INTRODUCTION

Human Metapneumovirus (HMPV) is a relative newly described virus. It was first isolated in 2001 and currently appears to be one of the most significant and common human viral infections. Retrospective serologic studies demonstrated the presence of HMPV antibodies in humans more than 50 years earlier. Almost all children are infected by HMPV below the age of five; the repeated infections throughout life indicate transient immunity ***(Kroll and Weinberg, 2011).***

Genetic and antigenic studies based on variations of the HMPV F gene have demonstrated the presence of two distinct HMPV groups, designated groups A and B, which can be further divided into five subgroups A1, A2a, A2b, B1, and B2 ***(Kim et al., 2012).***

Human Metapneumovirus (HMPV) is a member of the Paramyxoviridae family which also includes respiratory syncytial virus (RSV), measles virus, and mumps virus ***(Regev et al., 2012).***

The infection symptoms caused by HMPV are similar to those caused by RSV and patients infected with HMPV demonstrate symptoms ranging from upper respiratory tract infection to bronchiolitis and pneumonia ***(Matsuzaki et al., 2008).***

It has been suggested that HMPV is responsible for 5–10% of acute respiratory tract infections in neonates and children ***(Agrawal et al., 2011).***

Acute respiratory tract infections (ARI) are leading causes of morbidity and mortality worldwide. Of the 10 million deaths of children less than 5 years of age throughout the world, 1.9 million children died from acute lower respiratory tract infections (ALRI) in the year 2000 ***(Williams et al., 2002).***

Aim of the Work

This study aims at evaluating the burden of Human Metapneumovirus infection among outpatient and inpatient children below five years old suffering from acute respiratory illness attending Pediatric Hospital Ain Shams University and studying its relation to the severity of illness.

Chapter 1:
HUMAN METAPNEUMOVIRUS

Introduction

Human metapneumovirus (HMPV) was first detected at 2001 upon respiratory specimens collected from children with respiratory tract infection ***(Haas et al.,2013).***

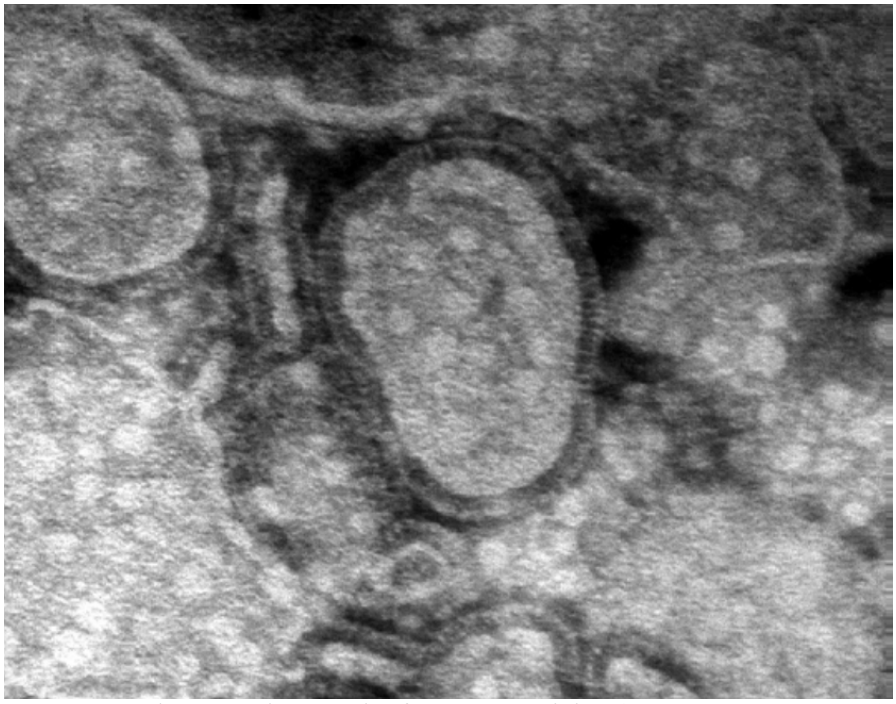

Figure (1): Electron micrograph of HMPV particles ***(Schildgen et al., 2011).***

Human Metapneumovirus is RNA virus belonging to the family of Paramyxovirus .The family Paramyxoviridae consists of a group of large, enveloped, negative-sense, single-stranded RNA viruses and contains many important human and animal

pathogens such as measles virus (MeV), mumps virus, respiratory syncytial virus (RSV) and the human Parainfluenza viruses (HPIV) in addition to animal viral agents.

