Human metapneumovirus: Emerging Threat in Respiratory Tract Infections – Virology, Diagnosis, and Future Directions

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ABSTRACT

Human metapneumovirus (HMPV), a member of the Paramyxoviridae family, is a significant global cause of acute respiratory tract infections (ARIs), primarily affecting infants, the elderly, and immunocompromised individuals. First identified in the Netherlands in 2001, it accounts for 4–16% of annual respiratory infections, ranging from mild upper respiratory tract illness to severe pneumonia and bronchiolitis. Due to overlapping symptoms with respiratory syncytial virus (RSV) and other pathogens, accurate diagnosis remains challenging. HMPV is a negative-sense single-stranded RNA virus with four main genotypes: A1, A2 (further divided into A2a and A2b), B1, and B2. Its pathogenesis involves viral fusion with epithelial cells, replication, and immune evasion through altered cytokine responses and suppression of long-term immunity. Diagnostic advances, particularly molecular methods such as multiplex PCR and real-time RT-PCR, have improved detection speed and sensitivity compared to conventional cell culture. Currently, no specific antiviral therapy or licensed vaccine exists for HMPV. Management is supportive, focusing on symptom relief. However, progress in reverse genetics and animal models has enabled the development of live-attenuated vaccine candidates, now under evaluation. Public health measures, including hygiene practices and surveillance, remain

essential to limiting spread. Despite notable progress, gaps persist in understanding the virus's molecular biology, epidemiology, and immune responses. Addressing these uncertainties through intensified research, improved vaccine development, and wider access to reliable diagnostic tools is crucial for reducing the global burden of HMPV, particularly in resource-limited regions and vulnerable populations.

Keywords

Human Metapneumovirus (HMPV), Acute Respiratory Tract Infections (ARIs), Respiratory Viruses, Virology, Genotypes, Molecular Diagnostics, RT-PCR, Vaccine Development

OVERVIEW ON HMPV VIRUS

Globally, acute respiratory tract infections (ARI) are a major cause of illness and death. In 2000 alone, ARIs accounted for 20% of all deaths in children under the age of five worldwide; additionally, Sub-Saharan Africa and southern Asia accounted for almost 70% of these deaths. Children of all economic backgrounds are affected by ARIs, which have comparable incidence rates in wealthy and developing nations but a greater death rate in the former. Children in underdeveloped nations have a higher risk of pneumonia (10-20%), as opposed to 3-4% in developed nations. Children's respiratory issues can be caused by a variety of etiological causes. Upper respiratory tract infections have substantial social costs in the form of missed work, missed school days, and increased medical expenses, despite the fact that they are typically less dangerous. Determining the etiological agent of these infections is crucial because of this. We have established the significance of recognized viral infections such as the coronavirus, rhinovirus, influenza virus, parainfluenza virus, and human respiratory syncytial virus (hrsv) via decades of study and epidemiological investigations. A significant percentage of respiratory tract infections, Nevertheless, are still unattributable to any recognized pathogen in spite of these investigations. In the Netherlands, the human metapneumovirus (hMPV) was initially identified in 2001 after it was recovered from a paediatric child with symptoms resembling those of a hrsv infection. since then, 4-16% of ARI patients have been found to have hMPV mainly in the same region, the prevalence of hMPV may change from year to year. hMPV mainly affects youngsters, although it can also infect adults and those with weakened immune systems. [1]

The sickness brought on by a hmpv infection might manifest clinically as anything from a minor upper respiratory tract infection to potentially fatal severe bronchiolitis and pneumonia. Pneumovirinae and Paramyxovirinae are subfamilies. Whole genome research has

demonstrated that hmpv occurs as two genotypes, A1, A2, B1, and B2 according to the sequence variability of the attachment (G) and fusion(F) surface glycoproteins. Subgroup A2 is further subdivided into A2a and A2b.[2]

There may be a new subgroup developing inside the A major subgroups A1 or A2. Twelve with the development of reverse genetics platforms, research into the molecular biology of hmpv made considerable strides, however a vaccine to prevent hmpv infection is still lacking. This review covers recent discoveries in hmpv molecular virology, diagnosis, and control methods when the 1960s respiratory virology explosion, including rhinovirus, coronavirus, enterovirus, adenovirus, and parainfluenza species.[3]

