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REVIEW ON HMPV DISEASE PATTERNS AND IMMUNE RESPONSE IN PEDIATRIC AND GENERAL POPULATIONS

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ABSTRACT

Acute respiratory tract infections (ARTIs) are a major cause of morbidity and mortality, particularly among young populations in developing nations. Their high transmissibility, widespread prevalence, and person- to-person spread pose significant risks to vulnerable groups, including children, the elderly, and immunocompromised individuals. According to the World Health Organization (WHO), ARTIs contribute to approximately 2.6 million pediatric deaths worldwide each year. Among the viral agents responsible, human metapneumovirus (HMPV) has emerged as a key contributor to the rising incidence of ARTIs in pediatric patients. Notably, HMPV is the second most common cause of infant bronchiolitis, following respiratory syncytial virus (RSV), affecting both the upper and lower respiratory tract. This underscores the urgent need for ongoing research and targeted public health interventions to mitigate the burden of ARTIs in high-risk populations.

KEYWORDS: *Human Metapneumovirus (HMPV), Epidemiology, Respiratory Viruses, Pediatric Infections, Respiratory Tract Infections, Antiviral Therapy, Vaccination, Public Health*

1. INTRODUCTION

Acute respiratory tract infection (ARI) continues to rank as a predominant cause of morbidity and mortality on a global scale. In the year 2000, approximately 20% of total deaths among children under five years of age were attributable to ARIs, with approximately 70% of these fatalities occurring in the regions of Sub-Saharan Africa and southern Asia. These infections impact children irrespective of their socioeconomic status, resulting in comparable incidence rates across both developed and developing nations; however, the mortality rates observed in developing countries remain significantly elevated.

The vulnerability of children in developing nations to pneumonia is markedly pronounced, with incidence rates estimated between 10% and 20%, in stark contrast to the 3% to 4% observed in developed countries. Such disparities in morbidity highlight the critical need for targeted public health interventions in high-risk areas.[1-3]

A multitude of etiological agents contribute to respiratory complications in children, encompassing both viral and bacterial pathogens. While upper respiratory tract infections are generally considered less severe, they impose substantial societal burdens due to lost productivity, decreased school attendance, and increased healthcare expenditures. Consequently, the identification of the etiological agents responsible for these infections holds substantial significance. [4] Extensive research and epidemiological investigations have underscored the relevance of several known viral pathogens, including human respiratory syncytial virus (hRSV), parainfluenza virus, influenza virus, coronavirus, and rhinovirus. Nevertheless, a considerable portion of respiratory tract infections remains unexplained, with no known pathogen identified.[5]

The discovery of human metapneumovirus (hMPV) in 2001 in the Netherlands marked a significant advancement in understanding respiratory infections. Isolated from a pediatric patient exhibiting symptoms akin to hRSV infection, hMPV has since been detected in 4% to 16% of patients suffering from ARIs. Notably, the incidence of hMPV may fluctuate annually within the same geographical area. Although primarily associated with pediatric disease, hMPV possesses the capacity to infect adults and individuals who are immunocompromised. The clinical manifestations of hMPV infection can vary widely, ranging from mild upper respiratory tract infections to severe conditions such as life-threatening bronchiolitis and pneumonia.[6,7]