Like other respiratory viruses HMPV is associated with upper and lower respiratory tract infection. Cytopathic effects morphologically indistinguishable from those induced by human respiratory syncytial virus (HRSV) were observed ***(Hoogen et al., 2001).***

Table (1): Classification of HMPV ***(Schildgen et al., 2011).***

Group	**Group V(negative single – stranded RNA)**
Order	Mononegavirales
Family	Paramyxoviridae
Subfamily	Pneumovirinae
Genus	Metapneumovirus

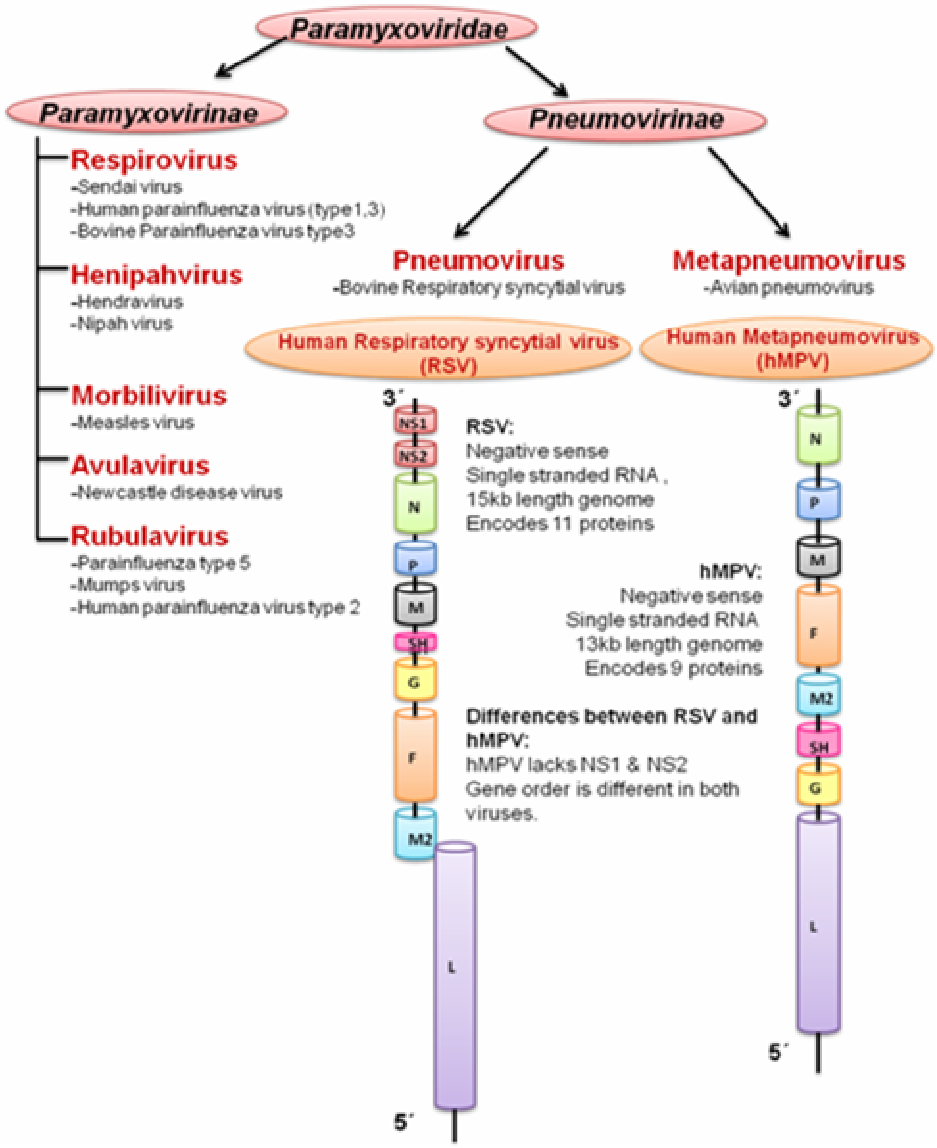

Figure (2): Representative members of Paramyxoviridae gene family and the genomic organization of respiratory syncytial virus (RSV) and human metapneumovirus (HMPV) ***(Kolli et al., 2013).***

