

Review Article

# The Global Perspective of Human Metapneumovirus

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**Summary:** Globally, human metapneumovirus (hMPV) constitutes a more significant proportion of acute respiratory tract infections (ARTIs), a primary cause of morbidity and mortality in children. A range of viruses, such as influenza viruses, respiratory syncytial virus (RSV), picornaviruses, coronaviruses, parainfluenza viruses, and adenoviruses, have been linked to various respiratory syndromes across all age categories. Notably, some of these viruses circulate and co-infect individuals, increasing the possibility of resulting in complex interactions that may affect disease severity, immune response, and epidemiology. It is also known that the majority of children contract hMPV by the age of 5, with the most severe cases found in infants, comprising both symptomatic and asymptomatic infections. Although hMPV is widely common, no approved vaccines or specific antiviral therapies are available, highlighting the need for more research into focused treatments and vaccine development. Improvements in molecular diagnostics have increased detection rates, though difficulties persist in disease monitoring and management. The 2024-2025 current outbreak in China commenced in December 2024 and has experienced a rapid rise in cases, especially among children aged 14 and younger. Additionally, other countries like the United Kingdom (UK), France, and Germany have reported cases of the virus, reflecting its extensive spread. Consequently, an understanding of the epidemiology of hMPV is essential for creating effective targeted interventions. This review provides a global perspective of hMPV and points out knowledge gaps to drive future research initiatives in its management, prevention, and control.

**Keywords:** Human metapneumovirus, Respiratory viruses, Epidemiology, Public Health.

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## INTRODUCTION

Human metapneumovirus (hMPV), although being a newly described virus, was first isolated in 2001 in the Netherlands from the nasopharyngeal aspirates (taken over 20 years) of 28 hospitalised children and infants with ARTIs (acute respiratory tract infections), with signs and symptoms similar to RSV (respiratory syncytial virus infection) (Mullins *et al.*, 2004; Haas *et al.*, 2013). However, findings from retrospective studies indicate that the virus has been in circulation since 1958 (Kroll & Weinberg, 2011) and has been found worldwide (Wolf *et al.*, 2003; Vinci *et al.*, 2018) (Table 1).

hMPV, a lipid-enveloped, negative-sense, single-stranded RNA virus, belongs to the subfamily Pneumovirinae within the Pneumoviridae (formerly Paramyxoviridae) family (van den Hoogen *et al.*, 2004; Vinci *et al.*, 2018; Uddin & Thomas, 2021). Other members of this subfamily include respiratory syncytial virus (RSV) and avian pneumovirus (van den Hoogen *et al.*, 2004). Based on genetic differences, the virus is divided into two

major groups (A and B) and four primary subtypes (A1, A2, B1, B2) (Boivin *et al.*, 2004). The genome of hMPV is around 13 kb and consists of eight open reading frames (ORFs) that encode nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion glycoprotein (F), transcription enhancer protein (M2), small hydrophobic protein (HP), adhesive glycoprotein (G), and large polymerase protein (L) (Kamau *et al.*, 2020).

The virus exhibits significant genetic diversity globally due to its evolving genome and regional circulation patterns (Kim *et al.*, 2016). This is evident by the genome-wide analysis of 103 complete genomes, which identified recombination events and divergent selection pressures across genes, particularly in the G gene (Kim *et al.*, 2016). Despite sparse hMPV genome sequence data and limited information on genome-wide diversity in Africa, the transmission of the virus shows strong local and regional clustering in Africa, with genotypes often circulating within subregions such as East Africa (Kenya), West Africa (Mali, Gambia), and Southern Africa (Zambia, South Africa) (Kamau *et al.*, 2020; Oketch *et al.*, 2021). This clustering

suggests localised outbreaks and limited intercontinental spread (Oketch *et al.*, 2021).