VIROLOGY

Viruses along with respiratory syncytial virus was added to the list of causes of respiratory tract infection like influenza and measles viruses. Members of the herpesvirus family, like human herpes virus 6, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, along with herpes simplex, have been linked to respiratory disorders. These disorders appear within immunocompromised individuals and also restricted patient groups. This pathogen list.[4]

The past fifty years have seen the meticulous and exquisite characterization of the epidemiology, molecular structure, cell tropism, and pathophysiology of several viruses that cause human illness. Differently effective vaccines and antiviral medications were created and tested. Even if measles and hepatitis B have been controlled and smallpox has been relegated to a freezer chest, the viruses that cause both occasional and severe respiratory illnesses in children still exist. The prevalence of influenza A and B, parainfluenza, respiratory syncytial viruses, and adenoviruses, as well as their effects on children and babies and the populations most at risk for morbid consequences, are examined.[5]

STRUCTURE AND ORGANISATION OF THE HUMAN GENOME

Diseases like some types of cancer, which may be linked to acquired somatic genetic changes rather than inherited defects, are not included in the estimate that at least 10% of human illness is a direct result of inheriting defective or disease-predisposing genes (UNSCEAR 1977). Major single gene abnormalities are inherited by around 1% of live newborns, and some of them are the result of novel mutations.[6]

A gene that causes a type of X-linked non-specific mental retardation has a mutation rate of approximately 1 per 104 gametes per generation, which is at one extreme of the spectrum. In contrast, inherited major single gene defects have a chromosomal abnormality that occurs in approximately 1 in 150 live newborn babies. This abnormality can be a change

in the number or structure of chromosomes, and most of these abnormalities are new mutations arising in parental germ lines Evans 1977.[7]

In fact, over 50% of early abortions are linked to a chromosomal mutation (boue et al 1975), and the total numbers would suggest that nearly 1 in 10 human gametes carry a chromosomal mutation. The incidence of chromosomal mutations in stillbirths and spontaneous abort uses is significantly higher. Human somatic cells can also easily exhibit chromosomal and, in some situations, gene mutations, and blood lymphocytes from healthy persons frequently have chromosomal abnormalities, occurring in 1 in 102 to 103 cells. Therefore, mutations in human somatic and germ cells are by no means uncommon, and the human genome may be less stable entity than is frequently thought.[7]

The hepatitis C virus (HCV) belongs to the Flaviviridae family and is a positive strand virus that belongs to the genus Hepaciviral. Hepatocytes, the main, if not exclusive, host cells, are where HCV replication begins when the virus attaches itself to them. HCV entrance is a laborious, multi-step procedure.[8] Primary binding of the virus particles to host cells is facilitated by interactions between glycosaminoglycans (GAGs) and HCV E1-E2 envelope glycoproteins.[9]

EPIDERMOLOGY

Global epidemiology examines the distribution of heath and disease in human populations around the world, as well as the factors that influence these outcomes. It takes into account the persons impacted, the time, and the location. Difficulties Access to data Worldwide epidemiology is limited by a paucity of date, particularly in developing nations. Standardized terminology comparing data across areas is challenging due to the absence of uniform classification for illnesses such as sepsis. Global epidemiology examples Infections illnesses: Worldwide, severe bacterial infections are a leading cause of admissions to intensive care units. Visceral leishmaniasis in dogs: Though the actual number of afflicted animals may be higher, this illness is present in roughly 50 nations. Dengue: Research has been done on dengue's worldwide dissemination. Group with spotted fever Rickettsiae: This disease's worldwide range has been charted. [10]

Epidemiology and risk factors of eating disorders: A two -stage epidemiologic study in a Spanish population aged 12-18 years in terms of morbidity and mortality, human metapneumovirus, or hMPV, is a relatively new virus 1 that seems to be just as harmful as hrsv. Understanding the pathophysiology of hMPV and the molecular limitations causing severe disease is crucial for both treating infections and creating an effective vaccine against this significant respiratory virus. Recent research has provided some insight into the

pathophysiology of hMPV enabled us to assess live vaccination candidates through the use of reverse genetics platforms and animal models for hMPV infection. Clinical trials must now be started in order to assess the various hMPV infections therapy options.[3]

PATHOGENESIS

MECHANISM OF INFECTION

Human Metapneumovirus Mechanism (HMPV) Human Metapneumovirus Mechanism (HMPV) The respiratory system is the preferred site of infection for HMPV, a negative stranded single stranded RNA virus belonging to the viral family Paramyxoviridae (Soto et al., 2018). [40]. With the aid of the viral fusion (F) protein, the virus fuses with the host epithelial cells in the upper respiratory tract to initiate the illness process (Leroy et al., 2020). [26]. In order for protein to be generated, the viral RNA genome is released into the cytoplasm after cell invasion and converted into mRNA by the host or viral RNA Dependent RNA polymerase (Ishiyama and Nagata, 1988).[11]