Structure of Human Metapneumovirus

HMPV structure and genome organization

HMPV consists of a helical nucleocapsid contained within a lipid bilayer envelope that is derived from the plasma membrane of the host cell ***(Easton et al., 2004).*** Inserted into the envelope three transmembrane surface glycoproteins were identified:-

1. An attachment glycoprotein (G) that differs from haemagglutinin-neuraminidase (HN) and haemagglutinin (H) attachment proteins in that it has neither haemagglutination nor neuraminidase activity.
2. F protein
3. A small hydrophobic (SH) protein ***(Bossart and Broder, 2011).***

Inside the envelope, there are approximately 13,000 nucleotide single stranded negative sense RNA genome that is encapsidated with the N protein and contains eight genes in the order 3'-N-P-M-F-M2-SH-G-L-5' that encode nine different putative protein analogous to Respiratory syncytial virus (RSV) and Avian pneumovirus (APV) ***(Biacchesi et al., 2003).***

The N protein and the genome RNA form the ribonuclease (RNase) resistant nucleocapsid core to which the phosphoprotein (P) and L protein are attached. This complex of proteins termed the ribonucleocapsid complex (RNP) has RNA dependent RNA

transcriptase activity and initiates intracellular virus replication (Figure 2) ***(Lamb and Parks, 2007)***.

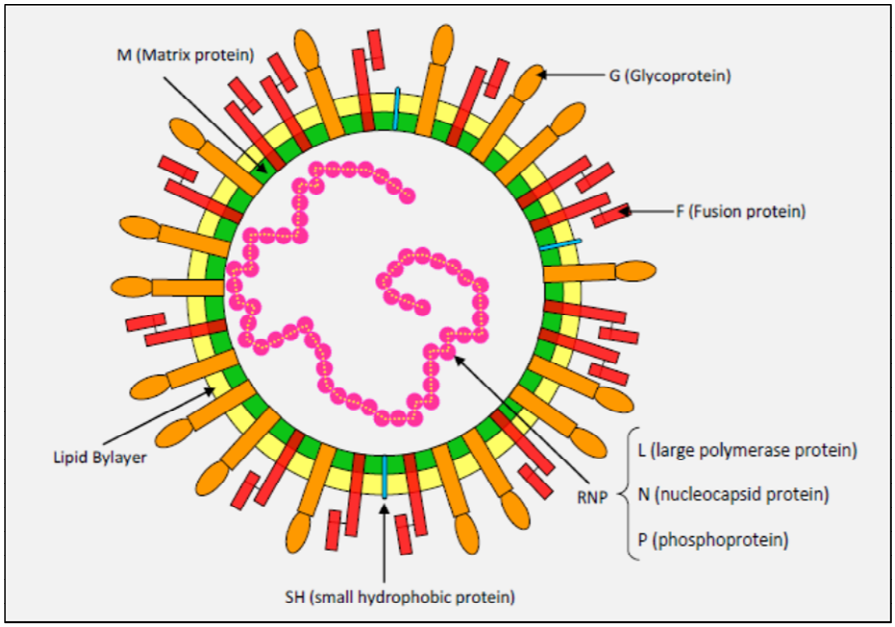

Figure (3): Schematic representation of the structure of members of the Pneumovirinae ***(Lamb and Parks, 2007).***

Genetic structure of HMPV resembles RSV however there are some differences in genome of (Avian Pneumovirus) APV/HMPV as compared to RSV, they lack the 2 nonstructural proteins NS1 and Ns2 located at the 3' end of RSV genomes. These proteins counteract host interferons; therefore the lack of these genes in the Metapneumoviruses may have important implications for the relative pathogenicity of these viruses compared with RSV strains ***(Collins and Murphy2007)***.

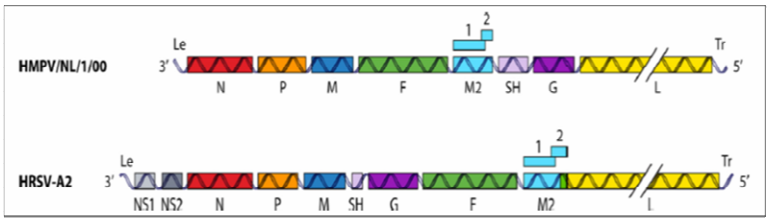

Figure (4): Genomic maps of HMPV and RSV showing the important differences between the two viruses ***(Schildgegen et al., 2011).***

