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Research Article

Global Insights into HMPV Infections: Clinical Patterns, Genetic Subtypes, and Public Health Implications

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A B S T R A C T

Human Metapneumovirus (HMPV) is a significant respiratory pathogen that poses a substantial health burden worldwide, particularly in young children, older people, and immunocompromised individuals. Although it was first identified in 2001, HMPV remains underdiagnosed due to clinical overlap with other respiratory viruses. It has recently garnered significant attention due to a notable outbreak in China during the 2025 winter season. According to data from the Chinese Centre for Disease Control and Prevention, HMPV accounted for 6.2% of positive tests for respiratory illnesses and 5.4% of hospitalisations due to respiratory diseases, outperforming the incidence of COVID-19, rhinovirus, and adenovirus during the same period. This review discusses a comprehensive study of HMPV, covering its epidemiology, pathogenesis, clinical manifestations, diagnostic approaches, and therapeutic strategies. HMPV is characterised by significant genetic diversity, which contributes to the variability in its pathogenicity and presents a challenge for vaccine development. Current management is mainly supportive because of the lack of specific antiviral therapies or approved vaccines. Molecular diagnostics have improved detection through PCR and multiplex panels; however, challenges persist in terms of accessibility. Emerging research identifies metabolic reprogramming and immune evasion as essential features of HMPV pathogenesis, thus opening new avenues for therapeutic intervention. This review emphasises the urgent need for enhanced surveillance, targeted prevention strategies, and expedited vaccine and antiviral development to mitigate the public health impact of HMPV. Future efforts must integrate molecular insights, public health measures, and innovative technologies to confront this evolving threat.

Keywords: Human Metapneumovirus, Respiratory Infections, Pathogenesis, Diagnostics, Antiviral

Introduction

Human Metapneumovirus (HMPV) is a significant human viral pathogen that causes respiratory infections in both children and adults. However, it is more severe in young children, older people, and individuals with immunocompromised conditions. Since its identification in 2001 as a member of the Pneumoviridae family, HMPV has been recognised as a significant cause of infections in the upper and lower respiratory tracts, resulting in substantial morbidity and mortality, particularly in high-risk populations. The global disease burden of HMPV is high but frequently not appreciated because of its clinical overlap with influenza and respiratory syncytial virus (RSV). HMPV is the primary pathogen implicated in the aetiology of acute lower respiratory infections (ALRI) in children aged less than five years. There were an estimated 14.2 million cases of HMPV-associated ALRI globally in 2018, which resulted in around 643,000 hospitalisations and 7,700 in-hospital deaths, and the overall number of deaths, including those occurring outside of hospitals, was approximately 16,100.[1] Children below one year of age contributed most to severe cases, with 58% of the hospitalisations and 64% of in-hospital mortality within this age group, and almost 79% of these deaths were seen in low- and lower-middle-income nations. In the United States alone, the hospitalisation rate was an estimated 231 per 100,000 older adults, or an estimated 122,000 admissions a year. Among adults at risk, for example, those with chronic disease or immunocompromised hosts, HMPV causes 3.4–4.0% of annual symptomatic respiratory infections, more than half of whom receive medical attention and are hospitalised, 6.6% who need intensive care, and 9.3% who die.[2] The virus has a year-round circulation with seasonal peaks in late winter to early spring in temperate climates and in variable timing in the tropics. Recent surveillance in China in 2024–2025 documented that HMPV was responsible for 6.2% of positive respiratory tests and 5.4% of respiratory hospitalisations, which surpassed detections for adenovirus, rhinovirus, and COVID-19 in the same time period.[3]

The virus belongs to the family Pneumoviridae, specifically to the genus Metapneumovirus, which shares many characteristics with other paramyxoviruses, such as RSV. HMPV infections first manifested clinically in the early 2000s; as a result, there was a drive to identify this new pathogen, and it has since emerged as an agent of viral respiratory tract infections. It affects a wide variety of individuals and is spread through respiratory droplets projected into the air when coughing and sneezing. Additionally, secondary transmission occurs through direct contact with fomites and personal belongings. Most infections occur during the colder months, although the outbreak typically peaks in winter and spring. Most people acquire the infection by the age of 5 years, but reinfections occur throughout life, typically resulting in less severe disease because some immunity is conferred from previous infections. The epidemiology of HMPV is quite complex, exhibiting significant year-to-year variability in infection prevalence.[4,5] Four major genetic subgroups of HMPV have been identified: A1, A2, B1, and B2. These differ in their genetic makeup, pathogenicity, and antigenic properties. An infection with one subgroup may provide partial protection against later infections with the other subgroups, but the immunity is not complete; thus, reinfections are common.[6]

The clinical presentation of HMPV infection varies widely, ranging from a simple cold-like condition to serious forms of respiratory disease, including bronchiolitis, pneumonia, and Acute Respiratory Distress Syndrome (ARDS). For children under the age of 5 years, HMPV is among the most significant aetiologic agents of bronchiolitis and pneumonia, characterised by inflammation and congestion of the lower respiratory tract. The clinical presentation includes fever, cough, wheezing, nasal congestion, and shortness of breath.[7] In adults, especially the elderly and those with comorbid conditions of chronic respiratory disease, the disease caused by HMPV is more serious. Immunocompromised states, such as cancer, recipients of organ transplants, and individuals with HIV, are more likely to be severely affected by the disease. The virus tends to worsen pre-existing diseases, leading to complications such as secondary bacterial infection or prolonged respiratory failure. The whole range of diseases caused by HMPV, a potentially lethal infection, has remained poorly recognised because the pathogen causes very similar viral respiratory infections, with its presence only reported in a few areas where extensive surveillance has been conducted.

