Metapneumovirus Infections and Respiratory Complications

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Abstract

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Acute respiratory tract infections (ARTIs) are the most common illnesses experienced by people of all ages worldwide. In 2001, a new respiratory pathogen called *human metapneumovirus* (hMPV) was identified in respiratory secretions. hMPV is an RNA virus of the *Paramyxoviridae* family, and it has been isolated on every continent and from individuals of all ages. hMPV causes 7 to 19% of all cases of ARTIs in both hospitalized and outpatient children, and the rate of detection in adults is approximately 3%. Symptoms of hMPV infection range from a mild cold to a severe disease requiring a ventilator and cardiovascular support. The main risk factors for severe disease upon hMPV infection are the presence of a high viral load, coinfection with other agents (especially human respiratory syncytial virus), being between 0 and 5 months old or older than 65 years, and immunodeficiency. Currently, available treatments for hMPV infections are only supportive, and antiviral drugs are employed in cases of severe disease as a last resort. Ribavirin and immunoglobulins have been used in some patients, but the real efficacy of these treatments is unclear. At present, the direction of research on therapy for hMPV infection is toward the development of new approaches, and a variety of vaccination strategies are being explored and tested in animal models. However, further studies are required to define the best treatment and prevention strategies.

Acute respiratory tract infections (ARTIs) are the most common illnesses experienced by people of all ages worldwide. Infants and young children are particularly vulnerable. The pediatric population is disproportionately affected by ARTIs, which represent a leading cause of morbidity and mortality in this demographic. Lower respiratory tract infections (LTRIs) are the second leading cause of death in children younger than 5 years,[1] and each year, 15% of all childhood deaths are caused by pneumonia; most of these deaths are preventable.[1,2] Although the global incidence of ARTIs appears similar on all continents, varying economic statuses heavily skew the mortality rate toward developing countries. As a result, two-thirds of these deaths occur in southern Asia and sub-Saharan Africa.[3] Considering these epidemiological data, the identification of the etiological agents of ARTIs is an essential requirement to establish an appropriate prevention strategy.

The majority of ARTIs are thought to be caused by viruses, such as human respiratory syncytial virus (hRSV), parainfluenza virus, influenza virus, coronavirus, and rhinovirus.[4] Unfortunately, in a significant proportion of cases, the infectious agent remains unknown because current diagnostic methods have proven deficient in detecting the etiology. This observation suggests that unknown pathogens may be circulating and may be responsible for a substantial number of respiratory tract diseases.

In 2001 in the Netherlands, van den Hoogen et al reported the discovery of a novel agent associated with upper and LTRIs, human metapneumovirus (hMPV).[5] The aim of this review is to summarize current knowledge regarding hMPV in terms of its epidemiology, pathogenesis, clinical manifestations, respiratory complications, risk factors for the development of severe disease, methods of diagnosis, and future perspectives in therapy and vaccination.

Classification

hMPV was first isolated from nasopharyngeal aspirates of 28 hospitalized children and infants with ARTIs for which the etiological agent could not be previously identified using diagnostic assays for known respiratory viruses.[5] It is an enveloped, single-stranded, nonsegmented, negative-sense RNA virus of the *Paramyxoviridae* family and *Pneumovirinae* subfamily. This family is made up of the genus *Pneumovirus*, which includes hRSV, and the genus *Metapneumovirus*, which includes two viral species: hMPV and avian pneumovirus.

A whole genome analysis has shown that hMPV exists as two genotypes, A and B, which are further divided into subgroups A1, A2, B1, and B2.[6] Subgroup A2 consists of two clusters, A2a and A2b.

hRSV is the human pathogen most closely related to hMPV. The negative-strand RNA genomes of both viruses contain frames that encode three envelope glycoproteins: the F (fusion), G (attachment), and SH (short hydrophobic) proteins. However, hMPV has certain differences from hRSV concerning the absence of nonstructural genes and the inversion of other genes.[7]

