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REVIEW ARTICLE

Human Metapneumovirus: A Critical Review of Its Impact on the Immune System and Clinical Implications

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Abstract

Human Metapneumovirus (HMPV) became known in 2001 as a major respiratory pathogen which triggers acute respiratory tract infections (ARTIs) in the population with particular impact on infants and elderly patients and individuals with impaired immunity. HMPV was recently identified but retrospective analyses show this virus has existed unnoticed throughout previous decades starting from the 1950s. The respiratory tract pathogen HMPV exists within the Pneumoviridae family with genomic and structural relationships to respiratory syncytial virus (RSV). The virus manifests differently from delicate upper respiratory conditions to dangerous bronchiolitis and pneumonia within the lower respiratory system. Medical practitioners discover it difficult to identify HMPV due to identical viral symptoms but RT-PCR now enhances testing precision. HMPV has a seasonal pattern which reaches its peak during late winter and spring through airborne respiratory droplet transmission. Most people acquire the virus before their fifth year but continued infections happen as natural protection weakens so there remains an urgent need to develop safe treatments and vaccines against HMPV. FDA-approved antiviral drugs along with vaccines do not exist for treatment so healthcare professionals must provide supportive care only. Studies of HMPV's spread have improved yet scientists have not resolved fundamental questions about lineage immunity protection and virus immune evasion behaviors and persistent immune responses. The prevention of HMPV transmission requires proper hand hygiene practice together with respiratory etiquette. Multidisciplinary research needs continuous investigation because it helps tackle the worldwide burden of HMPV while developing specific prevention methods for this enduring public health threat that affects vulnerable populations.

Keywords: HMPV, Respiratory Syncytial Virus, Acute Respiratory Tract Infections, SARS-CoV, Vaccination.

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INTRODUCTION

Several respiratory pathogens emerged at the start of the 21st century including SARS-CoV alongside HMPV. HMPV was first identified in the Netherlands in 2001. This enveloped virus belongs to the Metapneumovirus genus as a member of two specific species which include avian metapneumovirus and HMPV. This virus serves in the Pneumoviridae family and fits into the Mononegavirales order within the same group as respiratory syncytial virus (RSV). The discovery of HMPV occurred through electron microscopy and random reverse transcription-polymerase chain reaction (RT-P CR) assessments on nasopharyngeal samples taken from respiratory illness patients among children (Hasvold et al., 2016). The virus caused damage to monkey kidney cells while showing genomic similarities of 88% to avian metapneumovirus serotype C yet demonstrated effective replication in monkeys but failed to replicate in birds (Khan et al., 2024). Historical investigations revealed HMPV had been spreading unnoticed throughout different decades since antibodies from the 1950s existed in serum archives along with respiratory specimen samples dating from 1976 (Philippot et al., 2024).

HMPV drives numerous cases of acute respiratory tract infections (ARTIs) that result in significant worldwide mortality especially in underdeveloped nations and the under-five age group. Lower respiratory tract infections (LRTIs) develop from ARTIs which result in annual millions of deaths worldwide (Miyakawa et al., 2025). Medical investigators have proven HMPV as one of multiple viruses responsible for acute respiratory tract infections. The symptoms of HMPV infection that include fever combined with coughing and breathing difficulties align with symptoms of multiple respiratory viral infections but diagnosis thus becomes difficult. HMPV shows its most destructive effects as an infection primarily within young infants and aged individuals as well as people with compromised immune systems. More than two decades since HMPV discovery has passed without effective prevention methods making this virus still a major public health concern (Hamelin et al., 2004).

HMPV infects both upper respiratory tract and lower respiratory tract areas in children and adults but produces most severe outcomes among immunocompromised patients. The development of present-day viral diagnostic technologies led scientists to discover and identify unknown pathogens such as HMPV (van et al., 2001). Humoral immunity stands as the main factor against HMPV infections and research on HMPV antibodies reveals significant information regarding the extent of HMPV exposure and first infection age and protective effects across subgroups and immunization potentials and possible treatment benefits from monoclonal antibodies (mAbs) (Afonso et al., 2016).

Studies show that HMPV caused the recent rise in respiratory infections in China and India although it is an established virus that remains difficult to manage (Cevey-Macherel et al., 2009). Studies of HMPV genome structure showed connections between the virus and paramyxoviruses but particularly with avian pneumovirus while the earliest documented HMPV case occurred in 1956 (Boncristiani et al., 2009). Since its discovery HMPV continues to be a leading agent of respiratory diseases globally because it demands improved diagnostic testing and better prevention and therapeutic treatments (Ruiz et al., 1999).