HMPV pathogenesis is brought about by the interaction of the virus with airway epithelial cells. Like all other respiratory viruses, HMPV targets the respiratory epithelium, binds to specific receptors, enters the cells, and then replicates. The virus uses its glycoprotein (G) and fusion (F) proteins to attach to host cells and facilitate viral entry. Once inside, the virus disrupts the normal functioning of epithelial cells. This causes a host immune response and inflammation that contributes to infection symptoms such as fever, cough, and airway obstruction. One key feature of the infection caused by HMPV is the alteration in the metabolic pathways of host cells. Studies have demonstrated that HMPV infection causes significant changes in the cellular metabolism of airway epithelial cells, promoting glycolysis and reducing oxidative phosphorylation. This metabolic reprogramming appears to favour the virus, as it provides the cell with sufficient energy and precursors for viral replication. These metabolic changes are very valuable for gaining insight into the virus-host interaction, providing potential targets for antiviral therapy. Clinical

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manifestations, epidemiologic features, and laboratory investigations guide the diagnosis of HMPV infection. Usually, there is an overlap in presentation with other common respiratory pathogens, including RSV, influenza, and parainfluenza. Thus, confirmation is commonly necessary through laboratory evaluation. The detection of HMPV has become increasingly popular nowadays, primarily through the use of PCR-based tests that offers high sensitivity. These diagnostic methods include viral culture and serology, among others, and are less commonly applied in clinical settings due to either low sensitivity or longer turnaround times. The rapid detection of HMPV is critical in cases of patients admitted to a hospital or those with high-risk factors for severe illness. Early detection enables the proper management and implementation of isolation policies that prevent the transmission of infections, which in healthcare facilities may lead to nosocomial infections and outbreaks. Specific antiviral treatment is in limited supply; therefore, the appropriate use of diagnosis becomes crucial for managing HMPV infection, as well as differentiating it from other viruses that cause respiratory infections. There is currently no known antiviral therapy for HMPV, and management is essentially supportive. This includes the provision of oxygen, hydration, and mechanical ventilation in severe cases. Patients with chronic pre-existing respiratory conditions or immunosuppressed conditions are closely followed up, and antibiotics may be administered if a bacterial infection is suspected. The lack of a specific antiviral treatment emphasises the importance of a prevention strategy, which should be concentrated in the groups at highest risk.

Vaccination is still considered the most effective weapon against reducing the HMPV disease burden. Some candidates for the vaccine are being developed from the preclinical stage to the clinical phase, targeting various proteins, with most focusing on the F protein since it mediates entry and viral fusion. Early-stage trials of F protein-targeted monoclonal antibody therapies have shown promise and hold hope for severely ill patients as a potential treatment. HMPV exhibits high genetic diversity, which complicates the production of a universal vaccine. Some studies have revealed that HMPV is quite genetically heterogeneous within its subgroups and, therefore, develops various viral lineages over time. It also undergoes recombination events, where the genetic material of the virus is exchanged between two different strains, making its evolutionary dynamics somewhat complex. Phylogenetic analyses of HMPV genomes have shown continuous evolution, while distinct genetic lineages co-circulate in different geographic regions. Differences and variations in pathogenicity, antigenic features, and the possibility of severe disease are associated with different lineages. Understanding the change in HMPV is thus a key feature in developing effective vaccines and other therapeutic strategies. When the virus mutates, new types can emerge with new antigenic profiles that may potentially affect the effectiveness of vaccines or monoclonal antibodies. The evolution of HMPV genetic variants must be continuously monitored through surveillance to alert and guide efforts toward the development of future vaccines. This review provides a detailed overview of HMPV in the context of epidemiology, pathogenesis, clinical features, diagnosis, treatment, and the historical development of the virus.

Epidemiology and Clinical Features

The geographic distribution and seasonality of HMPV were influenced by multiple factors affecting its spread, such as climate-related variations and fluctuations in other respiratory virus cases, as evidenced by a specific study that documented distribution changes and regional differences impacting trends.