#### **TRANSMISSION AND PATHOGENESIS:**

The disease is transmitted through direct inhalation of infected droplets or indirectly via fomites (Boivin *et al.*, 2007). Upon entry into the host's respiratory tract, the virus binds to epithelial cells through its G and F glycoproteins. While the G protein helps in attaching to the virion of the host cell, the F protein facilitates the entry of the virus by promoting membrane fusion, which is subsequently followed by replication within the cytoplasm. This viral replication leads to cytopathic effects, including the formation of syncytia and the shedding of cells, which in turn contribute to inflammation and obstruction of the airways (Ballegeer and Saelens, 2020).

The pathogenesis of hMPV involves both direct damage caused by the virus and the response of the host's immune system. The infection leads to disruption of epithelial cells, excessive mucus production, and the infiltration of inflammatory cells, notably neutrophils and macrophages. The innate immune response is marked by the release of proinflammatory cytokines, such as IL-6 and IL-8, as well as interferons (Ballegeer and Saelens, 2020). However, hMPV has evolved strategies to evade or diminish these immune responses, including the disruption of Toll-like receptor signaling pathways (Ballegeer and Saelens, 2020). hMPV has been observed to mainly impact young children, the elderly, and immunocompromised individuals, presenting with symptoms that vary from mild upper respiratory infections to serious bronchiolitis and pneumonia (Deffrasnes *et al.*, 2007). In young children, common symptoms include fever, runny nose, cough, pharyngitis, otitis, wheezing, and hypoxia, while adults typically experience cough, nasal congestion, hoarseness, sore throat, and fever (Schildgen *et al.*, 2011). Nevertheless, the specific factors that confer protection and the immunopathological mechanisms underlying the severity of the disease are still not well understood.

#### **DIAGNOSIS AND DIAGNOSTIC ADVANCES:**

The infection can be diagnosed using various methods, such as culture, nucleic acid amplification tests (NAAT), antigen detection, and serological tests. Immunofluorescence also serves as a promising method for diagnosing hMPV infection, but it has not been implemented in clinical practice (Chiu *et al.*, 2007). Due to its slow growth in conventional cell culture and mild cytopathic effects, virus culture is usually difficult (Haas *et al.*, 2013). However, identifying viral RNA using NAAT techniques like reverse transcriptase-PCR (RT-PCR) is the most sensitive approach for hMPV diagnosis (Gray *et al.*, 2006; Haas *et al.*, 2013). Particularly, RT-PCR has established itself as the gold standard diagnostic method due to its exceptional sensitivity and specificity, as well as its capability to differentiate between the two hMPV genotypes, A and B (Haas *et al.*, 2013). Also, multiplex PCR assays have shown concurrent identification of hMPV along with a range of other respiratory viruses, such as respiratory syncytial virus (RSV), influenza, adenovirus, and parainfluenza viruses (Yoshida *et al.*, 2010). This capability is especially beneficial in clinical environments where co-infections are prevalent and symptoms often overlap (Yoshida *et al.*, 2010;

Popowitch *et al.*, 2022). Currently, commercially available respiratory pathogen panels, including those from BioFire, GenMark, and Luminex, are extensively utilized in both hospitals and research laboratories (Popowitch *et al.*, 2022).

#### **TREATMENT:**

Currently, there are no treatments and vaccines for this disease except supportive measures such as oxygen therapy, bronchodilators, corticosteroids, and mechanical ventilation (Yoshida *et al.*, 2010). However, ribavirin and intravenous immunoglobulins have shown in-vitro activity but are not standard treatments (Khan *et al.*, 2024). Research has been conducted on monoclonal antibodies (mAbs) that target the F protein, with several showing neutralizing effects in animal studies. Nevertheless, there are currently no mAbs approved for clinical application against hMPV (Proenca-Modena *et al.*, 2011). Consequently, prevention relies on hygiene practices such as frequent hand washing, sanitizing surfaces, wearing masks in crowded areas during peak seasons, and maintaining social distancing when feeling unwell (Khan *et al.*, 2024).

