

# Human metapneumovirus: a new pathogen in children and adults

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## ABSTRACT

In 2001, human metapneumovirus (hMPV) was discovered in young children with respiratory tract infection of unknown origin. In the two years since its discovery the clinical characteristics of this new virus have been clarified. In children, especially those younger than one year of age, hMPV is responsible for 5 to 10% of respiratory tract infections requiring hospitalisation; its clinical course is somewhat milder, but otherwise indistinguishable from respiratory syncytial virus (RSV) infection. Human MPV can also be found in adults, in influenza-like illnesses, but also as a cause of pneumonia. Especially in the latter cases immunosuppressive conditions may be present.

paramyxovirus-like particles. Sequence analysis and genomic organisation characterised the virus as a member of the genus *Metapneumovirus* of the family *Paramyxoviridae*, of which the only member until then was the avian pneumovirus (APV), the causative agent of an upper respiratory tract infection in turkeys. The most closely related human virus was RSV, also a paramyxovirus but belonging to the *Pneumovirus* genus. The isolated hMPV strains showed sequence variation, and two main clusters of isolates could be distinguished.<sup>1,2</sup> In the two years since its discovery, the epidemiology and clinical features of this virus have been the subject of further investigations.

## INTRODUCTION

Respiratory tract infections (RTI) are among the most common infections in humans. Many infectious agents can cause RTI. However, in a substantial proportion of RTI the aetiology is not established. For instance, in adult community-acquired pneumonia an aetiological agent is commonly identified in only 50% of cases. One explanation for this large proportion of unknown aetiologies is insufficient sensitivity of current diagnostic tests, but another explanation might be the presence of unknown pathogens. In 2001, human metapneumovirus (hMPV) was discovered in young children with respiratory tract infection of unknown origin.<sup>1</sup> Cytopathic effects of this virus in tertiary monkey kidney cells were comparable with those caused by human respiratory syncytial virus (hRSV), and electronmicroscopy of supernatant revealed the presence of

## EPIDEMIOLOGY

Human MPV is a common respiratory virus; 25% of Dutch children aged between six months and one year have antibodies to the virus, and at the age of five years almost all children have antibodies.<sup>1</sup> Investigation of samples stored at the National Influenza Centre showed that as early as in 1958, 100% of investigated persons had antibodies to hMPV, so the virus has been circulating for at least 50 years in the Netherlands. Comparable serological results were obtained in Japan.<sup>3</sup> Soon after its discovery the virus was also isolated in other countries in Europe, North America, Australia, and Asia.<sup>4-13</sup> In all these countries, the same two hMPV clusters as originally described were found. There is a clear seasonal distribution of disease, with almost all cases occurring between December and April.<sup>4,7-9,10,12,14,15</sup> In the Far East, the peak of hMPV activity is in spring and early summer.<sup>8,11</sup>

## DETECTION OF THE VIRUS

The virus can be isolated by cell culture. Originally, the virus was isolated from cultures of tertiary monkey kidney (tMK) cells, displaying cytopathological effects (CPE) within 10 to 14 days post-inoculation similar to those seen with RSV.<sup>1</sup> Boivin *et al.* only showed CPE in LLC-MK2 cells after a mean incubation time of 17.3 days, without large syncytia formation.<sup>14</sup> The virus could not, or only poorly, be propagated in other cell lines commonly used for isolation of respiratory viruses (such as Vero cells, MDCK or A-549). In human laryngeal carcinoma (HEp-2) cells hMPV could be detected from respiratory samples; however, since no CPE was found, RT-PCR examination of cell culture material was necessary.<sup>16</sup>

In clinical samples viral RNA can be detected by reverse-transcription polymerase chain reaction (RT-PCR). Several targets for amplification have been chosen in the design of the RT-PCR, and it has been suggested that amplifying the N and/or the L gene is particularly suitable for hMPV diagnosis.<sup>17,18</sup> Since several laboratories have started to implement PCR as routine diagnostic assay for respiratory virus infections, it can be expected that detection of hMPV RNA will be more widely used as part of a respiratory virus diagnosis package.

Antibodies against hMVP can be measured and serology studies have been performed, but since everyone over the age of five years has anti-hMPV antibodies, antibody detection is not currently implemented as a standard assay in most routine laboratories.