The HMPV infection has been observed among people in Taiwan from 2013 to 2023. The cases were highest in children younger than 4 years, at 68.4%. The highest infection rate was reported in Penghu County, followed by Changhua and Hsinchu Counties. Common presentations included fever (56.1%), cough (44.7%), rhinorrhoea (21.1%), and sore throat (14.9%). Rare, more serious central nervous system manifestations occurred in 1.8% of cases, and dyspnoea was reported in 0.9%. Phylogenetic analysis of the 114 isolated strains revealed genetic variability, with A2 being the most common lineage, accounting for 57.9%, and B2 accounting for 33.3% of the remaining. The study indicated that HMPV is one of the primary causes of severe breathing problems in Taiwan, particularly among young children. The work emphasises the need to continue observing and monitoring this disease and studying its epidemiology to inform prevention and control measures.[8]

A study done by Deval et al. on HMPV among 100 children suffering from Severe Acute Respiratory Infection (SARI) in Eastern Uttar Pradesh, India, showed that 4% of the children were infected with HMPV. Among the HMPV-positive, the mortality was significantly high, at 25%, which again points to potentially severe infections caused by this virus among children. The identified HMPV strains were highly related to clades from Singapore and the USA and may reflect the international transmission of these viruses or shared ancestral lineages.[9]

A prospective study conducted from 2013 to 2015 in a tertiary care hospital in Delhi, India, evaluated the epidemiology of respiratory viruses among children below 5 years of age hospitalised for SARI. The incidence showed that among children hospitalised due to SARI, respiratory viruses were detected in 69%, a much higher figure than in 33% of controls who remained asymptomatic.[10]

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A retrospective cohort study conducted by Jurkowicz et al. analysed the epidemiological and clinical characteristics of HMPV infections in hospitalised patients in Israel from 2015 to 2021. The study involved 990 patients, among whom 36.2% were under 18 years of age, with the highest incidence observed among children aged 0–2 years (25.6%). Adults older than 60 years comprised 51.6% of the cases, indicating vulnerability in both paediatric and elderly populations.[11]

A study carried out by Xie et al. on the seasonal and genetic characteristics of HMPV found that from 2017 to 2023, in Henan Province, China, among 2,707 cases of acute respiratory infection, 6.17% showed positive results, with the peak infection rate at 7.78% among children under five years of age. There were seasonal peaks in spring during 2018 and 2019 (Table 1).[12]

Table 1.Epidemiology of HMPV

Study/ Location	Period	Population	Key Findings	Genetic Lineages
Taiwan8	2013–2023	Children < 4 years (68.4%)	Year-round infections, peak in spring (March–May); most common symptoms: fever (56.1%), cough (44.7%); A2 lineage dominant (57.9%)	A2 (57.9%), B2 (33.3%)
Eastern UP, India9	Not specified	Children with SARI (4% HMPV)	Mortality in HMPV-positive cases (25%); Strains related to the Singapore and USA clades	Related to the Singapore and USA clades
Tertiary Care Hospital, Delhi10	2013–2015	Children < 5 years with SARI	Respiratory viruses detected in 69%; RSV most common (31%), HMPV not specified individually	Not specified
Israel11	2015–2021	Paediatric (36.2%) and elderly (51.6%)	Peaks in winter/ spring; severe cases in < 2 years and > 60 years; high coinfection with RSV	Not specified
Henan Province, China12	2017–2023	Children < 5 years (7.78%)	Seasonal peaks in spring (May 2018: 31.11%, May 2019: 19.57%) and winter (Nov 2020–Jan 2021: 42.11%)	A2c (46.91%), B2 (53.09%)

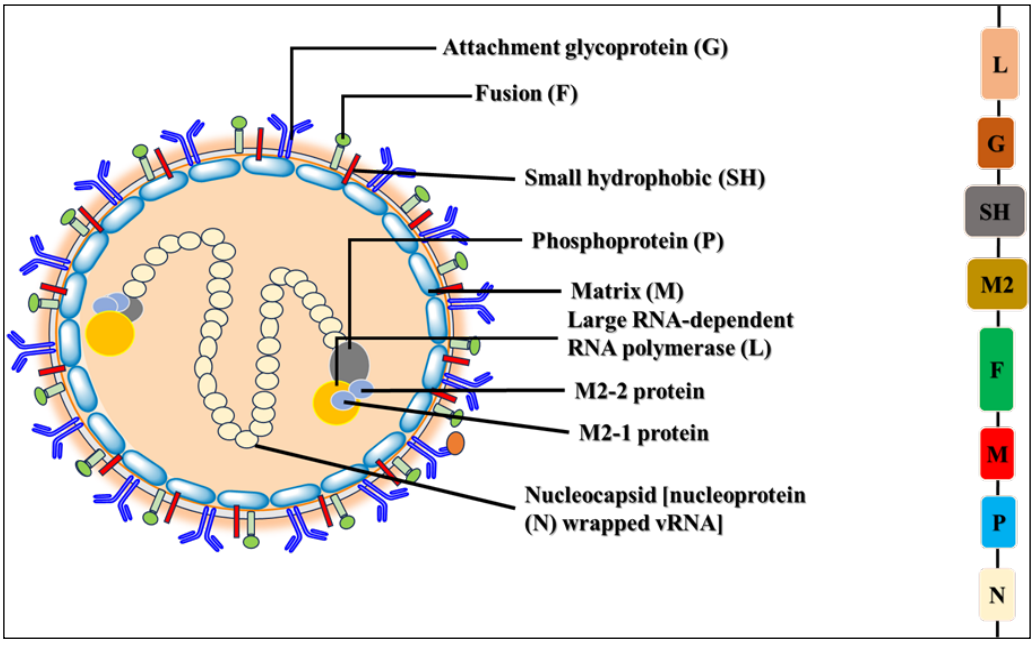

Figure 1.Genomic organization of human metapneumovirus (HMPV)