New negative strand RNA genomes are created from previously produced positive strand RNA intermediates while the viral replication cycle continues (Ahlquist, 2006). With the help of matrix M protein, these new genomes are then integrated into new virus particles that are partly wrapped and discharged from the infected cell's cell membrane (Cosset, F.L., & Lavallette, 2011).[12]

Both innate and adaptive immune responses are part of the immune system's reaction to HMPV (Kolli et al., 2012). Although neutralizing antibodies, natural killers, and interferons are crucial for controlling the virus, the virus also uses other techniques to evade protection, such as glycosylating the F protein (Klasse, 2014). Some children or newborns are more susceptible to HMPV than others, and those who are older or immunocompromised may experience symptoms that vary from a simple cold-like sickness to bronchiolitis or pneumonia. Persistent hMPV infection may result from a poor and delayed immune response, as well as delays in cytotoxic T-lymphocyte activity and viral clearance following the first infection. Dendritic cells are infected by 70 hmpv, which stops superantigen-induced T cell activation. As a result, the proliferation of antigen-specific CD4+T cells is restricted and the establishment of long-term immunity is impeded. 2.1 Respiratory viruses are known to modify cytokine responses. Hmpv is less potent than RSV and influenza at inducing the cytokines interleukin [IL]-12, tumor necrosis factor alpha [TNF-a], IL-6, IL-1B, IL-8, and IL-10.71. When BALB/C mice and cotton rats are infected with hmpv, the lungs and bronchoalveolar lavage fluid include greater amounts of interleukins [IL-2, IL-8, and I L-4], Monocyte chemotactic proteins, macrophage inflammatory protein 1A, and interferon [IFN-A].[13] Perivascular and

peribronchiolar infiltration and inflammation are further consequences of these alterations. Immunological and histological studies reveal the development of intra -alveolar foamy and hemosiderin -loaded macrophages, smudge cells, alveolar damage, and hyaline membrane disease. There is currently insufficient data to establish is required, but there is some indication that the latter is feasible. one study found hmpv in middle ear fluid, and another found HMPV RNA in the brain tissue of a patient who died of encephalitis.[14]

CLINICAL MANIFESTATIONS

Particularly in young infants, the clinical signs of an RSV infection and a hMPV infection are identical. Patients with hMPV are often diagnosed with pneumonia, bronchiolitis, and bronchitis. Common symptoms that they exhibit include fever, coughing, hypoxia, upper and lower respiratory tract infections, and wheezing.[15]

However, pneumonia and bronchiolitis are the most frequent reasons for hospitalization. Only a tiny percentage of infected individuals had fever, with the typical duration of fever in hMPV re-infection exhibiting mild cold and flu-like symptoms. However, in the case of elderly patients, re-infection can cause severe symptoms such as pneumonitis as well as even kill them. One study reported the finding that 50% of children with hMPV infection were diagnosed in cases with otitis media 56. [16]

One more study showed hMPV infection affected nearly 8% of wheezing children in hospitals. Doctors see wheezing often in studies about children who have hMPV and lower respiratory infections. Small children and also adults can develop asthma exacerbations from hMPV infections. hMPV improves COPD59 and COPD patients are more likely to get hMPV infection. Additionally, some of the findings have shown a variety of the disorders affect the central nervous system. These disorders, that range from severe encephalitis to febrile seizures, may be linked to hMPV infection within children.[15]

Although asymptomatic children exhibited far lower virus loads than symptomatic children, hMPV was nevertheless identified by real-time RT-PCR in these children. Regardless of genotype, there was a strong correlation between higher hMPV viral loads and the severity of the sickness and the duration of illness. Acute diseases was followed by one to two weeks of high levels of hMPV virus shedding. It has been suggested that a kid undergoing treatment for acute lymphoblastic leukaemia may develop hMPV-associated deadly pneumonia. An allogeneic hematopoietic stem cell transplant patient who developed interstitial and intra-alveolar pneumonitis along with significant alveolar cell destruction died from an infection caused by hMPV alone.[17]

