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Review Article

Human Metapneumovirus as an Emerging Respiratory Pathogen: A Comprehensive Review

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Abstract

Human metapneumovirus (hMPV) has emerged as a significant pathogen responsible for a wide spectrum of respiratory illnesses across all age groups, with the greatest burden observed in infants, older adults, and immunocompromised individuals. Since its discovery in 2001, extensive research has revealed its epidemiology, clinical manifestations, modes of transmission, and impact on public health. It is now recognized as a leading cause of both upper and lower respiratory tract infections. Despite significant advances in diagnostic technologies—particularly nucleic acid amplification methods such as RT-PCR—and a growing understanding of the virology and immune response, no licensed vaccine or specific antiviral therapy is currently available. Supportive care remains the mainstay of management. Co-infections with hMPV and other respiratory pathogens, such as RSV or SARS-CoV, present additional challenges and may complicate disease severity. Moreover, the limited understanding of hMPV immunopathogenesis, particularly in vulnerable populations, emphasizes the necessity for further research. In conclusion, hMPV represents an important target for future therapeutic and preventive interventions. With ongoing research and development, especially in vaccine design and antiviral therapy, there is hope for reducing the global disease burden of hMPV and improving outcomes for those most at risk.

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Introduction

Acute respiratory tract infections (RTIs) are the most prevalent illnesses affecting individuals of all ages across the world. They represent a major public health concern due to their significant contribution to both morbidity and mortality rates. Acute respiratory infections (ARIs) are a significant global health burden in low- and middle-income countries. According to estimates by the World Health Organization (WHO), ARIs are responsible for approximately 1.9 to 2.2 million childhood deaths each year, with about 70% of these fatalities occurring in Africa and Southeast Asia[1]. ARIs encompass infections involving any part of the respiratory tract; however, the majority of deaths are attributed to acute lower respiratory infections

(ALRIs), which are generally more severe. In children under five years of age, the incidence of ALRIs is estimated at 0.22 episodes per child per year[2]. The highest burden is observed in countries such as India, China, Pakistan, Bangladesh, Indonesia, and Nigeria[3]. Acute respiratory tract infections (ARTIs) represent the most frequently occurring illnesses across all age groups and genders. These infections encompass a broad spectrum of conditions, including pneumonia, influenza, and influenza-like illnesses (ILI), which collectively pose a significant health burden. In the United States, these diseases rank as the sixth leading cause of death, responsible for approximately 45,000 fatalities each year[4]. Annually, they account for an estimated 4 million visits to ambulatory care facilities and result in around 500,000 hospitalizations[4]. The global burden of ARTIs is evident beyond the United States as well. For example, in The Netherlands, the incidence of acute respiratory tract infections is notably high, with an estimated 5,445 cases per 10,000 person-years[5]. A substantial number of these infections are caused by viruses, making them one of the leading viral diseases affecting populations on a global scale.

The etiological spectrum of ARIs includes a wide range of pathogens, notably bacteria, viruses, and fungi. Among the bacterial agents, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* are most commonly associated with respiratory infections. Additionally, atypical bacteria such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Klebsiella pneumoniae* are also implicated, though less frequently[6]. Viral pathogens, however, play a dominant role in pediatric ARIs, accounting for nearly 60% of all ALRI cases in children[7]. Commonly identified respiratory viruses include respiratory syncytial virus (RSV), influenza viruses types A and B, human Parainfluenza viruses types 1, 2, and 3 (HPIV-1, HPIV-2, HPIV-3), rhinoviruses, adenoviruses (ADV), and human metapneumoviruses (HMPV).

In 2001, the identification of human metapneumovirus (HMPV) in nasopharyngeal aspirate samples collected over a ten-year period from 28 hospitalized infants and children suffering from respiratory tract infections[8]. These patients exhibited clinical signs and symptoms that closely resembled those typically associated with human respiratory syncytial virus (RSV) infections, including cough, wheezing, and difficulty in breathing. The study marked one of the earliest detections of HMPV and highlighted its potential role as a significant pathogen in pediatric respiratory illness. HMPV causes disease primarily in children but also can infect adults and immunocompromised individuals. The incidence of HMPV may vary from year to year in the same area[9]. The clinical features of the illness range from a mild upper respiratory infection to life-threatening severe bronchiolitis and pneumonia.

