experimental live-attenuated vaccines have demonstrated immunogenicity in preclinical investigations, with some moving on to early-phase clinical trials (10).
5.3.2.2. Subunit Vaccines: Vaccines based on the F protein are being developed to induce neutralizing antibody responses (42).

5.3.2.3. mRNA Vaccines: Using recent breakthroughs in mRNA vaccine technology, potential vaccines for HMPV are at the exploratory stage (43).

5.4. Future Directions in Therapy and Prevention

5.4.1. Prospects for Monoclonal Antibodies and Combination Therapies

5.4.1.1. Monoclonal Antibodies (mAbs): Advances in monoclonal antibody technology have permitted the development of mAbs that target the HMPV F protein. These are being tested for both preventive and therapeutic applications (44).

5.4.1.2. Combination Therapies: Combining antiviral with immunomodulators or mAbs may improve therapeutic success, especially in severe instances (45).

5.4.2. Emerging Technology and Personalized Medicine

5.4.2.1. Gene Editing: CRISPR-based methods to HMPV genomic areas may bring innovative antiviral tactics (46).

5.4.2.2. Host-Directed Therapies: attacking host components that are essential for viral replication is a promising option to directly attacking the virus (48).

6. Future Research Directions

6.1. Unanswered Questions in Virology and Pathogenesis

6.1.1. Immune Evasion Mechanisms: Although HMPV has been shown to decrease interferon signaling, the precise molecular mechanisms and viral components involved need to be investigated further (49).

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6.1.2. Persistence and Latency: It is currently unclear if HMPV causes a latent or persistent infection in some host groups (50).

6.1.3. Viral Proteins' Role in Pathogenicity: It is unknown what specific contributions HMPV proteins, such as SH and M2-2, provide to immune regulation and pathogenesis (51).

6.2. Emerging trends in diagnostics and therapeutic approaches.

6.2.1. Advanced Molecular Diagnostics: The development of quick, sensitive, and cost-effective diagnostic techniques, such as CRISPR-based assays, may improve the early detection of HMPV infections (52).

6.2.2. Point-of-Care Technologies: Portable nucleic acid detection technologies are evolving, allowing for reliable diagnosis in resource-constrained environments (53).

6.2.3Therapeutic innovations:

6.2.3.1. Host-directed therapies: Strategies aimed at host pathways crucial for viral replication, such as autophagy modulators, are gaining popularity (54).

6.2.3.2. Combination Therapies: Combining antiviral and immunomodulators may improve treatment outcomes, particularly in severe instances (55).

6.3. Research Gaps in Understanding HMPV-Host Interactions

6.3.1. Host Susceptibility Factors: A comprehensive knowledge of the genetic and immunological mechanisms that influence vulnerability to HMPV is needed (56).

6.3.2. Cytokine and Chemokines Dynamics: The involvement of specific cytokines and chemokines in illness severity and recovery requires additional investigation (57).

6.3.3. Immune responses vary with age: The differences in immunological responses between childhood and elderly populations have received little attention (58).
6.3.4. Microbiome-Virus Interactions: Emerging data suggests that the respiratory microbiome influences HMPV pathogenesis, but further research is required (59)

7. Conclusion

Human Metapneumovirus (HMPV) is a serious infection that causes respiratory disorders in people of all ages, with particularly severe consequences for susceptible groups such small children, the elderly, and immunocompromised people. This review focuses on the virology, pathophysiology, clinical implications, and therapeutic methods for HMPV, stressing its intricate interactions with the host immune system and capacity to escape immune responses. Despite advances in diagnostics and developing therapeutic options, significant gaps exist in our understanding of HMPV-host interactions, vaccine development, and effective antiviral therapy. Continued study is critical for understanding the molecular mechanisms underlying HMPV pathogenesis, improving diagnostic and therapeutic tools, and developing preventative methods, ultimately lowering the global burden of HMPV-associated disorders.

8. Declaration

8.1. Data Source: This review uses peer-reviewed literature from sources such as PubMed, Scopus, Web of Science, and Google Scholar. The most popular search phrases were "Human Metapneumovirus (HMPV)," "HMPV virology," "HMPV pathogenesis," "immune evasion mechanisms," "clinical manifestations of HMPV," "HMPV treatment," or "HMPV vaccine development." Relevant papers published between 2001 and 2025 were considered to provide both historical and current perspectives. Furthermore, reports from major health organizations such as the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control (ECDC) were examined. Only research published in English were examined, with a preference for articles containing experimental data, clinical trials, or systematic reviews.

8.2. Funding

This study received no external funding.

8.3. Institutional Review Board Statement

Not applicable.

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8.4. **Informed Consent Statement**

Not applicable.

8.5. Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

8.6. Conflicts of Interest

The authors declare no conflicts of interest.

8.7. Human and Animal Rights and Informed Consent

This article contains no studies with human or animal subjects performed by authors.

8.8. Author Contribution: All authors made significant contributions to the conception, design, drafting, and revision of this manuscript. **Mufakkir Aziz** conceptualized the study, supervised the overall process, and contributed to writing, critical review, and final editing. **Inam Ullah** was responsible for data collection, writing selected sections, and critically revising the manuscript for intellectual content. **Muhammad Asif** conducted an extensive literature review, prepared the tables and figures, and contributed to the sections on virology and pathogenesis. **Muhammad Nadeem** focused on the clinical implications and therapeutic strategies, providing substantial input during the revision phase. **Amna Ramzan** assisted in formatting, proofreading, and ensuring adherence to journal guidelines. **Muhammad Zubair** contributed to the analysis and interpretation of emerging treatment approaches and participated in manuscript editing. **Salwa M.A. Dahesh** offered insights into virological and immunological aspects, contributing to the discussion and refining the final draft. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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