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HUMAN METAPNEUMOVIRUS (HMPV): CURRENT INSIGHTS AND FUTURE PERSPECTIVES

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ABSTRACT

Human Metapneumovirus (HMPV) is a significant contributor to respiratory tract infections (RTI's), presenting a clinical spectrum that ranges from mild flu-like symptoms to severe pneumonia. The overlap of clinical features with other RTI's, often complicates its diagnosis. While HMPV predominately affects young children, the elderly and immunocompromised individuals, its true burden remains under-recognized due to diagnostic challenges. Currently there is no specific antiviral therapy or approved vaccine for HMPV, underscoring the urgent need for research into effective prevention and treatment strategies. Furthermore, the oral manifestations of HMPV infections remains an unexplored domain with potential correlations to viral kinetics and systemic spread. Investigating these oral signs could provide new insights into disease progression and serve as adjunctive diagnostic markers. The present paper provides a comprehensive review of the epidemiology, immunodynamics and diverse clinical manifestations of HMPV, while also shedding light on recent advancements in diagnostic approaches and vaccine development. By addressing these knowledge gaps, future research can pave the way for a more comprehensive approach to mitigate the global burden of HMPV-related respiratory illness.

Keywords: *Vaccination, Human Metapneumovirus (HMPV), Respiratory Tract Infections (RTI), Health Care Professionals*

INTRODUCTION

Acute respiratory tract infections (ARTIs) are the leading cause of symptomatic sickness globally. ARTI is primarily caused by viruses, while it can also be caused by certain bacteria and fungi (1). Researchers have established the significance of recognized viral infections such as the coronavirus, rhinovirus, influenza virus, parainfluenza virus, and human respiratory syncytial virus (RSV) via decades of study and epidemiological investigations (2,3,4). ARTI limited to the upper airway often cause moderate respiratory discomfort. Nevertheless, this might result in potentially fatal pneumonia if the infection advances to the lungs. HRSV and HMPV are common causes of viral pneumonia in young children (<5 years old), senior citizens (>65 years old), and immune compromised persons (1). Depiction and comparison between various aspects common viruses- Influenza, COVID-19, RSV and HMPV is provided in Table 1.

A recent outbreak of HMPV virus in China in December 2024 has raised global concerns prompting countries like India and Malaysia to closely monitor its transmission (5). Public awareness was raised when the Chinese Centre for Disease Control and Prevention released statistics, indicating a sharp increase in HMPV respiratory infections during the week of December 16–22, 2024. In China, HMPV was more common than COVID-19, rhinovirus, or adenovirus in late 2024, accounting for 6.2% of individuals with positive respiratory disease tests and 5.4% of respiratory-related hospitalisation (6). World Health Organization (WHO) has been providing health messages to the public on how to prevent the spread of this respiratory pathogen and has advised member states to maintain surveillance for HMPV through an integrated approach to combat its spread (7).

HMPV is categorized as the first human member of the Pneumovirinae subfamily of the Paramyxoviridae family, which includes the Metapneumovirus genus. It is a single-stranded, negative-sense RNA virus with an envelope (1). There are eight genes in the RNA genome that code for nine distinct proteins (Figure 1). The virus has been in circulation among humans for more than 50 years, according to serologic investigations of antibodies against HMPV, despite the virus being originally discovered in 2001 in Netherlands.

EPIDEMIOLOGY

HMPV exhibits a seasonal variation and has been discovered in every continent. In 2019, worldwide systematic investigation of monthly patterns of activity of various viruses from 246 sites (65 of which were HMPV impacted) revealed that in the majority of temperate sites, HMPV epidemics happened in the late winter and spring (6). The northern and southern

hemispheres have outbreaks primarily from January to March and June to July, respectively. Co-circulation of multiple respiratory pathogens during the winter season sometimes can lead to an increased burden on health care systems treating ill patients. The paediatric population is frequently affected by HMPV, with children under the age of two having the highest susceptibility rates (2). At age of five, seroprevalence is nearly 100% (8). However, reinfection happens, particularly in older and susceptible individuals, as a result of poor immune response or infection from a new genotype (9).