Virological Aspect

Human metapneumovirus (HMPV) is an enveloped, non-segmented, negative-sense single-stranded RNA virus belonging to the *Pneumoviridae* family, genus *Metapneumovirus*. Its genome is approximately 13 kilobases in length and encodes eight proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), M2 proteins (M2-1 and M2-2), small hydrophobic protein (SH), glycoprotein (G), and large polymerase protein (L). The virion is roughly spherical to pleomorphic in shape, measuring about 150 to 600 nanometers in diameter, and is surrounded by a lipid bilayer envelope derived from the host cell membrane[10]. Three of these are membrane-anchored glycoproteins, namely, the attachment (G), the small hydrophobic (SH), and the fusion (F) proteins. The F protein mediates fusion of the viral and cellular membranes during viral entry, induces syncytium formation in infected cells, and determines the cellular host range[4,10]. While F is highly conserved, is immunogenic, and induces protective antibodies, the other surface glycoproteins, G and SH, have been shown to be only weakly immunogenic[11]. The nucleocapsid within the envelope consists of the RNA genome tightly encapsidated by the N protein, along with associated P and L proteins, which are essential for replication and transcription. This structural organization supports the virus's ability to infect the respiratory epithelium, particularly in young children, the elderly, and immunocompromised individuals.[1]

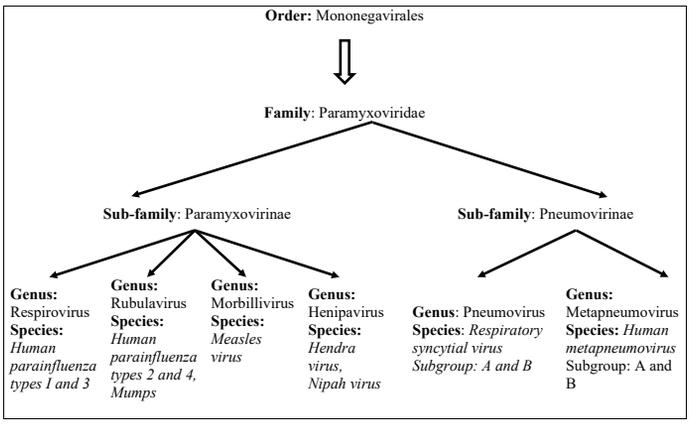

Figure I: human pathogens in the family Paramyxoviridae[3]

Genomic structure

The genomic structure of human metapneumovirus (hMPV) contains eight genes arranged in the order: 3'-N-P-M-F-M2-SH-G-L-5', which encode nine proteins, including nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), M2-1 and M2-2, short hydrophobic (SH),

attachment glycoprotein (G), and the large polymerase (L). Notably, while the F protein is highly conserved between hMPV and RSV (approximately 33% amino acid identity), the G and SH proteins differ substantially, with their amino acid sequences not align able due to low similarity[11]. The hMPV G protein is shorter than its RSV counterpart (236 vs. 299 amino acids) and is associated with multiple downstream open reading frames (ORFs), whose expression and function remain uncertain. Notably, the M2 gene contains two overlapping open reading frames (ORFs), M2-1 and M2-2, which play roles in transcription processivity and the regulation of the switch from transcription to replication, respectively[13]. The F, G, and SH genes encode surface glycoproteins, with F being highly conserved and essential for membrane fusion, while G and SH are more variable and dispensable for viral replication in vitro[12]. A key genomic difference is the absence of NS1 and NS2 genes in hMPV, which in RSV are major anti-interferon factors. The lack of these genes may influence hMPV pathogenesis, although their precise role is yet to be clarified. Recent advances in reverse genetics have allowed manipulation of the hMPV genome, demonstrating that both the G and SH genes are non-essential for replication in vitro and in vivo[14].