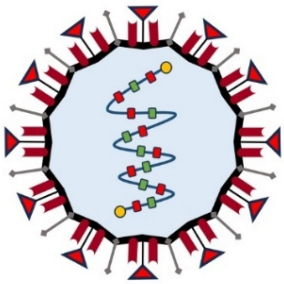
OVERVIEW OF STROKE

The seasonal pattern for Human metapneumovirus (HMPV) shows similarity to that of other respiratory viruses because it reaches its highest numbers during late winter and early spring periods in temperate climate zones beyond RSV and influenza timing (Williams et al., 2010). HMPV attacks particularly vulnerable individuals among infants along with young children, elderly persons and those who have underlying chronic illnesses or compromised immunity (Howard et al., 2018; Shafagati et al., 2018). HMPV infection occurs in almost all children worldwide before their fifth birthday but causes the most hospitalizations during six to twelve months of age (Walsh et al., 2008; van et al., 2004). The several genetically different HMPV subtypes that circulate simultaneously can produce severe illness and do not demonstrate any pattern linking genetic heterogeneity to illness intensity (Wei et al., 2013; Jain et al., 2015). The incidence of HMPV detection remains low in healthy children and this virus causes between 6 to 40 percent of acute respiratory diseases which lead patients to hospitalization or require outpatient treatment around the world (Edwards et al., 2013; Self et al., 2016). Adults contract HMPV infection for the first time before reaching age 5 but experience recurring infections throughout their lives (Williams et al., 2006; Panda et al., 2014). HMPV typically produces mild infections in fit adults under fifty but elderly patients and older residents of long-term care facilities experience extreme illness and high death statistics due to these infections (Aberle et al., 2010; Chano et al., 2005). Severe HMPV infection becomes more likely when a patient has asthma, COPD or weakened immune functions yet viral co-infections do not produce consistent modifications to disease levels (Ebihara et al., 2003; Kim et al., 2005). The complication of secondary bacterial pneumonia leads to higher death rates in patients (Anderson et al., 2012; Klein et al., 2006). Serologic testing has shown that HMPV spreads through respiratory droplets and has been present worldwide for over 50 years (Peiris et al., 2003; Madhi et al., 2003). Seasonal epidemics occur throughout northern winter months December to April in the northern hemisphere while RSV outbreaks may either happen before or simultaneously with these HMPV outbreaks (Wolf et al., 2003). Youthful children become sick from HMPV which creates 5–10% of lower respiratory tract infections (LRTIs) in infants and stands as the second main virus causing bronchiolitis after RSV (Pavlin et al., 2008). Regular contact with children through childcare duties raises the chances of HMPV infection as one of its risk factors (McAdam et al., 2004). HMPV outbreaks produce severe clinical consequences of bronchitis and pneumonia together with high death rates among elderly populations especially those in long-term care homes (Lüsebrink et al., 2010; Boivin et al., 2007). Scientists have found different infection rates between nations where Chinese provinces show the greatest levels of HMPV occurrence (Dunn et al., 2013; Howard et al., 2021). Medical surveys show periods of spring and winter generate the highest detection rates of HMPV while all genders demonstrate similar infection patterns (Bosis et al., 2005; Williams et al., 2005). HMPV continues to represent a major respiratory illness worldwide because it affects vulnerable groups and the disease patterns depend on both age and health conditions and seasonality (Boivin et al., 2003; García-García et al., 2007; Ahmed, 2025).

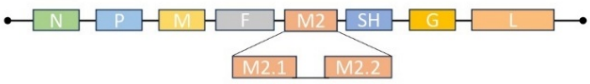
EPIDEMIOLOGY

The seasonal pattern for Human metapneumovirus (HMPV) shows similarity to that of other respiratory viruses because it reaches its highest numbers during late winter and early spring periods in temperate climate zones beyond RSV and influenza timing (Williams et al., 2010). HMPV attacks particularly vulnerable individuals among infants along with young children, elderly persons and those who have underlying chronic illnesses or compromised immunity (Howard et al., 2018; Shafagati et al., 2018). HMPV infection occurs in almost all children worldwide before their fifth birthday but causes the most hospitalizations during six to twelve months of age (Walsh et al., 2008; van et al., 2004). The several genetically different HMPV subtypes that circulate simultaneously can produce severe illness and do not demonstrate any pattern linking genetic heterogeneity to illness intensity (Wei et al., 2013; Jain et al., 2015). The incidence of HMPV detection remains low in healthy children and this virus causes between 6 to 40 percent of acute respiratory diseases which lead patients to hospitalization or require outpatient treatment around the world (Edwards et al., 2013; Self et al., 2016). Adults contract HMPV infection for the first time before reaching age 5 but experience recurring infections throughout their lives (Williams et al., 2006; Panda et al., 2014). HMPV typically produces mild infections in fit adults under fifty but elderly patients and older residents of long-

