INTRODUCTION

Acute bronchiolitis is defined as an *"acute inflammation of the bronchiolar airways"* secondary to viral infection, which causes airway obstruction and respiratory distress via bronchiolar wall oedema, spasm and mucous production within the bronchiolar lumens. [1] Bronchiolitis is predominately a viral illness. Several viruses have been implicated in it's etiopathogenesis. Respiratory syncytial virus (RSV), parainfluenza viruses (PIV) (mainly type 3), influenza type A, adenovirus, and rhinovirus are some of the common viruses found in hospital studies. RSV accounts for the majority of bronchiolitis (about 50-60%). [2, 3]

Mycoplasma pneumoniae is also responsible for some of the "atypical bronchiolitis" in older children. [4] Rhinoviruses and *Mycoplasma pneumoniae* are responsible for an increasing number of cases of bronchiolitis associated with wheezing, whereas RSV is known to provoke wheezing at all ages. [5, 6]

Epidemiology

Respiratory infection is observed in 25% of children younger than 12 months and 13% of children aged 1-2 years. Of these 25%, one half have wheezing-associated respiratory disease. RSV can be cultured from one third of these outpatients and from 80% of hospitalized children younger than 6 months. [7]

Nearly 100% of children experience an RSV infection within 2 RSV seasons, and 1% are hospitalized. Among healthy full-term infants, 80% of hospitalizations occur in the first year, and 50% of hospitalizations occur in children aged 1-3 months. Fewer than 5% of hospitalizations occur in the first 30 days of life, presumably because of transplacental transfer of maternal antibody. [8]

Descriptive analysis

Hospital Discharge Survey data from 1980 through 1996 showed that admissions associated with bronchiolitis totaled 1.65 million. [9] During this period, the hospitalization rate for children younger than 1 year increased from 12.9 to 31.2 per 1000 population, and the percentage of hospitalizations for lower respiratory tract illnesses among children younger than 1 year associated with bronchiolitis increased from 22.2% to 47.4%. [9]

In this analysis, the RSV-coded hospitalization rate in infants younger than 1 year old was 26.0 per 1000, with no significant difference between study years. The hospitalization rate was highest among infants younger than 3 months (48.9/1000), followed by infants aged 3 to 5 months old (28.4 per 1000), and was substantially lower among those older than 1 year (1.8/1000). [10]

The increase in hospitalizations is attributable not to increased aversion risk on the part of pediatricians but, rather, to physician's desire to treat the condition with bronchodilators. [11] The cost of hospitalization for bronchiolitis in children younger than 1 year is estimated to be more than$700 million per year. [12]

In the United States, the highest RSV activity usually occurs in winter, except in the subtropical areas of the southeastern United States (eg, Florida) where RSV is endemic

throughout the year, with peaks from October to February and relative subsidence only from March to July.[13, 14]

Secondary infections occur in 46% of family members, 98% of other children in daycare, 42% of hospital staff, and 45% of previously uninfected hospitalized infants.[15] Infection is spread through self-inoculation of fomites via direct contact and environmental surfaces to nasopharyngeal or ocular mucous membranes. RSV can survive for several hours on hands and surfaces; therefore, handwashing and using disposable gloves and gowns may reduce nosocomial spread. [16]

Statistics

Bronchiolitis is a significant cause of respiratory disease worldwide. According to the World Health Organization bulletin, an estimated 150 million new cases occur annually; 11-20 million (7-13%) of these cases are severe enough to require hospital admission. Worldwide, 95% of all cases occur in developing countries. [17] The frequency of bronchiolitis in developed countries appears to be similar to that in the United States. Epidemiologic data for underdeveloped countries are incomplete. Epidemiologic data from underdeveloped countries show that RSV is a predominant viral cause of acute lower respiratory tract infections and accounts for about 65% of hospitalizations due to viruses. [17]

However, less is known about RSV-associated mortality in developing countries. Morbidity and mortality may be higher in less-developed countries because of poor nutrition and lack of resources for supportive medical care.

In the northern hemisphere, RSV epidemics generally occur annually in winter and late spring, whereas parainfluenza outbreaks usually occur in the fall. Conversely, in the southern hemisphere, wintertime epidemics occur from May to September.

Descriptive epidemiologic data from a population-based cohort (Georgia Air Basin, Canada) reported by Koehoorn et al indicated that from 1999 through 2002, bronchiolitis was associated with 12,474 inpatient and outpatient physician contacts during the first year of life. This equates to 134.2 cases per 1000 person-years. In total, 1588 bronchiolitis cases resulted in hospitalization (17.1 cases per 1000 person-years). [18]

Age-related demographics

Although infection with the agents that cause bronchiolitis may occur at any age, the clinical entity of bronchiolitis includes only infants and young children. About 75% of cases of bronchiolitis occur in children younger than 1 year and 95% in children younger than 2 years. Incidence peaks in those aged 2-8 months.

Age is a significant factor in the severity of infection: The younger the patient is, the more severe the infection tends to be as measured by the lowest oxygen saturation. Infants younger than 6 months are most severely affected, owing to their smaller, more easily obstructed airways and their decreased ability to clear secretions.

Intrauterine cigarette-smoke exposure may impair in utero airway development or alter the elastic properties of the lung tissue. Second-hand cigarette smoke (eg, by a parent or family member) in the postnatal period compounds the severity of RSV bronchiolitis in infants.