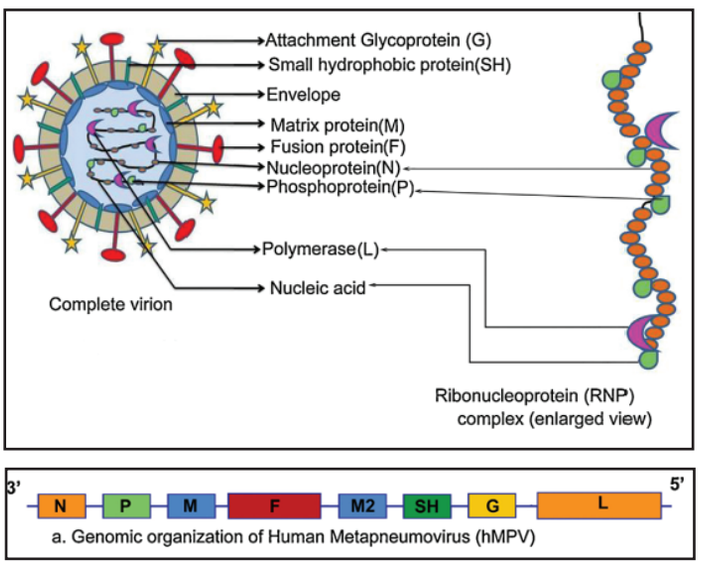

Figure II: Schematic diagram of the human metapneumovirus particle and the ribonucleoprotein (RNP) complex[14]

Moreover, the M2 gene of hMPV contains overlapping ORFs (M2-1 and M2-2), with M2-2 regulating the shift from transcription to replication. Deletion of M2-2 results in increased mRNA synthesis but attenuated viral replication, yet still elicits protective immunity, offering promise for vaccine development[11,13,14].

Epidemiology

Epidemiologically, hMPV is a significant cause of acute respiratory infections (ARIs), second only to respiratory syncytial virus (RSV) in pediatric populations. Unlike influenza, where uniform global strains tend to circulate annually, hMPV outbreaks are often localized, with strain variation between regions and across time[3]. In temperate climates, hMPV primarily circulates in the late winter and spring, often coinciding with or following the seasonal peak of respiratory syncytial virus (RSV) activity. Although peak activity is seasonal, low-level circulation of hMPV can be detected year-round in many communities, including during late spring, summer, and fall[12]. For example, strains from The Netherlands have shown genetic similarity to those identified in Australia, Canada, France, Israel, and the United States in different years[8,15]. Viruses of both genotypes and their subgroups often co-circulate in a single season, and shifts in predominant genotypes—such as a switch from genotype B to A in consecutive years—have been documented in places like St. Louis, Missouri16. However, no significant difference in illness severity has been observed between infections caused by genotype A or B. This circulation pattern closely mirrors that of RSV, where both subgroups A and B co-exist annually, and the dominant strains vary by location and year[16]. Additionally, a novel variant strain, genetically distinct from the known lineages and detectable only with N gene-targeted primers, was identified in 2004. This finding suggests potential for greater genotypic diversity than currently recognized, potentially requiring updates to diagnostic methods[17].

Seroepidemiological studies underscore the ubiquity of hMPV infection early in life. Multiple techniques—including immunofluorescence assays, ELISAs using recombinant proteins, and neutralization tests—have shown that over 90% of children have been infected with hMPV by the age of five[18]. In adults, the seroprevalence approaches 100%, indicating repeated exposure or reinfection throughout life[19]. Interestingly, infants under three months of age also exhibit high seroprevalence rates (>90%), reflecting the presence of maternally derived antibodies and these maternal antibodies confer protection or reduce disease severity remains unclear[7]. Collectively, these findings highlight the global reach, seasonal behavior, genetic diversity, and early-life exposure associated with hMPV, reinforcing its significance as a respiratory pathogen across all age groups[18].