term care facilities experience extreme illness and high death statistics due to these infections (Aberle et al., 2010; Chano et al., 2005). Severe HMPV infection becomes more likely when a patient has asthma, COPD or weakened immune functions yet viral co-infections do not produce consistent modifications to disease levels (Ebihara et al., 2003; Kim et al., 2005). The complication of secondary bacterial pneumonia leads to higher death rates in patients (Anderson et al., 2012; Klein et al., 2006). The respiratory droplet transmission path of HMPV has been identified worldwide since at least five decades according to serologic testing results (Peiris et al., 2003; Madhi et al., 2003). Seasonal epidemics occur throughout northern winter months December to April in the northern hemisphere while RSV outbreaks may either happen before or simultaneously with these HMPV outbreaks (Wolf et al., 2003). Youthful children become sick from HMPV which creates 5–10% of lower respiratory tract infections (LRTIs) in infants and stands as the second main virus causing bronchiolitis after RSV (Pavlin et al., 2008). Regular contact with children through childcare duties raises the chances of HMPV infection as one of its risk factors (McAdam et al., 2004). HMPV outbreaks produce severe clinical consequences of bronchitis and pneumonia together with high death rates among elderly populations especially those in long-term care homes (Lüsebrink et al., 2010; Boivin et al., 2007). Scientists have found different infection rates between nations where Chinese provinces show the greatest levels of HMPV occurrence (Dunn et al., 2013; Howard et al., 2021). Medical surveys show periods of spring and winter generate the highest detection rates of HMPV while all genders demonstrate similar infection patterns (Bosis et al., 2005; Williams et al., 2005). HMPV continues to represent a major respiratory illness worldwide because it affects vulnerable groups and the disease patterns depend on both age and health conditions and seasonality (Boivin et al., 2003; García-García et al., 2007).



Gene (Protein)	Symbol	Amino acid length	Function
N (Nucleoprotein)		394	RNA genome encapsidation
P (Phosphoprotein)		294	Polymerase co-factor
M (Matrix protein)		254	Aids in viral assembly and budding
F (Fusion protein)		539	Virus-cell binding and membrane fusion
M2 (M2.1)		187	RNS transcription processivity factor
M2 (M2.2)		71	Regulates RNA transcription/replication or associated with viral replication
SH (Small hydrophobic protein)		177–183	Possible viroporin or innate immune inhibition
G (Attachment glycoprotein)		229–236	Binds to cellular glycosaminoglycans
L (Large polymerase protein)		2,005	Catalytic activity for viral replication
Nucleic Acid			



Genomic organization of (a) human metapneumovirus (hMPV)

Figure 1: Approaches to treating and preventing the spread of human metapneumovirus (HMPV).

GENOME ORGANIZATION AND STRUCTURE

The genomic organization of human metapneumovirus (HMPV) closely resembles that of respiratory syncytial virus (RSV), though HMPV lacks the non-structural proteins NS1 and NS2 and exhibits a slightly different gene order (3'-N-P-M-F-M2-SH-G-L-5') in its antisense RNA genome, which contains eight open reading frames (Hermos et al., 2010; Yi et al., 2019). HMPV is genetically related to avian metapneumoviruses types A, B, and C, and it is classified into two main genetic lineages, A and B, with subgroups A1/A2 and B1/B2, respectively (Williams et al., 2004). Phylogenetic analysis has shown that HMPV subtype B is associated with more prolonged respiratory symptoms, such as cough, compared to subtype A. The virus primarily infects airway epithelial cells in the nose and lungs, utilizing its glycoprotein (G) to bind to heparan sulfate and other glycosaminoglycans on target cells (Biacchesi et al., 2003; Ye et al., 2023). Additionally, the fusion (F) protein of HMPV, which contains an RGD motif, facilitates viral entry by interacting with integrins and mediating membrane fusion in a pH-independent manner, likely within endosomes (Piyaratna et al., 2011; Amarasinghe et al., 2011). HMPV is a negative-sense, non-segmented, single-stranded RNA virus with a genome of approximately 13,000 nucleotides, encoding nine proteins, including the nucleoprotein (N), phosphoprotein (P), matrix protein (M), and large polymerase protein (L), which form the viral replication complex (Figure 1). Unlike RSV, HMPV and avian metapneumoviruses lack NS1 and NS2 proteins and exhibit a distinct gene order (Biacchesi et al., 2004; Divarathna et al., 2020; Banerjee et al., 2022). Structurally, HMPV resembles other paramyxoviruses, with an enveloped morphology ranging from 150 to 600 nm in size and short protein spikes. Recent studies have revealed that HMPV can form branched filamentous networks and intercellular extensions in human bronchial epithelial cells, facilitated by the P protein's interaction with the actin cytoskeleton (Derdowski et al., 2008). This enables direct cell-to-cell viral spread, even in the presence of neutralizing antibodies or the absence of heparan sulfate, mediated by actin, CDC42, and Rac1. Genetically, HMPV is divided into six lineages (A1, A2a, A2b, A2c, B1, and B2), with varying geographical distributions (Fearns & Collins, 1999; Nao et al., 2020; Tulloch et al., 2021). In China, for instance, A2b, B1, and B2 are the predominant lineages, though their prevalence

varies by region, with A2c dominating in Henan province and B1/B2 in Zhejiang province. Monitoring these genetic variations is crucial for understanding HMPV's pathogenicity and epidemiological patterns (Ren et al., 2012; Masante et al., 2014).