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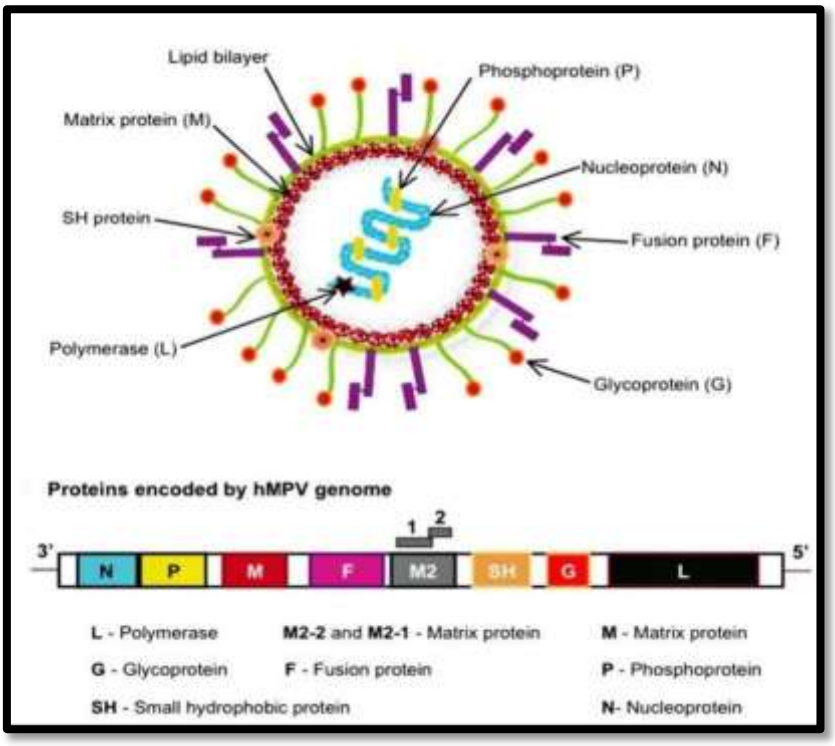


Figure.1: Structure of Human Metapneumovirus (Hmpv)

Human metapneumovirus (hMPV), identified in the year 2001, is predominantly responsible for both upper and lower respiratory tract infections, particularly affecting young children. Nevertheless, attention must also be directed towards its implications in elderly populations and individuals with compromised immune responses. Epidemiological data indicate that hMPV accounts for approximately 5% to 10% of pediatric hospitalizations due to acute respiratory infections. The clinical manifestations of hMPV infection can lead to severe conditions such as bronchiolitis and pneumonia in children, with symptoms that closely resemble those of infections caused by human respiratory syncytial virus.[8]

Initial exposure to hMPV typically occurs in early childhood; however, it is essential to recognize that re-infections are frequently observed throughout an individual's lifespan. The virus's poor viability in cell culture has led to the adoption of molecular diagnostic techniques, such as reverse transcriptase PCR (RT-PCR), as the preferred methods for the detection of hMPV. Although several vaccine candidates have demonstrated efficacy in preventing the onset of clinical disease, no vaccines have yet achieved commercial availability.

Recent advancements in the understanding of hMPV have significantly expanded the existing knowledge base regarding its molecular biology and epidemiology. This article aims to provide a thorough review of these developments, in addition to examining current therapeutic interventions and strategies implemented to manage hMPV infections. Moreover, an emphasis will be placed on exploring innovative approaches that could facilitate the eventual development of an effective vaccine against hMPV

II.DISCOVERY AND CLASSIFICATION OF HMPV

The identification of human metapneumovirus (hMPV) originated from the analysis of nasopharyngeal aspirates collected from 28 pediatric patients, all under the age of five, who presented with respiratory tract infections in the Netherlands over two decades ago Upon examination, the virus demonstrated a cytopathic effect akin to that of respiratory syncytial virus (RSV) and exhibited slow replication rates in tertiary monkey kidney cells.

Subsequent investigations utilizing electron microscopy revealed the presence of pleomorphic particles resembling paramyxoviruses within the superannuate of the infected cellular cultures. These particles displayed a size range of 150 to 600 nm in diameter, accompanied by short surface projections measuring between 13 and 17 nm. In contrast to other members of the Paramyxoviridae family, such as RSV and parainfluenza viruses, the characteristic nucleocapsid was not discernible in hMPV. Further analysis indicated that this virus did not induce agglutination of erythrocytes and was susceptible to inactivation by chloroform.[9,10]

Amplify the viral genome using various respiratory virus-specific primers in reverse transcriptase reactions yielded inconclusive outcomes. Based on its morphological attributes and genomic characteristics, hMPV was classified within the subfamily

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Pneumovirinae and the genus Metapneumovirus of the Paramyxoviridae family.