The epidemiology of hMPV is complex and dynamic. Based on current data from Institute of Epidemiology, Disease Control and Research (IEDCR) and other surveillance units there has been no unusual surge in Influenza-Like Illness (ILI) or Severe Acute Respiratory

Illness (SARI) cases in Bangladesh[20]. China is experiencing a surge in HMPV cases, particularly in children under 14 years of age. Symptoms include cough, fever, and shortness of breath, with potential complications like bronchitis and pneumonia[21]. India hadn't registered any unusual spike in winter respiratory diseases. However, they confirmed three cases of Human Metapneumovirus (HMPV)[22]. Hongkong and Malaysia also reported cases of HMPV[23]. HMPV can cause both upper and lower respiratory diseases in people of all ages, with young children, older adults, and those with weakened immune systems being most vulnerable. However, the risk of severe illness is higher for people who are younger than five or older than 65[24]. There is no vaccine or specific antiviral treatment for HMPV; treatment primarily involves managing symptoms. Like other similar viruses, HMPV usually spreads from person to person through droplets from coughing and sneezing, through human contact such as hugging or kissing, and through touching surfaces and objects contaminated with the virus and then the mouth, nose or eyes. The spike in cases coincides with colder weather and increased indoor activity, conditions that typically fuel the spread of respiratory viruses[22]. China's National Disease Control and Prevention Administration emphasize that this surge is consistent with seasonal trends[25].

Pathogenesis

Human metapneumovirus (hMPV) is recognized as a significant cause of severe respiratory infections, particularly in individuals with underlying pulmonary conditions such as chronic obstructive pulmonary disease (COPD). Experimental studies using animal models, including BALB/c mice and cotton rats, have demonstrated that hMPV infection induces airway obstruction and hyper responsiveness. Infected mice exhibit interstitial lung inflammation beginning around day 3 post-infection, peaking at day 5, followed by a gradual decline in inflammation; however, after 2–3 weeks, inflammation reemerges as prominent peribronchiolar and perivascular infiltrates[26]. In BALB/c mice, airway obstruction persists long after initial infection—up to day 70—indicating chronic pulmonary involvement, along with sustained airway hyperresponsiveness in response to methacholine challenge[27]. Another study showed that aged mice suffer from more severe disease and higher mortality rates despite similar rates of viral clearance when compared to younger mice [26]. Aged animals exhibited increased viral replication in the lungs but produced lower levels of virus-specific antibodies, neutralizing antibodies, and interferon-gamma, alongside elevated levels of IL-4 and CD4+ lymphocytes, suggesting a skewed immune response favoring a Th2 profile. However significantly lower TNF-α expression and NF-κB activity in aged mice following hMPV infection[28]. In human studies, found that the neutralizing antibodies are detectable across all age groups, their functional activity remains relatively stable with only a slight decline in individuals over 69 years old19. This observation, supported by findings from Sastre et al. using an F protein-based ELISA and corroborated by Falsey et al., indicates that the humoral immune response, particularly neutralizing antibodies, plays a relatively minor role in clearing hMPV infections[29,30]. Falsey et al. further noted that older adults exhibited higher baseline serum antibodies and more robust binding antibody responses than younger adults despite experiencing similar illness severity, suggesting immune dysregulation rather than protection[30]. Taken together, these findings point to the cellular immune response—particularly T-cell mediated mechanisms—as being more crucial than the humoral response in controlling hMPV infection, especially in aged individuals, where immune senescence may impair effective viral clearance.

Clinical Manifestations

Human metapneumovirus (HMPV) is a respiratory pathogen that can lead to both upper and lower respiratory tract infections in individuals of all ages, but it poses a greater risk of severe illness in children under five, adults over 65, and those with weakened immune systems[18]. With no available vaccine or specific antiviral treatment, care is focused on alleviating symptoms. HMPV spreads through respiratory droplets, close personal contact, and contaminated surfaces, with cases often surging during colder months due to increased indoor activity[22]. In young children, especially those under two, HMPV is a significant cause of lower respiratory tract infections (LRTIs) such as bronchiolitis, pneumonia, and bronchitis, often leading to hospitalization[8]. It is considered the second most common cause of LRTI-related hospital admissions after respiratory syncytial virus (RSV). While severe cases can require intensive care or even extracorporeal membrane oxygenation, HMPV generally causes less severe illness than RSV. However, infants, especially those born prematurely or with underlying health conditions, remain at heightened risk, underscoring the need for effective treatments and preventive strategies targeting this vulnerable population. Like other common respiratory viruses, human metapneumovirus (hMPV) is also associated with upper respiratory infections (URIs), accounting for an estimated 5 to 15% of pediatric URI cases, although this varies depending on the study and year[31]. A long-term study by Williams et al., which analyzed over 2,000 respiratory specimens from children under five with symptoms such as coryza, conjunctivitis, pharyngitis, otitis media (OM), or stomatitis, found that 1 to