PREVALENCE OF HMPV

Research-connected scientists detected Human metapneumovirus (HMPV) within 28 nasopharyngeal aspirates (NPA) harvested from Dutch young children suffering from respiratory illnesses during a 20-year observation period. When cultivated in tertiary monkey kidney cells HMPV showed an effect resembling the cytopathic changes of respiratory syncytial virus (RSV) with slow virus replication (Jallow et al., 2019). Electron microscopy of infected cell supernatant revealed particulatres that resembled paramyxoviruses and displayed pleomorphic shapes along with short surface projections of 13 to 17 nm in diameter which ranged from 150 to 600 nm. The properties of HMPV differed from other Paramyxoviruses like RSV and parainfluenza because it did not show visible nucleocapsid structures and failed to agglutinate red blood cells or become susceptible to chloroform exposure. The identification of the virus failed to detect results through reverse transcriptase reactions with respiratory virus-specific primers. The Paramyxoviridae family contains HMPV which belongs to Pneumovirinae subfamily and Metapneumovirus genus (Vinci et al., 2018).

The HMPV virus primarily affects young children whose median age falls at 22 months but mainly affects those who have not yet reached two years of age. The majority of children (90 to 100 percent) become infected with HMPV before they reach either five or ten years of age according to seroprevalence evaluations. Acute lower respiratory tract infections from the virus lead to hospitalization of 5 to 10 percent of pediatric patients. Infections with HMPV make hospitalization three times more probable for infants compared to children above six months up to five years of age. People can become infected with HMPV again since different viral strains or inadequate immune response from past infections might be present (Uche et al., 2018). Adults usually develop mild flu-like symptoms but elderly people combined with those who have weakened immune systems and chronic lung disease patients face higher risks for severe complications.

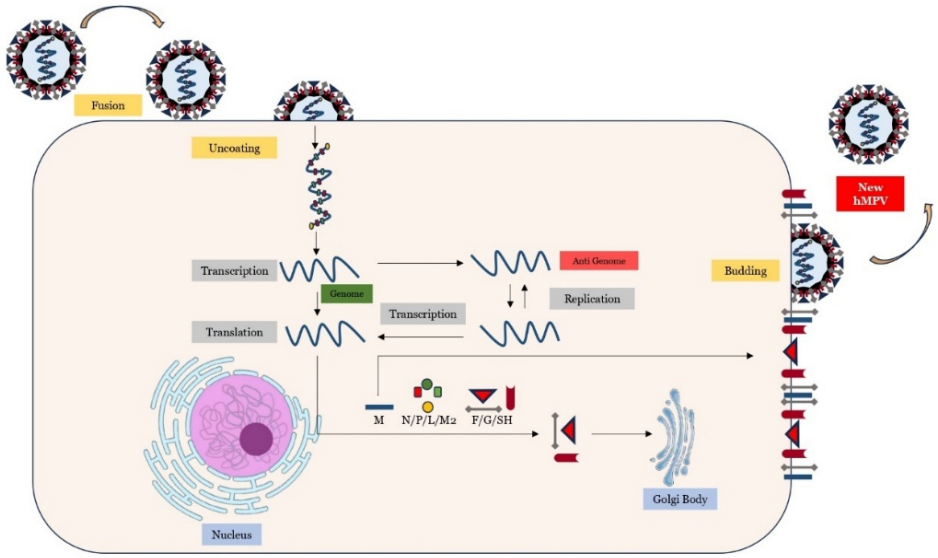


Figure 2: Schematic illustration of the viral cycle of HMPV.