## CLINICAL FEATURES IN CHILDREN

In most series, hMPV could be demonstrated in 5 to 10% (range: 1-25%) of children admitted with acute respiratory tract infections.<sup>4,8-13,15</sup> The incidence can vary substantially in consecutive years,<sup>7,10</sup> which partially explains the wide range of incidences found. In up to 30% of cases more than one respiratory virus was isolated.<sup>4,8,10,12,15,18</sup> In all series RSV was isolated more frequently than hMPV. The clinical picture is comparable with what is seen with RSV infections, with bronchiolitis being the most frequent manifestation, followed by (broncho)pneumonia, pneumonitis, wheezing, and otitis media. Most infections are seen in children younger than one year of age who are otherwise healthy. Compared with RSV infections, the affected children are somewhat older, and the severity of disease is usually somewhat less.<sup>11,12,15,18</sup> The detection of antibodies against hMPV in 100% of older children suggests that most infections in older children are not associated with serious disease.<sup>10</sup> Antibodies against strains from one cluster do not automatically confer

immunity against strains from the other cluster. This explains that in the same person more than one episode of hMPV infection can occur.<sup>6,19</sup>

## CLINICAL FEATURES IN ADULTS

In a cohort of mainly adult persons with an influenza-like illness of less than five days' duration hMPV was detected in 1.3% of cases.<sup>5</sup> In most of these patients there was evidence of lower respiratory tract involvement. In the Dutch ARIEL study (Acute Respiratoire Infecties in de Eerste Lijn) 448 patients were investigated who had gone to their general physician with an influenza-like illness or another acute respiratory infection. In 3% of cases (and in 0% of controls) hMPV was found.<sup>20</sup>

In several large cohorts respiratory material was collected during (unspecified) respiratory conditions.<sup>7,14,21</sup> Human MPV could be recovered from 2.3 to 14.8% of respiratory samples, and in 4.5 to 24% of patients with hMPV more than one respiratory pathogen was detected.<sup>7,14,21</sup> HumanMPV was detected in all age groups,<sup>21</sup> and during subsequent years substantial differences in hMPV incidence were noted.<sup>7</sup> The clinical characteristics of hMPV infections are not distinctive. Differentiating it from other respiratory viruses on clinical grounds is not possible,<sup>5,21</sup> although as compared with RSV infections hoarseness has been observed more frequently.<sup>7</sup> In around 18 to 50% of cases a pneumonitis was diagnosed, while in the other patients rhinitis, bronchitis or a flu-like syndrome were found.<sup>7,14,21</sup> Of the described patients with pneumonitis a substantial percentage had an immunosuppressive condition.<sup>14</sup> In a recently described Dutch cohort most adult patients also had another disease, or had recently received a bone marrow or kidney transplant.<sup>18</sup> As only hospitalised patients were investigated in this cohort, a population bias is likely to be present. In the described cohort of patients with influenza-like illnesses this association with underlying immunosuppression was not found.<sup>5</sup> Noteworthy is the fact that during the recent SARS epidemic in Hong Kong in patients with proven disease, hMPV could also be demonstrated in 52% of cases.<sup>16</sup> In the Canadian SARS cohort the same observation was done. It is not clear whether hMPV influenced the severity of disease, or whether the two viruses were merely co-circulating in the population during the epidemic.<sup>16</sup>

## HUMAN MPV IN IMMUNOCOMPROMISED PERSONS

Although the fatality rate of hMPV appears to be very low, hMPV can be responsible for fatal respiratory insufficiency in severely immunocompromised persons. One young

child with acute leukaemia was described who suffered from hMPV infection in two subsequent winters. The two strains that were recovered during these two episodes were genetically distinct, and the last episode was fatal.<sup>19</sup> Likewise, a fatal case of hMPV infection was described in an adult haematopoietic stem cell transplant recipient.<sup>22</sup>

## CONCLUSION

In the two years since its discovery, the clinical characteristics of this new virus have been clarified. In children, especially those younger than one year of age, hMPV is responsible for a substantial number of respiratory tract infections requiring hospitalisation; its clinical course is somewhat milder, but otherwise indistinguishable from RSV infection. Human MPV can also be found in adults, in influenza-like illnesses, but also as a cause of pneumonia. Especially in the latter cases immunosuppressive conditions may be present, and, like RSV, hMPV can be responsible for respiratory insufficiency under these conditions. The incidence of hMPV as a cause of respiratory failure in these patients needs further investigation. Identifying hMPV in such patients is relevant, because *in vitro* reports suggest that ribavirin and intravenous immunoglobulin have antiviral activity against hMPV.<sup>23</sup> Whether these agents have therapeutic value *in vivo* needs to be demonstrated in further studies.

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