III.HIGH-RISK POPULATION FOR HUMAN METAPNEUMOVIRUS (HMPV)

- **Young Children:** Infants and toddlers exhibit heightened susceptibility to severe respiratory illnesses, including bronchiolitis and pneumonia, which can significantly impact their health outcomes.
- **Increased Risk in Older Adults:** Individuals who are 65 years of age or older, particularly those suffering from chronic health conditions such as asthma or chronic obstructive pulmonary disease (COPD), face an elevated likelihood of experiencing complications related to HMPV infections.[11]
- **Pregnant Women:** The occurrence of HMPV during pregnancy poses risks for respiratory complications that can threaten the health of both the mother and the developing fetus, necessitating careful monitoring and management.
- **Impact on Immunocompromised Individuals:** Those with compromised immune systems, whether due to underlying medical conditions or as a consequence of treatments like chemotherapy, exhibit a greater risk of encountering severe symptoms associated with HMPV, warranting specific attention in clinical settings.[12]

IV.SYMPTOMS

Symptoms associated with human metapneumovirus (HMPV) typically encompass cough, fever, nasal congestion, and shortness of breath. In the course of HMPV infection, the clinical manifestations may evolve into more severe respiratory conditions, such as bronchitis or pneumonia. The symptomatology of HMPV infection bears resemblance to that of other viral infections responsible for both upper and lower respiratory tract illnesses.[12,13]

- **Symptoms In Adults**

HMPV symptoms in adults often resemble those of a common cold or flu. They include:

- Persistent cough, often accompanied by mucus production.
- Nasal congestion or runny nose.
- Fever, typically mild to moderate.
- Fatigue and general body aches.
- Sore throat.
- Shortness of breath in severe cases.

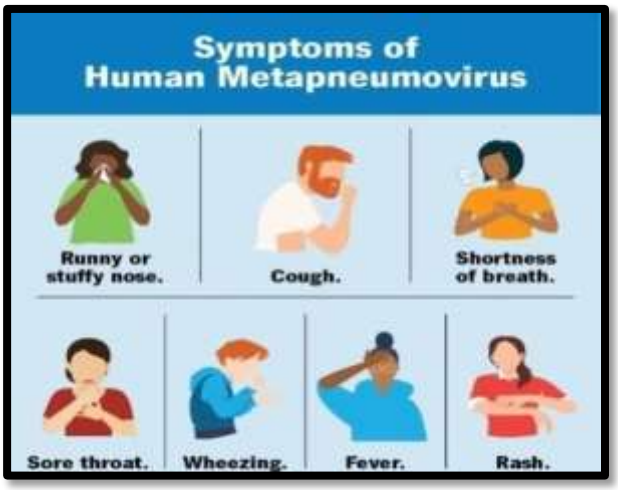
Symptoms In Children

Children are more likely to experience severe symptoms, including:

- Breathlessness
- Wheezing and persistent cough
- High fever and Poor feeding and dehydration, especially in infants.

HMPV typically causes symptoms similar to other respiratory infections, such as:

- Cough
- Fever
- Nasal congestion
- Wheezing
- Shortness of breath
- Sore throat
- Rush
- Runny or stuffy nose



When HMPV entry into the human body, human metapneumovirus (hMPV) targets the cells of the respiratory tract, which encompass the oral cavity, nasal passages, and pharynx. In response to the infection of these cells, the immune system elicits a variety of symptoms, including but not limited to discomfort, low-grade fever, cough, rhinorrhea, cephalalgia, and pharyngodynia. The pathophysiology of the disease may also extend to the bronchi or major airways in certain individuals, potentially resulting in exacerbated coughing and wheezing. [13]

In pediatric populations, particularly those younger than one year, additional symptoms such as decreased fever and weight loss may manifest. Furthermore, hMPV has been associated with severe disease presentations that necessitate hospitalization in select patient groups. This includes individuals with compromised immune systems, as well as those suffering from underlying cardiac or respiratory disorders. The propensity for these patients to experience acute respiratory failure requiring high-flow oxygen support is significantly elevated; in severe cases, deterioration may occur to a threshold demanding mechanical ventilation. Consequently, intensive monitoring and care within an intensive care unit setting is imperative for these high-risk individuals.[13,14]

V.HOW DOES HMPV SPREAD

HMPV is highly contagious and spreads through various means:

- **Respiratory Droplets:** The spread of the virus occurs when an infected individual engages in actions such as coughing,

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sneezing, or speaking, thereby releasing respiratory droplets into the atmosphere.

