



A Review on Human Metapneumovirus and Human Bocavirus Associated with Acute Respiratory Tract Infections

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRID/2023/v12i3247

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/96507>

Review Article

Received: 11/12/2022

Accepted: 17/02/2023

Published: 01/03/2023

ABSTRACT

One of the significant causes of morbidity and mortality among young children in developing nations is acute respiratory tract infections (ARTIs). It is also highly contagious, widely prevalent, and transmissible from person to person. It risks young children, the elderly, and those with immune system disorders. Acute respiratory infections are thought to cause 2.6 million child deaths annually worldwide, according to the World Health Organization (WHO) [1]. Infections in children with human metapneumovirus (hMPV) and bocavirus (HBoV) are linked to a high prevalence of ARTIs. It has been determined that hMPV is the second-leading cause of infant bronchiolitis, after the respiratory syncytial virus (RSV), of upper and lower respiratory tract infections. Although HBoV was first discovered in children's airways, the high detection rates of other viral pathogens and the discovery of HBoV in stool raise doubts about the virus's significance in respiratory tract infections. According to the published literature, only a few studies have identified ARTIs or demonstrated the

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importance of early diagnosis and treatment of ARTIs. This review article aims to thoroughly explain the aetiology, epidemiology, clinical characteristics, diagnostic approaches, and management of hMPV and HBoV.

Keywords: Communicable diseases; emerging; human metapneumovirus; human bocavirus; acute respiratory tract infections.

1. INTRODUCTION

"Viral and bacterial ARTIs, including the common cold, pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and bronchopneumonia, are very common. There is a high mortality rate and a high economic cost associated with these ARTIs." [2]. ARTIs are infections of breathing-related body parts, such as the lungs, sinuses, throat, or airways. The most frequent cause of pediatric respiratory illness is viral pathogens. Rhinoviruses, respiratory syncytial viruses, influenza, parainfluenza, hMPV, HBoV, measles, mumps, adenoviruses, and coronaviruses are among the culprits [3, 4]. Two crucial viruses for children with ARTIs are hMPV and HBoV. Children with high rates of mixed infection with other viral pathogens had the airways where HBoV was first discovered. Questions have been raised about the proper function of HBoV as a cause of respiratory diseases in light of the virus's detection in stool [5]. "Children's upper and lower respiratory tract infections have been linked to the human metapneumovirus (hMPV), which is second only to the respiratory syncytial virus as a cause of bronchiolitis in young children. These viruses are significant contributors to ARTIs in elderly and immunosuppressed patients. The hMPV is a member of the Paramyxoviridae family and has an eight-gene negative-sense single-stranded RNA genome that codes for nine different proteins" [6]. HBoV has single-stranded DNA and is a member of the Parvoviridae family [7]. The undiagnosed lower respiratory tract infections (LRTIs) and upper respiratory tract infections (URTIs) in children under five are now thought to be caused by the hMPV and HBoV, which are now regarded as critical viral pathogens. Research is being conducted on strategies for treatment and prevention and effective diagnostic tools for clinicians. This review focuses on the pathogenesis, clinical characteristics, epidemiology, and diagnostic methods for HBoV and hMPV.

2. ACUTE RESPIRATORY TRACT INFECTION

The respiratory tract is prone to many infections, including pleuritis (lasting for less than 30 days),

sinus infection, and rhinitis [8]. "Infections of the respiratory tract can be bacterial or viral in origin, with viral infections being more common and typically only affecting the upper respiratory tract. Depending on which organs are impacted, ARTIs can be divided into upper respiratory tract infections (URIs) or lower respiratory tract infections (LRIs). There are three categories of clinical severity for ARTIs: mild, moderate, and severe" [9]. "The constant contact that children have with other children who might be virus carriers puts them in particular danger. Children frequently rub their eyes, do not regularly wash their hands, and put their fingers in their mouths, all of which contribute to the spread of viruses. Acute respiratory infections are more common in people who have heart disease or other lung conditions. Anyone whose immune system may have been compromised by another illness is vulnerable. Smokers are more vulnerable and experience more difficulty in recovering" [10].

In the winter and wet seasons, URIs are a common cause of hospitalization due to cough, coryza, sore throat, or hoarseness, frequently associated with acute febrile illnesses. In children attending daycare facilities and schools, the number of URI episodes per year can range from six to eight, and they can even be more frequent [11]. The majority of these URIs are self-limited, mild, and rarely life-threatening. Infants with URIs may become lethargic and have trouble feeding. It can also result in clinical conditions such as acute otitis media, asthma flare-ups, and LRIs like bronchitis, bronchiolitis, and pneumonia [12].

"The most common symptom of an LRIs is cough, followed by dyspnea or wheezing, chest discomfort and pain (usually occurring within 21 days of the onset of the illness) (e.g., sinusitis or asthma). There are many clinical symptoms associated with LRIs, including tachypnea, fever, cough, hypoxia, bronchitis, bronchiolitis, and pneumonia" [13]. Chest radiograph changes include infiltrated hyperinflation and peribronchial cuffing. LRIs, particularly pneumonia, cause the most severe illnesses and deaths in ARTIs. In children under five years of age and immunocompromised individuals, the severity of the disease is very high [14].