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Pathophysiology of Human Metapneumovirus (HMPV)

The Pneumoviridae family is characterised by its negative-sense single-stranded RNA genome that carries eight proteins encoding structural proteins; F, G, N, M, and SH, non-structural proteins NS1 and NS2, and finally the RNA-dependent RNA polymerase L.[13] Each of these proteins plays a critical role in viral replication, immune evasion, and pathogenesis (Figure 1).[14]

Viral Entry and Replication

A crucial determinant of HMPV infectivity is the fusion (F) protein, which mediates viral entry into host cells by facilitating the fusion of the viral envelope with the host cell membrane.[15] After entering the cell, the viral RNA genome is transcribed and replicated in the cytoplasm with the RNA-dependent RNA polymerase (L) complex. New viral progeny are then produced, assembled, and released to infect the adjacent cells.[16]

Immune Evasion and Host Response

HMPV utilises multiple mechanisms to evade innate immunity. The virus inhibits the production of interferon (IFN) by interrupting the signalling pathways, which is primarily mediated by the functions of the NS1 and NS2 proteins. These proteins inhibit the activation of the retinoic acid-inducible gene I (RIG-I) and the mitochondrial antiviral signalling protein (MAVS), which are involved in recognising viral RNA and inducing the antiviral state. Therefore, HMPV reduces the host's capacity to develop an effective early immune response, thereby allowing unchecked viral replication and spread.[17]

Cellular Damage and Inflammatory Response

HMPV primarily infects the ciliated epithelial cells of the respiratory tract, and initially, cytopathic effects, such as rounding and detachment with cell death, are observed. The infection triggers a pro-inflammatory cytokine response through the stimulation of IL-6, IL-8, and TNF-α, resulting in the recruitment of neutrophils, macrophages, and other leukocytes to the site of infection. Although this response is crucial to the elimination of viruses, overactive inflammation can lead to tissue injury, airway constriction, and a clinical presentation characterised by wheezing and hypoxaemia.[13, 18]

Molecular Basis of Chronic Damage

In susceptible individuals, chronic infections or even prolonged inflammation may lead to structural changes in the airways that persist. The oxidative stress and protease activity of HMPV deteriorate epithelial barriers, inhibit mucociliary clearance, and predispose the lungs to secondary bacterial infections.[15] The continuous activation of macrophages and fibroblasts can lead to the development of fibrosis and remodelling in the airways, which are also implicated in chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease.[16]

The molecular pathogenesis of HMPV is driven by its ability to exploit host cellular machinery for replication while evading immune surveillance. Its reliance on the F protein for entry, NS1 and NS2 proteins for immune suppression, and its inflammatory cascade underlie the critical molecular targets for therapeutic intervention. Advancing our understanding of these mechanisms is crucial for developing antiviral drugs and vaccines to mitigate the impact of HMPV (Figure 2).

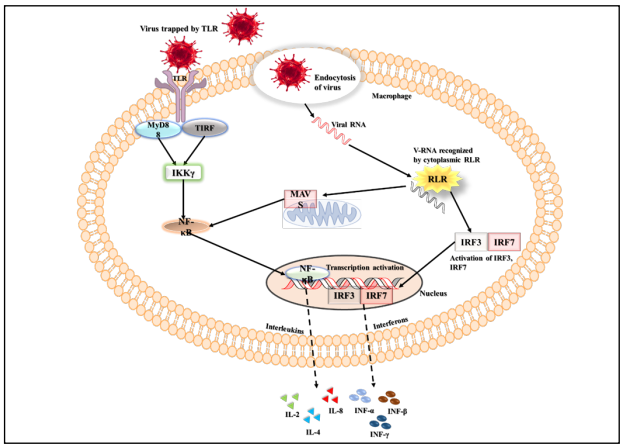

Figure 2.Molecular processes involved in the etiology of HMPV infection; Nuclear factor kappa beta (NF kb) is activated when a virus attaches itself to the toll-like receptors (TLR) of macrophages and/or dendritic cells, activating multiple immune system adaptor molecules (TRIF and MYD88). The cytoplasmic RIG1-like receptor (RLR) detects the RNA of the internalized virus and activates NF kb by activating the transcription activators interferon regulatory factors 3 and 7 (IRF-3 and IRF-7) and mitochondrial antiviral signaling protein (MAVS). Lastly, a number of interleukins and interferons are produced in response to NF kB and IRFs.

