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Human metapneumovirus: review of an important respiratory pathogen

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SUMMARY

Human metapneumovirus (hMPV), discovered in 2001, most commonly causes upper and lower respiratory tract infections in young children, but is also a concern for elderly subjects and immunocompromised patients. hMPV is the major etiological agent responsible for about 5% to 10% of hospitalizations of children suffering from acute respiratory tract infections. hMPV infection can cause severe bronchiolitis and pneumonia in children, and its symptoms are indistinguishable from those caused by human respiratory syncytial virus. Initial infection with hMPV usually occurs during early childhood, but re-infections are common throughout life. Due to the slow growth of the virus in cell culture, molecular methods (such as reverse transcriptase PCR (RT-PCR)) are the preferred diagnostic modality for detecting hMPV. A few vaccine candidates have been shown to be effective in preventing clinical disease, but none are yet commercially available. Our understanding of hMPV has undergone major changes in recent years and in this article we will review the currently available information on the molecular biology and epidemiology of hMPV. We will also review the current therapeutic interventions and strategies being used to control hMPV infection, with an emphasis on possible approaches that could be used to develop an effective vaccine against hMPV.

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1. Introduction

Acute respiratory tract infection (ARI) is a leading cause of morbidity and mortality worldwide. Globally, ARIs were responsible for about 20% of total deaths in children less than 5 years of age in 2000 alone; moreover, about 70% of these deaths occurred in Sub-Saharan Africa and the southern regions of Asia. ARIs affect children regardless of their economic status, with similar incidence rates in both developed and developing countries, but with a higher mortality rate in developing countries. The risk of pneumonia is higher in children in developing countries (10–20%), compared to 3–4% in developed countries. A wide range of etiological agents are responsible for respiratory problems in children. Although upper respiratory tract infections are generally less serious, they nonetheless carry significant societal costs in terms of lost work, lost school days, and additional health care costs. For this reason, determining the etiological agents of these infections is important. With decades of research and epidemiological studies, we have been able to establish the importance of known viral pathogens like human respiratory syncytial virus (hRSV), parainfluenza virus, influenza virus, coronavirus, and rhinovirus. However, despite these studies, a substantial proportion of respiratory tract infections still cannot be attributed to any known pathogen.

Human metapneumovirus (hMPV) was first discovered in 2001 in the Netherlands, when the virus was isolated from a paediatric patient who had symptoms similar to those of hRSV infection. Since then, hMPV has been detected in 4–16% of patients with ARIs. The incidence of hMPV may vary from year to year in the same area. hMPV causes disease primarily in children, but can infect adults and immunocompromised individuals as well. The clinical features of the illness caused by hMPV infection range from a mild upper respiratory tract infection to life-threatening severe bronchiolitis and pneumonia.
Belonging to the order Mononegavirales, the Paramyxoviridae family is divided into the subfamilies Paramyxovirinae and Pneumovirinae. The Pneumovirinae subfamily is further divided into two genera, Pneumovirus and Metapneumovirus. hMPV is placed under the genus Pneumovirus, while hMPV is placed under the genus Metapneumovirus. Whole genome analysis has shown that hMPV exists as two genotypes, A and B. Based upon the sequence variability of the attachment (G) and fusion (F) surface glycoproteins, these two genotypes are further divided into subgroups A1, A2, B1, and B2. Subgroup A2 is again subdivided into A2a and A2b.\textsuperscript{10,11} One study has described a strain that is under major subgroup A, but does not fall into subgroups A1 or A2, and hence there may be a new subgroup evolving in the A major subgroup.\textsuperscript{12} Study of the molecular biology of hMPV advanced significantly with the establishment of reverse genetics platforms, but we still lack a reliable vaccine to control hMPV infection. Recent findings in hMPV molecular virology, diagnosis, and control strategies are reviewed here.

