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REVIEW MICROBIOLOGY

Human Metapneumovirus (HMPV): A comprehensive review of its virology, epidemiology, clinical features, and advances in diagnosis and prevention

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ABSTRACT

Human Metapneumovirus (HMPV) is a leading viral cause of respiratory infections worldwide, particularly affecting children, elderly adults, and immunocompromised individuals. Since its discovery in 2001, HMPV has been recognized as a significant pathogen responsible for both upper and lower respiratory tract infections, often manifesting as bronchiolitis, pneumonia, and wheezing in infants, as well as acute respiratory distress syndrome (ARDS) in older adults and immunocompromised patients. Although it shares clinical features with Respiratory Syncytial Virus (RSV), HMPV is genetically distinct, posing unique challenges for diagnosis, treatment, and prevention. This review provides a comprehensive analysis of HMPV, focusing on its virus structure, genetic makeup, taxonomy, clinical features, and epidemiology. It also explores advances in diagnosis, prevention, and therapeutic strategies, highlighting the urgent need for continued research to address the global burden of HMPV.

Keywords: Diagnosis; epidemiology; human Metapneumovirus; pathogenesis; respiratory viruses; Turkiye; vaccine development.

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Human Metapneumovirus (HMPV) was first identified in 2001 and has since emerged as a leading cause of acute respiratory infections (ARIs) worldwide [1]. It primarily affects young children, the elderly, and immunocompromised individuals, causing symptoms ranging from mild upper respiratory tract infections to severe lower respiratory tract diseases such as bronchiolitis and pneumonia [2].

HMPV is transmitted through respiratory droplets, making it highly contagious in settings like hospitals, daycare centers, and nursing homes [3]. Despite its clinical significance, HMPV remains under-recognized due to nonspecific symptoms and limited routine diagnostic testing, often leading to misdiagnosis or underreporting [4].

Epidemiological studies indicate that HMPV is a year-round pathogen, with seasonal peaks during winter and early spring, similar to other respiratory viruses [5]. In Turkiye, HMPV has become a significant public health concern, particularly in pediatric populations, with high rates of hospitalization for bronchiolitis and pneumonia [6, 7].

VIRUS STRUCTURE AND MORPHOLOGY

HMPV is an enveloped, pleomorphic virus with an average diameter of 150-250 nm, displaying spherical, elliptical, or filamentous shapes under electron microscopy [8]. Its envelope contains two major glycoproteins:

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1. Fusion (F) Protein: Mediates viral entry into host cells and is a primary target for immune responses and vaccine development [9].
2. Attachment (G) Protein: Facilitates binding to respiratory epithelial cells, distinguishing HMPV from RSV, which lacks this protein [10].

The core structure includes the nucleocapsid (N) protein, which binds viral RNA, and the matrix (M) protein, which aids in viral assembly and budding [11]. The small hydrophobic (SH) protein plays a role in immune evasion, contributing to the virus's ability to persist in the host [12].

Highlight key points

- HMPV causes serious respiratory infections, especially in children, the elderly and immunocompromised individuals.
- Although it has similar symptoms to RSV, it is genetically and structurally distinct, making it difficult to diagnose and treat.
- It is globally prevalent and increases in winter/spring and is an important cause of pediatric hospitalizations in Turkey.
- PCR tests are the most sensitive method for diagnosis; there is no approved vaccine or specific antiviral treatment yet.
- Vaccine development is ongoing, but issues such as duration of immunity, genetic diversity and accessibility remain.

TAXONOMY AND CLASSIFICATION

HMPV belongs to the Pneumoviridae family and the Metapneumovirus genus, classified under Group V of the Baltimore Classification system for negative-sense RNA viruses [13]. It shares molecular and structural features with RSV but has distinct genomic organization and antigenic properties [14].

PHYLOGENETIC CLASSIFICATION

HMPV is classified into two genetic lineages, A and B, each further divided into sublineages (A1, A2, B1, B2). Studies in Turkiye have shown the co-circulation of both lineages, with periodic shifts in dominance between the sublineages during different epidemic seasons. This variability highlights the importance of ongoing genetic surveillance to inform vaccine strategies [15, 16].

