

Viral Infections of the Lower Respiratory Tract

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Abstract Lower respiratory tract infections (LRTIs) are a global burden to public health and are frequently caused by respiratory viruses. Advances in molecular diagnostic techniques have allowed the identification of previously undetected viral pathogens and have improved our understanding of respiratory virus infections. Here we review the epidemiological and clinical characteristics of recently identified viruses including human metapneumovirus, human coronaviruses NL63 and HKU1, human rhinovirus C, bocavirus, WU and KI polyomaviruses, and parechovirus. The roles of these viruses in LRTIs in children and adults are discussed.

Keywords Lower respiratory tract infection · Pneumonia · Bronchiolitis · Bronchitis · Symptoms · Clinical characteristics · Respiratory virus · Human metapneumovirus · Human coronavirus · Rhinovirus · Bocavirus · WU polyomavirus · KI polyomavirus · Parechovirus · Pathogenicity · Epidemiology · Seroprevalence · Seasonal distribution · Incidence · Percentage · Genotype · Coinfection · Age · Children · Adult

Introduction

Lower respiratory tract infections (LRTIs) are a global burden to public health. Among acute LRTIs, bronchitis is the most common reason for admission of infants to the hospital;

whereas pneumonia is the major cause of death in children and adults (most in those older than 65 years) worldwide, accounting for 1.05 million (11.3 %) in lower income countries and 3.46 million (6.1 %) deaths worldwide [1–3].

A large proportion of LRTIs are caused by respiratory viruses. It is well known that influenza virus (IFV) A and B, parainfluenza virus (HPIV), respiratory syncytial virus (RSV), adenovirus (AdV), enterovirus (EV) and coronavirus (HCoV)-229E and-OC43 are important causes of LRTIs [4•]. However, their influence in causing severe LRTIs was not underscored until the emergence of highly pathogenic H5N1 avian influenza and severe acute respiratory syndrome (SARS) [4•]. These outbreaks have attracted intensive attentions worldwide.

The diagnosis, detection and surveillance, of respiratory pathogens, particularly the newly emerging viral pathogens, have been unprecedented in the past decade. Advances in molecular diagnostic techniques have allowed the identification of previously undetected viral pathogens and have improved our understanding of the characteristic of respiratory virus infections. During the past decade, additional respiratory viruses or new species/strains related to human respiratory illness have been identified in addition to SARS-CoV, such as the human metapneumovirus (hMPV), HCoV-NL63, HCoV-HKU1, human rhinovirus (HRV) C, pandemic influenza A/H1N1 2009 virus, as well as the potential respiratory pathogens including human bocavirus (HBoV), WU and KI polyomaviruses (PyV), and parechoviruses (HPeVs) [5–14]. While the pathogenicity of IFV and SARS-CoV have been well characterized [6, 10], that of hMPV, HCoV-NL63, HCoV-HKU1, HRV-C, HBoV, WUPyV, KIPyV, and HPeV have not (Table 1). We review the epidemiology and clinical characteristics of hMPV, HCoV-NL63, HCoV-HKU1, HRV-C, HBoV, WUPyV, KIPyV, and HPeVs infections, and discuss their roles in LRTIs in children and adults.

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Table 1 Respiratory viruses discussed in the article

Family	Genus	Species	Abbreviation	Genotype
<i>Paramyxoviridae</i>	<i>Metapneumovirus</i>	Human Metapneumovirus	hMPV	A1, A2 (A2a, A2b), B1, B2
<i>Coronaviridae</i>	<i>Coronavirus</i>	Human Coronavirus OC43 Human Coronavirus 229E Human Coronavirus SARS-CoV Human Coronavirus NL63 Human Coronavirus HKU1	HCoV	
<i>Picornaviridae</i>	<i>Enterovirus</i>	Human Rhinovirus A Human Rhinovirus B Human Rhinovirus C	HRV	
	<i>Parechovirus</i>	Human Parechovirus	HPeV	1–16
<i>Parvoviridae</i>	<i>Bocavirus</i>	Human Bocavirus	HBoV	1–4
<i>Polyomaviridae</i>	<i>Polyomavirus</i>	WU Polyomavirus KI Polyomavirus	WUPyV KIPyV	

Human Metapneumovirus

hMPVs belong to the *Metapneumovirus* genus of the *Paramyxoviridae* family, and contain a single-stranded, negative sense RNA of 13 kb [14]. Since the first identification in children with LRTIs in the Netherlands in 2001, circulation of hMPV has been reported on all continents [14, 15]. Based on the F and G genes, hMPV has been classified into two genotypes, A and B, and four subtypes, A1, A2, B1, and B2 [16]. The subtype A2 is further classified into two lineages A2a and A2b [17].