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Diagnosis and Treatment

Diagnostic Methods

The detection of HMPV is crucial for effective clinical management and public health response. The methodologies for diagnosing it have undergone significant evolution, aiming to increase sensitivity, specificity, and accessibility in both clinical and community settings.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

RT-PCR remains the gold standard in diagnosing HMPV since it is more sensitive and specific compared to other methods.[19] It amplifies specific segments of the viral RNA, allowing even minimal viral loads to be detected. Mackay et al. claimed that its efficiency in distinguishing HMPV from other respiratory pathogens makes it invaluable in clinical laboratories. However, it requires specific equipment and expertise, which may not be readily available in resource-poor settings. Its cost and the time it takes to process samples also make it less suitable for point-of-care testing in community settings.[20]

Rapid Antigen Detection Tests (RADTs)

Rapid antigen detection tests offer a more accessible and time-efficient alternative for diagnosing HMPV, particularly in outpatient and community healthcare settings. These tests detect viral proteins and give results within minutes, thus supporting immediate clinical decisions. However, the sensitivity of these tests is lower than that of molecular methods, which means a higher chance of false negatives. According to Van Den Hoogen et al., the accuracy of RADTs has to be improved so that it can be relied upon, especially during outbreaks.[21]

Serological Tests

Serological tests detect antibodies produced after HMPV infection and are primarily used for retrospective diagnosis and epidemiological studies. These tests are not suitable for diagnosing acute infections due to the latency period before antibody production occurs. Boivin et al. discussed the role of serological tests in understanding the prevalence and spread of various diseases among different populations, emphasising that serology is essential to public health surveillance.[22] Promisingly, newly developed molecular reagents for the diagnosis of HMPV include Loop-Mediated Isothermal Amplification (LAMP) and Next-generation sequencing (NGS).[23] Based on observations, LAMP is available at a moderate cost and is relatively portable compared to RT-PCR. Like RT-PCR, it yields reliable results rapidly and without complicated thermal cycling. Most applications of NGS are specifically for research in the field; it allows genomics to delineate the characterisation of new isolates and the determination of co-infections.[24]

Multiplex Diagnostic Panels

Multiplex panels that also detect other common respiratory viruses have significantly improved the efficiency of diagnosis by integrating HMPV detection. As noted by Feuillet et al., these panels commonly reduce the cost and time taken to diagnose the individual pathogens and are mostly helpful during seasons marked by outbreaks.[25]

Current Management Approaches

HMPV is a significant respiratory pathogen, particularly in very young children, the elderly, and immunocompromised patients. Notwithstanding its immense impact, this agent remains severely underdiagnosed and many times misdiagnosed. It shares symptoms with other respiratory viruses like RSV and influenza that can make identification a bit complicated. Infections due to HMPV are generally upper respiratory tract infections, but can lead to severe forms of lower respiratory tract diseases, including bronchiolitis and pneumonia, particularly among those at risk.16 The epidemiology of HMPV demonstrates seasonal peaks, usually during the colder months, with a high prevalence in children under the age of five years, although adults can be significantly affected as well.[17, 26]

Currently, there are no antiviral therapies or vaccines specific to HMPV, so management is generally supportive in nature, meaning that treatment of symptoms and prevention of secondary bacterial infections define the current strategies.[27] A few research studies have used ribavirin, an antiviral drug for treatment, which was used in only a few cases; it is still controversial regarding its efficacy and thus warrants further investigation.[28, 29] Supportive care includes oxygen therapy, mechanical ventilation in severe cases, and hydration, with a focus on maintaining airway patency and respiratory function.30 Currently, there is an increasing focus on developing targeted therapies, such as fusion inhibitors, which could interfere with the entry process of the virus.[28] The vaccine remains a significant focus area due to the massive health burden associated with the virus across the world.[17]

Although tremendous progress has been made toward the disease's treatment, without an effective and solid diagnostic tool for HMPV, this would further worsen the management, as current molecular diagnostic techniques like RT-PCR can only be processed in advanced laboratories. Thus, to facilitate interventions promptly, more robust diagnostic platforms with rapid testing need to be developed.[31] Furthermore, detailed knowledge of HMPV's mechanisms of immune modulation and its mode of viral persistence will contribute significantly to vaccine design and development, along with designing new antiviral agents.[16]

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Impact of Outbreak

The clinical spectrum of HMPV infection is rather broad. It varies from simple upper respiratory infections to more serious forms like bronchiolitis and pneumonia, with potentially life-threatening courses in both elderly patients and in patients who may have chronic medical conditions.[16,32] Consistent with the reported incidents of outbreaks in nursing homes and hospitals, most cases have exhibited a significant level of morbidity, except during seasonal peaks, when occurrences have also been recorded in other regions of the Netherlands and Korea, outside these seasonal intervals.[32, 33] The removal of lockdown measures for COVID-19 has led to a resurgence of infections, despite HMPV being out of season, thereby increasing the healthcare burden.[34] The complexities of controlling outbreaks also result from the genetic evolution and variations of HMPV, for example, the A2c variant, which emerged during the COVID-19 pandemic, suggests an adaptation mechanism that enables escape from immune responses; therefore, surveillance and further studies are necessary.[31, 35] Other complications in the clinical picture arise with co-infection by other respiratory pathogens, including rhinoviruses or RSV.33 Surveillance efforts continue, and there is a critical need for effective preventive measures, including vaccines and antiviral treatments, to deal with the ever-growing threat posed by HMPV infections among different populations.