2. Molecular virology

The hMPV virion is pleomorphic in nature and its size varies from 150 nm to 600 nm.\textsuperscript{5} The genomic orientation of hMPV resembles other members of the Paramyxoviridae family (Figure 1). The genome organization of hMPV is quite similar to that of avian pneumovirus (aMPV), particularly type C. The genomes of hMPV and hRSV closely resemble each other, excluding a few differences in the order of the genes and the absence of the non-structural genes from the hMPV genome (Figure 2). For hRSV, the two non-structural proteins (NS1 and NS2) have been identified as potent multifunctional antagonists of the interferon (IFN) signalling pathways.\textsuperscript{13} The absence of these proteins may be the reason for the difference in level of host innate immune response observed during hRSV and hMPV infections.\textsuperscript{14} The hMPV genome is comprised of negative-sense single-stranded RNA and contains eight genes that code for nine proteins. The order of the genes in the genome (from 3’ to 5’ end) is N–P–M–F–M2–SH–G–L. The proteins are: the nucleoprotein (N protein), the phosphoprotein (P protein), the matrix protein (M protein), the fusion glycoprotein (F protein), the putative transcription factor (M2–1 protein), the RNA synthesis regulatory factor (the M2–2 protein), the small hydrophobic glycoprotein (SH protein), the attachment glycoprotein (G protein), and the viral polymerase (L protein).\textsuperscript{15} The RNA core is surrounded by M protein and covered by a lipid envelope. This envelope contains the three surface glycoproteins (F, SH, and G), in the form of spikes of approximately 13–17 nm. The core nucleic acids are associated with the P, N, L, M2–1, and M2–2 proteins and form a nucleocapsid 17 nm in diameter. With the help of the G and F proteins, hMPV attaches and fuses to heparan sulphate receptors on the cell surface. After the fusion process, the viral nucleocapsid enters into the cytoplasm of the host cell and undergoes replication. The newly synthesized viral genome assembles with the viral P, N, L, and M2 proteins, and moves towards the host cell membrane. The virion now buds out of the cell, with the F, SH, and G proteins exposed on the outer side of the membrane.\textsuperscript{16,17} The P protein acts as a co-factor to stabilize the L protein, allowing the formation of the virus ribonucleoprotein (RNP) complex during virus replication. The M protein plays a crucial role in virus assembly and budding by interacting with the RNP complex. The N protein encapsidates the viral genome and protects it from nuclease activity. In addition to regulating viral transcription and replication, the M2–2 protein plays a major role in virulence by decreasing the host’s innate immunity.\textsuperscript{18,19} Like other members of the Paramyxoviridae family, hMPV interferes with the host’s innate immune system using specific mechanisms. The virus antagonizes cellular responses by regulating pattern recognition receptors, such as toll-like receptor and retinoic acid-inducible gene-like receptors and other signalling molecules.\textsuperscript{20} Infection interferes with dendritic cell activity and reduces antigen-specific T cell activation.\textsuperscript{21} Thus, virus clearance remains incomplete and the chances of re-infection occurring increase.

Members of the two genotypes show much less amino acid and nucleotide similarity (nucleotide 84–86%, amino acid 94–97%) than members of the same subgroup (A1 and A2, or B1 and B2) within the same genotype (nucleotide 94–96%, amino acid 97–99%) based on the F gene sequence.\textsuperscript{8} Comparing all the subgroups (A1, A2, B1, and B2), the N gene is found to be most conserved at both the nucleotide and the amino acid levels (91.2% and 98.4%, respectively), while the G gene is the least conserved (79% and 59.2%, respectively).\textsuperscript{22}

3. Epidemiology

hMPV has been isolated on all continents and has a seasonal distribution. The geographic distribution of the various hMPV genotypes is given in Figure 3. Outbreaks occur mainly in the

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Figure 1. Schematic diagram of the human metapneumovirus particle and the ribonucleoprotein (RNP) complex.
spring and winter months – January to March in the northern hemisphere and June to July in the southern hemisphere. A recent study reported that the peak of the hMPV seasonal cases is observed between March and April following the RSV and influenza infection seasons. Another study reported that the hMPV infection season overlaps with that of the RSV infection season. Being a respiratory infection, hMPV is transmitted by infectious airborne droplets. Seroprevalence studies have shown that a high percentage (90–100%) of children have been infected by the time they are 5–10 years old, but re-infection can occur throughout adulthood. This may be due to insufficient immunity acquired during the initial infection and/or due to infection by different viral genotypes. The incubation period varies from individual to individual, but is commonly between 3 and 5 days. During animal experimentation, peak viral titres are seen between days 4 and 5 in BALB/c mice and cotton rats. hMPV is commonly found in the paediatric population, with high susceptibility rates in children less than 2 years old. hMPV infection in adults normally shows only mild flu-like symptoms. However, in some adult cases (especially elderly adults), severe complications such as chronic obstructive pulmonary disease (COPD) can occur. Dyspnoea is more likely in adults as compared to children. hMPV infection has also been reported in several immunocompromised patients, such as lung transplant recipients, patients with haematological malignancies, and hematopoietic stem cell transplant recipients. Two studies found that both genotypes of hMPV (A and B) co-circulated during a typical respiratory virus season and frequent re-infections with different hMPV genotypes occur.