Epidemiology

Since it was first detected, hMPV has been isolated on every continent and from individuals of all ages. Seroprevalence studies have revealed the presence of hMPV antibodies in samples obtained in 1958, suggesting that the virus has been circulating for at least the past 50 years.[5] hMPV infections are observed throughout the year, although a seasonal distribution has been thoroughly described.[8–14] In temperate climates, the epidemiological peak of hMPV is between December and February and often coincides with or follows the time of peak hRSV activity.

hMPV genotypes differ between communities, but similar strains may be identified in various locations in different years, and multiple lineages can exist in the same location during the same period.[6,10,15,16]

Because hMPV presents as a respiratory infection, transmission is most likely attributed to infectious airborne droplets.[17] The incubation period of the virus is between 4 and 6 days, and excretion of the virus lasts between 2 and 14 days.[8,18]

hMPV causes 7 to 19% of all cases of ARTIs in both hospitalized and outpatient children. The annual rate of hospitalization associated with hMPV infections is 1 per 1,000 children, which is lower than that reported for hRSV infections, but the same as the rate of hospitalization associated with the influenza virus.[19] The rates of clinic and emergency department visits due to hMPV infections are 55 per 1,000 and 13 per 1,000 children, respectively.[19] The rate of hMPV detection in adults is usually lower than that in children and is approximately 3% in the general community.[20] These data suggest that the majority of hMPV infections occur early in childhood with high susceptibility rates in children younger than 2 years old.[21] Heikkinen et al have found that the incidence of hMPV infections in children younger than 2 years is approximately twice the incidence observed in

children between 2 and 5 years of age and ten times higher than the incidence among children older than 9 years.[22]

The first hMPV infection appears to take place at the age of 6 months, although during this period, the documented presence of maternally derived specific antibodies seems to be protective against infection.[23] Compared with infections with hRSV, hMPV infections tend to occur in slightly older children.[8,24] However, seroprevalence studies revealed that more than 90% of children younger than 5 years have already been infected by hMPV.[21] Most of the infected children were previously healthy, although the risk of severe disease appears higher in patients with an underlying medical condition.[8,10,25–27]

Reports of hMPV infections in otherwise healthy adults are relatively rare; almost 100% of young adults are seropositive for hMPV with stable neutralizing titers.[5] Despite this fact, recurrences are most frequently observed in older adults (≥65 years) and in patients with a comorbid illness, such as chronic obstructive pulmonary disease (COPD), asthma, cancer, or lung transplantation.[28–30]

Pathogenesis

The conventional model of hMPV attachment involves the interaction of the G protein with a molecule or molecules on the host cell surface.[31] Then, the F glycoprotein promotes fusion of the cell membrane with the virus envelope. Following membrane fusion, viral ribonucleoprotein containing the negative-sense viral RNA genome is released into the cytoplasm. Genomic RNA can serve as a matrix for viral transcription and replication. The newly produced proteins associate with viral genome copies to form nucleocapsids, which will be incorporated into the virions as they bud from the surface of the cell membrane.[32]

Infected cells may also form syncytia via a mechanism similar to that observed for hRSV.[33] Several animal models have been developed to study hMPV infections, including mice, cotton rats, and primates. hMPV replicates to varying extents in the upper and lower respiratory tracts of these animals, but clinical symptoms have been observed only in chimpanzees.[34] hMPV infection increases perivascular and peribronchiolar infiltration and induces inflammatory changes and the formation of intra-alveolar foamy and hemosiderin macrophages. Moreover, alveolar damage and smudge cells have been observed.[35] One study reported histopathologic changes during hMPV infection in young patients.[33] The bronchoalveolar lavage samples and lung biopsy specimens of these patients displayed epithelial cell degeneration or necrosis with detached ciliary tufts and round red cytoplasmic inclusions, frequent neutrophils, and mucus.

hMPV can persist for several weeks in the lungs, but there is no evidence that it can cause a systemic infection. The detection of hMPV RNA in the brain tissue of a patient who died of encephalitis seems to confirm this hypothesis.[36]