VIRUS GENETICS AND PROTEIN FUNCTIONS

HMPV's genome is approximately 13.2 kb in length, encoding eight open reading frames (ORFs) that produce structural and non-structural proteins, including the N, P, M, F, G, SH, and L proteins [17]. The L protein, an RNA-dependent RNA polymerase, is essential for viral replication, while the NS1 and NS2 proteins modulate the host immune response to promote viral survival [18]. The genome of human metapneumovirus (hMPV) is organized in a 3′ to 5′ orientation and encodes at least nine proteins across eight sequential genes. These proteins include both structural and non-structural components vital to the virus's replication and interaction with the host [19].

Nucleoprotein (N)

The nucleoprotein (N) is the most abundant protein in hMPV. It encapsidates the viral RNA, forming a ribonucleoprotein (RNP) complex that protects the genome and serves as a template for transcription and replication [20].

Phosphoprotein (P)

The phosphoprotein (P) acts as a non-enzymatic cofactor. It binds to both N and L proteins, facilitating the recruitment and stabilization of the RNA polymerase complex on the nucleocapsid [21, 22].

Matrix Protein (M)

The matrix protein (M) associates with the inner envelope of the virion and plays a central role in virion assembly, budding, and structural integrity by bridging the RNP complex and the membrane [23].

Fusion Protein (F)

The fusion protein (F) mediates membrane fusion between the viral envelope and host cell. Initially synthesized as an inactive precursor (F0), it undergoes cleavage into F1 and F2 subunits, enabling viral entry. It is also a major target for neutralizing antibodies and a focus for vaccine design [24–26].

Glycoprotein (G)

The glycoprotein (G) facilitates viral attachment to host epithelial cells. Although not essential for replication *in vitro*, G contributes significantly to immune evasion and displays high antigenic variability, limiting cross-protective immunity across hMPV strains [27, 28].

Small Hydrophobic Protein (SH)

The small hydrophobic (SH) protein has an unclear function but is believed to play a role in modulating host