Risk factors associated with severe hMPV infection include prematurity birth, young age, pre-existing nosocomial infection, and underlying chronic pulmonary, heart, or neural disorders. Studies investigating the relationship between genotype and disease severity in children have not found any significant correlations. Vicente et al. reported that genotype A may be more virulent than genotype B, while Papenburg et al. indicated that it was genotype B that was associated with severe hMPV infection. Compared to hMPV-negative children, hMPV-infected children

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**Figure 2.** Genomic organization of (a) human metapneumovirus (hMPV) and (b) respiratory syncytial virus (RSV), showing the important differences between the two viruses. In comparison to hMPV, RSV expresses two extra proteins, NS1 and NS2, differs in the organization of SH and G proteins, and the reading frames for M2 and L overlap each other. N, nucleoprotein; P, phosphoprotein; M, matrix protein; F, fusion protein; SH, small hydrophobic protein; G, attachment protein; L, large polymerase protein; NS1 and NS2, non-structural proteins 1 and 2.

**Figure 3.** Geographical distribution of hMPV genotypes. Map showing the geographical distribution of hMPV genotypes among humans. Human metapneumovirus isolates are divided into four major subgroups (A1, A2, B1, and B2) and each has its own geographical localization.
were found to be more likely to require supplemental oxygen, to have a longer stay in the intensive care unit (ICU), and more likely to have undergone chest radiography. About 40% of children hospitalized with hMPV infection were found to have underlying high-risk conditions, like asthma and chronic lung disease.21 The average annual rate of hospitalization was about three times more in children less than 6 months old (3/1000) compared to children 6 months to 5 years old (1/1000). Nosocomial infection has been reported in several studies as a mode of transmission.24,25 The annual rate of hospitalization due to hMPV infection is equal to that of influenza and parainfluenza 1, 2, and 3 combined,26 and a recent analysis of an hMPV outbreak in two skilled nursing facilities showed an 11% mortality rate.27 The severity of disease caused by this recently discovered virus and the importance of hMPV pathogenesis and vaccine research is now becoming clear.

Many studies have reported co-infection of hMPV with other respiratory pathogens, including RSV,28,29 bocavirus,30 rhinovirus or enterovirus, parainfluenza virus,31 coronavirus,32 influenza A,33 and influenza B.34 hMPV co-infection has also been reported during an outbreak of severe acute respiratory syndrome (SARS).35 Studies have also found hMPV co-infection with bacterial pathogens like Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae.36 However, the interaction of hMPV with these other etiological agents is unclear, as co-infection does not seem to affect hMPV disease severity.10,48 There are conflicting reports on the association between RSV–hMPV co-infection and disease severity; some studies found that co-infection leads to an increased rate of ICU admission and hospital stay,20,50 but others found no association between co-infection and disease severity.51,52