Although RSV bronchiolitis is clearly a significant disease of the young child, immunity has been shown to wane over time [19] ; susceptible adults may be asymptomatic or mildly symptomatic and act as carriers. With the increasing use of treatment modalities that compromise cellular immunity, RSV infection may be life-threatening to older children and adults undergoing organ and bone marrow transplantation, as well as to the elderly. [20, 21]

Sex-related Bronchiolitis

Occurs as much as 1.25 times more frequently in males than in females; the exact reason for this difference is unknown. [22] Death is 1.5 times more likely in males. [23]

Race-related demographics

Race and low socioeconomic status may adversely affect outcome in patients with acute bronchiolitis. In one study, RSV bronchiolitis seemed to be more severe in white children than in black children. The reason for this finding is unknown. [31]

A study by La Via et al demonstrated that although more minority children than white children were hospitalized with RSV infection, Nothing indicated that the infections in minority children were more or less severe than those in white children. [24]

Lower socioeconomic status in USA may increase the likelihood of hospitalization. Hospitalization rates are higher in Native American, Alaskan, and Hispanic populations, but it is not clear if this is due to more severe infection or to a lower threshold for admission. [25]

Pathophysiology

Although bronchiolitis occurs throughout the year, it is more common in the winter. Peak incidences occur in February. These outbreaks parallel epidemics of RSV infection, which is the most common cause of acute bronchiolitis. In infected infants and young children there is direct viral invasion, an increase in goblet cell mucous production, and subsequent necrosis and desquamation of the ciliated respiratory epithelium, particularly in bronchioles. Cellular debris and fibrin form plugs in the bronchioles resulting in air flow obstruction. [26]

As the respiratory epithelium regenerates, the new, non-ciliated cells are poorly equipped to clear the products of inflammation. Thus, airway oedema, necrosis and mucous plugging are the predominant pathological features in bronchiolitis (Fig. 1).

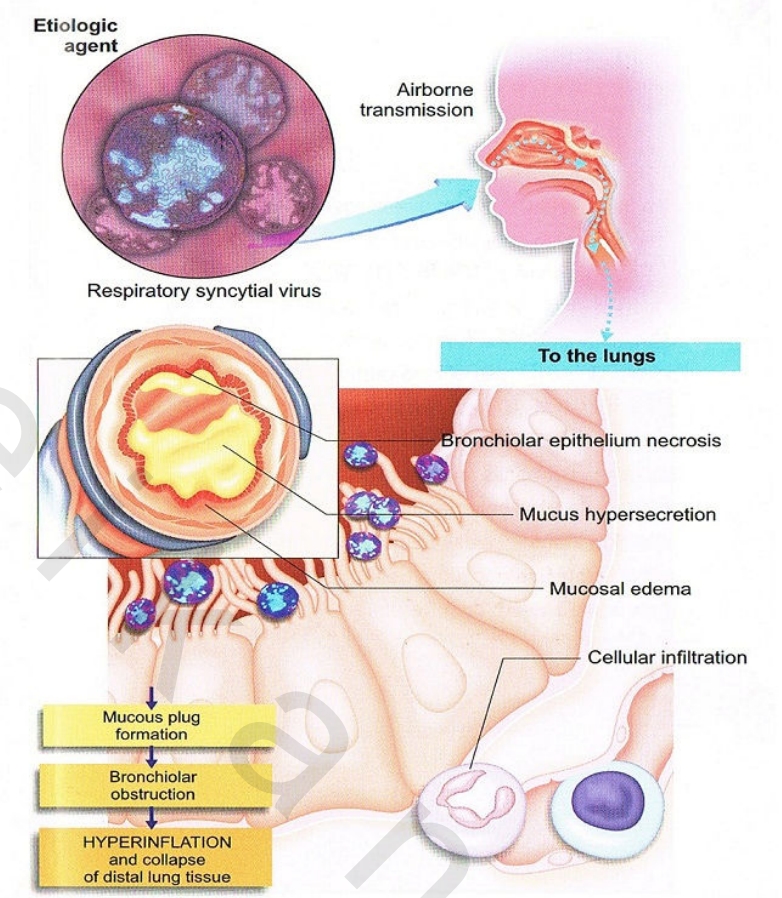

Figure (1): Pathological Features in Acute Bronchiolitis

Clinical picture

The key clinical features of viral bronchiolitis are acute respiratory distress with wheezing in a previously well infant and a concurrent history of fever, coryza or cough. Hypoxemia, defined as low blood oxygen tension, is the most significant immediate consequence. Affected infants and young children develop, to varying degrees, chest wall retractions, tachypnea and hyperinflation. Normal feeding and sleep patterns are disrupted because of the respiratory distress and nasal congestion. The inability of the infant to feed adequately and/or dehydration is a common consequence of the respiratory distress. [27]

Bronchiolitis clinical diagnosis is based on signs and symptoms from the history and physical examination. Since there is no confirmatory test or "gold-standard" for diagnosing bronchiolitis, laboratory testing is not helpful. Pulse oximetry is helpful in the identification of infants with moderate to severe hypoxemia associated with bronchiolitis. No study has demonstrated the utility of complete blood count in diagnosing bronchiolitis or directing therapy. [28] Elevated white blood cell counts have limited usefulness in diagnosing bacterial disease as well. Because human respiratory syncytial virus (hRSV) is the most common etiology in bronchiolitis, virology testing is frequently performed. Rapid viral antigen detection tests on nasopharyngeal specimens are 80% to 90% sensitive compared to viral cultures. These have limited usefulness except for epidemiologic

surveillance. Chest radiographs are not indicated for making the diagnosis of bronchiolitis, but can exclude other disease processes that may present with wheezing, such as foreign body or congestive heart failure. [29]