LIFE CYCLE AND REPRODUCTION

The expected incubation period for HMPV is 3–6 days and differs from one person to another. Attachment to a recipient cell, more especially, the respiratory tract's epithelial cells using the G protein is the initial stage of replication cycle of the HMPV. The fusing of the membranes of the host and virus, mediated via the F protein, follows the cycle. The virus nucleocapsid then replicates after entering the cytoplasm of the recipient cell (10). The Golgi apparatus transports viral glycoproteins to the membrane, where they aggregate for the production of new viruses. When viral protein synthesis reaches a certain level, RNA polymerase copies the entire genome producing positive-sense RNA. After being enclosed inside the new virus particles, the novel negative-sense RNA genome is going to be created using this positively-sense RNA as a template. Finally, via budding across the membrane, assembled virus particle expelled from the surface of the cell with the help of the M protein (11).

TRANSMISSION

It is believed that HMPV spreads mostly by airborne droplets, being in close proximity with infected secretions which could include saliva or large particle aerosols. It can also enter the human body by touching contaminated surfaces like doorknobs or handles and then touching the eyes, nose or mouth (6). Within five days or two weeks following the onset of manifestations, HMPV's RNA is detected in excretions. However, since the presence of RNA of HMPV in breathing specimens from patients recuperating from illness does not necessarily indicate live infectious virus particles, the degree of contagiousness is uncertain. A retrospective study was conducted in Japan to study the transmission of HMPV. Children enrolled in primary school, day-care centres, or nursery homes comprised all index-patients among the 15 families under study. The median time for contact cases to showing symptoms was five days (range: three to seven days) following the index cases (12).

PATHOGENESIS

The virus can quickly propagate into the airways after being inoculated in nasopharyngeal mucosa. Airway epithelial cells, alveolar macrophages, and dendritic cells are the main cell types that may detect HMPV in a case of acute infection, which cause an initial antiviral response that is primarily defined by the generation of Interferons (IFN) (1) (Figure 2). Through a number of immunological repressive ways, mainly carried out by its G and SH proteins, HMPV immediately attempts to reverse the response (Table 2). T cells, including CD4⁺ and CD8⁺ T cells, are essential for the removal of HMPV along with innate immune system agents. It should come as no surprise that HMPV has developed strategies to hinder dendritic cell activity in order to postpone the cytotoxic T cell activity and the elimination of the virus. Following the infection's course, the humoral response - the B cells' generation of virus-specific antibodies is another crucial stage in controlling the virus (1).

CLINICAL MANIFESTATIONS

It is impossible to make accurate differences between the clinical manifestations of HMPV infection compared to other frequently occurring respiratory viruses. Despite the fact that symptoms typically overlap, variations in clinical presentation can happen (12). While producing sputum, bleeding, irregular bowel movements, and headache are less frequent symptoms; a high-grade fever, dyspnoea, body pains, and a persistent cough are typical initial symptoms.

1. Manifestations affecting Respiratory Tract

People with HMPV typically exhibit manifestations of upper and/or lower airway infection, although the latter is generally more prevalent. Cough, rhinorrhoea, congestion, and sore throat are typical signs of upper respiratory tract infection. Symptoms of lower airway infection include coughing, fever, hypoxia, dyspnoea, and wheezing. Children who have lower respiratory tract infection are more likely to develop pneumonia, croup, bronchiolitis, and acute asthma flare-ups (10).

2. Extra pulmonary manifestations

The epidermis, olfactory system, along with oral cavity is among the other organs that this virus may impact with similar symptoms. An ulcer, erosion, vesico-bullous lesions, pustule, fissured tongue with de-papillation, pallor, bad breath, whitish patches, haemorrhagic crust, tissue necrosis, blisters, inflammation, redness, and spontaneous bleeding are among the oral signs (13). Additional extra-pulmonary symptoms including as encephalitis, focal epileptic seizure, otitis media and viral cardiomyopathy have also been linked to HMPV. An HMPV

transmission in an immune-deficient adult who presented as a mononucleosis-like disease was reported by Li et al (14). According to Williams et al., otitis media was identified in 50% of children infected with HMPV (15). Additionally, some findings have indicated that a variety of disorders affecting the central nervous system, from serious encephalitis to febrile seizures, are possibly linked to HMPV infected children (16). According to a case report, an allogeneic hematopoietic stem cell transplant recipient who developed interstitial & intra-alveolar pneumonitis along with significant alveolar cell destruction died from an infection caused by HMPV solely (17). The first instance of HMPV inducing viral myocarditis was reported by Weinreich et al. in 2015 (18). In 2024, Toyin et al. reported a case of a 43-years-old individual who had no known cardiovascular history and was diagnosed with HMPV-related sepsis-induced dilated cardiomyopathy (19).