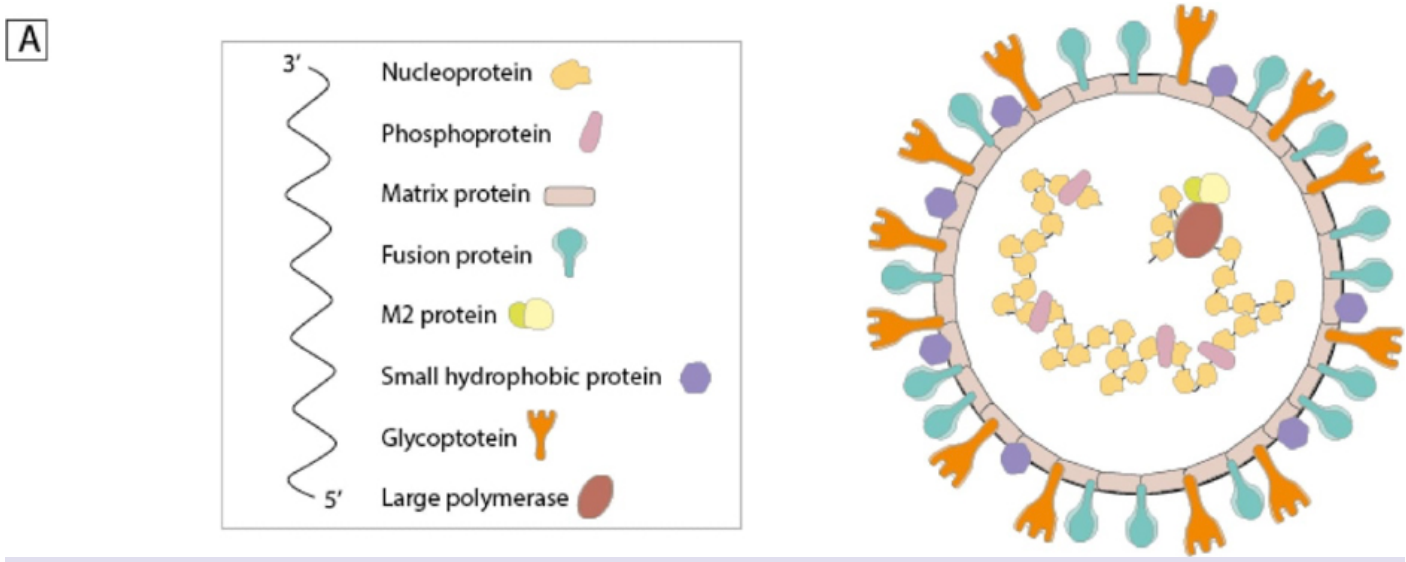


FIGURE 1. HMPV structure.

immune responses. Animal studies suggest that SH may suppress tumor necrosis factor-alpha (TNF-α) signaling and contribute to viral persistence [22, 29].

M2 Gene Products (M2-1 and M2-2)

The M2 gene encodes two proteins. M2-1 functions as a transcriptional antiterminator, enhancing mRNA synthesis. M2-2 regulates the balance between transcription and replication, promoting the synthesis of full-length genomes by downregulating mRNA production [22, 29, 30].

Large Polymerase Protein (L)

The large (L) protein is the catalytic subunit of the viral polymerase complex. It is responsible for RNA synthesis, including mRNA capping, methylation, and replication of the viral genome [22].

Proteins and structure of the virus are shown in Figure 1.

VIRAL REPLICATION CYCLE

HMPV enters host cells through receptor-mediated endocytosis. The F protein facilitates membrane fusion, allowing the viral genome to enter the cytoplasm for replication and transcription. Newly assembled virions are released by budding from the host cell membrane [31]. Human metapneumovirus replicates in the cytoplasm, following a process similar to other non-segmented negative-strand RNA viruses (NNSVs), such as RSV and measles [21, 22].

Attachment to Host Cells

Viral attachment is primarily mediated by the G protein, although the exact host receptor remains unclear. Heparan sulfate proteoglycans and integrins have been implicated in facilitating viral binding [22, 27].

Membrane Fusion and Entry

Fusion between the viral envelope and host cell membrane is facilitated by the F protein after it is cleaved into its active subunits. This allows the ribonucleoprotein complex to enter the cytoplasm [22, 24].

Transcription

Transcription begins at the 3′ end of the viral genome, with the L protein and its cofactor P synthesizing capped, polyadenylated mRNAs in a sequential gradient—a process termed transcriptional attenuation [22, 29].

Translation and Protein Synthesis

Viral mRNAs are translated by host ribosomes. The resulting proteins are trafficked to appropriate cellular compartments for assembly [22].

Genome Replication

When sufficient N protein accumulates, the polymerase switches from transcription to genome replication. A full-length antigenome is synthesized and used as a template to produce new negative-sense genomes [22, 29].