Following a donation of hematopoietic stem cells, hMPV infection may be linked to significantly increased rates of morbidity and death in the first week. A low to moderate increase in C-reactive protein (CPR) levels, decreased peripheral blood lymphocytes, and an elevated monocyte ratio were the early signs of hMPV infection. In lung transplant recipients, hMPV can cause a variety of illnesses, ranging from a mild upper respiratory tract infection to severe motor and intellectual disabilities. As symptoms subsided, the ratio of peripheral blood lymphocytes to monocytes returned to normal, but the CPR levels remained elevated for a while. Leukopenia and leucocytosis were also recorded in a small number of hospitalized children infected with hMPV, in addition to high serum CPR levels.[18]

DIAGNOSIS:

Different cells lines like Vero cells,75 Hep-2 cells, Hep G2 cells, 76 293 cells,29 and LLC-MK2 cells5 have been employed for the cultivation and isolation of hMPV. In a recent study where 19 cell lines were employed for the cultivation of hMPV, it was demonstrated that the most appropriate cell lines to employ for the cultivation of hMPV, it was demonstrated that the most appropriate cell lines to employ for the cultivation of hMPV were a human Chang conjunctiva cell line (clone 1-5C4) and a feline kidney CRFK cell line. hMPV is slowly growing during cell culture, with late cytopathic effects that vary from cell rounding and detachment from the culture matrix to formation of small syncytia. For this reason, detection of hmpv antigen with anti-hmpv antibody by direct fluorescence or ELISA- based assays is common alongside cell culture methods. 75 Sensitivity and specificity of cell culture detection methods were 68% and 99%, respectively, compared to real-time RT-PCR are employed more frequently.[19]

Two studies have established and validated multiplex PCR assays with the objective of providing a tool that is capable of detecting an increasingly complete panel of respiratory viruses. Following the establishment of multiplex RT-PCR (mRT-PCR), it is now feasible to design a more sensitive and quicker assay for the detection of hmpv. mRT-PCR methods have a sensitivity and specificity of 100% and 96%, respectively, compared to 54.6% and 100% for rRt-PCR. Another benefit of mRT-PCR is that it is possible to detect co-infections, even with very low viral loads that are undetectable with cell culture or immunostaining.[20]

However, most of the clinical laboratories are not yet in a position to conduct routine diagnostic RT-PCR for the diagnosis of hmpv. In order to perform the rapid and correct diagnosis of hmpv infection, the combination of direct fluorescent antibody test and immunofluorescence test is utilized as the initial diagnosis, which is followed by RT-PCR on

the negative test. Shell vial centrifugation culture and hmpv monoclonal antibodies will be of invaluable use in the rapid diagnosis of hmpv in the near future for clinical laboratories.[21]

TREATMENT AND MANAGEMENT

Numerous therapy plans have been studies by researchers. Conventional immunoglobulin preparations have prevented hmpv from replicating in vitro and in animal experiments. No particular treatment or cure exists. You will just require supportive treatment to manage your symptoms while you recover because the majority of them are minor and reasoning on their own. In the interim, you can do the following to assist manage your symptoms: To treat symptoms like fever, pain, and coughing, take over-the-counter medications such as ibuprofen an acetaminophen. To relieve stiffness or a runny nose, use decongestants. For respiratory issues like wheezing or coughing, use an inhaler. To relieve pressure within your nose, use a nasal spray that contains corticosteroids. To aid with inflammation, your doctor can also recommend a steroid, such as prednisone.[22]

PREVENTION AND CONTROL

VACCINATION DEVELOPMENT

An estimated 45% of mortality among children under five in underdeveloped nations are attributed to malnutrition, primarily as a result of illnesses. Therefore, children who are malnourished stand to gain much from immunization; but, as malnutrition has been identified as the most prevalent immunodeficiency worldwide, it is possible that these children may not be able to react well to vaccinations. Malnutrition's immunology and adaptive immune dysfunction persist. Although the timing, quality, and length of responses may be compromised, most malnourished children are still able to develop a protective immune response after vaccination. In addition to highlighting evidentiary gaps in our existing understanding, this research analyses the data supporting vaccination immunogenicity.[23]