When compared with an infection with hRSV, an hMPV infection in humans induces lower levels of inflammatory cytokines such as interleukin (IL)-12, IL-8, IL-10, and tumor necrosis factor-α (TNF-α).[37]

Clinical Features

hMPV preferentially targets ciliated epithelial cells and causes a variety of clinical syndromes localized in the respiratory tract. hMPV infection presents clinical manifestations that make it difficult to differentiate from infections with other winter viruses, especially hRSV.[38,39]

hMPV infection is rarely asymptomatic in pediatric patients. hMPV is the cause of 5 to 15% of upper respiratory tract infections (URTIs) in children,[22,38–40] is the second leading cause of bronchiolitis in infants, and is the etiological agent of a substantial proportion of LRTIs. Compared with the children most commonly infected with hRSV, children who develop an hMPV infection are older and present with a less severe disease.[22,38–40]

URTIs associated with hMPV infection are characterized by rhinitis, pharyngitis, conjunctivitis, and acute otitis media (AOM). The duration of symptoms is usually less than a week.[41]

LRTIs associated with hMPV infection frequently require hospitalization. It is reported that 10% of hospitalizations among children are attributable to hMPV infections.[19,42–44] Clinical features include tachypnea; fever; cough; hypoxia; wheezing; and chest X-ray abnormalities, such as infiltrates, hyperinflation, and peribronchial cuffing.

As a respiratory pathogen, hMPV may be implicated in the pathogenesis of AOM. The inflammatory reaction following viral infection most likely leads to a partial or complete obstruction of the Eustachian tubes, which increases the risk for bacterial invasion of the middle ear.[45,46] Williams et al have found that one-third of the pediatric hMPV-associated LRTIs have a diagnosis of AOM.[21] In another study, hMPV was detected in 6% of children who presented with AOM as the primary diagnosis; no bacterial pathogen was isolated from 25% of the patients in this study, suggesting that hMPV may be implicated as a unique infectious agent in cases of AOM.[47]

hMPV infection has also been associated with febrile seizures, rash, diarrhea, vomiting, and altered liver function.[27] A few reports have suggested a connection with central nervous system diseases, such as encephalitis[48] and status epilepticus.[49]

The overall rates of hMPV infection in adults are lower than those described in children. Asymptomatic infections in adults are common, accounting for at least 40% of cases, and young adults usually experience a mild cold or influenza-like symptoms.[50] However, elderly and immunocompromised patients may present with severe pneumonia that may be fatal in some circumstances.[28,51] In addition, 6 to 12% of COPD exacerbations have been associated with hMPV, and the presence of an underlying lung disease is common in patients hospitalized with hMPV infection.[29,52,53] In long-term facilities, a high mortality rate due to hMPV infection is reported. Boivin et al observed a 50% fatality rate in patients of a long-term care facility who had a PCR-confirmed hMPV infection and a 9.4% fatality rate among elderly institutionalized persons with a possible hMPV infection.[54]

Respiratory Complications

hMPV infection may cause severe morbidity in both the pediatric and adult populations. Children admitted to a hospital may develop a severe disease requiring an advanced ventilator and cardiovascular support. Among hospitalized children, bronchiolitis is the most frequent diagnosis upon admission, followed by pneumonia.[55] Respiratory distress is the most common reason for admission to the pediatric intensive care unit (PICU).[55] A few cases of apnea, shock, or status epilepticus have been reported.

Paget et al have compared children admitted to the PICU with hMPV infections to those admitted with hRSV infections.[56] They have observed that children with hMPV infections were significantly older and presented less commonly with bronchiolitis and more commonly with pneumonia than those with hRSV infections. During the study period, hMPV was the second leading cause of bronchiolitis after hRSV. Both infections displayed a similar severity of disease.