4. Clinical features

The clinical manifestations of an hMPV infection are indistinguishable from those of an RSV infection, especially in young children. hMPV patients are generally diagnosed with bronchiolitis, bronchitis, and pneumonia. They show common symptoms like fever, cough, hypoxia, upper respiratory tract infection, lower respiratory tract infection, and wheezing.53 However, the most common causes of hospitalization are bronchiolitis and pneumonia.54 The average duration of fever in hMPV-positive cases is about 10 days, with a peak during the course of the illness.55 Young adults with hMPV re-infection show mild cold and flu-like symptoms, with fever in a small proportion of infected cases. However, in the case of elderly patients, re-infection can lead to severe symptoms (such as pneumonitis) and even to death.56 One study reported that 50% of children with hMPV infection were diagnosed with otitis media56 and another study reported that hMPV infection was found in about 8% of children who came to the hospital with wheezing.57 Wheezing is a common clinical symptom observed in multiple studies of children with hMPV-associated lower respiratory tract infections.58 hMPV infections can lead to asthma exacerbations in small children and adults.31 hMPV acts as an enhancer of COPD59 and patients with COPD are more prone to hMPV infection.60,61 A few reports have also suggested that hMPV infection in children may be associated with a spectrum of central nervous system diseases ranging from febrile seizures to severe encephalitis.62 hMPV was detected by real-time RT-PCR in asymptomatic children, but they had significantly lower viral loads that those found in symptomatic children.59 Higher hMPV viral loads were significantly correlated with the course of illness and disease severity, irrespective of genotype.60 High levels of hMPV viral shedding lasted from 1 to 2 weeks after acute illness.55,56 hMPV-associated fatal pneumonia has been indicated in the case of a child receiving chemotherapy for acute lymphoblastic leukemia.34 hMPV was found to be the sole etiological agent responsible for the fatal infection of an allogeneic haematopoietic stem cell transplant patient showing interstitial and intra-alveolar pneumonitis with profound alveolar cell damage.65 hMPV infection during the first week after haematopoietic stem cell transplant may be associated with much higher morbidity and mortality rates.66 hMPV can cause a range of illnesses in lung transplant recipients, from a mild upper respiratory tract infection to a severe lower respiratory tract infection.67,68 In a prospective study involving patients with severe motor and intellectual disabilities, the early stages of hMPV infection were characterized by a low to moderate increase in C-reactive protein (CRP) levels, reduced peripheral blood lymphocytes, and an elevated monocyte ratio.65 Although the peripheral blood lymphocytes and monocyte ratio normalized with the mitigation of symptoms, the CRP levels persisted for some time.62 Along with elevated serum CRP levels, a few hospitalized children infected with hMPV were also reported to have leukenopia and leukocytosis.69

5. Pathogenesis

Persistent infection by hMPV may be attributed to a minimal and late immune response, as well as delayed cytotoxic T-lymphocyte activity with impaired virus clearance during primary infection.60 hMPV interferes with superantigen-induced T cell activation by infecting dendritic cells. Thus, the proliferation of antigen-specific CD4+ T cells is restricted and the production of long-term immunity is impaired.61 Respiratory viruses are known to modulate cytokine responses. Compared to RSV and influenza, hMPV is a less effective inductor of different cytokines like interleukin (IL)-12, tumour necrosis factor alpha (TNF-α), IL-6, IL-1β, IL-8, and IL-10.71 hMPV infection induces pulmonary inflammatory changes in BALB/c mice and cotton rats and leads to an increase in the levels of interleukins (IL-2, IL-8, IL-4), interferon (IFN-α), macrophage inflammatory protein 1α, and monocyte chemotactic proteins in the bronchoalveolar lavage fluid and in the lungs. These changes further lead to perivascular and peribronchial infiltration and inflammation.31,72 The formation of intra-alveolar foamy and haemosiderin-laden macrophages, smudge cells, alveolar damage, and hyaline membrane disease are seen in immunological and histopathological investigations.67 It is known that hMPV infection induces toll-like receptor-dependent cellular signalling. However, the role of toll-like receptor-mediated signalling in the host’s defence against pulmonary hMPV infection and pathogenesis is unknown. In a recent study, MyD88-deficient mice were shown to have significantly reduced pulmonary inflammation and associated disease compared to wild-type C57BL/6 mice after intranasal infection with hMPV.73 The molecular events in the pathogenesis of hMPV are shown in Figure 4. To date, there is no clear evidence to determine if hMPV remains limited to the respiratory tract during infection or if the virus can cause a systemic infection. There is some evidence that the latter is possible – one study showed the presence of hMPV in middle ear fluid66 and another showed the presence of hMPV RNA in the brain tissue of a patient who died of encephalitis,74 but further investigation is needed.

6. Diagnosis

Various cell lines, such as Vero cells,75 HEP–2 cells, Hep G2 cells,76 293 cells,77 and LLC-MK2 cells76 have been used for the growth and isolation of hMPV. In a recent study using 19 different cell lines to grow hMPV, it was shown that the most suitable cell lines for the growth of hMPV were a human Chang conjunctiva cell line (clone 1-5C4) and a feline kidney CRFK cell line.77 In cell culture, hMPV has a slow growth rate, with late cytopathic effects varying from the rounding of cells and their detachment from the
culture matrix to small syncytium formation. For this reason, the detection of hMPV antigen using anti-hMPV antibody in direct fluorescence or ELISA-based assays is widely used along with cell culture methods. The sensitivity and specificity of cell culture detection methods were found to be 68% and 99%, respectively, as compared to real-time RT-PCR detection of hMPV. Currently, the use of cell culture for the diagnosis of hMPV infection is uncommon and molecular methods like RT-PCR and/or real-time RT-PCR are more widely used.