PUBLIC HEALTH MEASURES TO CONTROL SPREAD

PERSONNAL PREVENTIVE STRATEGIES

Eliminating carcinogenic exposures should lower the chance of getting cancer later on. The magnitude of the decline and its rate of occurrence are of importance. Depending on the stage of the process at which the carcinogen is only slowly apparent, multistage models with more than two stages for tumor development predict different patterns of changing risk after removing a carcinogenic exposure. In contrast, removing a late-stage carcinogen reduces excess risk more quickly. Both early and late-stage effects are observed, and experimental and epidemiologic data are discussed. The long-term risk of early-stage carcinogen exposure is

examined, and it is demonstrated that individuals who have previously been exposed may have amassed their fully effective dosages by the time there is human proof that a hazard does exist.[24]

RECENT ADVANCES IN RESEARCH

NEW TECHNIQUES IN LABORATORY ASSAYS FOR HUMAN METAPNEUMOVIRUS DETECTION

One of the main causes of acute respiratory tract infections (ARIs), human metapneumovirus (HMPV) has a high morbidity and fatality rate, especially in young patients and those with weakened immune systems. Clinical laboratories have developed and used a variety of HMPV detection techniques.[25]

Upon reviewing the literature, we discovered that the most common and reliable methods for detecting HMPV have been assays based on polymerase chain reaction (PCR). Multiplex reverse transcriptase-PCR (RT-PCR; 57.4%) was the most often employed technique, with real-time RT-PCR coming in second (938.3%). Between 2011 and 2019, multiplex RT-PCR gained popularity (69.7%), compared to 2001 to 2009 (28.6%).[26]

The shift in user choice was driven by the development of multiplex PCR, which can identify coinfected viruses and larger viral pathogens in a single run. Additionally, from 2011 to 2019, ionization mass spectrometry and recently developed microarray technologies were introduced. Fluorescence immunoassays (with or without culture) and viral culture (including shell vial assays) used to be the standard.[27]

Nonetheless, the proportion of research using culture and fluorescence immunoassays dropped from 21.4% between 2001 and 2010 to 15.2% between 2011 and 2019. In the meantime, the percentage of HMPV detections using PCR-based techniques rose from 78.6% in 2001–2010 to 84.8% in 2011–2019. The rise of PCR-based techniques may have been due to the fact that PCR techniques outperformed older techniques in terms of diagnostic performance, run and hands-on times, risks to lab staff, and reliability.

It is crucial to get a thorough awareness of the concepts, benefits, drawbacks, and data interpretation concerns while utilizing these assays. Future HMPV infection patients will benefit from the effective therapeutic intervention made possible by the combination of nanotechnology and cutting-edge genetic platforms like next-generation sequencing. New methods must first undergo analytical and clinical validation before being used in clinical laboratories.[24]

NEW DIAGNOSTIC TECHNIQUES:

A brief overview of China's human metapneumovirus epidemiology and diagnostic methods Acute respiratory tract infections in newborns worldwide are caused by the recently discovered human metapneumovirus (HMPV). Chinese students have worked hard to prevent and control HMPV since the first reports of the virus's presence in China in 2003. They have developed diagnostic tools, vaccinations, and antiviral drugs, as well as carried out epidemiological studies.[28]

Since there are presently no licensed vaccines or particular antivirals that are effective against HMPV, it will be helpful to manage the virus by developing early detection techniques and understanding its epidemiological features. In order to improve future disease control and public awareness, we have compiled the most recent research on the epidemiological features of HMPV in China and the diagnostic techniques that are now available.[29]