CLINICAL MANIFESTATIONS & TRANSMISSION OF HMPV

Transmission of Human metapneumovirus (HMPV) occurs primarily by means of respiratory secretions caused by coughing or sneezing and through personal contact interactions and contact with surfaces that transmit infection to subsequent eye and mouth and nasal contacts (Figure 2) (Wang et al., 2021). The transmission of Human metapneumovirus through respiratory secretions constitutes a major concern for healthcare facilities due to the essential requirement of strict hand hygiene together with surface disinfection protocols to stop hospital-acquired infections (Wyde et al., 2005). Healthcare workers need to exercise greater caution because the virus stays infectious during one week post the start of symptoms (Williams et al., 2005). HMPV clinical manifestations mirror those of other respiratory viruses since the infection affects both upper respiratory tract and lower respiratory tract systems (Zhang et al., 2014). The set of upper respiratory symptoms includes cough together with rhinorrhea and sore throat and fever while patients showing lower respiratory symptoms exhibit wheezing dyspnea and hypoxia (Darniot et al., 2005). The virus serves as a major pathogen of bronchiolitis and pneumonia and asthma exacerbation and croup in children while it worsens chronic obstructive pulmonary disease (COPD) in adults. The respiratory condition from HMPV infection becomes severe in immunocompromised patients leading to acute respiratory failure that necessitates high-flow oxygen support and occasionally requires mechanical ventilation (Kolli et al., 2008). Pathological research demonstrates that HMPV infection produces acuteumatic lung organ deterioration and diffuse alveolar destruction and multiple severe pulmonary ramifications (Wang et al., 2021). The clinical course along with severity of HMPV infections exhibits different patterns between infants under one year who display lower fever and weight loss symptoms and immunocompromised patients together with those with existing heart or lung problems who face elevated risks of serious disease outcomes (Oong et al., 2018). Medical staff

frequently relies on empirical antibiotic and corticosteroid administration as a diagnostic approach because accurate HMPV infection detection remains challenging. The overlap in clinical and radiological findings between HMPV and other respiratory pathogens, such as SARS-CoV-2 and RSV, underscores the need for precise diagnostic tools, particularly in the post-pandemic era (Jeong et al., 2020).

PATHOGENESIS

Antibodies that neutralize human metapneumovirus (HMPV) develop in both humans and animals. These antibodies are first seen in mice about five to seven days after infection, and they reach their peak around four to six weeks later. Protection against reinfection is shown in mouse models by an initial HMPV infection, and in small animal models, protection may be conferred by antibodies alone (Feng et al., 2018). But even with serum antibodies, macaques could still detect viral replication 12 weeks after initial infection, and eight months later, they showed no protection when challenged (Erickson et al., 2012). This provides further evidence that antibody levels in humans and primates decrease with time, making re-infection easier (Darniot et al., 2009; Afrin, 2023). This is corroborated by a human investigation that found that older persons with fewer baseline HMPV antibodies had a higher infection risk, suggesting that antibodies have a protective function (Hamelin et al., 2008).

The clearance of HMPV infection in mice is facilitated by cytotoxic T lymphocytes (CTLs). The perivascular and peribronchial regions of the lungs are infiltrated by lymphocytes, monocytes, and other mononuclear cells during the first day after infection (Williams et al., 2007). On day 7, the total number of cells in the bronchoalveolar lavage reaches its peak, and by day 21, it has returned to almost normal levels. Day 3 sees an increase in neutrophils and mononuclear cells, which persists until day 14 (Corti et al., 2013). While CD8+ T cells reach their peak between days 8 and 10, CD4+ T cells reach their peak around day 6. While T-cell epitope immunization may decrease viral titers on its own, T-cell depletion prolongs viral replication (Schuster et al., 2015). Studies using various depletion strategies have shown inconsistent findings, leaving the function of natural killer (NK) cells uncertain.

Despite their need for defense, T cells may amplify the impact of illness. Mice without CD4+ or CD8+ T cells lost less weight, had less inflammation in the lungs, and had less airway blockage when these cells were removed, demonstrating that these cells exacerbate clinical illness and lung pathology (van et al., 2007). The specific ways by which HMPV, similar to other respiratory viruses, suppresses the immune response remain unknown. Several viral proteins are involved in the way that HMPV disrupts the type I interferon (IFN) response, according to studies. The significance of the IFN pathway in viral clearance and illness was highlighted by the observation that IFN receptor-deficient animals had elevated viral titers together with reduced inflammation and airway dysfunction (Falsey et al., 2010).

Dendritic cells may be infected with HMPV in vitro, which changes their signaling, cytokine generation, migration, and CD4+ T cell activation abilities. The effect of these interactions on illness and protection in living organisms, however, is not yet known (Alvarez et al., 2004). Additionally, HMPV is able to elude the adaptive immune response because it enhances CD8+ T-cell activity by upregulating programmed cell death-1 (PD-1). This process, which is analogous to the depletion of T cells in cancer and persistent infections (Erickson et al., 2014; Bao et al., 2013), occurs when PD-1 and its ligand, PD-L1, are overexpressed in the lungs. More functional HMPV-specific CD8+ T cells were seen in PD-1-deficient animals, and CD8+ T-cell activity was restored by blocking PD-1 ligation (Wen et al., 2015). Lung CD8+ T-cell effector activities were compromised after secondary infection due to elevated PD-1 expression; however, their function was restored after inhibiting PD-1 ligation (Bao et al., 2008; Afrin et al., 2024). In the case of human metapneumovirus (HMPV), the overexpression of PD-1/PD-L1 in lung tissue has been shown to suppress CD8+ T-cell responses, limiting the immune system's ability to clear the virus. Studies in animal models suggest that blocking PD-1/PD-L1 interaction can restore T-cell function, highlighting this pathway as a potential target for enhancing antiviral immunity and reducing the risk of reinfection (Goutagny et al., 2010).