Public Health and Healthcare Systems

The outbreak of HMPV has significant repercussions for public health and healthcare settings worldwide, taking into account that it can readily cause widespread acute respiratory illness involving all age ranges. In any case, particular vulnerable populations include young children, the elderly, and immunocompromised individuals—all of whom could be at an enhanced risk of illness, thus leading to the establishment of targeted interventions in healthcare strategies for these higher-risk groups of patients.[16, 32] HMPV, which seasonally peaks traditionally in the winter, is therefore very challenging in planning health services as the disease creates pressure on health facilities in instances where peak periods coincide with influenza and RSV infection, similar to the off-season outbreaks such as that reported in the Netherlands and Korea, when COVID-19 restrictions were relaxed putting further pressure on strained health facilities.[33, 34] Apart from direct medical complications, co-infections with other pathogens increase the clinical complexity of HMPV infections, leading to more extended hospital stay periods and higher complication rates that place a greater burden on healthcare systems. The growing awareness of the role of HMPV in public health, combined with its ability to evolve genetically and the appearance of new strains, requires the development of integrated surveillance systems that will track its spread and predict future outbreaks. Such systems should be flexible enough to respond quickly to off-season surges and adapt to changes in viral dynamics.31, 35 Public health efforts should also focus on strengthening preventive measures, such as developing vaccines and antiviral drugs, to help reduce the burden of HMPV on healthcare systems, considering that the virus continues to evolve in response to environmental and social changes.[32, 34]

Social and Economic Consequences

The economic burden of HMPV infections arises from both direct and indirect costs, including medical expenses, hospitalisation, outpatient care, lost productive time, and long-term use of healthcare services, particularly those related to complications such as pulmonary sequelae.[36, 37] Carrico et al.'s study, which captures the yearly economic burden of RSV in adults in the United States, will help inform the effects of respiratory viruses, such as HMPV, on the economy. Typically, RSV leads to severe illness in infants and children. It is a requirement to point out that even adults, older adults, or persons with certain medical conditions can readily succumb to potentially deadly health issues and even death from RSV and other lung infections, including HMPV. This provides an in-depth review of both direct medical costs (hospitalisations, outpatient visits, diagnostic testing, and medications) and indirect costs (lost productivity and long-term care) of RSV in adults, with findings that can be extrapolated to HMPV, given their clinical similarities.[37]

The economic cost of HMPV is primarily related to the frequency of occurrence. Wang et al. reported on the frequency of HMPV occurrence in children under 5 years of age worldwide. It describes many cases of lower respiratory tract infections related to HMPV, which resulted in increased hospitalisation and healthcare expenses.[38] Furthermore, a study on HMPV in Canada showed that the virus imposes a heavy burden on healthcare, thus requiring strong healthcare systems to cope with the seasonal peaks.[39] In regions like Beijing, China, it was reported that the seroprevalence of viral infections, including HMPV, further emphasising the widespread nature of these infections and the potential societal costs associated with widespread morbidity.[38] Coinfections with bacteria, such as Streptococcus pneumoniae, or other viruses, like influenza, can exacerbate the severity of HMPV infections and result in more complex clinical outcomes.[40] According to Pacheco et al., coinfections may worsen clinical prognosis, necessitate extended hospitalisation or intensive care, and contribute to increased healthcare costs and resource utilisation. This highlights the importance of timely diagnosis and effective management strategies, which can help reduce both

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direct healthcare costs and indirect societal costs.[39,40] The molecular biology of the HMPV attachment protein has relevant findings that might guide the design of vaccines and antiviral treatments. Vaccination and prophylactic treatment against other common respiratory pathogens, such as influenza and pneumococcal infections, can also diminish the risk of coinfections and help lessen the societal burden associated with HMPV.

Prevention and Control

Although there is no specific vaccine for HMPV,[41] several approaches can be taken to reduce the transmission and severity of this disease.[39] These include vaccination, antiviral treatment, infection control measures, and public health interventions.[42]

Vaccination and Immunisation

The residual development of a functional vaccine for HMPV thus constitutes one area that researchers are keenly focusing on in the field of respiratory viruses. Although a vaccine targeting HMPV has not yet been licensed, the molecular biology of the virus, particularly the attachment protein, is of vital interest in developing potential vaccines. It provides an opportunity for designing vaccines that can evoke immunity, which could block infection, as the attachment protein helps the virus gain entry into host cells.