CHALLENGES AND FUTURE PERSPECTIVES

LIMITATIONS IN CURRENT RESEARCH

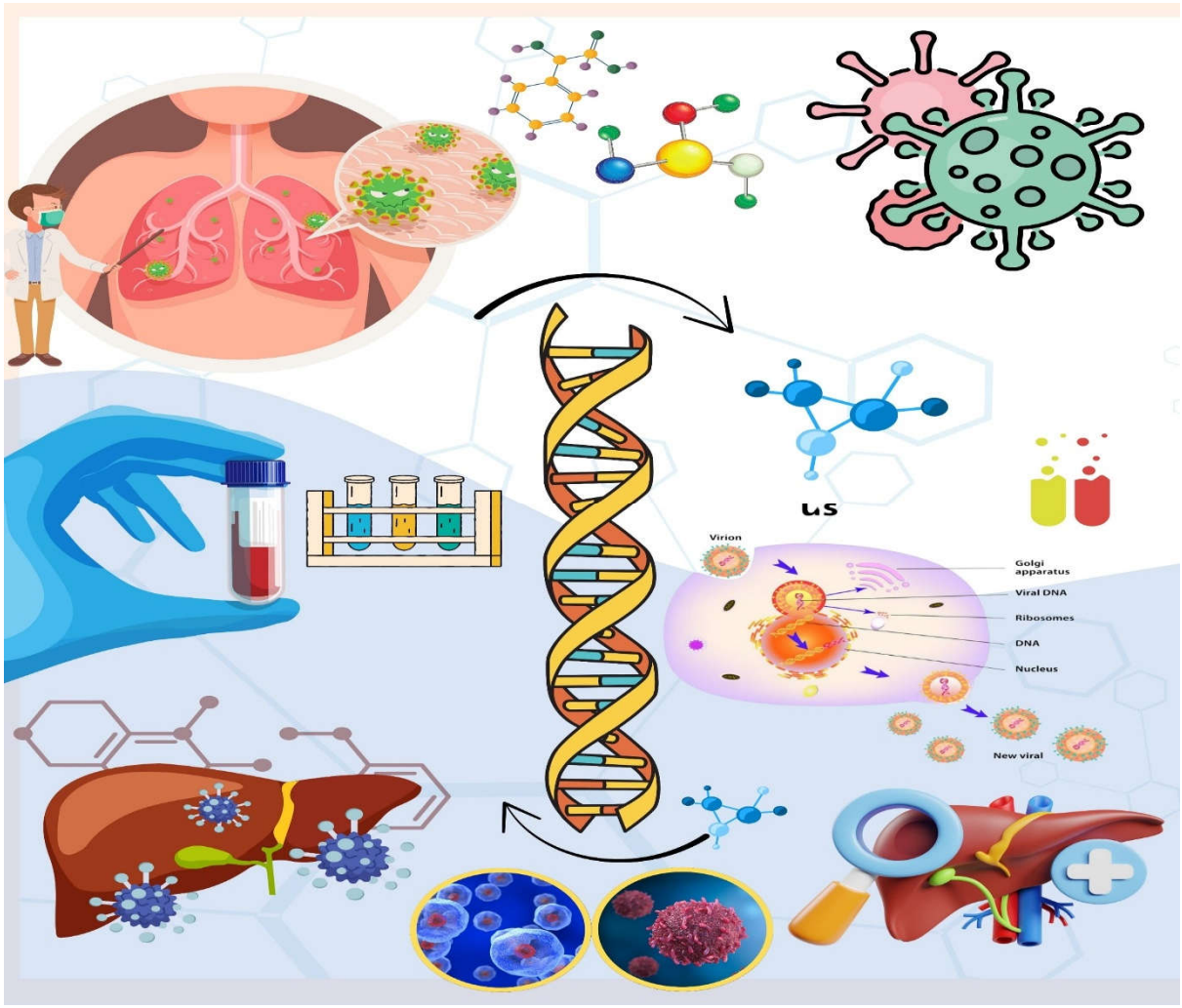
Human Metapneumovirus (HMPV) is a respiratory infection that has resurfaced and is causing a great deal of morbidity and mortality, especially in small children and elderly people with impaired immune systems. First identified in 2001, HMPV has been recognised as a leading cause of acute respiratory tract infections (ARTIs) worldwide. Its transmission occurs through droplets, direct contact, and surface contamination, with crowded spaces and healthcare facilities serving as key environmental amplifiers. HMPV'S clinical manifestations, ranging from mild cold-like symptoms to severe pneumonia, often overlap with those of other respiratory pathogens like RSV and COVID-19, complicating timely diagnosis and management. Despite advancements in molecular diagnostics, the limited accessibility of these tools in low-resource settings presents a challenge. Preventive measures, such as hygiene practices and physical distancing, remain promising innovations, including AI-guided vaccine design and portable diagnostic tools, highlight the potential for future breakthroughs. This article highlights the urgent need for enhanced surveillance, scalable diagnostics, and intensified research into vaccines and therapeutic strategies. By addressing these gaps, HMPV's global burden can be significantly mitigated, improving outcomes for high-risk populations, and strengthening preparedness against respiratory virus outbreaks.[30]