In another study, 18% of pediatric patients hospitalized with hMPV infections required PICU care, and 69% required respiratory support. Mechanical ventilation was necessary in 5% of children, and noninvasive positive pressure ventilation, as maximal support, was required in 9% of patients.[57] Oxygen supplementation was used in 55% of patients. In comparison to previously healthy children, those who suffered from a chronic medical condition needed respiratory noninvasive support for a longer period and were more frequently admitted to the PICU.[57]

Estrada et al reported the occurrence of apparent life-threatening events (ALTEs) in three hMPV-infected patients before hospital admission.[58] An ALTE is defined as cyanosis associated with prolonged apnea spells. These episodes involved three infants younger than 3 months.

Moreover, some fatal events have been reported. Schlapbach et al described the case of a 20-month-old healthy child who died after experiencing acute respiratory distress syndrome (ARDS) due to hMPV infection.[59] The patient developed multiorgan failure and required venoarterial extracorporeal membrane oxygenation (ECMO). The risk of ARDS is higher in children affected by underlying conditions, especially prematurity and chronic lung diseases.[19,60]

Episodes of severe disease have been observed in adult patients as well. It seems that hMPV can have a significant effect in some specific categories of fragile subjects. Elderly and immunocompromised patients, including pregnant women, are especially at risk. Although remarkably rare, a few cases of severe disease in healthy adult individuals have been observed. Contentin et al described a case of ARDS secondary to hMPV infection in a healthy 58-year-old woman. The patient required mechanical ventilation for 7 days and was discharged from the hospital after 23 days.[61]

In general, because hMPV infection is quite common it should be considered as a possibility for every patient with respiratory failure admitted to the ICU.[62]

Risk Factors Related to Severe Disease

The severity of disease caused by hMPV infection may be predicted by the coexistence of certain risk factors, some of

which are associated with characteristics of the pathogen and others of which depend on the clinical and demographic features of the patient.

The correlation between viral load (VL) and clinical characteristics of hMPV infection has been investigated in several studies. Roussy et al observed that a high VL is associated with severe disease: in effect, a VL higher than 1,000 copies/10^4 cp/mL is independently associated with hospitalization and is correlated with typical signs of LRTIs, such as rales on auscultation and use of bronchodilators and inhaled glucocorticoids.[63] These data confirmed findings from previous studies, which associated with a high VL with severe disease.[64,65]

In addition to these results, Peng et al observed that the VL is correlated with the duration of illness.[65] The number of viral copies is significantly different in patients who have symptoms lasting between 6 and 11 days than in those with symptoms of infection lasting less than 5 days.

To evaluate the connection between hMPV genotype and the severity of respiratory infection, clinical features of hospitalized children infected with hMPV have been correlated with the detection of different hMPV genogroups. A study by Vicente et al suggested that hMPV genotype A may be more pathogenic than genotype B, because a diagnosis of pneumonia is more commonly associated with genotype A and the illness severity index is higher in patients with an hMPV genotype A infection.[66] In contrast, Pitoiset et al found that the majority of pathological chest X-rays are observed in patients infected by serotype B rather than A.[42] Moreover, Matsuzaki et al found that genotypes B1 and B2 are associated with wheezing more frequently than genotype A2 is.[67] Beyond the apparently conflicting results of these clinical studies, the available data focusing on the correlation between disease severity and hMPV genotype indicate, for the most part, a lack of significant differences in terms of clinical features in patients infected with different hMPV lineages.[13,42,66,68,69]

Because of the overlapping seasonal distributions of hMPV and hRSV, there is potential for coinfection. Many studies evaluating hMPV infection have tested for the simultaneous presence of other viruses. hRSV was detected in 5 to 17% of patients infected with hMPV.[25,70–72] Most results have not described an exacerbation of the disease when multiple pathogens were detected. However, one study reported a 10-fold increase in risk of admission to the PICU in children coinfected with hRSV and hMPV, and the dual infection has been described as being capable of augmenting severe bronchiolitis.[73] On the other hand, bacterial coinfection is not commonly observed during hMPV infections. hMPV appears primarily as a respiratory pathogen, and the majority of respiratory diseases are not associated with bacterial agents.