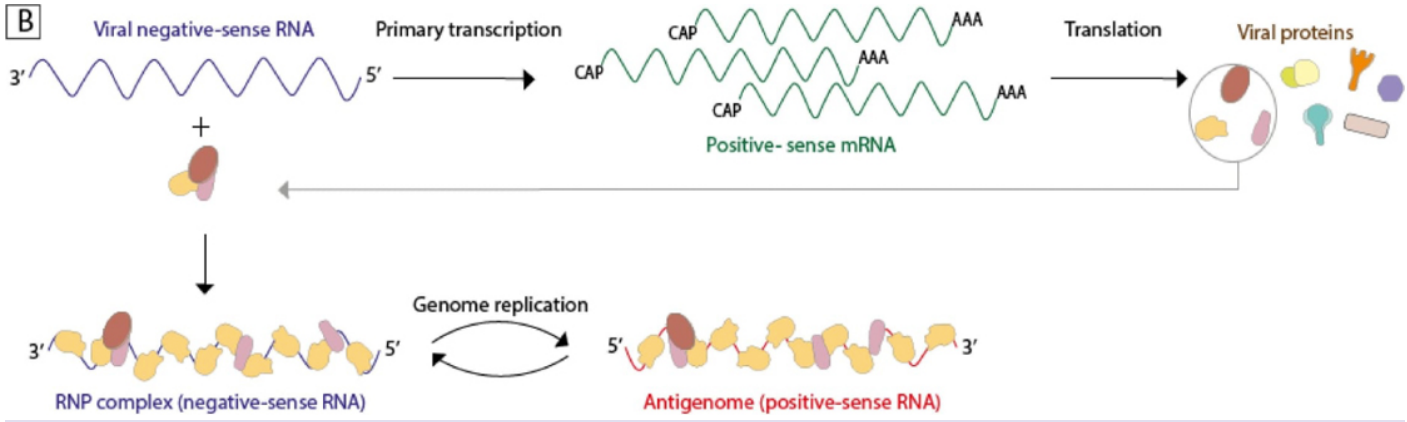


FIGURE 2. HMPV replication.

Virion Assembly and Budding

Assembly occurs at the plasma membrane where M protein coordinates packaging of the viral components. Budding takes place at lipid rafts, and the virion exits the cell by acquiring a host-derived envelope [22, 23]. The replication mechanism of the virus is shown in Figure 2.

EPIDEMIOLOGY

Human Metapneumovirus (HMPV) infections are distributed globally, affecting individuals across all age groups, with the highest burden observed in young children, the elderly, and those with underlying health conditions. Nearly all children are exposed to HMPV by the age of five, with reinfections occurring throughout life [32, 33]. Seasonal peaks typically occur in late winter and early spring, mirroring the patterns of other respiratory viruses such as respiratory syncytial virus (RSV) and influenza [34].

CLINICAL FEATURES

HMPV infections typically present with mild to moderate upper respiratory symptoms, such as fever, cough, and nasal congestion [35]. In severe cases, particularly in young children and elderly adults, HMPV can cause bronchiolitis, pneumonia, and ARDS, often requiring hospitalization [36]. Immunocompromised individuals are at higher risk of severe outcomes, including prolonged respiratory failure [37]. HMPV causes a wide range of respiratory symptoms, particularly severe in infants, elderly individuals, and immunocompromised patients. Common symptoms include fever (~80%), cough (60–70%), and wheezing (30–50% in pediatric cases) [38–40]. Nasal congestion is also frequent [38]. Bronchiolitis and pneumonia account for 10–20% of hospitalizations, while acute respiratory distress syndrome (ARDS) is observed in vulnerable populations [3, 34, 41, 42]. Co-infection with viruses such as RSV and influenza can exacerbate clinical severity, occurring in up to 20% of cases [43, 44].

GLOBAL PATTERNS

Studies conducted worldwide have shown that HMPV accounts for 5–15% of respiratory tract infections requiring hospitalization, with the highest rates in pediatric populations. In a meta-analysis spanning multiple countries, HMPV was identified in 10–20% of children hospitalized with lower respiratory tract infections (LRTIs), with a notable prevalence in low- and middle-income countries where access to advanced diagnostic tools is limited [7, 16]. In high-income countries, such as the United States and parts of Europe, the introduction of advanced molecular diagnostics like RT-PCR has improved HMPV detection rates in community-acquired pneumonia and bronchiolitis cases [45]. In the elderly, HMPV contributes significantly to hospitalizations and mortality rates, often in combination with chronic conditions such as chronic obstructive pulmonary disease (COPD) or cardiovascular diseases [15].