The relevance of vaccines to respiratory viruses like HMPV highlights their potential as a means of pre-exposure prevention against pathogens like RSV, which presents strong similarities to HMPV. Vaccine intervention against RSV has already been proven to lower the attack rate of severe disease, especially in high-risk populations, which would be infants and the elderly. A similar strategy for HMPV may be very effective at preventing not only direct healthcare costs but also indirect productivity losses that occur with severe infections.[37]

Antiviral Treatments

Although HMPV vaccines are in development, antiviral therapy remains one of the effective control strategies against the virus.[26] Antiviral drugs that target the viral replication process or its attachment to host cells are being developed.[43] In this regard, Pacheco et al. have described bacterial and viral coinfections with RSV, emphasising the importance of initiating antiviral therapy as soon as possible to mitigate the severity of the infection and its complications. For HMPV, early antiviral intervention would help lower the duration and intensity of symptoms and reduce hospitalisation and healthcare costs.[40]

Infection Control Measures

Infection control in healthcare settings is crucial for preventing the transmission of HMPV, particularly in paediatric or geriatric units, where patients are most vulnerable to respiratory infections. The importance of infection control practices, such as hand hygiene, isolation of infected patients, and the use of personal protective equipment (PPE), helps in controlling the clinical and economic burden. These are just as effective for HMPV. It is worth noting that implementing proper respiratory hygiene measures, such as the use of masks and tissues to cover coughs and sneezes, can effectively reduce the incidence of HMPV transmission within community settings during seasonal peaks of respiratory infections.[44]

Public Health Interventions

Public health campaigns are crucial for raising awareness about HMPV and its prevention strategies.[45,46] Early diagnosis and treatment of HMPV infections are effective ways to reduce the healthcare burden and enhance patient outcomes. Surveillance systems monitoring the incidence of HMPV can help inform public health responses and resource allocation. These systems also allow for the identification of at-risk groups, such that interventions, such as antivirals or potential vaccines, will be targeted toward those most likely to suffer from severe disease.[38]

Community and Environmental Measures

These measures will control the environmental spread in school settings, daycares, and hospitals by ensuring proper cleaning and disinfection of all surfaces where the virus may be present.[47] The children may face pulmonary sequelae following HMPV infection; therefore, the risk of transmission at this initial phase must be halted as much as possible.

Integrated Approach to Prevention

Shared clinical features of HMPV and other respiratory viruses, such as RSV, influenza, and parainfluenza, require a concerted approach for prevention and control.48 Preventing coinfections by HMPV and other respiratory pathogens will likely reduce disease severity and improve clinical outcomes. The approach would involve concomitant vaccination with a range of multiple respiratory viruses, as well as the use of broad-spectrum antiviral drugs.[40]

Even though the development of vaccines and antiviral treatments for HMPV remains an open challenge,[49] the combination of infection control measures, public health strategies, and research into antiviral therapies will be important in controlling the spread of HMPV.[50] Seroprevalence analysis, which examines the patterns of HMPV transmission and its prevalence in the population, is crucial for effective prevention planning.[51] In conclusion, only a comprehensive intervention involving vaccination, antiviral treatment, infection control, and public health measures can effectively diminish the clinical and economic burdens that HMPV places on the individual, the family, and the healthcare system (Figure 3)

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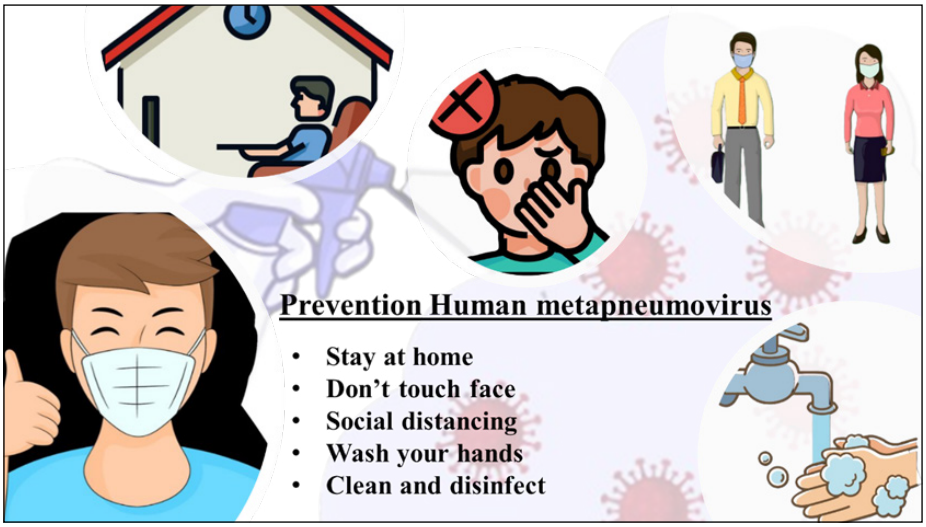