Treatment

Infants with respiratory distress should be hospitalized; the mainstay of treatment is supportive. If hypoxemic, the child should receive cool humidified oxygen. Sedatives are to be avoided because they may depress respiratory drive. The infant is sometimes more comfortable if sitting with head and chest elevated at a 30-degree angle with neck extended. The risk of aspiration of oral feedings may be high in infants with bronchiolitis owing to tachypnea and the increased work of breathing. The infant may be fed through a nasogastric tube. However, if there is any risk for further respiratory decompensation potentially necessitating tracheal intubation, the infant should be kept NPO and maintained with parenteral fluids.[2]

A number of agents have been proposed as adjunctive therapies for bronchiolitis. Bronchodilators produce modest short-term improvement in clinical features, but the statistical improvement in clinical scoring systems seen with them is not always clinically significant. Several studies have included both infants with first-time and recurrent wheezing, complicating interpretation of the data. [2]

Corticosteroids, whether parenteral, oral, or inhaled, are widely used despite conflicting studies. Differences of diagnostic criteria, measures of effect, timing and route of administration, and severity of illness complicate these studies. In a meta-analysis of steroid use, pooling of all studies and length-of-stay (LOS) plus duration-of-symptoms as outcomes yielded mean reduction in LOS of less than 1 day per patient. This effect disappeared if studies were used measuring LOS only or clearly excluding patients with previous episodes of wheezing. Thus, the theoretical benefits of corticosteroids do not outweigh their risks, side effects, and expense, and they are not indicated for previously healthy infants with RSV. [2]

Newly Emerging Respiratory Viruses:

Until recently, most viral lower respiratory infections in children were attributed to RSV, parainfluenza virus, adenovirus, and influenza viruses. However, two newly discovered viruses, human metapneumovirus (hMPV) and human bocavirus (HBoV), have joined the list of significant contributors. Both viruses, discovered in 2001 and 2005 respectively, constitute up to 13% of previously undiagnosable respiratory infections in children.[30,31] Additionally, both coronavirus and rhinovirus, traditionally regarded as causes of URIs, now have been shown to be present in LRTIs and, therefore, should be included in studies looking at all respiratory tract infections. [32] Identifying the viral etiology of respiratory infections in children can be challenging, especially due to concurrent infections. A Swiss study by Regamey et al. (2008) followed 197 children during their first years of life and found that 122 (62%) had at least one acute respiratory infection in that first year. [33] Fifteen (15%) had dual infections (infections due to 2 distinct pathogens), and three (3%) had triple infections. Together, rhinoviruses, coronaviruses, and the newly discovered hMPV and HBoV accounted for 49% of cases, highlighting the role that hMPV and HBoV play in the etiology of respiratory tract

infections in children. Gaining a better understanding of these newly discovered viruses is important in gaining a better understanding of respiratory infections in children. [34]

The human metapneumovirus

Throughout the years, clinicians have considered RSV followed by influenza as the most common pathogens responsible. Over the past decade, new viruses have been discovered. One of these was the human metapneumovirus, which leads to clinical symptoms similar to that caused by hRSV. [35] The hMPV is an enveloped, single-stranded negative-sense RNA virus that has been recently identified as a new cause of upper and lowers RTIs in children and adults, precisely in patients in whom screening tests for other viral pathogens had been negative. [36]

1. History of Discovery:

In 2001, van den Hoogen et al. reported the discovery of a novel virus from children with respiratory tract illness in The Netherlands. This agent was detected in the nasopharyngeal aspirates (NPAs) of 28 children that were collected during a 20-year period. The clinical syndromes of these infected children encompassed illnesses ranging from mild respiratory problems to bronchiolitis and pneumonia. This virus was distinct from common respiratory viruses, as immunological assays using virus-specific antibodies and polymerase chain reaction (PCR)-based methods using virus genome-specific primers, failed to identify this agent. The genetic characterization of this agent remained a mystery until the tools of molecular biology were applied to identify portions of the genomic sequence. Using a technique known as randomly primed PCR, Dutch researchers were able to obtain genomic sequence of this novel pathogen. [37] Based on limited sequence data, this virus appeared to be closely related to the avian pneumovirus, a member of the *Metapneumovirus* genus, and it was called human metapneumovirus (hMPV). [38] Several lines of evidence suggested that hMPV was a common human respiratory pathogen. Seven of 68 respiratory specimens (10%), collected in the winter of 2000 by van den Hoogen et al., were screened and tested positive for hMPV by reverse transcription-PCR (RT-PCR). [36]

2. Epidemiology:

The epidemiology and seasonality of hMPV infections is similar to that of hRSV, with most episodes occurring during the winter months. [39] It is worldwide in distribution, and since it's initial report by the Dutch researchers in 2001, hMPV has been found in most parts of the world, with reports from Canada, Australia, Denmark, Tunisia, France, Italy, Hong Kong, Japan, Brazil, the United States, Argentina, South Africa, Thailand, and Israel. [40] The frequency of hMPV detection in patients with respiratory tract infections ranged from 2 to 25%. [41, 42] Several studies suggest that it may be responsible for ~10% of viral respiratory infections in which the common respiratory viruses are not diagnosed. [43, 44]