In contrast to these data, Madhi et al demonstrated that the 9-valent pneumococcal conjugate vaccine may prevent the development of hMPV-associated pneumonia. They reported a 58% reduction in hospitalization for hMPV-associated LRTIs in vaccinated children. These results suggest involvement of hMPV as a viral copathogen in bacterial pneumonia. Further studies are necessary to clarify the nature of this association.[74]

The immune status of infected patients is important in determining the severity of illness. hMPV is capable of causing severe infections in immunocompromised hosts, a phenomenon that has been described for the majority of respiratory viruses and is probably related to a reduced capability to control viral replication in such individuals. Several studies have suggested that hMPV is a common cause of ARTIs in the adult and pediatric immunocompromised populations, including patients infected with human immunodeficiency virus (HIV), subjects with a malignancy and hematopoietic stem cell (HSC), or solid-organ transplant recipients.[49,75–79] Some fatalities have been reported in these populations.

In adult patients with hematological malignancies, 9% of ARTIs have been attributed to hMPV,[49] and hMPV has been associated with 6% of ARTIs in lung transplant recipients.[80] Among HSC transplant recipients, hMPV infection mortality rates range from 10 to 80% in different studies. In the majority of patients, hMPV is the only pathogen found, and most of the patients required hospitalization. The progression from upper to lower respiratory disease has been very frequently observed.[81–84]

Among immunocompromised children, Chu et al reported an hMPV-attributable mortality rate of 5%, and 23% of patients were classified as having a severe disease.[85] Those who developed severe pneumonia were more likely to be neutropenic.

Moreover, hMPV has been detected in children with HIV infection. In this group, it is difficult to determine if the disease is more severe.[79]

The association between children's ages and disease severity has also been investigated. In the pediatric population, being between 0 and 5 months in age is linked to a higher risk of hospitalization, whereas prematurity and low birth weight are associated with a more frequent occurrence of severe disease in hospitalized patients.[86] Edwards et al conducted surveillance for ARTIs among inpatient and outpatient children younger than 5 years in three U.S. states.[19] They found a correlation between hospitalization for hMPV infection and the presence of other children between 5 and 17 years old in the home. Moreover, members in households of hMPV-positive children fell ill significantly more and required more visits and drug prescriptions than did those in households of hRSV-positive children, with a frequency similar to that observed among members of households where influenza virus infections were present.[71]

The presence of an underlying medical condition is a risk factor associated with increased disease severity. Hahn et al found that the chronic lung diseases of prematurity (i.e., bronchopulmonary dysplasia, respiratory distress syndrome), an anatomic or congenital lung disease (i.e., trachea-laryngomalacia), a congenital heart disease, a neuromuscular disorder (i.e., hypoxic-ischemic encephalopathy, cerebral palsy, traumatic brain injury, spinal muscular atrophy), and trisomy 21 increase the risk for a more severe disease.[57] Moreover, children with comorbidities who present with an hMPV infection are significantly more likely to be admitted to the PICU.[57]

In the case of asthma, a biunique association has been observed. It is known that the previous presence of asthma is a risk factor, predisposing an individual to severe respiratory

disease during hMPV infection, but, in the acute phase, hMPV itself can cause wheezing in young children.[87–89] Bosis et al found that almost 26% of children with hMPV infections presented with wheezing,[71] and Jartti et al reported that hMPV has been detected in 8% of children who were admitted to the hospital with exacerbation of wheezing.[90] hMPV is also associated with an exacerbation of asthma in adult patients who required hospitalization.[88] According to some authors, hMPV plays a role not only in acute asthma exacerbation but also in the development of recurrent wheezing and asthma in the medium term.[91–93] One retrospective study showed an association between hMPV infection during infancy and the subsequent diagnosis of asthma or another bronchial obstructive disease.[91] The nature of this association remains to be determined, because it is difficult to establish a diagnosis of asthma in the first year of life when wheezing is commonly observed during viral ARTIs. In light of these reflections, further studies are required.