Figure 3.Prevention and Control of HMPV

Conclusion and Future Prospects

The future of HMPV research and management holds both promise and challenge simultaneously, due to increased global awareness of the clinical and economic burden on healthcare systems. It is mainly due to the continued focus on vaccine development that will grow further into maturity, since early-stage progress has been considerable. Notably, efforts such as the investigational IVX-A12 combination vaccine for RSV and HMPV, which is currently undergoing clinical trials, represent a significant step forward in reducing the global burden of the disease. These vaccines, if successful, will greatly impact society, especially high-risk groups including infants, and elderly and immunocompromised patients. While vaccine research will be going forward, there is also hope that antiviral therapies, such as targeting a specific lifecycle phase of HMPV, will move forward rapidly. The inhibitors of viral replication and entry under investigation, together with the advances of structure-guided drug design, can lead to treatment options in line with current supportive care approaches. Furthermore, integrated multiplex diagnostic panels, capable of detecting HMPV and other respiratory pathogens simultaneously, will probably become the new gold standard. In parallel, AI and machine learning algorithms are expected to be increasingly used for epidemiological data analysis, identification of trends, and prediction of outbreaks. These predictive models, combined with real-time genomic surveillance, will enhance preparedness and response strategies, mitigating the impact of seasonal and off-season surges. Further, community awareness about HMPV and promoting preventive measures such as hand hygiene, respiratory etiquette, and vaccination campaigns for other respiratory pathogens will be essential. In healthcare settings, infection control practices, such as the use of personal protective equipment and isolation protocols, must be strictly followed to prevent nosocomial transmission. Scientifically, host-pathogen interactions at the cellular and molecular levels are expected to reveal new therapeutic targets. Research into the metabolic reprogramming induced by HMPV infection, which favours viral replication, could lead to innovative approaches that disrupt these pathways. Similarly, elucidation of mechanisms of immune evasion by the virus, such as interference with interferon responses, will guide immunomodulatory therapies that bolster host defences. Animal models and organoids will help in studying the pathogenesis of HMPV in a controlled setting, which can be useful for understanding disease progression and potential intervention. Looking further ahead, the integration of nanotechnology and biotechnology into HMPV research holds transformative potential. Nanoparticle-based delivery systems for vaccines and therapeutics can enhance their stability, efficacy, and targeted delivery, reducing side effects and improving patient outcomes. CRISPR-Cas, which has already revolutionised genetic research, could be leveraged to edit viral genomes or boost host immunity against HMPV.[52] Advances in synthetic biology may facilitate the development of attenuated or inactivated viral strains, leading to safer and more effective vaccine candidates.

HMPV is an emerging respiratory pathogen that particularly impacts young children, the elderly, and individuals with impaired immune systems. With such high prevalence, it continues to be underdiagnosed and underrecognised since it has clinical features that are similar to other respiratory viruses. Even with advancements in molecular diagnostics, such as PCR and multiplex panels, improved detection remains a challenge because access remains limited in resource-poor settings. The lack of specific antiviral therapies and a licensed vaccine further underscores the need for urgent targeted research and development efforts. The recent increase in HMPV infections, such as the recent outbreak in China, emphasises the need for

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robust surveillance systems to track viral evolution and epidemiological trends. This, coupled with real-time genomic analysis and predictive modelling, could guide an appropriate public health response. Promising research in the area of vaccine development, such as the investigational IVX-A12 combination vaccine, and new approaches targeting the viral fusion and attachment proteins, can lead to a significantly decreased burden of HMPV globally. Future directions include incorporating nanotechnology, synthetic biology, and immunotherapy into the management of HMPV, with further development of rapid point-of-care diagnostics. Translation of the research findings to practical interventions would require collaboration among academia, industry, and public health agencies. Access to healthcare resources in low- and middle-income countries must be equitable to provide benefits to all affected populations.

Although global evidence points toward millions of cases, hundreds of thousands of hospitalisations, and substantial mortality annually, the Indian situation is not well described because of sparse surveillance and underdiagnosis. Epidemiologic studies from the Indian setting, which are accessible, indicate HMPV accounts for 5–15% of paediatric respiratory illness, with an annual peak in late winter and early spring, patterns similar to those observed internationally. Considering India's enormous paediatric population, high burden of chronic respiratory diseases, and disparities in access to healthcare, the hidden HMPV burden may be huge. It is imperative to enhance molecular diagnostic capability, incorporate HMPV testing in routine respiratory virus surveillance, and undertake multicentric epidemiological research to ascertain its real prevalence. Raising clinician awareness, ranking high-risk individuals for preventive interventions, and participating in international vaccine and monoclonal antibody development programmes will be the initial steps to limiting morbidity, mortality, and healthcare burden due to HMPV in India. This requires a multidisciplinary and proactive approach at all levels, harnessing scientific innovation, sound public health measures, and global coordination to mitigate the impact of HMPV and enhance respiratory health outcomes worldwide.

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