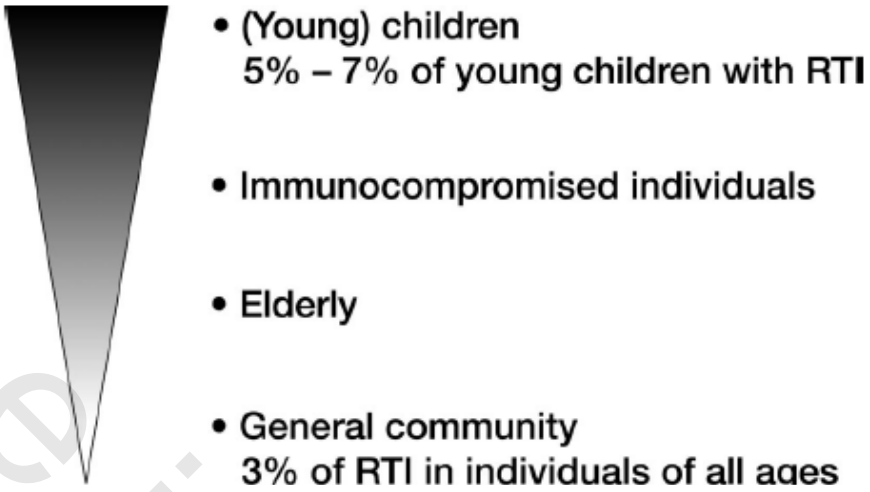

Figure (2): Prevalence of hMPV in Different Populations (Percentages are probably underestimates, because of the choice of inclusion criteria and diagnostic tests). [45]

Infants and young children are the most commonly affected, but the virus has also been documented in adults and the elderly. Globally, hMPV infections account for at least 5-7% of the RTIs in hospitalized children, but in the general community hMPV infections account for at least 3% of patients who visit a general practitioner for RTIs (Fig. 2). [45] The disease associated with hMPV may be slightly milder than for hRSV. Human RSV is detected most frequently in children younger than 2 months of age, whereas children between 6 and 9 months of age have the highest proportion of hMPV infection. Whether this reflects the biologic properties of these viruses or the immunity of their hosts requires further research. [45]

- **Seasonality of hMPV Infections:**

Whereas some of the respiratory viruses, such as parainfluenza viruses and rhinoviruses, may circulate throughout the year, others, such as hRSV and influenza viruses, circulate mainly during the winter season in temperate regions and in the late spring-summer season, also called the respiratory season, in the subtropics (Fig. 3). Studies focusing on specimens collected in this season, often within a two-month period, found high percentages of hMPV-positive specimens. [45] Year round surveillance studies confirmed that hMPV circulates primarily during the respiratory season in the temperate regions, peaking between December and February in the winters of 2000 and 2001. [46, 47]

hMPV is primarily found in the spring and summer months in Hong Kong, where RSV and sometimes influenza virus infections may have the same seasonality. [46] However, in the temperate regions, patient samples have tested positive for hMPV from October until May, with an occasional virus isolated in August. [47, 48] In addition, as observed for RSV and influenza virus infections, the incidence of hMPV infections may vary by year or location. In a North American study among adults in the general community, hMPV was detected more frequently in 2001 than in 2000 (7% vs. 1.5%). [49] In an Italian study, hMPV was detected considerably less frequently in hospitalized children younger than 2 years of age with RTIs in 2001 than in 2000 and 2002 (7% vs. 37

and 43%). [41] More comprehensive and long term studies are needed to determine the seasonality of hMPV infections around the world. [45]

- **Seroepidemiology**:

Seroepidemiologic studies, based on both immunofluorescence and viral neutralization assays, revealed that by the age of five nearly all individuals had evidence of hMPV infection. [37] Studies have shown a 52% sero-prevalence rate by two years of age in Israel [50], and 100% by 10 years of age in the Netherlands and Japan. [51] hMPV has been circulating in humans for at least five decades, [36] but it was not until 2001 when Dutch scientists discovered the virus in children and adults. Reasons for this delay in discovery include, among others, the use of continuous cell lines for viral isolation in many laboratories (in which hMPV does not appear to have an efficient replication) and slow replication kinetics in vitro. [39]