The symptoms of hMPV infection are similar to those of other common respiratory viruses and range from mild respiratory illness to severe LRTIs [18, 19]. hMPV also causes nosocomial infection [20]. The LRTI caused by hMPV mainly affects children under 5 years old, adults with underlying conditions, and immunocompromised patients [15, 18].

The global epidemic patterns of hMPV are complex. hMPV epidemics have a biennial rhythm peaking in the winter-spring season in one year and in the spring-summer season in the next year in temperate climates [18, 21, 22]. In tropical climates, hMPV is most prevalent in the rainy season [23•]. The incidence of hMPV ranges from 4 % to 25.9 % in patients diagnosed with LRTIs [15, 25]. In pediatric patients hMPV is the second most common etiological pathogen after RSV [15, 19, 25]. A high rate of co-infections of hMPV with RSV have been reported, as the epidemic cycles of both viruses overlap [25, 26]. However, it is not clear if the severity of symptoms is highest with a single infection of hMPV or with a co-infection with RSV or other respiratory virus [26].

Circulation of hMPV genotypes varies annually and the predominant genotype shifts every 1–3 years, although co-circulation of several genotypes is common [22, 23•, 24]. A significant association between infection with sub-genotype A2b and severe illness has been reported [23•]. However, a larger number of patients are required to elucidate the severity of symptoms with respect to the regional genetic variability.

Sero-epidemiological studies suggest that infection with hMPV occurs during the first 2 years of life and nearly all individuals have been exposed to hMPV by 5 years of age [14, 23•]. A lower IgG antibody against hMPV in children 6 months to 6 years old than in older children or adults may suggest a different number of repeat infections or a different response to repeat infections with increasing age [27]. Re-infection with hMPV appears to be due to incomplete immunity [28].

Human Coronavirus NL63 and HKU1

HCoVs are positive-stranded, enveloped RNA viruses in the *Coronavirus* genus of the *Coronaviridae* family [29]. Three groups of HCoVs have been identified and are associated to a wide range of illness in human beings, mammals and avian species [29]. HCoVs are commonly associated with respiratory symptoms in children and adults [29]. The HCoVs 229E and OC43 were first characterized in the 1960s [30, 31]. HCoV has not attracted the attention in LRTIs until the identification of SARS-CoV in 2003.

HCoV-NL63 (NL63 represents the sample code) was first detected in a 7-month-old child with bronchiolitis in 2004 in the Netherlands; like HCoV-229E, HCoV-NL63 belongs to

group I of HCoV-NL63 [5]. HCoV-HKU1 (HKU means the Hong Kong University), clustered with OC43 in group II, was first detected in a 71-year-old with chronic obstructive airway disease and pneumonia in 2005 in Hong Kong [8]. At least three genotypes A, B and C were observed [8, 32, 33]. HCoV-NL63 and HCoV-HKU1 have been detected worldwide and are associated with upper respiratory tract infections (URTIs), bronchiolitis, and pneumonia [34, 35]; HCoV-NL63 has also been associated with laryngotracheobronchitis (croup) [34, 46]. Both HCoV-NL63 and HCoV-HKU1 have been associated with deaths [36, 37].

The epidemics of HCoV-NL63 and HCoV-HKU1 fluctuate between years and peak primarily in late autumn, winter, and early spring; occasionally, they also peak in summer [35, 38, 39]. The average incidence of HCoV-NL63 varies from 0.6 % to 9.3 % in patients diagnosed with LRTIs, while that of HCoV-HKU1 varies from 0.1 % to 4 % [32, 35, 37, 39]. The study period, geographical location and cohort might be responsible for the differences observed in the incidence. Large-scale and long term studies are required to clarify the epidemiology of HCoV-NL63 and -HKU1.

HCoV-NL63 and HCoV-HKU1 infection are more frequently detected in infants, young children, elderly adults, immunocompromised adults, and in adults with underlying diseases; transplantation is the most common risk factor in adults infected with HCoV-NL63 and -HKU1 [40, 41].