Two studies have developed and evaluated multiplex PCR assays with the aim of providing a tool capable of detecting an increasingly complete panel of respiratory viruses. With the development of multiplex RT-PCR (mRT-PCR), it is now possible to design a more sensitive and rapid 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 advantage of mRT-PCR is the ability to detect co-infections, even with very low viral loads that are undetectable via cell culture or immunostaining.

However, many clinical laboratories do not at present have the capability to perform routine diagnostic RT-PCR for hMPV detection. For rapid and accurate diagnosis of hMPV infections, a combination of immunofluorescence assays and direct fluorescent antibody methods is used as the first-line of diagnosis, followed by RT-PCR on the negative samples. In the future, the availability of shell vial centrifugation culture and hMPV monoclonal antibodies will be of significant benefit for the rapid diagnosis of hMPV in clinical laboratories.

7. Treatment and control strategies

Currently, the treatments available for hMPV infection are primarily supportive. But a few reports have raised the possibility of using ribavirin, immunoglobulin, fusion inhibitors, and small interfering ribonucleic acids for the treatment and control of hMPV infection. The different strategies used to treat hMPV have undergone testing in rodent models and non-human primate models. Although they have shown promising results, none has yet been tested in human volunteers. There may be problems—a heat inactivated viral vaccine against hMPV enhanced lung disease when tested in mice.

T cell epitope vaccines have been shown to reduce immunomodulation by hMPV challenge. Murine animals immunized with an hMPV cytotoxic T lymphocyte epitope vaccine produced less Th1 and Th2 type cytokines compared to non-immunized mice following hMPV challenge. A few studies have also evaluated immunization by chimeric vaccines against hMPV infection. When tested in hamsters and African green monkeys, chimeric vaccines for hMPV were shown to induce the production of neutralizing antibodies and confer immunity against a challenge with the wild-type. A subunit vaccine, using the fusion protein of hMPV, has been shown to induce cross-protective immunity against hMPV challenge in the hamster. Several hMPV F subunit vaccines have given strong levels of protection when tested in rodents, hamsters, and non-human primates. In a recent study, hMPV virus-like particles (VLPs) mimicking the properties of the viral surface of both subgroups A and B were tested as a vaccine candidate. When tested in mice, these VLPs were able to induce a strong humoral immune response against both heterologous and homologous strains. Although an hMPV-VLP vaccine seems to be a promising approach, more research is still warranted to develop a vaccine that will be effective against all of the subgroups of hMPV.

The emergence of plasmid-based reverse genetics systems has given a significant boost to efforts to develop a live vaccine against hMPV infection. Recombinant hMPVs with SH, G, or M2-2 gene
Table 1
Different treatment strategies under development for the prevention of human metapneumovirus (hMPV) infection