3. Risk Group

Older people, immuno-compromised individuals, and young ones are the groups mostly at risk of contracting HMPV. According to research, between 30 and 85 percent of kids admitted to hospitals with HMPV suffer from long-term illnesses like asthma or chronic lung disease brought on by prematurity, cancer, or congenital heart disease. Patients with underlying illnesses including asthma, persistent obstructive pulmonary disease (COPD), HIV-positive, impaired immune state, or preterm are more likely to be admitted to the hospital (12).

DIAGNOSIS

The following methods can be used to diagnose HMPV infection:

1. Molecular Diagnostics

The most sensitive technique for diagnosing HMPV infection is the reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which detects viral Ribonucleic acid (RNA), particularly during the acute phase of illness. Multiplex RT-PCR is the most commonly used method found in the literature followed by real-time RT-PCR. Multiplex RT-PCR became the most popular method in 2011–2019. This technique enables detection of a broader range of respiratory viruses in a single test run. Commercial multiplex PCR kits, cleared by the Food and Drug Association (FDA), are now available (20). Optimal sample collection should occur within the first 3–5 days of symptom onset, when viral load is highest. Commonly used specimens include nasopharyngeal swabs (NPS), nasopharyngeal aspirates (NPA), and nasal washes. NPS is preferred in children for its balance of diagnostic yield and ease of collection. NPAs, though more invasive, offer higher viral yield and are often used in infants. Throat swabs may serve as supplementary samples but are less sensitive. In severe or hospitalized cases,

specimens such as endotracheal aspirates or bronchoalveolar lavage (BALF) may be used. Combined nasal and throat swabs are a non-invasive alternative that can enhance detection rates, especially in older children and adults. (Table 3) (20).

2. Virus Culture

HMPV has been grown and isolated using a variety of cell lines, including Vero cells, Hep G2 cells, Monkey Kidney cells, HEp-2 cells, BEAS-2B cells, HepG2 cells, 293 cells and LLC-MK2 cells (2). Because HMPV has minor cytotoxic effects and develops slowly in standard cell culture, virus cultivation is comparatively challenging. Cell culture detection techniques were shown to have 68% sensitivity and 99% specificity.

3. HMPV Antigen Detection

A number of investigations have documented high sero-prevalences utilizing enzyme-linked immunosorbent assays (ELISAs) or micro-neutralization assays. Rapid diagnostic tests using immune-chromatography (IC) are now available for detecting HMPV. These tests, for eg. Biopanda HMPV Rapid Test, utilize a lateral flow assay to detect HMPV antigens in nasopharyngeal swab samples. They are relatively easy to perform and can be done in point-of-care settings (POCR). Moreover, different types of bio sensors for rapid identification of respiratory viruses have been developed recently with promising results (21).

4. Serologic Testing

Serological testing for HMPV is primarily utilized in epidemiological research rather than routine clinical diagnosis, as IgM and IgG antibodies typically appear several days to weeks post-infection. By the age of five, most children have detectable IgG antibodies, indicating early-life exposure. Due to this delayed antibody response, serology is not suitable for diagnosing acute infections. Instead, molecular techniques such as RT-PCR are preferred for rapid and accurate detection (8).

5. Radiographic Investigations

Imaging using computed tomography (CT) and chest X-rays reveal that symptoms of acute interstitial pneumonia (air-space consolidation with ground glass opacification) give way to symptoms of inflamed bronchi (thickening of the bronchial wall). Other cutting-edge technologies are presently being developed for the diagnosis of respiratory viruses include microfluid chips, RT-PCR in conjunction with electrospray ionization mass spectrometry, and essays like surface-enhanced Raman spectroscopy (12).

TREATMENT STRATEGIES

Currently, there is no particular treatment for HMPV which is a major cause of paediatric pneumonia globally. The majority of HMPV infection therapies now available are mainly supportive. In case of infants and children who require hospitalization, the primary therapies are oxygen supplementation and intravenous hydration (22). Antiviral drugs are considered an option of last resort to treat a severe HMPV infection. At present, only ribavirin and immunoglobulins have been used in humans for treatment of HMPV infections.