The burden of HCoV-NL63 infections has been described by three independent studies. The annual incidence of HCoV-NL63 is 2.2 per 10,000 hospitalized children under the age of 3 years in Germany [42], 22.4 per 10,000 hospitalized children under the age of 6 years in Hong Kong, China [43], and 12.3 per 1,000 children with LRTIs under the age of 5 years in the USA [44]. There are no definite reports on the burden of HCoV-HKU1.

HCoV-NL63 and -HKU1 infections occur singly or with other respiratory viruses including IFVA, hMPV, HPIV, and especially with RSV [35, 45]. The viral load of HCoV-NL63 is lower in co-infected patients than in single infections, but co-infected patients are more likely to be hospitalized [46]. However, Gaunt et al. reported similar clinical outcomes and viral loads for patients with RSV and HCoV co-infections as for patients with HCoV single infections [45].

Sero-epidemiological analysis indicates that HCoV-NL63 and HCoV-HKU1 infections occur in early childhood [47]. HCoV-NL63 and HCoV-OC43 infections show a higher frequency of seroconversion than HCoV-HKU1 and HCoV-229E in newborns [39]. The seroconversions of HCoV-HKU1 and HCoV-229E are absent after seroconversions of HCoV-OC43 and HCoV-NL63, respectively [39]. Further investigations are needed to determine if the

seroconversions of HCoV-NL63 and HCoV-OC43 elicit cross protective immunity against HCoV-229E and HCoV-HKU1.

Human Rhinovirus Type C

HRVs are non-enveloped, positive single-stranded RNA viruses belonging to the *Enterovirus* genus of the *Picornaviridae* family [48]. HRVs were previously classified into two species, HRV-A (containing 74 serotypes) and HRV-B (containing 25 serotypes), according to partial sequences of the viral capsid-coding regions, noncoding regions, and a limited number of complete genomes [49]. In 2007, a novel HRV was identified in infants with bronchiolitis [9]. Other new strains have subsequently been detected [50]. These novel HRV strains are now designated as HRV-C based on the viral genomic sequences, as recommended by the International Committee on Taxonomy of Viruses (ICTV).

HRV infections occur throughout the year and have a high incidence in spring and autumn, with variation in the dominant serotype according to area and year [51, 52]. HRVs have been recognized as a pathogen responsible for the common cold but have also been detected in the nasopharynx of asymptomatic individuals [53]. HRVs appear to be able to replicate also in the lower airways and cause bronchiolitis and pneumonia, commonly leading to hospitalizations [54, 55].

All three species of HRVs have been epidemiologically associated with respiratory tract illnesses and HRV-A and HRV-C have caused severe respiratory disease outbreaks [56]. In addition, HRVs exacerbate asthma and other diseases such as chronic obstructive pulmonary disease (COPD) [57, 58]. In an investigation on asthma exacerbation, the detection rate of HRV-C was 69.8 % in 128 children with exacerbated asthma and 18.8 % in 192 controls [59]. In a study of 136 patients with exacerbations of COPD, 68 stable COPD patients, and 16 non-obstructed smokers, McManus et al. found that the incidence of HRVs was 23.5 %, 4.4 % and 0 in these cohorts, suggesting an association of HRVs with exacerbations of COPD [58].

Aside from their connection to the common cold, asthma and COPD, HRV-C have also been associated with other childhood wheezing illnesses, even in children without a known history of asthma [59]. Furthermore, HRVs have been detected at a high rate in adult patients with community-acquired pneumonia [55]. As well, multiple HRV serotypes have been detected in outpatients and hospitalized patients suffering from acute respiratory tract infections [51, 52, 54].

HRV-C does not grow in standard tissue culture; mucosal organ culture is the only medium to date that supports HRV-C infection in vitro [60]. This restriction has hindered the

identification of HRV-C receptor and the development of effective antivirals.

Currently, no effective vaccines against HRV infections exist in humans, and vaccination is considered impractical given the large number of HRV serotypes [57]. Long-term population-based studies are needed to define the diversity and relative virulence of HRV-C.

Human Bocavirus

HBoVs are members of the genus *Bocavirus* of the family *Parvoviridae*. HBoV, first identified in 2005, is the second parvovirus found to be pathogenic to humans [7]. HBoV is a small, non-enveloped virus with a linear single-stranded DNA genome of approximate 5 kb. Three open reading frames have been identified. One of these open reading frames encodes a nonstructural protein (NS1), another encodes a nonstructural protein (NP1) with unknown function, while the third encodes two overlapping capsid proteins (VP1/VP2). The VP2 protein has been expressed in insect cells and can form virus-like particles, which have been successfully used in the detection of specific antibodies against HBoV infection [61].