3. PREVALENCE OF ARTIS

The most common cause of ARTI deaths in children under the age of five is pneumonia (which is responsible for 20% of deaths). As a result of neonatal pneumonia, the mortality rate for children under the age of five rises to 35-40%, or 2.04 million deaths per year. The countries of sub-Saharan Africa have the second-highest incidence of ARIs, and together they account for more than 80% of all cases worldwide [15]. "The morbidity and mortality of ARI in children are affected by a variety of social and environmental factors. Poverty, poor nutrition, inadequate housing, indoor air pollution (including parental smoking), poor ventilation, overcrowding, industrialization, sociocultural values, excessive and inappropriate use of antibiotics, a lack of essential health services, and a lack of awareness are some of the contributing factors"[16]. "It's also crucial to remember that a quarter of child ARI deaths can be linked to passive smoking. According to the National Family Health Survey, which was conducted in 2019–2020, the prevalence of ARIs in the two weeks prior was 2.4% in urban areas and 3.8% in rural areas of Maharashtra state. Over two-thirds of all paediatric illnesses are caused by ARIs in Indian slum areas" [17]. "Almost 2, 65,000 hospital deaths of young children were attributed to ARI globally in 2010, with 99% of these deaths being reported in developing nations. Over two-thirds of all paediatric illnesses occur in urban slum areas. In India, ARTIs account for 15.9% of deaths among children aged 1 to 5 and 14.3% of deaths among infants, the majority of which are preventable. Because of the high rates of morbidity and mortality linked to ARTIs, the healthcare system continues to face significant difficulties in controlling individuals" [18].

4. AETIOLOGY OF ARTIS

"Infections of the respiratory tract can be brought on by a variety of microorganisms, the most common of which are bacteria and viruses. Most upper respiratory tract infections are caused by viruses, whereas bacterial infections can be either primary or secondary to infections with measles, influenza, or respiratory syncytial virus (RSV)" [19]. "*Streptococcus pneumoniae*, *Haemophilus influenzae* (type B), *Streptococcus pyogenes*, and *Staphylococcus aureus* are the most prevalent bacteria linked to ARTIs. Atypical pneumonia can also be caused by *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*" [20].

"A significant cause of morbidity and mortality is ARTIs in viruses. Respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses (PIV), adenoviruses, human rhinovirus (hRV), hMPV, HBoV, coronaviruses, and picornaviruses are the main viral etiological agents of ARTIs in all age groups" [21,22]. RSV, hMPV, hRV, and PIV are the most common among them and are seasonal illnesses that can occur with or without co- infection in children under the age of five [23].

5. DIAGNOSIS OF VIRAL RESPIRATORY TRACT INFECTIONS

It is practically impossible to distinguish the cause of a respiratory tract infection based on clinical circumstances. To treat and stop the spread of viral respiratory infections, a quick and accurate diagnosis of the etiological agent is crucial [24]. Based on the appropriate diagnostic approach selected by the medical staff when performing the test, laboratory diagnosis can significantly improve care. Numerous techniques for identifying respiratory tract infections include molecular-based nucleic acid amplification assays, immunofluorescence tests for antibody detection, conventional and quick cell culture techniques, and rapid antigen testing [25]. Nasopharyngeal aspirates, nasopharyngeal washes, nasopharyngeal swabs, and oropharyngeal swabs in viral transport media are among the specimen types used to identify respiratory viruses. Tubes are used to collect sputum, endotracheal aspirates, and bronchioalveolar lavages. Each method's sensitivity is influenced by various elements, including the type of sample, the moment the sample was taken, the onset of the patient's symptoms, their age, the antigen target, and the characteristics of the virus [26, 27]. Immunocompromised individuals shed low titers of the virus over a long period, making non-molecular methods of detection challenging. As a result, molecular-based methods for nucleic acid amplification have gained popularity because they are quick and susceptible assays for identifying respiratory viruses [28, 29]. Each method for detecting respiratory viruses has benefits and disadvantages.

"Although it takes days and frequently weeks to see results, the traditional tube culture method is useful for growing a wide variety of viruses, including new or unidentified ones. The turnaround time has been lowered from 10 days to 24 hours, thanks to modified cell culture techniques like the centrifugation-enhanced

shell-vial method" [30]. "Compared to traditional culture, shell-vial culture using combination cell lines enables the simultaneous detection of multiple respiratory viruses. It has similar sensitivity for parainfluenza 1 -3 (87% vs 83%) and influenza A/B (78% vs 75%) and noticeably higher sensitivity for RSV (73% vs 42%)" [31].