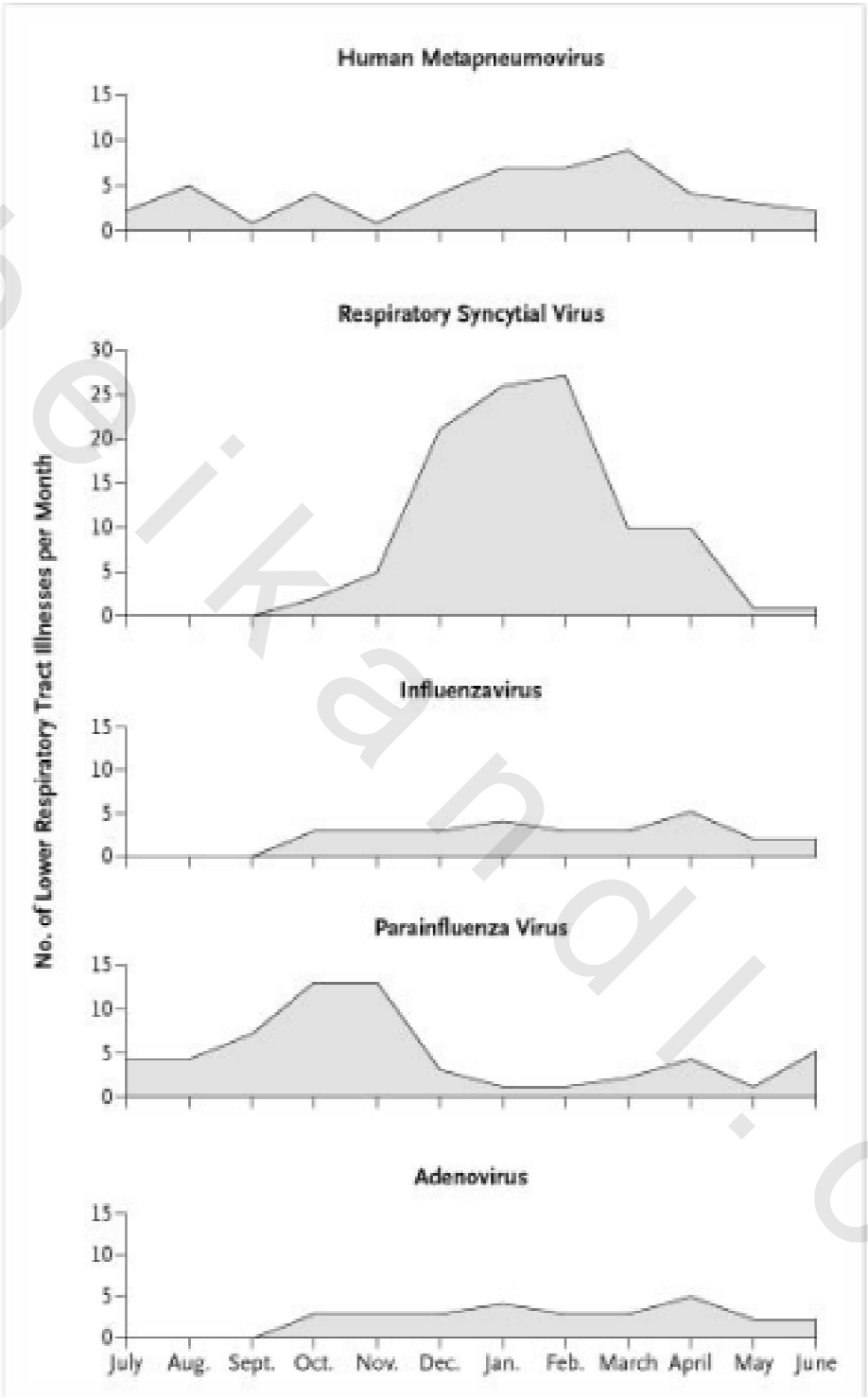

Figure (3): Epidemiologic Pattern of LRTIs with hMPV and Other Viruses [52] (Data are combined from 25 years of surveillance in the Vanderbilt Vaccine Clinic).

3. Taxonomy:

On the basis of morphological, biochemical, and genetic features, hMPV was classified as the first non-avian member of the *Metapneumovirus* genus.[63] This genus, together with the *Pneumovirus* genus is part of the *Pneumovirinae* subfamily within the *Paramyxoviridae* family (International Committee on Taxonomy of Viruses, 2000).

Order: Mononegavirales
Family: Paramyxoviridae
Sub-family: Paramyxovirinae
Genus: Respirovirus
Species: Human parainfluenza types 1 and 3
Genus: Rubulavirus
Species: Human parainfluenza types 2 and 4, Mumps
Genus: Morbillivirus
Species: Measles virus
Genus: Henipavirus
Species: Hendra virus, Nipah virus

Sub-family: Pneumovirinae
Genus: Pneumovirus
Species: Respiratory syncytial virus
Subgroup: A and B
Genus: Metapneumovirus
Species: Human metapneumovirus
Subgroup (?serogroup): A and B

Figure (4): Human Pathogens in the Family *Paramyxoviridae* [38]

As shown in figure (4), the *Paramyxoviridae* family also includes hRSV, hPIV, measles virus, and the mumps virus. [54] Belonging to the subfamily *Pneumovirinae*, hRSV and hMPV share some general characteristics. Both viruses are indistinguishable under the electron microscope, with similar cytopathic effects, as both of them induce syncytia in cell cultures. [36, 55] However, hRSV replicates relatively quickly in many cell lines, whereas hMPV has a more restricted in vitro host range, which includes Tertiary Monkey Kidney cells (tMK), Vero and Rhesus Monkey Kidney Epithelial cells (LLC-MK2). [36] In contrast to hRSV, many hMPV isolates require trypsin in the culture media for efficient replication. [36, 56]

The phylogenetic distribution of viruses belonging to the *Paramyxoviridae* family is shown in figure (5). Genetic analysis was performed using the gene encoding the nucleoprotein N. The scale represents the number of nucleotide changes.

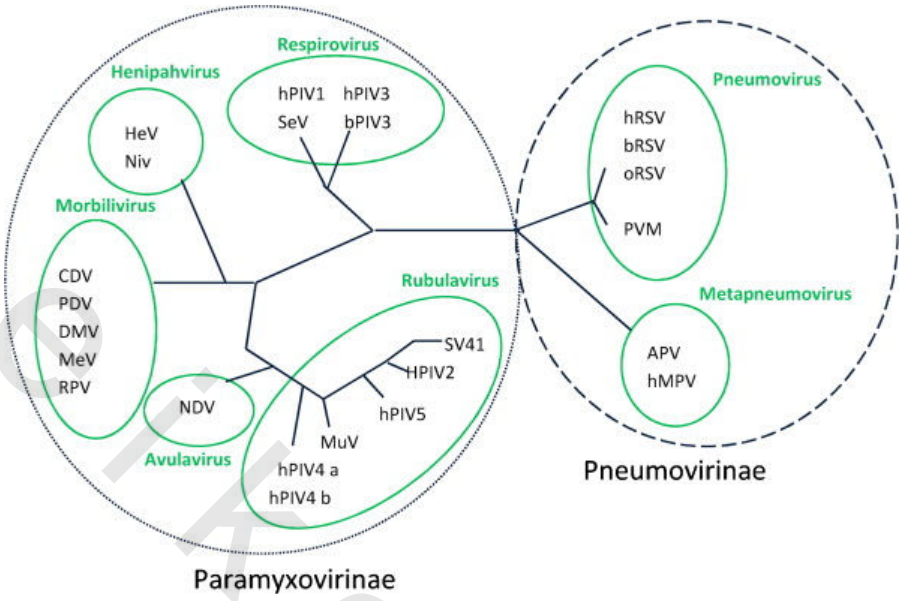

Figure (5): Phylogenetic Distribution of Viruses in the *Paramyxoviridae* Family [57]