Four species of HBoVs (HBoV1–4) have been identified to date based on phylogenetic analysis of the viral genome [7, 62, 63, 67]. HBoV1 is prevalent in respiratory tract samples and has been shown to cause respiratory tract diseases [64], while HBoV2 and HBoV3 have been detected in fecal and in respiratory specimens [65, 66]. HBoV4 has also been detected in fecal samples [67]. The signs and symptoms of patients with HBoV1 and HBoV2 do not differ clinically and include cough, sputum production, fever, rhinorrhea, wheezing, and diarrhea [66].

The global prevalence of HBoV, as determined by PCR analysis, ranges from 1.5 % to 19 % in children suffering from acute respiratory tract infections [66, 68], depending on the season, geographic location, and subjects studied. Although HBoV infections occur in both children and adults, children under the age of 2 years are at highest risk for infection [68].

Human antibodies against HBoV1–4 VP2 virus-like particles are cross-reactive between species. After depletion of cross-reactive antibodies, the approximate seroprevalences of HBoV1, 2, 3, and 4 in adults are 59 %, 34 %, 15 %, and 2 %, respectively. After depletion of HBoV1 reactive antibodies, the seroprevalences of HBoV2, 3, and 4 among children aged 1–2 years are 25 %, 10 %, and 5 %, respectively [61], indicating a differential prevalence of HBoV species. HBoV1 may be predominant in human populations.

As HBoVs are frequently co-detected with other viral infections associated with LRTIs [64, 69], the clinical significance of HBoV in LRTIs is not yet clear. However,

Körner et al. reported that a HBoV single infection caused a severe and life-threatening LRTI in an 8-month-old girl [70]. The transmission route of HBoVs to human beings has not been fully established. The lack of cell culture and animal model systems also limit the understanding to HBoV pathogenicity.

WU and KI Polyomavirus

Belonging to the *Polyomaviridae* family, PyVs are small non-enveloped viruses with a circular double-stranded DNA genome [71]. The PyV species BK virus (BKV) and JC virus (JCV) have been known to be common in humans and are related to PyV nephropathy, hemorrhagic cystitis, and progressive multifocal leukoencephalopathy, respectively [71]. WUPyV and KIPyV were first identified in respiratory specimens from patients with acute respiratory tract infections [11, 12]. Their viral nucleic acids have been confirmed in respiratory specimens worldwide by PCR methods with varying detection rates of 0.4 % to 27.5 % for WUPyV and 0.5 % to 8 % for KIPyV [72, 73].

However, the pathogenic roles of WUPyV and KIPyV in respiratory disease remain speculative, as there is no significant difference between the detection rates in patients with respiratory infection and healthy controls [74–76]. For example, Wattier et al. reported that WUPyV was detected at a rate of 7.1 % in symptomatic cohorts and 6.3 % in asymptomatic cohorts, while KIPyV was detected at a rate of 2.2 % in symptomatic cohorts and 0 % in asymptomatic cohorts [74]. Similarly, van de Pol et al. detected WUPyV at rates of 2.6 % and 2.4 % and KIPyV at a rate of 0 % and 4.8 % in children with or without LRTI, respectively [76]. High co-infection rates of WUPyV (26.7 % to 100 %) and KIPyV (33.3 % to 50 %) with other respiratory viruses convolutes the relationship between these viruses and respiratory diseases [72, 75–77]. However, an etiological role of WUPyV and KIPyV in LRTIs has been suggested, because single WUPyV or KIPyV infections have been detected at different titers in patients diagnosed with pneumonia, bronchitis, or bronchiolitis [78, 79]. In immunocompromised groups, especially stem cell transplant patients with respiratory disease, the viral load and frequency of KIPyV are higher than those in control groups (17.8 % vs. 5.1 %), suggesting an increased potential pathogenicity of KIPyV [80]. In addition, WUPyV has frequently been identified in HIV-infected patients with acute respiratory tract infections, with more cases showing moderate to severe LRTIs [81]. Furthermore, IgM antibodies against WUPyV have been detected at a higher rate in children born to mothers infected with HIV than in infants infected with HIV (27.4 % vs. 8.3 %) [82], indicating the early infection of WUPyV in children born to mothers with HIV.