Among adult patients, hMPV causes a more severe disease in fragile elderly individuals, and the infection can result in death in this population. Apart from advanced age, the major risk factor associated with hMPV infection is the presence of an underlying cardiopulmonary disease, especially COPD.[8,28–30,50,53,54,88,94–96] Infections in patients with COPD frequently evolve to become LTRIs, leading to development of fatal respiratory failure. The fundamental reasons for the higher morbidity in older adults have not been determined. The most likely explanation is that aging causes impairment of innate and adaptive immunity.[97] Moreover, inflammation as an exaggerated immune response to viral infection plays an important role in severe disease.[98] Finally, the existence of multiple hMPV lineages may lead to insufficient cross protection against different genotypes. The available data focusing on this aspect have reported conflicting results.[7,99] Additional studies are necessary to determine the nature of age-related defects in the immune response during hMPV infections and to establish if, after infection with a virus belonging to a single subgroup, cross protection occurs. This last question has a significant implication for vaccine development.

Diagnosis

hMPV replicates poorly in conventional cell cultures and is relatively difficult to isolate.[5,100–102] For these reasons, reverse transcriptase polymerase chain reaction (RT-PCR) and real-time RT-PCR have become the methods of choice to detect hMPV.[103]

RT-PCR is a powerful method that allows amplification and quantification of this pathogen in clinical samples. The development of multiplex RT-PCR has the advantage of supplying a complete panel of respiratory viruses, which allows the detection of coinfections with two or more pathogens, even those with very low VLs.[104–106]

Direct immunofluorescence or enzyme-linked immunosorbent assays (ELISAs) are rapid methods to detect respiratory viruses, but they are not as sensitive as the molecular techniques. Because infections with hMPV are universal, serological tests used for the diagnosis of a recent infection are only useful if fourfold increases in antibody titers or a recent seroconversion are demonstrated.[107,108] The option of serological tests may be useful in epidemiological evaluations to understand the worldwide seroprevalence of hMPV-specific antibodies in both pediatric and adult populations.[109]

Therapy against hMPV Infection

Currently, the available treatments for hMPV infection are mostly supportive. For infants and children who are hospitalized, the primary therapies are oxygen supplementation and intravenous hydration. Bronchodilators and corticosteroids are used empirically, but no data support their efficacy.[18,57,110,111] 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. Ribavirin is an analogue of guanosine triphosphate (GTP) that may limit viral transcription and lead to a reduction in the intracellular concentration of GTP.[112] Moreover, it appears to have an immunomodulatory effect in the containment of a viral infection.[112] Immunoglobulins are available in two types of preparations, specific and nonspecific: nonspecific polyclonal immunoglobulins have been administered in severely affected patients, usually along with ribavirin, with conflicting results.[113] Most of the treated cases were adults and children who were heavily immunocompromised because of a malignancy or an HSC or solid-organ transplant: all the patients received oral or, less frequently, intravenous (IV) ribavirin, usually with IV immunoglobulins.[77,82–84,86,113–116] The results obtained by Chu et al in a study of immunocompromised children affected by hMPV were negative: patients who received antiviral treatment demonstrated a 22% mortality rate.[85] Dokos et al reported the occurrence of fatal hMPV-associated pneumonia in a 10-year-old girl with chronic graft-versus-host disease despite the administration of IV ribavirin and IV immunoglobulins.[82] Another retrospective study, involving 145 hematologic adult patients infected with paramyxoviruses, suggested that oral ribavirin therapy may not improve clinical outcomes.[114] Positive results have been reported by other authors. Kitanovski et al presented the case of a 2-year-old girl undergoing intensive chemotherapy for Burkitt lymphoma who developed severe hMPV-associated pneumonia.[115] Rapid and complete recovery has been observed after treatment with oral ribavirin and IV immunoglobulins. Raza et al described a case of hMPV-associated pneumonia in a lung transplant recipient presenting with respiratory failure and sepsis syndrome.[116] The patient was treated with IV ribavirin with a successful outcome. Favorable results have been observed among adult HSC transplant recipients as well.[83,113]

Recently, a humanized monoclonal antibody (mAb 338) against the hMPV fusion protein has been developed. Studies have shown its preventive and therapeutic efficacy in mice.[117,118]