DIAGNOSIS & TREATMENT

Medical experts use four diagnostic methods to test for human metapneumovirus (HMPV) including cell culture alongside nucleic acid amplification and antigen detection and serological methods. Regular cell cultures prove unsuitable for HMPV diagnosis because the virus reproduces poorly and causes weak damage to cells while being expensive to maintain and requiring specialized trypsin-based procedures (Schuster, 2014). Cytopathic effects in tertiary monkey kidney, LLC-MK2, and Vero cells manifest only after infection times between 10 to 21 days in these three cell lines among HMPV growth-compatible cell lines including tertiary monkey kidney cells, Vero cells, LLC-MK2 cells, BEAS-2B cells, A549 cells, and HepG2 cells (González et al., 2018). Two rapid HMPV diagnosis methods exist: shell vial culture incubates specimens under centrifugation using fluorescent staining and the direct immunofluorescence assay detections hMPV surface antigens in patient samples through antibody labeling (You et al., 2017). The microarray and ELISA techniques are available but can only be acquired through commercial transactions. Reverse transcriptase PCR (RT-PCR) diagnostic tests using F and N gene sequences have become the preferred methods for HMPV detection because of their great ability to detect very small HMPV quantities while minimizing false results (Larsson et al., 2021).

RT-PCR represents the most commonly used diagnostic mechanism for HMPV testing alongside available commercial multiplex molecular testing methods. Viral culture along with serological testing remain less sensitive since the growth of HMPV in cell culture demands exogenous trypsin and uses 14 days or longer to propagate (Koo et al., 2019; Ahmed et al., 2023). The FilmArray Respiratory Panel demonstrates successful identification of HMPV through its testing of induced sputum that gives better assessment of lower respiratory secretions than nasopharyngeal swabs. RT-PCR testing functions as a standard diagnostic method worldwide but Brazil's lack of advanced diagnostic technologies poses challenges when trying to successfully implement these assessments.

The current identification challenge between viral and bacterial pneumonia requires doctor-patient-clinical assessment in addition to radiological findings to achieve maximum patient care. The clinical algorithm RT-PCR serves as the leading diagnostic tool for HMPV detection with high accuracy levels based on PERCH research findings about underreported viral actors in substantial pneumonia areas. Thrombocytopenia occurs frequently in severe viral infections and indicates poor disease progression as well as negative health results among critically ill patients (You et al., 2017).

Table 1: Approaches to treating and preventing the spread of human metapneumovirus (HMPV).