5% of these URIs were linked to hMPV, a lower rate compared to influenza, parainfluenza, adenovirus, and RSV[31,32]. hMPV has also been implicated in the development of acute OM, a common complication of viral URIs in children. Research shows that up to 50% of children with hMPV-associated URIs and about one-third with hMPV-related lower respiratory tract infections (LRTIs) were diagnosed with concurrent OM. Although hMPV is detected in nasal washes of children with OM in about 6% of cases, its presence in middle ear fluid is rare, suggesting that the virus likely contributes to OM indirectly. The inflammation caused by hMPV may obstruct the eustachian tubes, creating an environment conducive to secondary bacterial infections, thereby playing a role in the pathogenesis of virus-induced OM[22].

Clinical Manifestations in Immunocompromised Patients

Although HMPV is typically associated with mild to moderate respiratory illness in healthy individuals, immunocompromised patients, including organ transplant recipients, hematopoietic stem cell transplant (HSCT) recipients, patients undergoing chemotherapy, and those with primary or acquired immunodeficiencies, are at increased risk for severe and potentially fatal outcomes. In immunocompromised populations, HMPV infections can range from asymptomatic viral shedding to life-threatening lower respiratory tract infections (LRTIs), including pneumonia and acute respiratory distress syndrome (ARDS). Symptoms often include fever, cough, rhinorrhea, dyspnea, wheezing, and hypoxia. However, the disease can progress rapidly in these patients, sometimes requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) support. The severity of HMPV in immunocompromised hosts has been well-documented. In a study of adult HSCT recipients, HMPV was identified as the causative agent in 4–7% of respiratory viral infections, with mortality rates reaching up to 40% among those who developed lower respiratory tract disease[19]. A retrospective analysis by Peck et al. (2010) involving cancer patients found that HMPV was associated with a 30-day mortality rate of 17%, especially among those with hematologic malignancies and concurrent LRTIs[33]. Patients with underlying pulmonary comorbidities or recent allogeneic HSCT were found to be at particular risk for progression to severe pneumonia. Immunocompromised patients often exhibit prolonged viral shedding, sometimes for weeks, increasing the risk of nosocomial outbreaks in hospital settings. Cases of hospital-acquired HMPV infections have been reported in transplant units and oncology wards, underscoring the need for rigorous infection control practices[28]. Unlike immunocompetent individuals, where viral shedding typically resolves within a week, shedding in immunocompromised hosts can persist, contributing to ongoing transmission and reinfection risks[34]. Co-infections with other respiratory pathogens, including respiratory syncytial virus (RSV), influenza, cytomegalovirus (CMV), or bacterial pathogens, are common and often complicate the clinical picture[22]. These co-infections can exacerbate inflammation and pulmonary damage, leading to worse outcomes and complicating treatment strategies.