New frontiers of therapy are directed toward the development of drugs that act by inhibiting the fusion of the virus with the cell membrane. One fusion inhibitor is currently used in the case of HIV- infected patients and has shown promising results against hRSV infection.[119,120] Fusion inhibitors against hMPV have only been employed in animal

models. Deffrasnes at al tested several inhibitor peptides that have sequence homology with some domains of the hMPV F protein. One of these peptides has shown efficacy after intranasal administration in mice; these mice appeared to be protected from clinical symptoms and mortality due to hMPV infection.[121]

Another interesting approach is based on the natural phenomenon of RNA interference. There are some small, noncoding, endogenous micro-RNA sequences that inhibit the expression of specific genes by avoiding mRNA translation or by inducing mRNA cleavage. The use of exogenous small interfering RNAs (siRNAs) that act similarly toward targeted viral genes may produce an inhibitory effect. siRNAs against the hMPV N and P proteins have been tested in vitro with success.[122]

Vaccines

Several studies have focused their attention on developing vaccines against hMPV. A perfect vaccine should be safe and well tolerated and should produce a strong and long-lasting immune response. A variety of vaccination strategies have been explored and tested: inactivated viruses, live attenuated viruses, and recombinant proteins.

Inactivated Vaccines

A formalin-inactivated hMPV vaccine is not a suitable vaccine because it induces enhanced pulmonary disease and a Th2 cell response in animal models. Other inactivation methods have been investigated for the development of a safe vaccine. An opportunity is offered by a nanoemulsion-inactivated hMPV vaccine that appears immunogenic and protective in mice.[123,124]

Viral Protein-Based Vaccines

Subunit vaccines contain purified viral proteins, which may be either full- or partial length. These proteins are usually assembled in the form of virus-like particles (VLPs) or with the addition of adjuvants that may enhance the immune response.[125] Several animal studies using hMPV protein-based vaccines have been conducted. Among the viral proteins, the F and G proteins have been used in the majority of cases.

The results obtained using G protein–based vaccines are still controversial. Their role in the immunization process is unclear. According to some authors, the glycoprotein G itself has low immunogenicity.[126] One possibility is that the combination of this glycoprotein with some carriers reduces its capability to promote an intense immune response.

On the other hand, immunization techniques that employ the hMPV F protein–based vaccines are promising. There are potential candidates for an hMPV vaccine that elicit specific and strong humoral immunity in nonhuman primates, although a rapid decay in antibody titers has been observed.[127,128] Further studies are required to identify the most appropriate combination of carriers and to obtain effective and long-lasting protection.

Live, Attenuated Vaccines

A live, attenuated vaccine may be recombinant or non-recombinant. These vaccines may be produced during passages of cells under experimental stress such as cold or chemical mutagenesis or by using viruses genetically modified by reverse genetics. The major risk is in the potential recovery of viral pathogenicity and subsequent disease development in vivo. A perfect balance between attenuation and immunogenicity is the first goal. The majority of vaccine candidates that used live, attenuated viruses have shown good immunogenicity and have guaranteed protection against subsequent infections in animal models.[129] Recently, a wild-type recombinant hMPV strain has been approved as a parent virus for the development of live, attenuated hMPV vaccine candidates because it has been shown to be infectious in a trial that involved 21 healthy adults.[130]

Conclusion

Since the discovery of hMPV, a large amount of data has been obtained in numerous studies. Considerable progress has been made toward understanding the molecular basis of its replication, evaluating its clinical impact, characterizing the disease pathogenesis, and improving diagnostic methods. Despite this progress, other goals remain to be achieved. More work is required to understand the role of hMPV antigenic variability in human populations, to clarify the mechanisms of innate and adaptive immunity after infection, and to confirm the existence of a real and long-lasting cross protection against different hMPV genotypes after first contact with the virus. The results obtained from additional studies focusing on these aspects may offer a true perspective on the future of the development of effective therapeutic and preventive measures against hMPV.

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