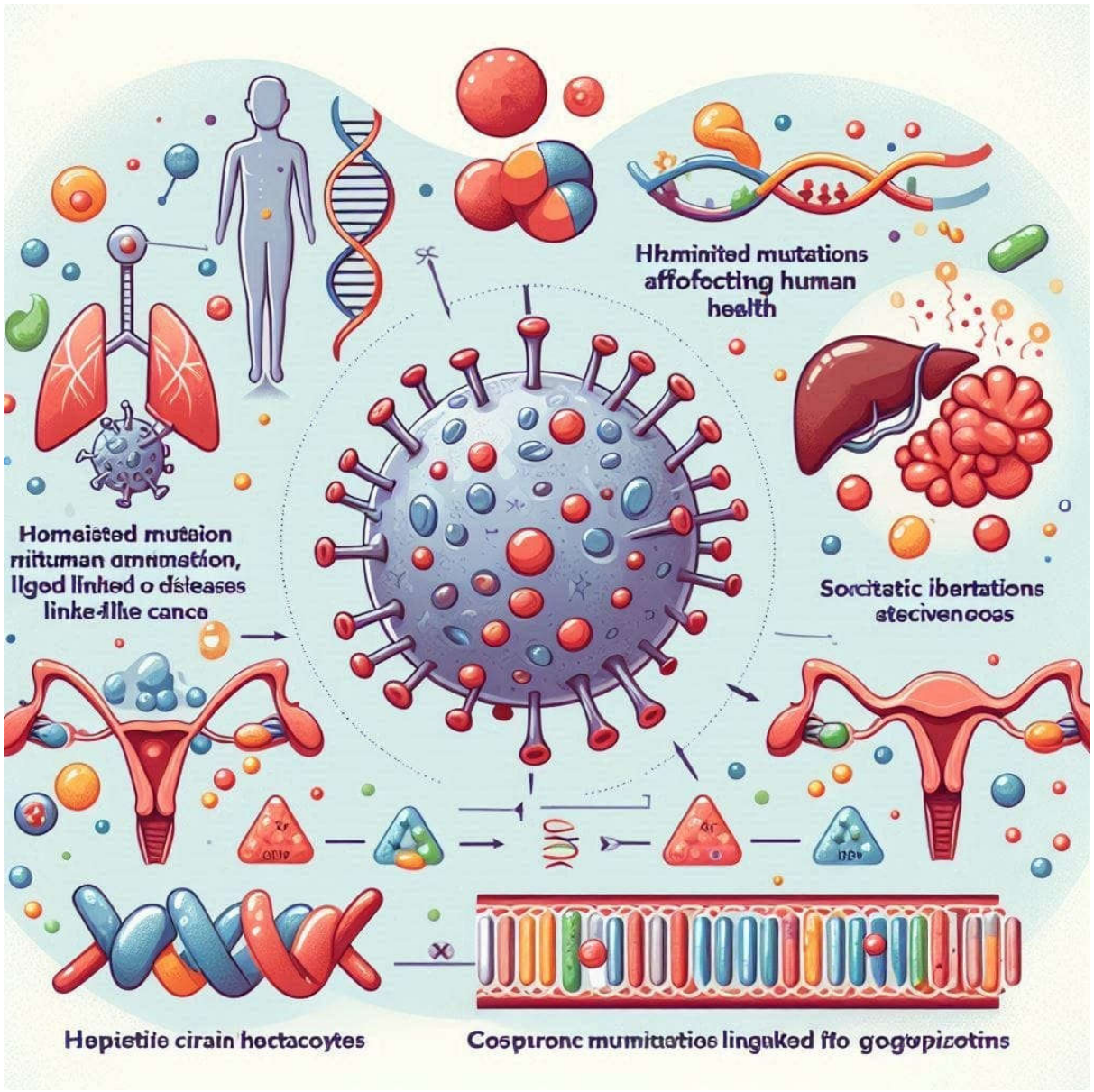
KNOWLEDGE GAPS IN UNDERSTANDING HMPV

A prominent member of the paramyxoviridae family, Newcastle disease virus (NDV) is responsible for epidemics and considerable financial losses in poultry around the globe. Six structural proteins (N, P, M, HN, and L) and two non-structural proteins (V and W) are the main proteins encoded by the NDV RNA genome. The ribonucleoprotein complex, which is

made up of the polymerase-associated proteins (N, P, and L) and the viral RNA (vRNA) genome, is essential for the synthesis and transcription of NDV vRNA.