Avian metapneumovirus (aMPV, or APV) is the only other member of the genus *Meta-pneumovirus*. This virus has been found to infect domestic poultry worldwide, causing acute respiratory disease in turkeys as well as the so-called 'Swollen Head Syndrome' in chickens. [58] The aMPV genome consists of ~13 kb of a non-segmented, linear, negative-sense strand RNA. [59] The absence of the two non-structural (NS) proteins found in the respiratory syncytial pneumo-viruses, and the unique gene order 3'-N-P-M-F-M2-SH-G-L-5' distinguish aMPV and hMPV as "metapneumoviruses". [60] The aMPVs have been classified into 4 subgroups; A through to D. [61] Subgroup C is more closely related to hMPV than to any other aMPV subgroup. [62]

- Structure and Morphology:

Initial electron microscopic examination revealed that the viral isolate had morphology similar to paramyxoviruses with spherical enveloped particles varying in size and having a mean diameter of 209 nm. [63] In addition, filamentous and pleomorphic particles were also present. The nucleocapsid has a length varying from <200 to ~1000 nm and a diameter of 17 nm. The mean length of the projections on the particles was 15 nm. Filamentous particles averaged 282 x 62 nm in size. [63]

The virion is surrounded by a lipid envelope derived from the plasma membrane of the host cell into which the three virus glycoproteins, the attachment (G), fusion (F), and small hydrophobic (SH) proteins, are inserted.[64] The RNA genome associates with viral proteins to form the helical nucleocapsid (as represented on the right and in the centre of the virion on the left in figure 6). The proteins associated with the viral RNA consist of the nucleocapsid protein (N), the phosphoprotein (P), and the large polymerase (L) protein. The M2-1 transcriptional enhancer protein is also thought to be associated with the nucleocapsid. [59]

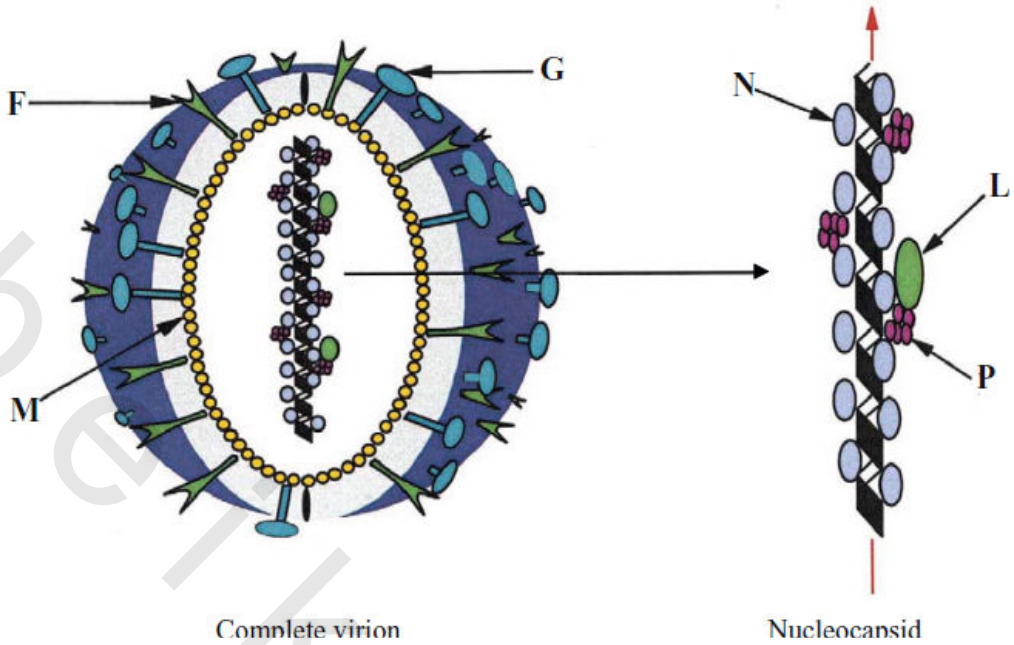

Figure (6): Schematic Diagram of a Pneumovirus Particle [58]

The nucleocapsid is surrounded by the matrix (M) protein, which forms a link between the nucleocapsid and the lipid membrane of the virus particle. Embedded in the viral lipid membrane are the attachment (G) glycoprotein, the fusion (F) protein and the small hydrophobic (SH) protein. [59]

- Clinical Features of Infections:

Infection with hMPV causes a broad spectrum of respiratory illness, from mild symptoms to severe cough, bronchiolitis and pneumonia. The clinical symptoms are similar to those seen with hRSV infection and may also include high fever, myalgia, rhinorrhea, dyspnea, tachypnea, and wheezing.[65] For most, the symptoms are similar to a mild cold. Yet in some children, hMPV can be the cause of severe respiratory infection requiring hospitalization and mechanical ventilation due to respiratory failure. [66]