#### **GLOBAL EPIDEMIOLOGY AND BURDEN OF HUMAN METAPNEUMOVIRUS:**

Since its first isolation, cases of hMPV have been recorded in individuals of all ages across North America, South America, Europe, Africa, Asia, and Oceania, with seasonal variations in these regions (WHO, 2025). For instance, Rodriguez *et al.* (2020) reported that hMPV displays a seasonal distribution, with peaks noted at the end of winter and in spring, following RSV and Flu in temperate areas. The study further reported that the virus circulates alongside the parainfluenza virus throughout winter and into late spring (Rodriguez *et al.*, 2020). In contrast, many other regions experience year-round circulation with reduced activity in late spring, summer, and fall (Kahn, 2006). However, the onset of the COVID-19 pandemic disrupted its circulation. While enveloped viruses continued to circulate from the summer of 2020, hMPV and RSV were not among the dominant strains. In the summer of 2021, hMPV and RSV were again in circulation and caused two epidemic peaks, the second of which started in the autumn (Kivit *et al.*, 2022; Piñana *et al.*, 2023). For instance, in China, there has been a surge surpassing pre-pandemic levels (World Health Organization, 2024). Also, reports from the UK Health Security Agency (UKHSA) indicated a slight increase in HMPV positivity, reaching approximately 4.5% among the respiratory samples analyzed in the United Kingdom (UK GOV, 2025).

Similarly, Japan saw a notable increase in hospital admissions related to hMPV from July 2022 to June 2023 following the relaxation of COVID-19 restrictions (Fukuda *et al.*, 2023). According to seroprevalence studies, around 90 to 100% of children get infected with hMPV by the age of 5 to 10 years (Arnott *et al.*, 2011; Banerjee *et al.*, 2011; Uddin & Thomas, 2021). Furthermore, the PERCH study, which identified the leading cause of severe pneumonia in hospitalised children across seven countries in Africa and Asia over two years, found viruses to be the predominant (61%) cause (O'Brien *et al.*, 2019). This study also found that hMPV is third after RSV and Rhinoviruses (O'Brien *et al.*, 2019). Additionally, a 2018 systematic review reported that the disease accounts for 6.1–6.4% of hospital

admissions related to ALRI (acute lower respiratory tract infections) in patients under 20 years old globally (Wang *et al.*, 2021). The findings of this review further revealed that between 1990 and 2015, the mean hMPV-associated ALRI incidence was 22.1 per 1000 children per year in children aged 0–59 months in settings with high child mortality, and 18.9 in settings with low child mortality (Wang *et al.*, 2021).

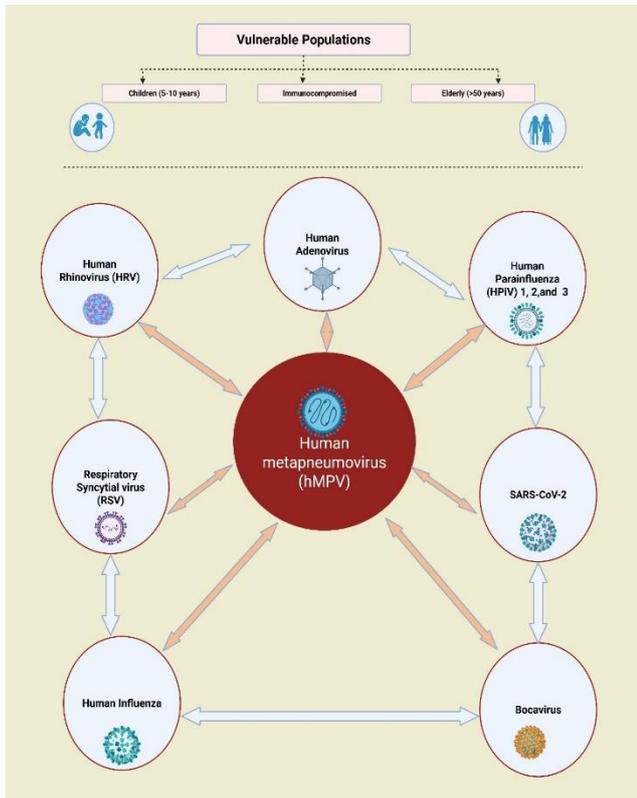
Although, in Africa, the true burden of hMPV is not known due to underreporting, studies conducted in countries like South Africa, Kenya, Uganda, Yemen, and Senegal (Table 1) have revealed that the virus is a notable cause of lower respiratory tract infections (LRTIs), often co-