In the last two decades, numerous studies have demonstrated that the polymerase-associated proteins and host proteins are closely related to the NDV's replication and pathogenicity. Research on the structure and function of NDV polymerase-associated proteins is less thorough than that of other NDV proteins, and the knowledge that is currently accessible is frequently dispersed, despite tremendous advancements in our understanding of their distinct and similar roles.[31]

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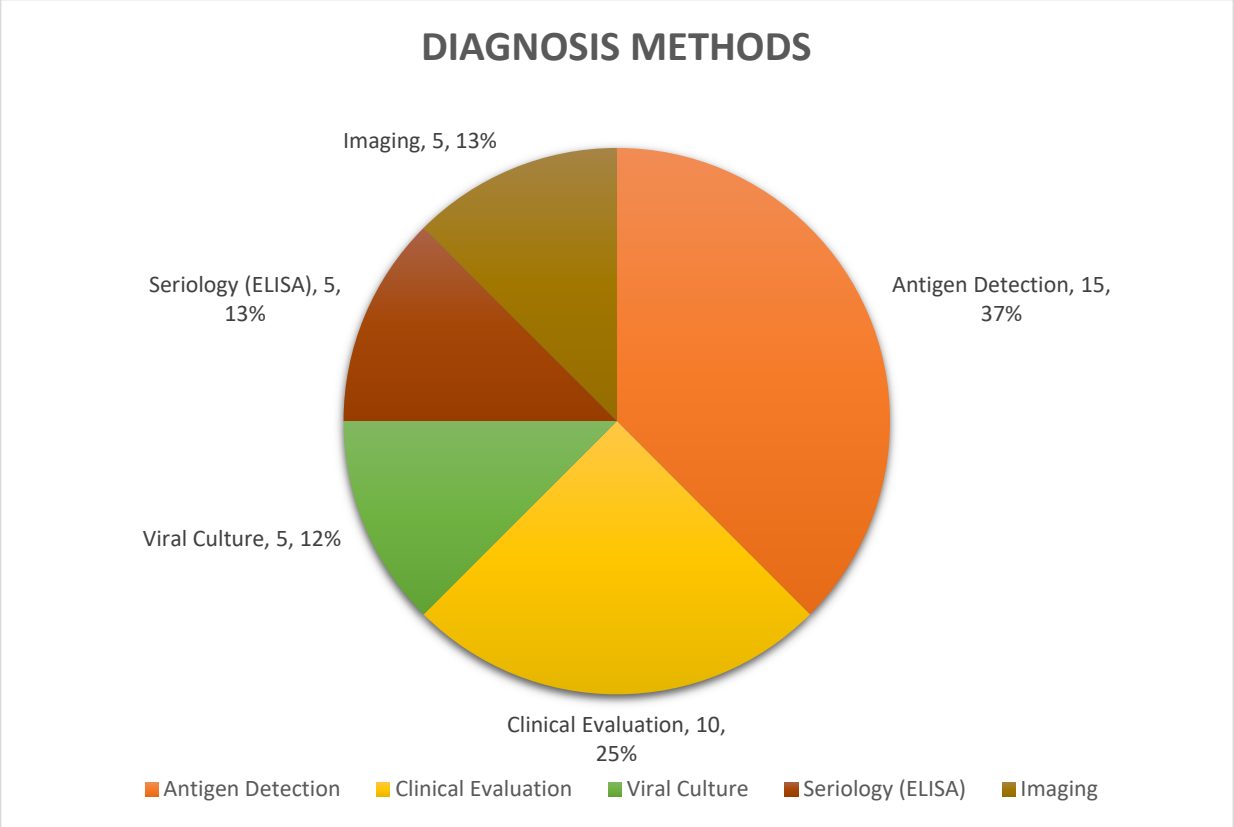

ASPECT	DETAILS
Diagnosis Methods	PCR testing, antigen detection, viral culture
Common symptoms	Cough, fever, wheezing, sore throat, shortness of breath
Treatment approach	No specific antiviral; supportive care including oxygen therapy, hydration, and fever management
Prevention strategies	Good hygiene, avoiding close contact with infected individuals

CONCLUSION

In terms of morbidity and mortality, human metapneumovirus, or HMPV is a relatively new virus that seems to be just as harmful as hRSV Treating infections and developing a successful vaccination against this important respiratory virus need on an understanding of the HMPV and the molecular constraints producing severe illness. Recent research has provided some insight into the pathophysiology of HMPV and enabled us to access live vaccination candidates thorough the use of reverse genetics platforms and animal models for HMPV infection. Clinical trials must now be started in order to access the various HMPV infection therapy options.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the support and guidance of the faculty and staff of the Department of Pharmacy and the Department of Pharmaceutical Analysis, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Anantapur. We also thank our colleagues for their valuable suggestions and constructive feedback that contributed to the improvement of this review.

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