- **Transmission through Direct Contact:** The dissemination of the virus may occur via physical interaction with an individual who is infected. This risk is particularly pronounced when tactile contact is made with the face, eyes, or mouth.
- **Surface Contamination:** The persistence of the virus on various surfaces poses a considerable risk of infection. Contact with contaminated objects, including doorknobs and mobile devices, significantly increases the likelihood of transmission.
- **Airborne Particles**: It has been observed that small respiratory particles can maintain a suspended state in the atmosphere, especially in environments characterized by high density of individuals or inadequate ventilation.

Human metapneumovirus (hMPV) exhibits a higher incidence of detection in pediatric populations, particularly among children under the age of two, with a mean age of 22 months at diagnosis. Evidence provided by seroprevalence studies indicates that by the ages of five to ten, a substantial majority, ranging from 90 to 100%, of children have experienced infection with hMPV. The presence of acute lower respiratory tract infections attributable to hMPV has been observed to constitute approximately 5 to 10% of hospital admissions among pediatric patients. Furthermore, a comparative analysis reveals that infants diagnosed with hMPV are three times more likely to require hospitalization relative to their counterparts aged between six months and five years.[15,16]

VI.EPIDEMIOLOGY

Human metapneumovirus (hMPV) is a pathogen associated with respiratory infections, exhibiting a global presence across individuals of various age groups. The historical prevalence of hMPV has been confirmed through serological studies, which identified antibodies in samples dating back to 1958, thereby indicating its existence for over five decades.

In terms of seasonal variation, hMPV infections are encountered throughout the year; however, in temperate climates, there is a discernible increase in cases during the months of December to February. This peak period often coincides with the emergence of another respiratory virus, human respiratory syncytial virus (hRSV). It is noteworthy that distinct genotypes of hMPV may circulate within different populations, and multiple strains can coexist in a singular geographic location. [17]

Transmission of the virus occurs primarily through aerosolized droplets, expelled by individuals during coughing or sneezing. The incubation period following exposure typically spans 4 to 6 days, with a contagious period extending from 2 to 14 days.

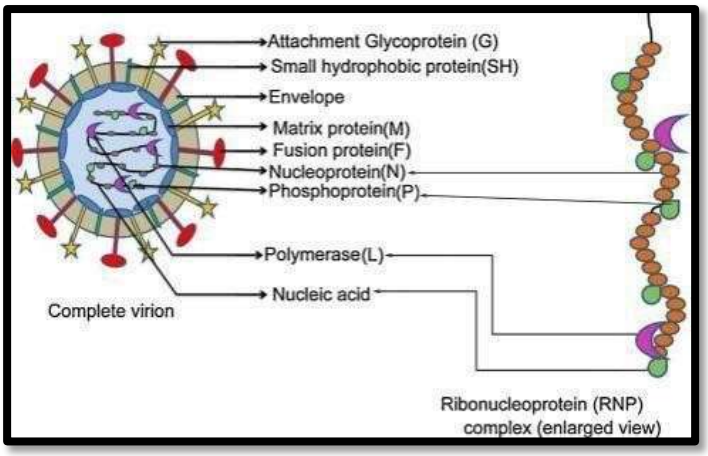


FIGURE 2 : Schematic diagram of the human metapneumovirus particle and the ribonucleoprotein (RNP) complex.

Epidemiological data reveal that hMPV is implicated in 7% to 19% of acute respiratory tract infections (ARTIs) among pediatric populations, including both hospitalized and outpatient presentations. Annually, approximately 1 in 1,000 children is admitted to a hospital due to hMPV infections, a rate comparable to influenza but lower than that of hRSV. Among 1,000 children, 55 tend to seek outpatient care, while 13 may require emergency medical services as a result of hMPV. In adult populations, the detection rate of hMPV is significantly lower, estimated at around 3%.