circulating with RSV and influenza viruses (Kahn, 2006). For instance, Ramocha *et al.* (2021) discovered that hMPV is responsible for 4.7% of LRTIs and severe acute respiratory infections (SARI) in African children under five years, with the case fatality rate estimated at 1.3%. Similarly, Owor *et al.* (2016) reported that the hospitalization incidence in Kenyan children under five due to hMPV ranged from 1.2% to 8.7% annually, with children under one year mostly affected. Malnourishment, HIV infection, and other immunosuppressive conditions further contribute to the risk of severe disease in African populations (Madhi *et al.*, 2007; Groome *et al.*, 2015).

**Table 1:**  
Historical Overview of Human Metapneumovirus

Continent	Countries	Year of isolation/detection	Outbreaks/incidences observed	Key findings	References
Europe	Netherlands	2001	Initial isolation of hMPV from respiratory samples of Dutch children.	First identified in 2001; the prototype strain was isolated.	(van den Hoogen <i>et al.</i> , 2004)
	United Kingdom	2000-2001	Sentinel general practices in England and Wales gathered samples from patients of every age exhibiting influenza-like illnesses (ILI) during the winters of 2000-2001.	hMPV was identified in 9 (2.2%) patients, and appeared to be associated with community-acquired ARTI.	(Stockton <i>et al.</i> , 2002)
	Finland	2001	The detection of hMPV by PCR in ten (8%) of 132 consecutive children admitted to Turku Hospital, Finland, for acute expiratory wheezing.	hMPV accounted for 8% of the total patients investigated. Co-infection with other respiratory viruses was also reported.	(Jartti <i>et al.</i> , 2002)
	Spain	2000s	Reported cases among pediatric populations; seasonal peaks like RSV.	hMPV prevalence rates was reported alongside RSV and other respiratory viruses.	(Kahn, 2006)
	Italy	2000-2002	The study examined nasal swab specimens from 90 infants with acute respiratory tract infections in Pisa, Italy, throughout three respiratory virus seasons.	The incidence of infection varied in each of the 3 years, with the rates of positivity for hMPV being 7% in 2001 but 37 and 43% in 2000 and 2002, respectively.	(Maggi <i>et al.</i> , 2003)
	Austria	2000-2007	Yearly surveys showed that seasonal hMPV activity varied substantially from year to year, with the majority of hMPV infections occurring in winter or spring.	The hMPV seasonality showed a biennial pattern of alternate winter versus spring activity.	(Aberle <i>et al.</i> , 2008)
	Switzerland	2004-2008	A total of 3,934 Nasopharyngeal aspirates (NPAs) were tested for hMPV, of which 198 (5%) were positive.	hMPV epidemics follow a biannual variation in the study.	(Heininger <i>et al.</i> , 2009)
South America	Argentina	2004	Prevalence of 20.3% among respiratory infections in children under one year old.	Local strains show high genetic similarity with those from neighbouring countries.	(Kahn, 2006)
	Brazil	2000s	hMPV was detected in pediatric cases; seasonal patterns were observed.	Similar trends in respiratory infections were noted across various age groups.	(Kahn, 2006)
North America	United States	2002	The first documented study of the occurrence of hMPV in the United States.	The study confirms that hMPV infection occurs in young adults as well as elderly persons.	(Falsey <i>et al.</i> , 2003)
	Canada	2000-2002	Children aged <5 years and elderly subjects aged 165 years represent 35.1% and 45.9% of the hMPV-infected cases, respectively.	In hospitalised children, the most frequent diagnoses were pneumonitis (66.7%) and bronchiolitis (58.3%), whereas bronchitis and/or bronchospasm (60%) and pneumonitis (40%) were most commonly seen in elderly subjects.	(Boivin <i>et al.</i> , 2002)