Coinfection of hMPV with Other Respiratory Pathogens

Coinfection involving human metapneumovirus (hMPV) and other respiratory viruses is a clinically recognized occurrence, particularly given the overlapping seasonal circulation of hMPV and respiratory syncytial virus (RSV). Numerous studies have reported that hMPV-RSV coinfection rates are generally low[4]. However, some findings indicate that when coinfection does occur, it may contribute to more severe clinical outcomes[7]. For instance, Greensill et al. reported that 70% of children infected with RSV and admitted to intensive care units in Liverpool, UK, were also coinfected with hMPV—suggesting that hMPV may amplify the severity of RSV-related illness even in otherwise healthy pediatric populations[34]. Supporting this, another UK-based study found that coinfection significantly increased the likelihood of admission to pediatric intensive care[7]. Conversely, larger population-based and case-control studies suggest that such dual infections are relatively uncommon. In a study by Mullins et al., none of the 668 hospitalized children tested positive for both hMPV and RSV concurrently[35]. Similarly, Lazar et al. evaluated children with both severe and mild RSV disease during a known period of hMPV circulation and found no evidence of hMPV in either group[36]. These discrepancies highlight the variability in coinfection prevalence and suggest that while hMPV-RSV coinfections may contribute to disease severity in select cases, they do not represent a widespread phenomenon across pediatric populations. Beyond RSV, coinfection with hMPV has also been observed in patients during the 2002 outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus (SARS-CoV). In certain regions of China and Canada, a notable proportion of SARS patients were also found to be infected with hMPV[21]. However, this pattern was not consistently observed in other regions. The clinical impact of such dual infections remains unclear, and it is unknown whether hMPV played a direct role in exacerbating SARS-related illness[7]. Unlike influenza virus, which is frequently complicated by secondary bacterial pneumonia, hMPV infections appear to have a lower risk of bacterial superinfection. While bacterial coinfections are a well-established concern in influenza and, to a lesser extent, RSV, current evidence suggests they are relatively rare in

the context of hMPV[37]. A study conducted among under five years children whose were infected with different types of respiratory pathogen in Dhaka city, Bangladesh[22].Nevertheless, comprehensive studies focusing specifically on bacterial complications in hMPV-infected individuals are lacking, leaving this area of investigation incomplete and in need of further research.

Diagnosis of Human Metapneumovirus (hMPV)

The accurate diagnosis of human metapneumovirus (hMPV) infection primarily relies on nucleic acid amplification techniques, with reverse transcription polymerase chain reaction (RT-PCR) being the gold standard. RT-PCR is highly sensitive and specific, capable of detecting low levels of viral RNA in respiratory specimens such as nasopharyngeal swabs, aspirates, or bronchoalveolar lavage fluid[38]. This method is widely used in both clinical and research settings and can be performed using either laboratory-developed tests or commercially available diagnostic kits. In recent years, the development and approval of multiplex molecular panels have enhanced diagnostic capabilities. These panels can simultaneously detect a range of respiratory pathogens, including hMPV, respiratory syncytial virus (RSV), influenza viruses, adenovirus, rhinovirus, and coronaviruses, among others. This multiplex approach is especially valuable during respiratory virus season or in hospital outbreaks, allowing for rapid identification of co-infections and informing appropriate infection control measures and clinical management.

Viral culture, although historically important, is now largely considered impractical and insensitive for routine hMPV diagnosis. One of the key reasons behind the late discovery of hMPV was the difficulty in isolating and cultivating the virus. hMPV requires the presence of exogenous trypsin to support replication in vitro, and while it is capable of replicating in several cell lines, it shows more robust cytopathic effects in tertiary monkey kidney cells and LLC-MK2 (rhesus kidney) cells[39]. Even under optimized laboratory conditions, viral propagation can take 14 days or longer, which significantly limits its utility in acute clinical settings. Serological testing, which detects antibodies to hMPV, has limited clinical application due to its low sensitivity and the fact that antibody responses may take days to weeks to become detectable, making it unsuitable for diagnosing acute infections. Additionally, cross-reactivity and prior exposure to the virus can complicate interpretation, particularly in older children and adults who may have been previously infected. while traditional methods like viral culture and serology have contributed to the understanding of hMPV, RT-PCR and multiplex molecular assays remain the most reliable tools for timely and accurate diagnosis. These advancements have significantly improved the ability to detect hMPV and distinguish it from other viral respiratory pathogens, ultimately aiding in patient management and epidemiological surveillance[38].

Treatment and Management

Currently, there are no licensed antiviral therapies specifically approved for the treatment of human metapneumovirus (hMPV) infections. As a result, supportive care remains the cornerstone of clinical management, focusing on symptom relief, oxygen therapy when necessary, and hydration. Among the potential antiviral agents studied, ribavirin and immunoglobulin therapies have shown some promise in preclinical settings. Ribavirin, a broad-spectrum nucleoside analog with activity against various RNA viruses, has demonstrated in vitro activity against hMPV[40] and exhibited modest efficacy in animal models, particularly in mice[26].