HMPV IN TURKIYE

Human Metapneumovirus (HMPV) has emerged as a significant respiratory pathogen in Turkiye, contributing to a substantial burden of acute respiratory infections (ARIs), particularly in pediatric populations. While HMPV affects individuals of all ages, its impact is most pronounced in young children, elderly adults, and immu-

nocompromised individuals. Despite its growing recognition as a key player in respiratory illnesses, HMPV remains underdiagnosed and underreported in many parts of Turkiye due to limited awareness, diagnostic challenges, and overlapping clinical symptoms with other respiratory viruses such as Respiratory Syncytial Virus (RSV), influenza, and parainfluenza virus [7, 16, 46]. In Turkiye, HMPV is increasingly recognized as a significant cause of acute respiratory tract infections in children and the elderly. Studies conducted in various regions, including Istanbul and Ankara, have demonstrated that HMPV accounts for approximately 7–10% of respiratory tract infections requiring hospitalization, particularly during the winter and early spring months [16, 46–48]. Data from Eastern Anatolia indicated that HMPV contributes significantly to seasonal respiratory outbreaks, often in combination with environmental factors such as air pollution and lower socioeconomic conditions [49].

EPIDEMIOLOGY AND PREVALENCE

Turkiye experiences seasonal peaks in HMPV infections, with the virus circulating primarily during the winter and early spring months, aligning with patterns observed in other parts of the world [5, 16]. Epidemiological studies indicate that HMPV is one of the leading causes of lower respiratory tract infections (LRTIs) in young children, with significant morbidity and hospital admissions due to diseases like bronchiolitis and pneumonia [50]. Recent research conducted in major Turkish cities, including Istanbul and Ankara, has shown that HMPV infection rates among hospitalized pediatric patients can reach as high as 20%, underscoring its clinical significance [16, 45, 51]. A 2020 study published in a Turkish medical journal revealed that HMPV was detected in approximately 17% of respiratory samples from children with acute respiratory symptoms, a rate comparable to other prominent viruses like RSV [16, 45, 52]. The study also highlighted that co-infections with multiple pathogens (including RSV, influenza, and HMPV) were relatively common, complicating diagnosis and treatment. Co-infections often result in more severe disease outcomes, requiring more intensive medical care [53]. In Ankara, the capital city, data suggests that HMPV infections are widespread but underreported due to diagnostic challenges. Real-time PCR testing, the gold standard for HMPV detection, has only become widely accessible in some Turkish hospitals in recent years [7, 15, 54]. Prior to this, many cases went undiagnosed, and the virus was often mistaken for other respiratory pathogens. The expansion of molecular diagnostics for respiratory viruses is now improving diagnostic accuracy and helping to determine the true burden of HMPV in Turkiye [16, 55].

CLINICAL FEATURES AND IMPACT ON CHILDREN

In Turkiye, the clinical manifestations of HMPV infections mirror global trends. The virus is most commonly associated with bronchiolitis, a viral infection of the small airways in the lungs that primarily affects infants and young children [7, 16, 46]. Pneumonia, another severe complication, is more common in infants under the age of 1 year and can lead to hospitalization and prolonged recovery [50]. Studies show that HMPV-related hospitalizations in Turkish children often involve a range of symptoms, including wheezing, fever, and cough, which are also seen in RSV infections [7, 16, 51]. Children with pre-existing respiratory conditions, such as asthma or chronic lung disease, are particularly vulnerable to severe outcomes when infected with HMPV. In some cases, these children require intensive respiratory support, including mechanical ventilation, due to the exacerbation of their underlying respiratory symptoms [52]. A multi-center study conducted in Izmir in 2021 analyzed the clinical characteristics of children admitted with acute respiratory infections caused by HMPV. The study revealed that approximately 25% of the children with severe ARI had HMPV infections, making it one of the leading viral causes of respiratory illness in the pediatric cohort [16, 53]. The study also noted that most children exhibited wheezing and required oxygen therapy due to acute hypoxemic respiratory failure, reinforcing the importance of early diagnosis and timely intervention [54].

HOSPITALIZATION AND INTENSIVE CARE

Hospitalization rates for HMPV in Turkiye are relatively high compared to other viral respiratory pathogens, especially for infants and children under two years of age [16, 55]. Intensive Care Unit (ICU) admissions due to respiratory failure, particularly in infants with bronchiolitis, are not uncommon. A study conducted at a major Turkish teaching hospital observed that children with HMPV infections often required extended ICU stays due to the severity of their respiratory distress [7, 16, 46]. These findings suggest that early identification and aggressive management of the disease can significantly improve outcomes

for these patients [50]. In adults, HMPV has been associated with pneumonia and worsening chronic obstructive pulmonary disease (COPD), especially in elderly individuals. A study from Istanbul demonstrated that older adults with comorbidities, such as diabetes, heart disease, or immunosuppression, were more likely to develop severe disease upon contracting HMPV [16, 45, 51, 55]. This highlights the importance of recognizing HMPV as a possible cause of severe respiratory illness in adults, particularly in those who are immunocompromised or elderly [52].