Therapeutics	Compounds	Model	Consequences
Antiviral Agents	Ribavirin	Tissue culture assay (TCA)	In vitro studies against HMPV demonstrated that ribavirin and intravenous immunoglobulin had antiviral effects.
		Human	An immunocompromised youngster having Burkitt's lymphoma treatment made a full and speedy recovery after receiving intravenous immunoglobulin in addition to oral ribavirin.
Antibody	Monoclonal Antibody	Mice	After being injected into BALB/c mice, the results demonstrated a significant reduction in lung viral titres, histological alterations, and airway obstruction after HMPV exposure.
		Mice	As a potential prophylactic measure and treatment for severe cases of hRSV and HMPV, a human monoclonal antibody was found to cross-neutralize both viruses.
		Hamster	Hamsters were protected from heterologous HMPV challenge by monoclonal antibodies against the HMPV F protein.
Fusion inhibitors	Inhibitory Peptide Compound	Mice	Fusion peptides targeting heptad repeat A and B domains of F protein offered protection against deadly HMPV intranasal exposure in BALB/c mice. Post-challenge there was a significant decrease in lung viral load, pulmonary inflammation, levels of proinflammatory cytokines, and airway obstruction
RNA interference	SiRNA	LLC-MK2 cells	In vitro, replication of all subgroups of HMPV was inhibited by siRNA targeting the P and N genes of HMPV.
		Mice	Minimized viral load in mice lungs after challenge by using Dicer substrate siRNA
Inactivated vaccine	Heat inactivated vaccine	Mice	After receiving an immunization, BALB/c mice were protected against an intranasal challenge with a homologous strain of HMPV.
Subunit vaccine	HMPV F subunit vaccine	Hamster	Recombinant human PIV-1 vaccines expressing the F protein of HMPV were more protective and produced a strong immune response when administered intramuscularly than vaccines expressing the G and SH proteins.
		Syrian golden hamsters	High viral neutralization titres against homologous viruses were produced by immunization. Additionally, it demonstrated a substantial decrease in viral titres in the nasal turbinates.
		Cotton rats	Lung histology was similar to that of control mice, and cotton rats who were immunized had less viral shedding in their noses after a HMPV challenge.
		Cynomolgus macaques	A strong cellular immunological response, HMPV F-specific antibodies, and neutralizing antibodies were all produced by the immune system after vaccination. The generated humoral reaction, however, quickly faded with time.
Chimeric vaccine	HMPV antigen on parainfluenza vaccine	Rhesus monkey	African green monkeys were completely protected against a wild-type HMPV challenge after receiving an intranasal vaccine that produced an immunological response unique to HMPV. This vaccination was determined to be attenuated to an adequate level in rhesus monkeys.
Epitope vaccine	T lymphocyte epitope vaccine	Mice	Viral load, lung pathology, and production of Th2-type cytokines (IL-10, IL-4) during HMPV challenge were all decreased following vaccination.
Live attenuated vaccine	G, SH, M2-2	African green monkeys	The attenuation of G and M2-2 was adequate. Viral shedding in the lower respiratory tract remained undetectable after challenge with wild-type HMPV.
	M2-2	Hamster	Hamsters show protection against wild type HMPV and show attenuation of strain
	M2-2	Mice	Total protection against a homologous strain challenge and cross-protection against a heterologous strain were both produced via immunization.
Virus-like particles		Mice	Immunization resulted in a decrease in viral titres in the lungs of inoculated animals and produced cross-protective immunity in mice against both homologous and heterologous strains.

Although cell culture played a crucial role in the discovery of HMPV in the past, it is not often used for diagnosis due to its slowness and lack of sensitivity. The LLC-MK2 cell line is the most sensitive for HMPV, and immunofluorescent labeling of shell vial centrifugation culture (SVCC) allows for speedier detection. Although they have not yet received FDA approval, commercial assays from companies like Biotrin Ltd. demonstrate promise as immunoassays, which include immunofluorescent staining and enzyme immunoassay (EIA), offer moderate sensitivity and high specificity. The xTAG Respiratory Viral Panel and the pro HMVP+ test are real-time RT-PCR assays that provide excellent sensitivity and specificity (Larsson et al., 2021). PCR methods, especially RT-PCR, are more sensitive than culture and immunoassays. Even though cross-reactivity between different serotypes of HMPV is still a problem, serological approaches such as enzyme-linked immunosorbent assays (ELISAs) that use recombinant N or F proteins may identify antibodies to the virus. In order to effectively treat patients, molecular diagnostics, especially

RT-PCR, are essential for HMPV diagnosis; nevertheless, these data need to be understood in conjunction with clinical findings.

Currently, there is no specific FDA-approved antiviral treatment for human metapneumovirus (HMPV) infection. Management primarily involves supportive care, including symptomatic treatment and respiratory support when necessary (Karron et al., 2018). Patients with fever are typically given antipyretic drugs such as acetaminophen or ibuprofen, while those who are dehydrated and unable to tolerate oral hydration may require intravenous fluids (Talaat et al., 2013). In severe cases, particularly among individuals with pre-existing respiratory or cardiac conditions or those who are immunocompromised, additional oxygen support, such as high-flow nasal cannula or mechanical ventilation, may be necessary. Most patients recover fully, but droplet precautions are recommended to prevent disease transmission (Russell et al., 2017). Despite the absence of a licensed vaccine, several promising candidates have been tested in animal models, including live-attenuated, recombinant, and vectored vaccines, though none have yet been evaluated in human trials. Subunit vaccines, particularly those targeting the HMPV F protein (Bates et al., 2016), have shown encouraging results without inducing enhanced disease, although their protective immunity may wane over time (de Swart et al., 2007). Other approaches, such as virus-like particles and peptide vaccines, have also demonstrated potential in generating immune responses. However, non-replicating vaccines, such as heat-killed or formalin-inactivated viruses, have raised concerns due to the risk of enhanced respiratory disease, as seen with similar RSV vaccines in the past (Schuster, 2014).

Antiviral treatments for HMPV remain limited, with no licensed options currently available. Ribavirin and intravenous immunoglobulin (IVIG) have shown some efficacy in vitro and in animal models, but their use in humans is anecdotal and lacks controlled trials or formal guidelines. Other experimental therapies, such as small interfering RNAs and peptides targeting the F protein, have shown promise in preclinical studies but have not been tested in humans (Pham et al., 2005). Passive immunization with humanized monoclonal antibodies, similar to those used for RSV, may also be considered, though their effectiveness for HMPV remains unproven. While supportive measures, oxygen therapy, and mechanical ventilation remain the mainstays of treatment, ongoing research into vaccines and antiviral therapies offers hope for future advancements in managing HMPV infections (Mok et al., 2008).