WUPyV and KIPyV have been identified in patients aged <15 years with URIs or LRIs and in patients aged >45 years with URIs; WUPyV has been detected more frequently in older children than in children ≤5 years old [75, 83]. These findings are consistent with the observation that the antibody levels against WUPyV are high in children <6 months old, decreased in children 6–12 months old, and then steadily increase in subsequent age groups, reaching a high titer in healthy adults [85]. In contrast to WUPyV, KIPyV seropositivity appears to increase further with increasing age in adults [85]. The age-related patterns of WUPyV and KIPyV infections may reflect reactivation of latent or persistent infections similar to the patterns of infection seen for BK and JC viruses [83]. More extensive data are needed to establish a definite role of WUPyV and KIPyV in respiratory disease.

Human Parechovirus

HPEVs are members of the *Parechovirus* genus, *Picornaviridae* family, with single-stranded, positive-sense RNA [85]. Since the first two genotypes of HPEV (formerly echovirus 22 and 23) were found 50 years ago [86], 14 additional genotypes/serotypes of HPEVs have been identified in recent years [13]. Among the 16 genotypes, only HPEV-1, -2, -3, -4, -5, and -6 circulate worldwide [85]. In contrast, reports of HPEVs-7-16 are limited [85].

The clinical manifestations of HPEV infections are thought to range from mild gastroenteritis and respiratory tract illnesses to less frequent, serious diseases such as meningitis and neonatal sepsis [85]. HPEVs-1-6 are the common genotypes related to respiratory diseases. HPEV-1 is thought not to be a major pathogen in a report by Harvala et al. as HPEV-positive samples showed a clinical profile with approximately equal frequencies of LRI, URI, and non-respiratory symptoms that most closely matched that of HPEV-screen-negative samples, which was distinct from those of other routinely screened respiratory viruses [87].

Yet the importance of HPEV-1 in respiratory infection is underscored in Abed's retrospective studies where 20 out of 28 children infected with HPEV-1 were diagnosed with either bronchiolitis, pneumonia, or both [88]. In another case, one child who received consolidation chemotherapy for acute lymphoblastic leukemia died from an HPEV-1 infection [88].

HPEV-2 (formerly echovirus 23) has been related to mild respiratory illness, but with a low frequency [88]. HPEV-3 is the second most common genotype of HPEVs [89]. HPEV-3 is an important etiological agent of respiratory infections according to a report in Japan, where HPEV-3 was detected in 14 out of 25 HPEV-positive patients diagnosed with

respiratory illness [89]. HPEV-4, -5, and -6 were retrospectively investigated in the Netherlands, and 31 (11 %) patients were diagnosed with HPEV-4-6 in 277 HPEV-positive samples. Among these, 18 (58 %) of the 31 patients presented with respiratory symptoms, and 6 were diagnosed with pneumonia [90]. The clinical significance of HPEV-6 and -10 in lower respiratory infections is unclear. Importantly, HPEV-3 and -6 have been detected in specimens including lung, spleen, colon, and nasopharyngeal swabs collected upon autopsy of infants who died suddenly of unexplained causes, underscoring the role these viruses may play in respiratory illnesses as well as in systematic infections [91].

The seasonal distribution of HPEVs occurs in late summer and early winter with a biannual rhythm [85]. HPEV infections are commonly observed in the general population, but symptomatic infections are restricted to children less than 3 years old, especially to neonates [92]. In adults, a high level of antibodies against HPEV suggests that many HPEV infections are asymptomatic or subclinical. Analysis of a larger number of samples positive for other HPEV genotypes is needed to further our understanding of the age distribution of HPEVs.

Conclusions

Although the presence of the recently identified viruses discussed here has been detected in the respiratory tract, the relationships between many of these viruses (e.g. HBoV, WU and KI PyV and HPEV) and respiratory illness have not been investigated in detail. In contrast to their relatively low incidence, a high seroprevalence in adults suggests frequent infections that may be asymptomatic or subclinical in humans. As the transmission routes of these viruses are not completely established, the detection sites of these viruses may act as transportation sites and may not be the target organs. Accordingly, the pathogenicity of these viruses should be investigated further. However, as not all viruses can be cultured or replicated in animals, determinations of associations between virus infections and diseases are difficult. Large-scale epidemiology studies containing control groups would be important to determine such associations. New strategies such as infectious full-length cDNA clones or recombinant viruses and molecular evolution analysis may be required to investigate fully the pathogenic mechanisms of these viruses to elucidate their roles in LRIs.

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