1. Antivirals

Ribavirin, a broad-spectrum nucleoside analogue, has shown antiviral activity against RNA viruses like HMPV. In vitro and animal studies suggest it may reduce viral replication and modulate immune responses by lowering pro-inflammatory cytokines. Clinically, its use is limited and largely experimental. In rare cases, such as in immune-compromised patients, ribavirin combined with intravenous immunoglobulin has been used with reported success, though further clinical validation is needed. Human clinical data on its efficacy in HMPV is limited, and concerns regarding its toxicity and narrow therapeutic window have restricted widespread adoption (20,23).

2. Immunoglobulins

It includes humanized monoclonal antibodies like Palivizumab capable of identifying a highly preserved neutralizing domain on the viral fusion protein. Palivizumab has been shown to be effective mainly against RSV mainly in infants. It is being studied further to be used in the treatment of HMPV infections (24). MAb 338, an antibody designed specifically for targeting the fusion protein of HMPV. In animal trials, it demonstrated efficacy by lowering the respiratory viral titre considerably, reducing severe acute symptoms, and bronchial hyper-reactivity (25). Fusion (F) protein plays an important role in the HMPV life cycle, making it an attractive antiviral drug target. Blockade of these F-mediated processes is expected to reduce HMPV infection and ultimately reduce global health care burden (26). The use of RNA interference targeting essential viral genes via small interfering RNAs (siRNAs) offer the ability to directly and rapidly treat viral infections including HMPV. N and P gene of HMPV can be effectively targeted by siRNAs, thereby proving to be a novel therapeutic agent for HMPV control (27).

VACCINATION

Vaccination is regarded as the most efficient technique of combating epidemics. However, there are currently no accessible vaccines and no human experiments have been

conducted. Numerous HMPV vaccines had been researched, such as inactivated vaccine, epitope vaccine, chimeric vaccine, subunit vaccine, virus like particles and live attenuated vaccine. Russell et al. reported the production of a Sendai virus (SeV) recombinant that carries a gene for a truncated HMPV fusion (F) protein (SeV-MPV-Ft). The vaccine induces binding and neutralizing antibody responses toward HMPV and protection against challenge with HMPV in a cotton rat system (28). Another promising option is a VLP-based vaccination. Cox et al. created a VLP vaccine centred around the proteins F and M (29). Trinite et al. compared the immunogenicity of RSV-F or hMPV-F based immunogens delivered either as soluble proteins or displayed on the surface of VLPs (30). Both vaccinations protected experimental animals infected with HMPV. Numerous attenuated live vaccines have already been created in recent decades, and the majority of them shown promising results in preclinical testing. Although rHMPV-Pa reached a clinical trial, excessive attenuation prevented it from producing the desired results (31,32). The research is still ongoing to generate an effective vaccine.

FUTURE PROSPECTIVE AND ROLE OF DENTAL PROFESSIONALS

While much has been explored regarding the clinical impact of HMPV, its oral manifestations remain largely under-reported, presenting a unique area for dental professionals to consider. As oral health providers, it is essential to recognize that HMPV may produce oral symptoms similar to those seen with other respiratory infections, such as mucosal lesions or xerostomia, which could potentially be overlooked without awareness. Dentists play a pivotal role in identifying these oral signs early, especially in at-risk populations like children, the elderly, and immuno-compromised individuals. Further research into the oral implications of HMPV, along with advancements in diagnostic tools and vaccines, will enable dental practitioners to better manage and support patients with this infection highlighting the importance of integrating oral health into the broader context of respiratory viral infections.

CONCLUSION

In conclusion, HMPV remains a significant respiratory pathogen, with diverse clinical manifestations. Despite extensive research into its clinical features and pathogenesis, HMPV continues to present diagnostic and therapeutic challenges. As our understanding of HMPV evolves, particularly in its immune responses and genetic variability, future studies need to focus on advancing diagnostic tools, improving treatment options, and exploring the potential role of vaccines in preventing HMPV-related morbidity. Collaborative efforts across medical

and dental disciplines will be essential in addressing the full scope of this virus, ultimately leading to better patient outcomes and more informed management strategies.

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Received: 30.01.2025

Accepted for publication: 06.06.2025

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Table 1. Overview of other common respiratory viruses.