AT-RISK POPULATIONS

Certain populations are at increased risk of severe HMPV infections, including:

- Children under five years old: HMPV is a leading cause of bronchiolitis and pneumonia in this group, second only to RSV in many regions, including Turkiye [15, 45, 56].
- Elderly individuals: Age-related declines in immune function increase susceptibility to severe HMPV infections. In nursing home settings, HMPV outbreaks can cause significant morbidity and mortality [57].
- Immunocompromised patients: Individuals undergoing chemotherapy, organ transplantation, or those with primary immunodeficiencies are at high risk for prolonged and severe HMPV infections [58].

IMPACT OF ENVIRONMENTAL AND SOCIOECONOMIC FACTORS

Environmental factors, such as air pollution and seasonal variations, play a critical role in the epidemiology of HMPV. Urban areas in Turkiye, such as Istanbul and Ankara, report higher rates of HMPV-related hospitalizations, potentially linked to pollution and higher population density. Conversely, rural areas experience challenges due to limited access to healthcare and diagnostic resources, resulting in underreporting of HMPV cases [15, 45, 56].

SURVEILLANCE GAPS

Despite its clinical significance, HMPV remains underdiagnosed in many regions, including Turkiye, due to a lack of routine surveillance and reliance on clinical symptoms that overlap with other respiratory viruses. Establishing robust surveillance systems and integrating molecular diagnostics into routine clinical practice are critical for better understanding the true burden of HMPV [16, 57].

ECONOMIC BURDEN

The economic impact of HMPV is substantial, with direct costs stemming from hospitalizations, outpatient visits, and supportive care. Indirect costs, including lost productivity and long-term complications in vulnerable populations, further underscore the need for preventive measures. In Turkiye, seasonal peaks in respiratory infections strain healthcare systems, with HMPV contributing significantly to this burden [16, 58].

CLINICAL FEATURES

HMPV infections range from mild upper respiratory tract infections to severe lower respiratory tract infections. Symptoms include rhinorrhea, cough, fever, and wheezing [56]. Severe manifestations such as bronchiolitis, pneumonia, and respiratory failure are more common in high-risk populations, including young children and the elderly [57].

DIAGNOSIS AND SURVEILLANCE IN TURKIYE

While molecular diagnostics like PCR testing have greatly improved the accuracy of HMPV diagnosis in Turkiye, significant barriers to widespread testing remain, particularly in regional hospitals [16, 53]. In many areas, viral cultures and rapid antigen tests are still the primary methods used to diagnose respiratory infections, but these are not sensitive enough to detect HMPV accurately. As a result, many cases are either missed or misdiagnosed as RSV or influenza [54]. To address this issue, several academic hospitals in Turkiye have begun collaborating on surveillance programs aimed at monitoring HMPV circulation. These programs often focus on seasonal trends and investigate the incidence of co-infections with other respiratory pathogens [16, 55]. National guidelines are being developed to encourage broader adoption of molecular diagnostics for HMPV in both inpatient and outpatient settings [46].

PREVENTIVE MEASURES AND VACCINE DEVELOPMENT

Despite the growing recognition of HMPV's impact in Turkiye, there is currently no licensed vaccine or antiviral therapy for its prevention or treatment [7, 16, 50]. Supportive care, including oxygen therapy and mechanical ventilation, remains the mainstay of treatment for severe

cases. Research into monoclonal antibodies and vaccine development for HMPV is still in its early stages globally, including in Turkiye, but the country is actively involved in clinical trials investigating potential therapeutic agents [15, 45, 49, 51]. Prevention strategies in Turkiye primarily involve hygiene measures and supportive care to manage symptoms. Health campaigns are increasingly emphasizing hand hygiene, respiratory hygiene, and the importance of vaccination against other common respiratory viruses like influenza and RSV [16, 52]. However, the development of a vaccine specifically for HMPV remains a critical goal for the Turkish public health system, particularly given the virus's ability to cause severe disease in vulnerable populations [16, 53].