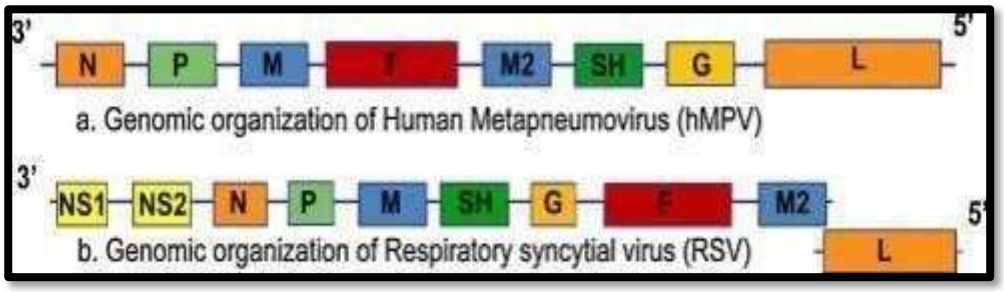


FIGURE 3 : A. Genomic organization of Human Metapneumovirus (HMPV)

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B. Genomic organization of Respiratory syncytial virus (RSV)

The majority of hMPV infections are observed in early childhood, particularly among children younger than 2 years. The initial infection commonly occurs around the age of 6 months, although maternal antibodies can provide some degree of protection during infancy. By the age of 5, it has been estimated that over 90% of children will have been infected with hMPV. While most children experience mild illness, those with preexisting health conditions are at an elevated risk for severe clinical manifestations.[18.19]

In the adult demographic, particularly among healthy young adults, hMPV infections are infrequent due to the presence of antibodies acquired during earlier exposure. Conversely, older adults aged 65 and above, as well as individuals with chronic conditions such as chronic obstructive pulmonary disease (COPD), asthma, cancer, or those who have undergone lung transplants, exhibit a heightened susceptibility to reinfection by hMPV.

VII.DIAGNOSIS

Diagnosing HMPV (Human Metapneumovirus) is important but can be tricky because its symptoms are similar to other respiratory viruses. Here are the main ways to diagnose it:

1. Molecular Methods

- RT-PCR (Reverse Transcription-Polymerase Chain Reaction): This is the best method to detect HMPV RNA. - Multiplex PCR Panels: These tests can detect HMPV and other viruses at the same time. [19.20]

2. Serological Testing

- This checks for HMPV-specific antibodies (IgM and IgG) in the blood.

3. Antigen Detection

- Rapid tests targeting the F protein of HMPV are being developed, but they are less accurate than PCR.

In short, RT-PCR is the most reliable method, while rapid tests are quicker but less sensitive.[20]

The isolation and growth of human metapneumovirus (hMPV) have been accomplished utilizing a variety of cell lines, which include Vero cells, Hep-2 cells, Hep G2 cells, 293 cells, and LLC-MK2 cells. A recent investigation involving the cultivation of hMPV in 19 distinct cell lines identified the human Chang conjunctiva cell line (clone 1-5C4) and the feline kidney CRFK cell line as the most effective for hMPV propagation. The growth dynamics of hMPV in cell culture are characterized by a slow growth rate, with cytopathic effects that manifest late in the culture process. These effects range from cellular rounding and subsequent detachment from the culture matrix to the formation of small syncytia.[18,20]

Due to the challenges presented by cell culture methods, the detection of hMPV antigens has increasingly relied on the use of anti-hMPV antibodies in direct fluorescence or enzyme-linked immunosorbent assay (ELISA) techniques. The effectiveness of cell culture-based detection methods has been quantified, revealing sensitivity and specificity rates of 68% and 99%, respectively, in comparison to real-time reverse transcription polymerase chain reaction (RTPCR) methods. Despite this, the application of cell culture as a diagnostic approach for hMPV infection remains relatively rare, with molecular techniques such as RT-PCR and real-time RT-PCR currently being favored.[21]