Aspect	Influenza	SARS-CoV-2 (COVID-19)	RSV	HMPV	Reference No. (In Text)
Virus Family	Orthomyxoviridae	Coronaviridae	Paramyxoviridae	Pneumoviridae	2,3,4
Genome	Negative-sense, single-stranded RNA; 8 segments	Positive-sense, single-stranded RNA; ~30 kb	A single-stranded, negative-sense RNA molecule approximately 15.2 kb in length	A non-segmented, single-stranded, negative-sense RNA virus	2,3,4
Key Proteins	Hemagglutinin (HA), Neuraminidase (NA), RNA polymerase, NP, M1, NS1	Spike (S), Membrane (M), Envelope (E), Nucleocapsid (N)	G protein and the F protein	Nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), small hydrophobic protein (SH), glycoprotein (G), and large polymerase protein (L)	3,4,8
Entry Mechanism	HA binds to sialic acid on host cells; endocytosis	S protein binds ACE2 receptor; TMPRSS2 or cathepsin L facilitates entry	G protein binds to specific receptors on host cells, like heparan sulfate proteoglycans (HSPGs), initiating the entry process	Enters host cells primarily through its F protein, which acts as both the attachment protein and the fusion protein	3,4,10,11
Transmission	Droplets, aerosols, contact with contaminated surfaces	Droplets, aerosols, contact; highly transmissible	Respiratory droplets, contaminated surfaces and also via large droplet transmission	Primarily through respiratory droplets or aerosols, direct contact with contaminated surfaces or objects	3,4,6
Incubation Period	1–2 days	2–14 days (typically ~5 days)	Typically 2-8 days, usually 4 to 6 days	Typically 3-6 days	3,4,12

Common Symptoms	Fever, chills, myalgia, headache, dry cough, sore throat	Fever, cough, dyspnea, fatigue, GI symptoms; loss of smell/taste common	Fever, severe cough, wheezing, rapid breathing	Cough, fever, rhinorrhoea, congestion. Children may develop pneumonia in severe infection	3,4,9,13
Elderly Presentation	Atypical (e.g., confusion without fever)	Increased risk of severe disease, multi-organ involvement	Mild cold like symptoms. Can severe and require hospitalization	Wheezing, difficulty breathing, and chest pain, potentially leading to pneumonia or bronchitis	3,4,8,9
Complications	Viral/bacterial pneumonia, myositis, myocarditis, encephalitis	ARDS, pulmonary fibrosis, thromboembolism, myocarditis, long COVID	Severe respiratory issues like pneumonia, bronchiolitis, respiratory failure, hypoxia.	Pneumonia, bronchiolitis, and exacerbation of chronic conditions like asthma or COPD	3,4,5
Pandemic History	Multiple pandemics (e.g., 1918 H1N1, 1957 H2N2, 1968 H3N2, 2009 H1N1)	2020-2023. Not a pandemic now.	Nil, first identified in 1956	Nil, first identified in 2001	3,4,7

Table 2. HMPV protein's impact on host immunity.

HMPV Protein	Effect on Host Immunity	Reference (in Text)
Nucleoprotein	A defensive response is facilitated by a fragment from this protein. This is a significant part of the inclusion bodies found during HMPV infection, associated with the P protein.	1,2
Phosphoprotein	Reduces the production of IFN-I by limiting RIG-I's capacity to detect 50-triphosphate viral RNA.	1,2,10
Matrix Protein	It causes the release of inflammatory cytokines and is released by affected cells in a soluble state.	1,2,10
M2-1 protein	This protein's domain triggers a defensive CTL response.	1,2,11
M2-2 Protein	Inhibits the homodimerization of IRF7, which stops the TLR7 signalling pathway from inducing IFN- α . Interferes with TLR-driven signalling by forming a compound with MyD88.	2,11
Small Hydrophobic Protein	Lowens the transcription levels of ISGs via blocking the phosphorylation process of STAT1. Reduces IFN expression by blocking the TLR7 signalling pathway. It may have a role in reducing CD4 ⁺ T cells activation.	2,10

Glycoprotein	<p>May contribute to lowering CD4+T cell activation.</p> <p>Combines with RIG-I to prevent viral sensing.</p> <p>Helps attract neutrophils by secreting more CXCL2, CCL3, CCL4, IL-17, and TNF.</p>	2,10
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*IFN-Interferon,

RNA- Ribonucleic Acid,

RIG- Retinoic acid-inducible gene,

CTL-Cytotoxic T Cell,

IRF- Interferon Regulatory Factor,

TLR- Toll-like receptor,

MyD88- Myeloid-Differentiation Factor 88,

ISG- Interferon Stimulated Genes,

STAT1- Signal transducer and activator of transcription 1,

IL- Interleukin,

TNF- Tumor necrosis factor

Table 3. Different types of Sample swabs for molecular testing of HMPV (Reference no. 20).