| Control strategy      | Product                          | Human/animal model used                                                                 | Results                                                                                                                                                                                                 | Reference |
|-----------------------|----------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Antivirals            | Ribavirin                        | Tissue culture assay                                                                  | Ribavirin along with intravenous immunoglobulin was found to have antiviral activity against hMPV in vitro                                                                                              | 84        |
|                       | Human                            | Oral ribavirin combined with intravenous immunoglobulin led to rapid and complete recovery in an immunocompromised child who was undergoing chemotherapy for Burkitt’s lymphoma |                                                                                                                                                                                                        | 85        |
| Antibodies            | Monoclonal antibody              | Mice                                                                                   | On immunization in BALB/c mice, showed significantly reduced lung viral titres, decreased histopathological changes, and decreased airway obstruction post challenge with hMPV                                                                 | 86        |
|                       |                                   | Hamster                                                                               | Monoclonal antibodies against hMPV F protein showed protection against heterologous hMPV challenge in hamsters                                                                                         | 87        |
|                       |                                   | Mice                                                                                  | Human monoclonal antibody was able to cross-neutralize hMPV and hRSV and may be used as prophylaxis and therapy for severe hRSV and hMPV                                                             | 88        |
| Fusion inhibitors     | Inhibitory peptides              | Mice                                                                                   | Fusion peptides against heptad repeat A and B domains of F protein gave protection against lethal hMPV intranasal challenge in BALB/c mice. Post-challenge there was a significant decrease in lung viral load, pulmonary inflammation, levels of proinflammatory cytokines, and airway obstruction | 89        |
| RNA interference      | SiRNA                            | LLC-MK2 cells                                                                          | SiRNA targeting F and N genes of hMPV was able to inhibit replication of all subgroups of hMPV in vitro                                                                                               | 90        |
| Inactivated vaccine   | Heat inactivated vaccine         | Mice                                                                                   | Dicer substrate SiRNA reduced lung viral titre post-challenge in mice                                                                                                                                 | 91        |
| Epitope vaccine       | T lymphocyte epitope vaccine     | Mice                                                                                   | Immunization gave protective immunity against a homologous strain of hMPV followed by intranasal challenge in BALB/c mice                                                                             | 92        |
| Chimeric vaccine      | hMPV antigen on parainfluenza    | African green monkeys, rhesus monkey                                                    | Intranasal immunization of African green monkeys induced hMPV-specific humoral and cell-mediated immune response and complete protection from wild-type hMPV challenge | 94        |
| Subunit vaccine       | hMPV F subunit vaccine           | Hamster                                                                               | Intranasal immunization with recombinant human PIV-1 expressing hMPV F protein vaccine showed high immunogenicity and protection in comparison to the ones expressing G and SH proteins                          | 95        |
|                       |                                   | Cotton rats                                                                           | Immunization showed reduced nasal viral shedding in cotton rats after hMPV challenge, while the lung pathology was comparable to that of control mice                                                  | 96        |
|                       |                                   | Syrian golden hamsters                                                                | Immunization induced high virus neutralization titres against homologous virus. It also showed significantly reduced viral titres in nasal turbinates | 97        |
|                       |                                   | Cynomolgus macaques                                                                   | Immunization induced hMPV F specific antibody response, neutralizing antibody, and a robust cellular immune response. However, the induced humoral response waned rapidly over time | 98        |
| VLP                   | Virus-like particles (VLPs)       | Mice                                                                                   | Immunization induced cross-protective immunity in mice against both homologous and heterologous strains, along with reduced viral titres in the lungs of immunized animals | 99        |
| Live attenuated vaccine | ΔM2-2                           | Hamster                                                                               | Attenuated and protective in hamsters against Wild-type hMPV challenge                                                                                                                             | 102       |
|                       | ΔG, ΔSH, ΔM2-2                   | African green monkeys                                                                  | ΔG and ΔM2-2 were sufficiently attenuated. After challenge with wild-type hMPV, virus shedding in the lower respiratory tract was undetectable                                                                 | 101       |
|                       | ΔM2-2                            | Mice                                                                                  | Immunization induced complete protection against challenge with a homologous strain and cross-protective immunity against a heterologous strain | 102       |

hRSV, human respiratory syncytial virus; SiRNA, small interfering RNA; IL, interleukin.

deletions have been evaluated for virus replication levels and it has been shown that the deletion of these genes does not affect the immunogenicity or the antigenicity of the virus. In a recent study, a live attenuated vaccine strain of hMPV was developed by changing the glycosylation site of the F protein. This vaccine was found to give complete protection against homologous virus challenge and some protection against heterologous viral challenge, even with a challenge at 56 days post-inoculation. All these findings suggest that before an effective vaccine against hMPV can be developed, more detailed knowledge of the molecular pathogenesis of hMPV is required.

8. Conclusions

Human metapneumovirus is a relatively recently described virus and hMPV appears to be as dangerous a pathogen as hRSV in terms of morbidity and mortality. As an important respiratory pathogen, understanding hMPV pathogenesis and molecular constraints for severe disease is essential for the treatment of infection and for the development of an effective vaccine against hMPV. Recent studies using animal models for hMPV infection and reverse genetics platforms have shed some light on hMPV pathogenesis and have allowed us to evaluate live vaccine candidates. Now we need to initiate the clinical trials to evaluate the different modalities of treatment available for hMPV infection.

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