<b>Asia</b>	Thailand	2001-2002	The study investigated the prevalence of hMPV in Thai children by RT-PCR, using primers specific for the N gene.	The results showed a prevalence of hMPV in 4.2% of the patients tested.	(Thanasugarn <i>et al.</i> , 2003)
	Israel	2002	A high prevalence of anti-hMPV antibodies among young children in southern Israel. By age 2 years, >50% of children have been exposed to the virus.	Studies indicated circulation and genetic diversity.	(Wolf <i>et al.</i> , 2003)
	Japan	2000s	Frequent transmission with China noted.	Close phylogenetic relationship with strains from China; regional transmission dynamics observed.	(Liu <i>et al.</i> , 2019)
	India	2003	The study suggests the importance of hMPV in causing mild and severe respiratory infections among children, especially infants in India.	First detection of hMPV in Children with ARIs in India.	(Rao <i>et al.</i> , 2004)
	Singapore	2005-2007	The first attempt to assess the importance of hMPV among the pediatric population in Singapore.	An estimated infection rate of 5% observed in this study indicates that hMPV is a notable contributor to illness in Singapore's children.	(Loo <i>et al.</i> , 2007)
	China	2013-2017	Increasing incidence, especially in Guangzhou; peak detection rates around 11% in 2017.	Emergence of B1 lineage; substantial seasonal patterns.	(Liu <i>et al.</i> , 2019)
	Malaysia	2010-2012	hMPV is an important, although relatively infrequent, cause of respiratory virus infection in hospitalised children in Malaysia, with prematurity and asthma as the commonest predisposing conditions.	The prevalence rate of hMPV between 2010 and 2012 was 1.1%, and it contributed 6.5% of confirmed viral respiratory infections.	(Nor'e <i>et al.</i> , 2014)
	Vietnam	2009	Hospitalized Vietnamese children with ARIs were investigated for 13 viral pathogens using multiplex-PCR	hMPV accounted for 4.5% of the confirmed viral respiratory pathogens.	(Yoshida <i>et al.</i> , 2010)
<b>Oceania</b>	Australia	2001	Three hMPV isolates were identified from 200 nasopharyngeal aspirate samples collected in 2001 from children with respiratory illness in Brisbane hospitals. These samples, initially negative for common respiratory viruses via antigen testing and culture, were screened using PCR. The PCR results confirmed hMPV presence, with sequences showing 100% homology to known hMPV strains.	The first report of the presence of hMPV infection in Australian children and described a new viral respiratory syndrome.	(Nissen <i>et al.</i> , 2002)
<b>Africa</b>	Yemen	2002-2003	This is the first report of hMPV from the Arabian Peninsula and confirms its importance as a cause of ARI in Yemen.	hMPV had marked seasonal variations with an RSV peak in December and January and an hMPV peak in February and March.	(Al-Sonboli <i>et al.</i> , 2005)
	Kenya	2007	The study was on the viral aetiology of severe pneumonia among Kenyan young infants and children.	hMPV accounted for 3.0% of the total sample.	(Berkley <i>et al.</i> , 2010)
	Uganda	2008	The study investigated the presence of viruses associated with (ILI) in Uganda.	hMPV accounted for 1.4% of the total sample.	(Balinandi <i>et al.</i> , 2013)
	South Africa	2009-2012	The description of LRTI hospitalizations among South African children aged <5 years.	hMPV (5%) was detected alongside other respiratory pathogens during outbreaks.	(Cohen <i>et al.</i> , 2015)
	Senegal	2012-2016	hMPV detection rates in the different age groups varied significantly with the children under 5 years group accounting for 71.7% of positive patients.	The temporal distribution pattern for hMPV infection showed a clear seasonal pattern with higher activity during the rainy period (July-September). Phylogenetic analyses revealed that hMPV specimens circulating in Senegal were distributed into the two main genetic lineages, A and B.	(Jallow <i>et al.</i> , 2019)



**Figure 1:** Interrelationship between human metapneumovirus and other respiratory viruses

### HUMAN METAPNEUMOVIRUS AND OTHER RESPIRATORY VIRUSES:

hMPV usually circulates and co-infects people with other respiratory viruses (including RSV, influenza viruses (types A and B), parainfluenza viruses, rhinoviruses, bocaviruses, and adenoviruses), resulting in complex interactions that may affect disease severity, immune response, and epidemiology (Etemadi *et al.*, 2019; Jallow *et al.*, 2019; Yew *et al.*, 2019) (Figure 1). Semple *et al.* (2005) indicated that co-infections of hMPV and RSV may lead to more severe respiratory diseases, especially in children and those with weakened immune systems. Conversely, an earlier study by Bosis *et al.* (2004) observed that a small group of children co-infected with hMPV and RSV or influenza viruses showed no signs of greater disease severity.