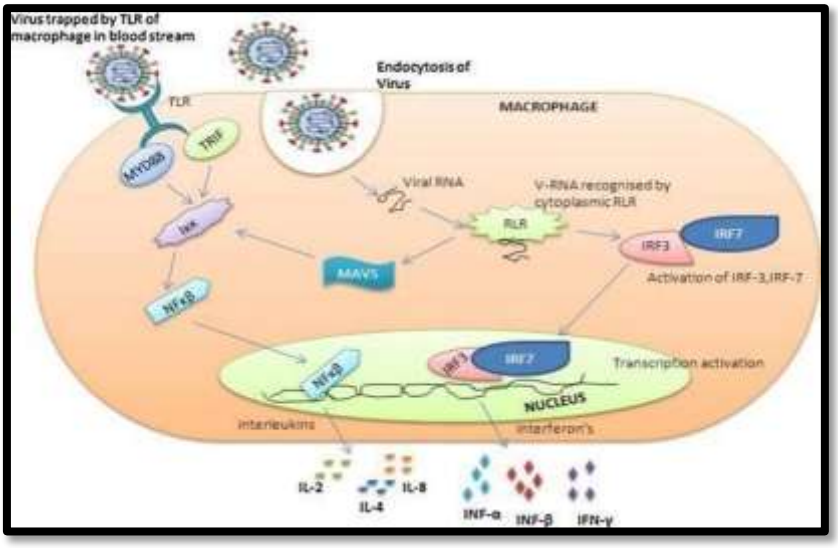


FIGURE 4. Molecular events in the pathogenesis of hMPV infection

Molecular events in the pathogenesis of hMPV infection. Virus attachment to toll-like receptors (TLR) of macrophage and/or dendritic cells activates several adapter molecules of the immune system (TRIF and MYD88), which in turn activates Nuclear

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factor kappa beta (NFkB). RNA of internalized virus is detected by cytoplasmic RIG1-like receptor (RLR), which in turn activates NFkB by activation of mitochondrial antiviral signaling protein (MAVS) and transcription activators interferon regulatory factors 3 and 7 (IRF-3 and IRF-7). Finally NFkB and IRFs induce the production of several interferons and interleukins.[20,21]

The advancement of multiplex PCR assays has facilitated the detection of a broader array of respiratory viruses. In particular, multiplex RT-PCR (mRT-PCR) has been developed to enhance sensitivity and speed in the identification of hMPV, demonstrating sensitivity and specificitrates of 100% and 96%, respectively. In contrast, the corresponding rates ki for traditional rRT-PCR are 54.6% and 100%. One of the significant advantages of mRT-PCR is its capability to detect co-infections, including those with low viral loads that might remain undetectable through conventional cell culture or immunostaining techniques.[21,22] Nevertheless, numerous clinical laboratories currently lack the infrastructure to routinely conduct diagnostic RT-PCR for hMPV detection. As a viable first-line diagnostic approach for hMPV infections, a combination of immunofluorescence assays and direct fluorescent antibody methods has been recommended, with subsequent RTPCR performed on samples that yield negative results. The prospective integration of shell vial centrifugation culture and monoclonal antibodies specific to hMPV may significantly enhance the efficiency of rapid diagnostic protocols for hMPV in clinical laboratory settings.[22]

VIII.TREATMENT

There is currently no FDA-approved antiviral treatment for hMPV infection. The main approach to treating hMPV is supportive care, which helps manage symptoms. If a person has a fever, they are given medications like acetaminophen or ibuprofen. If the patient becomes dehydrated and can't drink fluids, they may receive fluids through an IV. In severe cases, where breathing becomes difficult, patients may need oxygen support through a high-flow nasal cannula or a ventilator. This is especially important for people with existing heart or lung problems or those with weakened immune systems. Most patients fully recover.[23,24]

To prevent spreading hMPV, patients are placed under droplet precautions. There is no vaccine for hMPV yet, but some vaccines have shown promise in animal tests. These vaccines have not yet been tested on humans.[24]

At present, the treatment modalities available for human metapneumovirus (hMPV) infection primarily consist of supportive care. However, evidence from various reports suggests the potential therapeutic application of ribavirin, immunoglobulin, fusion inhibitors, and small interfering ribonucleic acids in the management of hMPV infections. A summary of the diverse therapeutic strategies employed for hMPV is provided .[25]

In the realm of immunization, several vaccine candidates targeting hMPV have undergone evaluation in rodent and non-human primate models. Despite the promising outcomes observed in these studies, none of the vaccine candidates has progressed to human clinical trials. Concerns have arisen regarding safety; for instance, a heat-inactivated viral vaccine demonstrated an enhancement of lung disease when assessed in murine models.