Similarly, commercial intravenous immunoglobulin (IVIG) preparations have been found to contain neutralizing antibodies against hMPV[18]. Experimental studies have shown that antibodies alone can be effective against hMPV in murine models, both in prophylactic and therapeutic settings[26]. Despite these encouraging findings in laboratory and animal studies, clinical evidence in humans remains extremely limited. There are anecdotal reports describing the use of ribavirin and IVIG in human cases of severe hMPV infection; however, no randomized controlled trials have been conducted to assess their efficacy or safety in this context. Consequently, no formal clinical guidelines recommend the use of ribavirin or IVIG for hMPV treatment in humans at this time[18].

Vaccine Development for Human Metapneumovirus (hMPV)

The development of a safe and effective vaccine against human metapneumovirus (hMPV) represents a critical goal in mitigating the global burden of respiratory illness, particularly among vulnerable populations such as infants, older adults, and immunocompromised individuals. Although no hMPV vaccine has been licensed to date, several promising candidates have demonstrated protective efficacy in preclinical models. One approach involves the use of live recombinant viruses. For instance, a recombinant human parainfluenza virus engineered to express the hMPV fusion (F) protein has been shown to induce robust hMPV-specific antibody responses and confer protection in experimental animals[34]. Another candidate, a chimeric bovine/human parainfluenza virus type 3 expressing the hMPV F protein, was also found to elicit neutralizing antibodies against both parainfluenza and hMPV[11].

In addition, recombinant hMPV strains with deletions of

non-essential genes—such as G, SH, M2, or combinations thereof—have been evaluated. These genetically modified viruses are attenuated in vitro but remain immunogenic and capable of inducing protective immunity in animal models[11,12]. These strategies mirror approaches used in the development of recombinant RSV vaccines, some of which have progressed into human clinical trials[41]. Another innovative strategy involves chimeric viruses created by replacing hMPV genes with those from avian pneumovirus. For example, chimeras in which the N or P gene of hMPV was substituted with the avian pneumovirus counterpart have shown attenuation in African green monkeys, with the P-gene chimera being significantly more attenuated—by a factor of 10 to 1,000—compared to the N-gene chimera[42]. Importantly, both retained immunogenicity comparable to wild-type hMPV, suggesting their potential utility as live attenuated vaccine candidates. Animal models of hMPV infection have many limitations. The virus is highly host-restricted, so results from animals do not always predict outcomes in humans. This problem has also been seen with recombinant RSV vaccines. In early clinical trials, some of those vaccines were either too weak or too strong. Although researchers have made progress in finding possible hMPV vaccine platforms, more studies are needed. In particular, human clinical trials are necessary to check their safety, immune response, and protection. Work on recombinant and chimeric virus technologies, together with lessons from RSV vaccine development, will help guide the creation of a successful hMPV vaccine.

Conclusion

Human metapneumovirus (hMPV) is a significant cause of respiratory tract infections across all age groups, particularly affecting young children, older adults, and immunocompromised individuals. Since its discovery in 2001, considerable progress has been made in understanding the epidemiology, clinical manifestations, and virology of hMPV. It is now recognized as a major contributor to both upper and lower respiratory tract infections, often second only to RSV in pediatric hospitalizations for lower respiratory tract disease. Despite these advancements, no specific antiviral therapies or licensed vaccines are currently available. Management remains largely supportive, and while preclinical studies have identified promising candidates for both antivirals and vaccines, translation into effective human treatments is still ongoing. Furthermore, the role of coinfections, especially with RSV and other respiratory pathogens, and the potential for severe disease in high-risk populations, continues to warrant further investigation. To reduce the global burden of hMPV, future efforts must focus on closing the existing gaps in pathogenesis, host immune response, long-term immunity, and vaccine development. A better understanding of these areas, supported by continued surveillance and translational research, is essential to develop effective strategies for prevention and treatment.

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