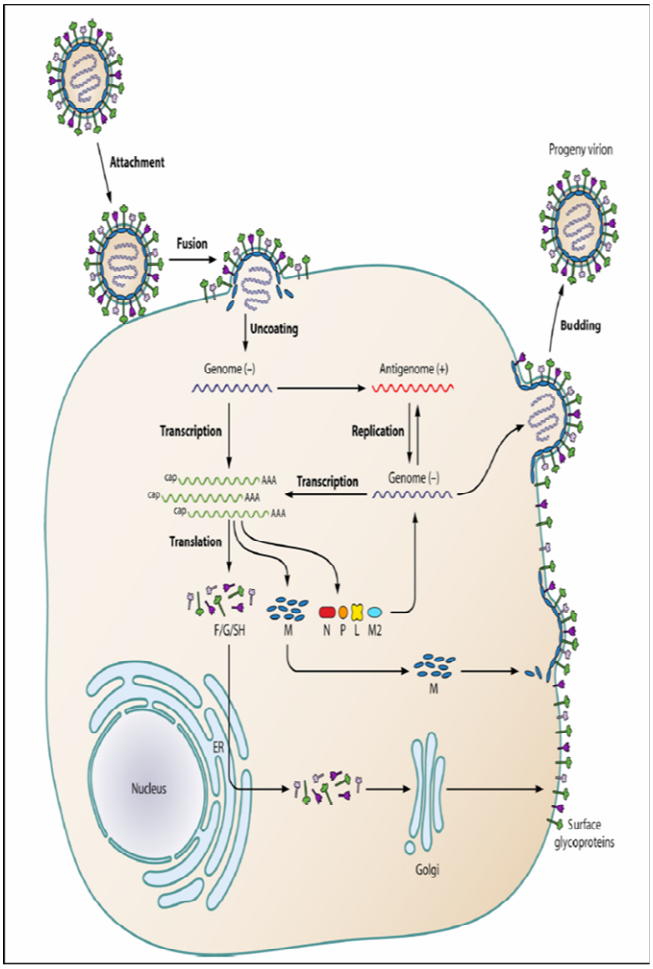

Figure (5): Schematic representation of the life cycle of members of the family Paramyxoviridae ***(Schelding et al., 2011).***

Epidemiology

Since its initial description in 2001, HMPV has been isolated from individuals of all ages with ARTI, and has been identified in every continent.

Incidence:-

- Incidence ranges from 1.5% to 25 % in different studies.
- In USA winter 2001 HMPV was detected in 6.4% in children less than 5 years old.
- In Italy winter of 2002 incidence was 43% in hospitalized children less than 2 years old with ARTI.
- In France winter 2001-2002 incidence was 6.6% in hospitalized children with ARTI.
- In Germany winter 2002 incidence was 17.5% in hospitalized children less than 2 years old with ARTI.
- In Canada winter 2001-2002 incidence was 14.8% in Persons of all ages.
- In United Kingdom winter of 2001 incidence was 2.2% in Persons of all ages with influenza like illness.

(Hamelin et al., 2004)

In Egypt HMPV was detected in13.5 % of adult population while in children incidence was 8% ***(Yahia et al., 2012).***

Risk factors of acquiring HMPV infection include:-

- **Age:-**Most HMPV infections occur in < 5 years of age, with children <2 years of age being most at risk for serious HMPV infections ***(Broor et al., 2008).***
- **Gender**:-several studies have reported a trend toward male predominance in children with HMPV infection ***(Sternak et al., 2008).***
- **Season of Birth:** in the spring
- **Order of birth:** older siblings.
- A history of premature birth.
- Underlying heart or lung disease
- Gastrointestinal reflux disease or aspiration
- Compromised immune system
- Exposure to household tobacco smoke or other indoor air pollution.

(Chen et al., 2010)

- **Social class:-**low stable monthly per capita household income (<US$30.00 per capita was hospitalized at least 1.6 times more frequent than better income).
- Large number of persons in the household (6–9 persons).
- Indoor exposure to fumes from burning firewood used for cooking.