Research into T cell epitope vaccines has indicated a reduction in immuno-modulation following hMPV challenges. Specifically, murine subjects that received an hMPV cytotoxic T lymphocyte epitope vaccine exhibited diminished production of Th1 and Th2 cytokines in comparison to their non-immunized counterparts after exposure to hMPV. Furthermore, investigations into chimeric vaccines against hMPV have yielded promising results. Tests conducted on hamsters and African green monkeys revealed that chimeric vaccines induced the generation of neutralizing antibodies and conferred immunity during subsequent challenges with wild-type hMPV.[26,27]

Additionally, subunit vaccines utilizing the hMPV fusion protein have been shown to elicit cross-protective immunity in hamster models against hMPV challenges. Multiple hMPV F subunit vaccines have demonstrated significant levels of protection in tests involving rodents, hamsters, and non-human primates. In a recent study, virus-like particles (VLPs) that mimic the viral surface characteristics of both hMPV subgroup A and B were evaluated as vaccine candidates. The results indicated that these VLPs were capable of inducing a robust humoral immune response against both homologous and heterologous strains when tested in murine subjects. Despite the promising nature of the hMPVVLP vaccine approach, further research is imperative to establish a vaccine that effectively targets all hMPV subgroups.[28]

The advent of plasmid-based reverse genetics systems has markedly advanced efforts aimed at developing a live attenuated vaccine for hMPV infection. Recombinant hMPVs featuring alterations in the SH, G, or M2-2 genes have been generated, further contributing to the exploration of potential vaccination strategies against this virus.[29]

IX.PREVENTION

HMPV prevention involves general measures to reduce the transmission of respiratory viruses:

- Practice good hand hygiene
- Wash your hands frequently with soap and water for at least 20 seconds.
- Use an alcohol-based hand sanitizer when soap and water are not available.
- Avoid close contact with sick individuals
- Maintain a safe distance from people who are coughing or sneezing.
- If you are sick, stay home to avoid spreading the virus to others.
- Clean and disinfect surfaces regularly

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- ➢ Wipe down frequently touched surfaces, such as doorknobs, light switches, and countertops, with A disinfectant
- ➢ Follow general vaccination guidelines
- ➢ While there is no specific vaccine for HMPV, staying up-to-date with other respiratory virus Vaccinations, such as the flu shot, can help reduce the overall burden of respiratory infections.
- ➢ Wearing masks during outbreaks or flu season can help reduce exposure to respiratory droplets.

The implementation of preventative strategies aimed at reducing the transmission of hMPV is of paramount importance. These strategies should encompass a range of measures that are effective in mitigating the spread of various respiratory illnesses. For instance, the practice of covering the mouth and nose with a tissue when coughing or sneezing is recommended; alternatively, one may opt to use the upper sleeve. [29,30]

Following the disposal of used tissues, it is essential that proper hand hygiene is maintained. This involves washing hands with soap and water for a duration of no less than 20 seconds. Moreover, individuals are advised against touching their mouth, nose, or eyes with unwashed hands, as this behavior can facilitate the transfer of pathogens.

In addition to personal hygiene practices, maintaining a safe distance from individuals exhibiting symptoms of illness is advisable. By observing these preventive measures, the risk of contracting hMPV and other respiratory infections can be significantly reduced.[30-33]

X.CONCLUSION

Human metapneumovirus (HMPV) is an often-overlooked pathogen with significant implications for both pediatric and general populations. Its ability to cause severe respiratory illnesses, particularly in vulnerable groups, underscores the need for heightened awareness and stronger public health measures.

Recent outbreaks in China and Malaysia emphasize the importance of regional and global collaboration in strengthening surveillance, improving diagnostic capabilities, and developing effective prevention strategies. Additionally, ongoing research into vaccines and antiviral therapies is crucial to mitigating the worldwide impact of HMPV infections.

Addressing the challenges posed by HMPV requires continued scientific advancements and coordinated public health efforts to protect global health.

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