### KNOWLEDGE GAPS IN HMPV DIAGNOSIS, TREATMENT, AND PREVENTION:

Despite two decades of research since the identification of hMPV, several critical knowledge gaps persist, hindering advancements in its diagnosis, treatment, and prevention. Addressing these gaps is vital for informing public health strategies, driving innovation in clinical management, and ultimately reducing the global disease burden associated with hMPV infections. A huge gap in knowledge exists regarding the pathogenesis of hMPV and the corresponding host immune responses. While it is established that hMPV can disrupt innate immune signaling, particularly by inhibiting interferon production, the precise viral-host interactions that influence the severity of the disease are not well understood (Ballegeer and Saelens, 2020). Also, current epidemiological insights into hMPV are primarily

from hospital-based studies, which may not accurately reflect the actual incidence and impact of the disease within the community. There is therefore a pressing need for longitudinal, population-based studies that will focus on geographic and socioeconomic factors as well as other risk factors to enhance our understanding of the transmission dynamics of hMPV.

As revealed by the reviewed studies, the lack of specific antiviral treatments for hMPV constitutes a considerable challenge in patient management. Future research should focus on the development of targeted therapies, such as small-molecule inhibitors, immunomodulators, and monoclonal antibodies (Proenca-Modena *et al.*, 2011). There is an urgent requirement for well-structured clinical trials to assess the safety and effectiveness of these treatments across diverse patient groups (Li *et al.*, 2024). Although promising vaccine candidates in the preclinical phase exist, no licensed vaccine for hMPV is currently available. Research efforts should aim at developing broadly protective and long-lasting vaccines that can effectively address the virus's genetic diversity (Li *et al.*, 2024).

While molecular diagnostics have become the standard for detecting hMPV, their accessibility remains limited in low-resource environments, where the disease burden is often the highest. It is vital to develop cost-effective, rapid, and point-of-care diagnostic tools that retain high sensitivity and specificity to support global surveillance and outbreak management

### DISCUSSION

Human metapneumovirus has gained increased attention in the post-COVID era due to its role in respiratory infections, particularly in vulnerable populations. Although hMPV was not as widely recognized as COVID-19 or influenza viruses initially during the pandemic era due to stringent control measures suppressing its spread along with other viruses like RSV, however, it poses great risks now that many countries have relaxed their infection control strategies. Studies also suggest that hMPV is associated with a substantial morbidity affecting both pediatric and adult populations. The virus usually presents its epidemic peak in late winter and early spring in pre-pandemic seasons, but its epidemic nature in 2020 was subtly interrupted by the SARS-CoV-2 pandemic (Piñana *et al.*, 2023). Furthermore, according to Piñana *et al.* (2023), two unexpected epidemic peaks occurred in the summer and autumn of 2021, with the latter associated with an increase in both the virus's prevalence and the median age of affected pediatric patients.

### CONCLUSION

The hMPV is an important respiratory pathogen with clinical similarities to RSV and influenza but with distinct epidemiological characteristics. Given its global impact, especially among vulnerable populations, focused public health strategies and research are vital to mitigate its burden. Additionally, genomic surveillance is essential in monitoring hMPV evolution by enabling the identification of new variants and linking these discoveries to the clinical attributes of confirmed cases, which is important for public health purposes. Furthermore, there is the need for the incorporation of molecular assay as a routine diagnostic in

the hospitals as this can improve the diagnosis and management of respiratory tract infections among the vulnerable populations, particularly children. This will ensure the development of effective treatment, prevention, and control strategies against this respiratory virus.

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