Evidence from many studies has demonstrated that hMPV is responsible for a substantial proportion of LRTIs in infants and young children and is second only to hRSV as a cause of bronchiolitis in early childhood. [67, 68] In 2004, Williams et al. screened respiratory specimens from >2,000 children <5 years old, collected during a 20-year period at the Vanderbilt University Medical Center (USA), for hMPV. [52] In 20% of cases of LRTIs (characterized by wheezing, crackles, tachypnea, and dyspnea) which could not be attributed to a culturable respiratory virus, hMPV was detected. The incidence of hMPV-associated LRTIs in young children varies with geographical location and time of year. The incidence estimates range from 5 to 15% in most studies, [45, 47, 48, 52, 69] but higher rates have been reported in other studies. [41, 70]

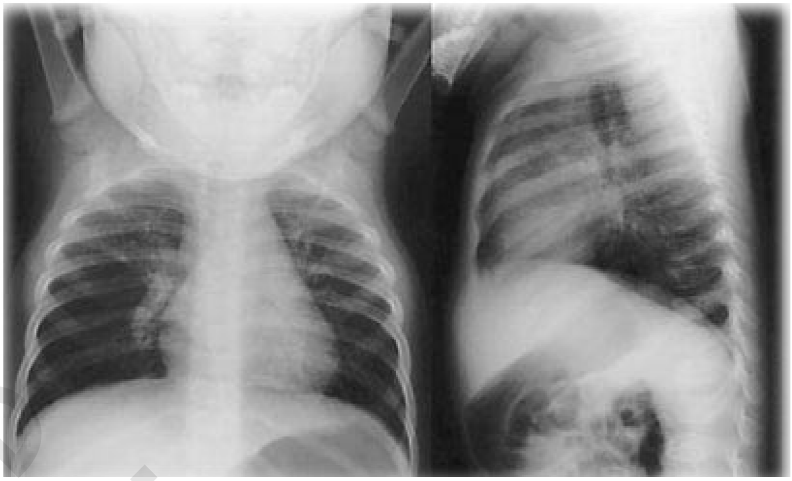

Figure (7): Chest Radiograph of a Six-Month-Old Infant with hMPV Bronchiolitis [52]

The clinical manifestations of hMPV infection in young children are indistinguishable from the clinical manifestations of RSV infection. Common features of hMPV infection included tachypnea, fever, cough, hypoxia and changes on chest radiographs such as infiltrates, hyper-inflation and peribronchial cuffing [30, 45, 47, 52, 63] (Fig. 7). Irritability, pallor, apnea and febrile seizures may also occur. [39] Asymptomatic infection with hMPV in young children appears to be uncommon. In the study by Williams et al. (2004), only one of 86 asymptomatic children (1.2%) tested positive for hMPV, indicating a causal role of hMPV in LRTIs. [52]

LRTIs associated with hMPV in infants and young children are a frequent cause of hospitalization. [37] hMPV likely accounts for ~10% of LRTIs hospitalizations and is second to hRSV as a cause of LRTIs requiring hospitalization. [46, 48, 69, 71] The most common diagnoses in hospitalized children who test positive for hMPV are bronchiolitis, pneumonia and bronchitis. hMPV has been associated with severe LRTIs requiring intensive care. Ulloa-Gutierrez et al. [72] reported a case of a 3-month-old premature child with hMPV pneumonia who required extracorporeal membrane oxygenation for survival, though data from some studies suggest that, in general, the severity of disease associated with hMPV may be less than that observed with hRSV. [48] Although the mean age for hMPV-associated LRTIs is slight greater than the mean age for RSV-associated LRTIs in some studies[73], but not in others [52], it is now clear that infants and young children are the groups in the pediatric population that are most susceptible to severe disease caused by either hRSV or hMPV. Risk factors for severe hRSV disease, such as a history of premature birth, underlying heart or lung disease, and a compromised immune system and are likely risk factors for severe hMPV disease. [30, 47, 74]

Upper Respiratory Infections (URIs):

Like other common human respiratory viruses, hMPV is also associated with URIs. While the definition of URIs varies among studies, hMPV may be responsible for 5 to 15% of cases of URIs in children. [52, 75] In a study in 2006, Williams et al. [75] screened respiratory specimens collected over a 20-year period from children <5 years old with URIs, characterized by coryza, conjunctivitis, pharyngitis, otitis media (OM), or stomatitis. These children did not have a prior virological diagnosis. Of the >2,000 specimens screened by

real-time RT-PCR, the percentage of URIs attributed to hMPV was 1 to 5%. This varied from year to year. Overall, the percentage of URIs associated with hMPV was lower than that observed with influenza virus, parainfluenza viruses, adenovirus, and RSV. [75]

Respiratory viruses have been also implicated in the pathogenesis of OM. Therefore, it was not surprising that hMPV has been identified in children with acute OM. [76-78] In one study, 50% of the children with hMPV-associated URIs were diagnosed with OM. [75] In another study, one-third of children with hMPV-associated LRTIs were diagnosed with concomitant acute OM. [52] hMPV was detected in the nasal washes of 6% of children who presented with acute OM, [78] suggesting that hMPV may be responsible for a small but significant percentage of cases of acute OM. Detection of some respiratory viruses in the middle ear fluid of children with OM suggests a role of the virus in the pathogenesis of OM. Of eight children with OM whose nasal wash specimens tested positive for hMPV, only one had middle ear fluid that also tested positive for hMPV. [78] Similar findings were observed elsewhere. [77] These findings suggest that the inflammatory reaction to the virus, leading to blockage of the Eustachian tubes and subsequent bacterial invasion, is a likely mechanism for virus-induced OM. [37]

Wheezing and Asthma:

The role of viral respiratory tract infections in acute and chronic asthma has been a subject of much debate and research. Viruses such as RSV and rhinoviruses in particular have been suggested as the principal trigger of asthma exacerbation in older children and adults. Several studies have reported the association of hMPV and asthma exacerbations,[47,52,79,80] while this association was not observed in one study [81]. According to the van den Hoogen et al. study in 2003, hMPV was found more frequently in asthmatic children than hRSV, where 16% of the hMPV-infected patients had asthma and 67% of them had a family member with asthma, whereas none of the hRSV-infected patients had asthma and only 30% of them had a family member with asthma. [47]

Another study of children hospitalized with acute expiratory wheezing demonstrated hMPV in 8% of the 132 children tested, [82] suggesting that hMPV is a causative agent of acute wheezing in young children. In contrast, Rawlinson WD et al. have found asthma to be more frequently associated with rhinoviruses than with hMPV. [81] Studies aiming at the identification of an association between hRSV and/or hMPV and asthma are problematic because asthma is a difficult clinical diagnosis in children younger than two years of age, the most susceptible population for both hMPV and hRSV. Nevertheless, these preliminary results on the association between asthma and hMPV infections warrant further research. [83]

Clinical Severity of hMPV Infections:

Whether hMPV infections are more or less severe than those caused by hRSV is not clear. [46, 48, 84] Some authors have found milder clinical courses than those of patients with hRSV, whereas others have noted no differences or have reported longer hospitalizations in children with hMPV infections compared to those infected with hRSV. [46, 84] In some reports none of the children infected with hMPV required admission to the intensive care unit, others indicate that 15–25 % of children required this. [43, 48, 73] In the study by van den Hoogen el al. in 2003, comparison of the medical files of hMPV-infected children with those of hRSV-infected children revealed that the clinical symptoms associated with these viruses were quite similar. [47] Dyspnea, feeding difficulties and hypoxemia were recorded

more frequently in hRSV-infected children than in hMPV-infected children, but all other recorded symptoms were found at the same frequency in both groups. In addition hMPV patients had 38% of all recorded symptoms compared with 50% for the hRSV-infected children, indicating that hMPV infections are slightly milder than hRSV infections. [47]

Coinfection of Human Metapneumovirus with other Respiratory Viruses

Many respiratory viruses share seasonality and susceptible populations; therefore it is not surprising that coinfections are detected at a rate of 1 to 3% in various sample sets. Care should be taken with the diagnosis of coinfections, as sensitive RT-PCR assays may enable the detection of viral genomes during two consecutive infections, which may be mistaken for double infections. Because the seasonal distributions of hMPV and RSV overlap, the potential for dual infection exists. Several studies have found hMPV-RSV coinfection rate of approximately 5-10%.[30,52,85] Greensill et al. (2003), however, reported a high frequency of coinfections by hMPV and hRSV, where 90% of RSV-infected infants with severe bronchiolitis were found coinfected with hMPV, [86] suggesting that coinfection with hMPV and hRSV may predispose for severe disease.[86]

In another study by Semple et al. (2005), dual infection with hMPV and hRSV conferred a ten-fold increase in the relative risk (RR) of admission to a pediatric intensive-care unit for mechanical ventilation. [87] In contrast to the previous studies, van Woensel et al. (2006) reported the absence of hMPV co-infection in any of the 30 mechanically ventilated children with RSV lower respiratory tract infection, [88] suggesting that hMPV coinfection is not very common in severe RSV respiratory tract infection.

Prevention and Control:

Human metapneumovirus has been detected in patients with both community and hospital -acquired respiratory tract illness, but no nosocomial outbreaks have been reported. Common respiratory transmission precautions and measures are suggested. [39] The development of a safe and effective vaccine to protect against hMPV is a reasonable goal. Several promising vaccine candidates have been tested in animal models. A live recombinant human parainfluenza virus that contains the hMPV fusion (F) protein gene has been shown to induce hMPV-specific antibodies and to protect experimental animals from hMPV challenge. [89] A chimeric bovine/human parainfluenza virus 3 expressing the hMPV fusion (F) protein elicits neutralizing antibodies against both parainfluenza virus and hMPV. [90] However, the results of these animal challenge studies should be interpreted cautiously. There are many limitations of the small-animal model for testing potential hMPV vaccines, not the least of which is that the pathogen is highly host restricted. The safety and efficacy of a recombinant hMPV vaccine may be difficult to predict. [37]

Treatment:

Other than influenza virus, antiviral therapy for respiratory viruses has not shown tremendous potential. The effectiveness of ribavirin therapy for hRSV remains a controversial issue. Currently, there is no specific therapy for hMPV. [91] It is unknown what role the host's inflammatory response plays during hMPV disease. Nonetheless, antiviral compounds have been tested with hMPV. [37] The antiviral activity of ribavirin to inhibit the replication of hMPV is equivalent to that observed with RSV. [92] Other

compounds, such as $NMSO_3$, a sulphated sialyl lipid that has been shown to have potent antiviral activity against RSV in tissue culture cells, have been shown to have anti-hMPV activity in vitro. [92]

It is likely that an hMPV-neutralizing monoclonal antibody for prophylaxis of high-risk infants (similar to the anti-RSV fusion [F] protein humanized monoclonal antibody currently used for prevention of severe RSV disease) will be developed and tested. The progress towards an effective antiviral strategy for hMPV is currently limited by the scant data on pathogenesis of the virus in the natural host. [37] Supportive therapy is recommended as in other viral respiratory infections of childhood. Mechanical ventilation has been used in severe cases. [39]