REINFECTION AND IMMUNITY

Different researchers maintain conflicting opinions about whether HMPV genetic lineages A and B should be recognized as distinct serotypes. Van den Hoogen et al. conducted in vitro tests which showed ferrets developed antisera from HMPV lineage A or B infections showed weak neutralization towards lineage heterologous strains despite maintaining efficient neutralization against homologous strains (van et al., 2004; Guerrero-Plata et al., 2006). The researchers demonstrated that lineage A and B show potential features of different serotypes. The work by Skiadopoulos and colleagues produced contradictory findings by demonstrating substantial heterologous protection between HMPV types A and B through reduced viral replication in respiratory tissue of hamsters and nonhuman primate subjects (Biacchesi et al., 2004; Céspedes et al., 2013). The high level of antigen similarity between lineages A and B stands in opposition to the hypothesis of separate serotypes. Scientists need to study human populations to determine if the same pattern of cross-protection exists because current information is unknown (Hamelin et al., 2006).

Universal exposure to HMPV exists across human populations due to the detection of neutralizing antibodies in every adult population whereas reinfection frequency ranges between 1% to 9% per year (Herfst et al., 2008). The continuous reinfection pattern across human lifespans serves as the primary cause of wide-ranging anti-HMPV antibody detection in the adult population. The typically brief duration of HMPV immune response combined with ongoing high serological detection patterns in childhood indicates that immune protection against HMPV is insufficient and short-lived (Herfst et al., 2008). Medical evidence shows that children experience documented reinfections of HMPV from both identical and different strains within their bodies. Young children and cynomolgus macaques who experience multiple infections with HMPV demonstrate repeated infections according to observation reports (Tedcastle et al., 2014). Developing successful HMPV vaccines proves difficult because strong persistent immunity needs to be generated in order to provide substantial protective benefits against HMPV infections (Zhang et al., 2014).

FUTURE DIRECTION

Strategies for prevention play an essential role in controlling the spread and diminishing the incidence of Human Metapneumovirus (HMPV) disease together with other respiratory infections. The combination of tissue or upper sleeve covering during coughing or sneezing together with proper tissue disposal and hand washing activities lasting at least 20 seconds helps prevent transmission. Both hand contact prevention with the mouth and eyes and maintaining physical distance from sick patients play an essential role in HMPV transmission reduction. Hygiene practices prevent both HMPV infections and other respiratory infections at the same time. Scientists have studied HMPV since its identification in 2001 to determine its harm-causing processes and historical origin giving evidence of long-term undiscovered circulation. Research investigators have developed strong animal models alongside recent developments in vaccine and antiviral antibody creation programs. Additional research is necessary to understand HMPV's pathogenesis together with immune mechanisms and antiviral measures as well as vaccine production because key knowledge gaps persist.

CONCLUSION AND RECOMMENDATIONS

The medical world achieved breakthroughs in respiratory pathogen research when Human Metapneumovirus (HMPV) was discovered in 2001 but also exposed this virus to have secretly diffused among populations during past decades. The respiratory infection agent HMPV belonging to Pneumoviridae family triggers major acute respiratory tract infections among vulnerable patient groups that include young children and older adults along with immunodeficient people. Clinical diagnosis proves difficult because HMPV symptoms are identical to RSV and influenza thus demanding better diagnostic technologies. Protecting against HMPV spread depends on essential preventive steps that combine hand cleanliness with nose and mouth etiquette and staying away from sick people. Knowledge-based improvements of HMPV genomic

structure, pathogenesis and immunity methods have not propelled substantial progress in vaccine and antiviral development. The current standard of care for treatment is supportive because appropriate FDA-approved medical interventions do not exist at this time. HMPV control proves challenging because of high reinfection rates and incomplete immunity thus necessitating ongoing research of the virus along with labyrinthine protection studies and extended-duration vaccine development. HMPV leads to significant respiratory illness burdens across the world especially in poorer nations so it requires a multidisciplinary approach with epidemiology and molecular testing and pharmaceutical innovation to minimize its effects and defend vulnerable communities.

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Dr. Syed Mahmood Shahidul Islam & Dr.Nourjahan Laskar: Supervised the Data Collection Process, And Checked Writing, Approved Methodology, Manuscript Editing and Supervised All Steps, Final Editing;
Md.Shajalal Reza: Researched Literature, Web-Survey Design, Coordinate and Monitor the Data Collection Process with Collaborators, Wrote the First Draft of The Manuscript;
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