Sample Type	Details	Recommended For
Nasopharyngeal Swab (NPS)	Deep nasal swab which reaches the nasopharynx	First-line in children; most ideal for PCR/antigen tests
Nasopharyngeal Aspirate (NPA)	Obtained by Suction of nasal secretions	Significantly higher viral yield than swabs; commonly used in infants/young children
Throat Swab	Swab taken from oropharynx (back of throat)	Less sensitive than NPS; can be used as supplementary
Sputum	Expectorated or induced sample	Older children/adults; rarely used in young kids
Endotracheal Aspirate	Collected from intubated patients	Mostly used in critically ill children in Intensive Care Units
Bronchoalveolar Lavage (BALF)	Collection of sample via bronchoscopy	Invasive; for severe lower respiratory infections
Combined Nasal + Throat Swabs	Simultaneous collection from both sites	This improves diagnostic yield; non-invasive alternative

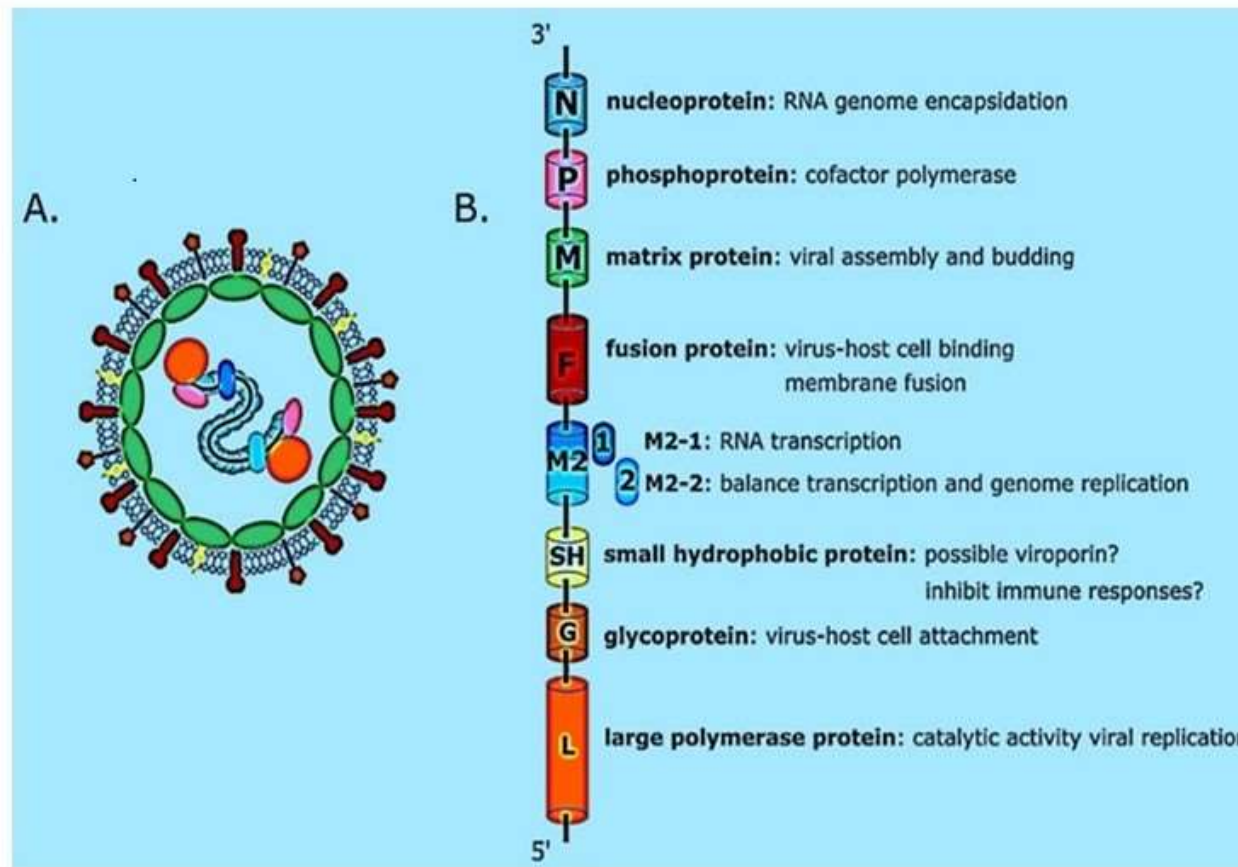


Figure 1. Virion Structure of HMPV (A. HMPV Genome, B. Encoded Proteins). Source- (1). Ballegeer M, Saelens X. Cell-Mediated Responses to Human Metapneumovirus Infection. *Viruses*. 2020;12(5):542. doi: 10.3390/v12050542

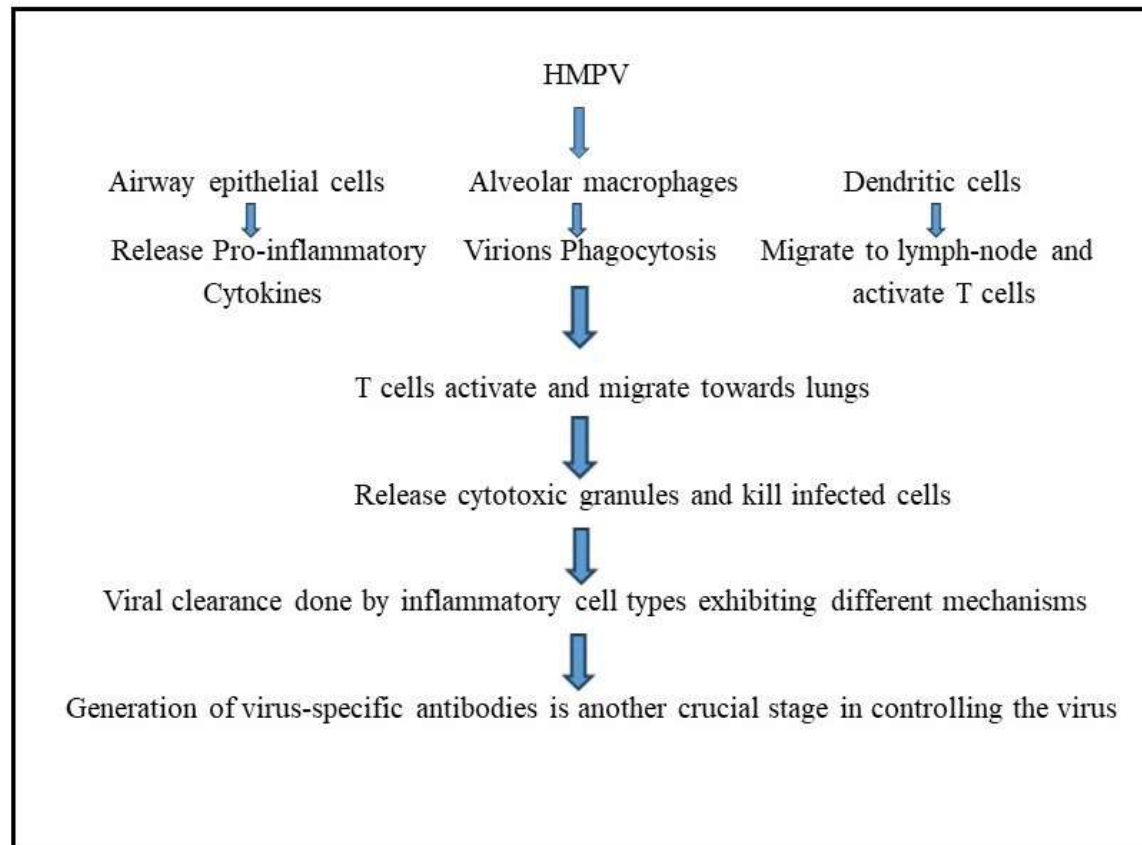


Figure 2. Anti-viral (immune) response after HMPV infection. Source- (1). Ballegeer M, Saelens X. Cell-Mediated Responses to Human Metapneumovirus Infection. *Viruses*. 2020;12(5):542. doi: 10.3390/v12050542