VACCINE DEVELOPMENT AND CLINICAL TRIALS

Several vaccine candidates targeting HMPV are in various stages of development, with promising progress seen in preclinical and early clinical trials. These include live-attenuated vaccines, subunit vaccines, vector-based platforms, and multivalent approaches designed to address the high burden of HMPV infections across different populations [7, 16, 24, 25].

Live-Attenuated Vaccines

Preclinical studies and early-phase trials of live-attenuated HMPV vaccines have shown robust immunogenicity, eliciting strong neutralizing antibody responses with minimal adverse effects [16]. These vaccines mimic natural infection, stimulating both humoral and cellular immune responses. However, achieving an optimal balance between attenuation and immunogenicity remains a challenge, especially for immunocompromised populations [45].

Subunit Vaccines

Subunit vaccines focusing on the prefusion conformation of the F protein have emerged as promising candidates. The prefusion F protein is the most immunogenic form and is crucial for neutralizing antibody generation. Recent advances in structural biology have enabled the stabilization of the prefusion F protein, improving vaccine efficacy [7, 15]. Subunit vaccines also offer safety advantages, particularly for older adults and those with underlying health conditions [31].

Multivalent Vaccines

Multivalent vaccines combining antigens from both RSV and HMPV have garnered attention due to the overlapping epidemiology and similar clinical impact of these pathogens [5]. These vaccines aim to provide broad protection, reducing the burden of both viruses in pediatric and elderly populations. Early studies have demonstrated cross-neutralizing activity and acceptable safety profiles, making them viable candidates for further development [5, 7].

Vector-Based Platforms

Viral vector-based vaccines leveraging replication-deficient adenoviruses or other platforms are being explored [49]. These platforms can deliver HMPV antigens efficiently and have the potential to induce strong cellular immunity. Vector-based vaccines are versatile and have been shown to work effectively in preclinical models [59].

Challenges and Future Directions

Despite these advancements, challenges remain, including addressing the antigenic diversity of HMPV, ensuring long-lasting immunity, and overcoming potential interference from preexisting immunity to related viruses such as RSV [60]. Large-scale clinical trials are essential to confirm the safety, immunogenicity, and efficacy of these vaccines across diverse populations. Furthermore, prioritizing vaccine accessibility and affordability in regions with high disease burden, such as Turkiye, will be critical to maximizing their public health impact [49, 61].

DIAGNOSIS AND ADVANCES IN PREVENTION

Current diagnostic methods for HMPV include polymerase chain reaction (PCR), immunofluorescence, and enzyme-linked immunosorbent assays (ELISA), with PCR being the gold standard due to its high sensitivity and specificity [54]. Rapid PCR assays for point-of-care testing are emerging as valuable tools for early diagnosis [55]. Prevention remains a challenge, as no licensed vaccine or specific antiviral therapy for HMPV is currently available [46]. Supportive care, including oxygen therapy and ventilation, remains the primary management strategy. In Turkiye, supportive care protocols for HMPV align with those for RSV and other respiratory viruses, focusing on symptom relief and the prevention of complications [15, 60].

CONCLUSION

Human Metapneumovirus (HMPV) is a significant respiratory pathogen with a growing impact on global public health, particularly in vulnerable populations such as children, the elderly, and immunocompromised individuals. Despite advances in diagnostic tools, challenges remain in prevention and treatment, underscoring the need for continued research into vaccine development and therapeutic strategies.

In Turkiye, HMPV has become a major cause of respiratory infections, highlighting the importance of enhanced surveillance, improved diagnostic infrastructure, and public health interventions. Global collaboration and investment in research are essential to address the challenges posed by HMPV and reduce its associated morbidity and mortality.

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