- Young maternal age (12-25 years).
- Low birth weight (more than 6 times likely to be hospitalized than full term babies) ***(Cardoso et al., 2013).***

Risk factors for hospitalization of HMPV patient

High risk groups were premature, children below 24 months, chronic lung disease, congenital lung disease, immunocompromised and other underlying abnormalities ***(Fenwick et al., 2007).***

Day care attendance and more than 3 older siblings are risk factors of HMPV infection ***(Roussy et al., 2014).***Severe and even fatal cases had been described in immune compromised patients ***(Sivaprakasam et al., 2007).***Apnea related to HMPV had been reported with maximum occurrence in prematurely born ***(Wilkesmann et al., 2007).***

HMPV is recognized as a leading cause of hospitalization for ARTI in children <5 years of age. However, children <2 years of age are at greatest risk of hospitalization ***(Williams et al, 2010).*** Nevertheless, it is evident that children with HMPV infection are significantly older than those which have HRSV infection ***(Baer et al., 2008).*** This is attributed to longer-lasting maternal immunity to HMPV compared to HRSV or perhaps the pathogenesis of HMPV disease favors older children ***(Mullins et al., 2004).*** Children with HMPV were older (8.4 VS 4 months), were born premature (27 Vs 33 weeks) ***(Andreson et al., 2012).***

Mortality rates in immunocompromised patients

HMPV infections can cause severe and fatal disease in immunocompromised patients , with reported mortality ranging from 10% to 80%in different small cohort studies of cancer and/or hematopoietic cell transplant (HTC) patients ***(Renaud et al., 2013).***

Geographical and seasonal distribution

HMPV has a worldwide distribution and has been identified on every continent. In temperate climates, HMPV circulates predominately in the late winter and spring, and the peak of activity at any given location often coincides with or follows the peak of RSV activity in many communities, HMPV has been detected throughout the year ***(Kahn ,2006).***

Despite the absence of winter season in the tropics, there are consistent seasons of respiratory infection ***(Shek and Lee, 2003).***

Seroepidemiology

Primary infection with HMPV occurs during early childhood ***(Okamoto et al., 2010),*** later than infection with HRSV ***(Lu et al., 2011),*** and by 5 to 10 years of age virtually all children are seropositive for the virus ***(Okamoto et al., 2010).***

The decline in the proportion of seropositive individuals during the first year of life likely represents waning maternally

acquired antibody. However, it appears that two periods of acquisition of HMPV infection in childhood also occur. The first period occurs within the first 3 years of life. During this period, the percentage of individuals who are seropositive essentially remains constant at 35 to 45% for children 12 to 47 months of age as the decline in maternal antibody is superimposed on the increase in antibody acquired during this first period of acquisition of HMPV infection ***(Leung et al., 2005).***

The second period occurs in children of >48 months of age. The percentage of seropositive individuals increases to 77.3% in children aged 48 to 59 months old and to >90% in children who are >5 years old. This second peak likely reflects increased exposure to the virus, perhaps at day care or preschool environments ***(Leung et al., 2005).***

Despite near-universal exposure in childhood, re-infection can occur in all age groups throughout life ***(Pavlin et al, 2008)*** due to incomplete protective immunity and/or acquisition of new genotypes ***(Hamelin et al., 2004).*** Immunocompromised, very young, and frail elderly hosts are at highest risk of serious sequels because of HMPV reinfection ***(Boivin et al., 2007).***

It was suggested that antibody may play a role in protection from infection with HMPV since serum antibody levels were significantly lower in adults who subsequently became infected with HMPV compared to those who remained infection free ***(Falsey et al., 2010)***.

Seasonal circulation pattern of HMPV lineages and Subclusters

The circulation of the 4 genetic lineages of HMPV was confirmed in studies throughout the world, most notably in long-term retrospective studies conducted in the United States from 1981 to 2001. From these studies, it can be concluded that (i) the prevalence of particular lineages is not restricted to certain locations and times and (ii) multiple lineages can circulate in the same period at a given location ***(Schildgen et al., 2011).***

In Germany:-

Predominance of subgroups A or B, respectively, was observed both for a single season (1982, 1983, 1987, 1993, 1994, 2000, 2001, and 2003) and a maximum of three consecutive seasons (1984–1986, 1989–1991, and 1996–1998). Besides, there were seasons with a co-dominance of HMPV subgroups A and B (1988, 1992, 1995, and 1999).

With the exception of the seasons 2000–2001 and 2006–2007, all seasons were characterized by the circulation of HMPV A2, only A2b circulated in all seasons.

A2a viruses circulated from 2001–2002 to 2003–2004 and reappeared in the season 2007–2008.

Epidemic seasons are further characterized by the recurrent appearance and disappearance of lineage B2.Whereas