"Rapid immunoassays (RIAs), which are frequently used in point-of-care testing (POCT), can deliver test results in less than 30 minutes and allow the test results to be incorporated into the clinical decision-making algorithm. Commercially available immunoassays have shown high sensitivity (93%) for the detection of RSV in the paediatric population. Further research has shown that the sensitivity of RSV RIAs is comparatively higher for children (81%) than for adults (29%), according to a systematic review of published studies. The higher sensitivity can be attributed to the fact that children frequently shed higher titers of respiratory viruses for a longer period of time than adults" [32, 33]. Serological tests can identify pathogen-specific antibodies that typically appear two weeks after the initial infection. Most respiratory pathogens, including RSV, adenovirus, influenza A and B, parainfluenza 1-3 virus, etc., can be successfully detected by serological tests. Except for infants, for whom an antibody response is typically undetectable, it can also identify mixed infections in hospitalised children with acute respiratory infections [34]. In contrast to molecular techniques like RT-PCR, serological assays have been found to be significantly less sensitive for detecting parainfluenza virus and adenovirus [35]. Compared to fluorescent antibody assay, RT-PCR can identify 40% more samples from paediatric patients who tested positive for at least one respiratory virus (FA). In epidemiological studies, FA testing is beneficial in addition to RT-PCR because it improves the likelihood of detecting acute viral infections and has been used to precisely assess respiratory viruses other than influenza in children [36-38].

6. HUMAN METAPNEUMOVIRUS

6.1 Discovery and Classification of hMPV

The hMPV was first discovered in 28 nasopharyngeal aspirates (NPA) taken from children under five who had respiratory tract infections over 20 years in the Netherlands [39, 40]. The virus produced a cytopathic effect similar to RSV and replicated very slowly in

tertiary monkey kidney cells. The supernatant from the infected cells revealed by electron microscopy contained paramyxovirus-like pleomorphic particles with diameters ranging from 150 to 600 nm and short projections of 13 to 17 nm in length. Unlike other Paramyxoviruses like RSV and parainfluenza, the nucleocapsid was not apparent. It did not agglutinate erythrocytes and was inactivated by chloroform. Different respiratory virus-specific primers used in a reverse transcriptase reaction failed to yield promising results. The morphological characteristics and genomic pattern placed it in the Paramyxoviridae, Pneumovirinae subfamily, and Metapneumovirus genus [41, 42].

6.2 Genotypes of hMPV

"The genomic organisation of hMPV and RSV is similar, but hMPV lacks NS1 and NS 2, and the antisense RNA genome of hMPV has eight open reading frames in a slightly different gene order than RSV (3'-N-P-M-F-M2-S H-G-L-5')" [43]. The avian metapneumoviruses A, B, and type C, particularly, are genetically related to the human metapneumovirus (hMPV). The two main genetic lineages of hMPV, designated subtypes A and B, with their respective subgroups A1/A2 and B1/B2, have been identified through phylogenetic analysis. Compared to hMPV-A, subtype B of the virus was associated with longer-lasting coughs and general respiratory systems, according to genotyping based on the F and G gene sequences [44]. In the nose and lungs, the hMPV infects cells that line the airways. The glycoprotein (G) protein of hMPV, in addition to interacting with heparan sulphate and other glycosaminoglycans, allows it to affix to the target cell. To mediate the fusion of the cell membrane and viral envelope in a pH-independent manner, most likely inside endosomes, the hMPV fusion (F) protein encodes an RGD (Arg-Gly-Asp) motif that engages RGD-binding integrins as cellular receptors [45- 47].

6.3 Prevalence of hMPV

The hMPV is more frequently detected in children, mainly in those under two years old, with an average age of 22 months. According to seroprevalence studies [48], by the ages of 5 to 10, 90 to 100% of children have contracted hMPV. Acute lower respiratory tract infections brought on by hMPV account for 5 to 10% of paediatric hospitalisations. In general, infants with hMPV infection were three times more likely

to be hospitalised than infants between 6 months and five years [49, 50]. Different viral genotypes or insufficient immunity from the initial infection may cause re-infection. Although adults typically only have mild flu-like symptoms, older people, people with compromised immune systems, and people with chronic lung diseases may experience complications [51, 52].

6.4 Clinical Manifestations of hMPV

When the hMPV enters the body, it infects the cells of the respiratory tract, including the mouth, nose, and throat. The immune system responds whenever these cells become infected, producing symptoms like pain, low-grade fever, cough, runny nose, headache, and sore throat. The disease may impact some people's bronchi or significant airways. The virus's spread may bring on coughing and wheezing. Reduced fever and weight loss can occur in children under one year old [53, 54]. In some patient populations, it's possible that hMPV can lead to severe illness that necessitates hospitalization. Patients with compromised immune systems and those with cardiac or respiratory conditions are among them. These patients are more likely to experience acute respiratory failure that necessitates high-flow oxygen support; in some cases, these patients may even deteriorate to the point where mechanical ventilation is necessary. Patients must be constantly observed in the intensive care unit [55].

6.5 Diagnosis of hMPV

Techniques like cell culture, nucleic acid amplification, antigen detection, and serological methods can be used to diagnose hMPV infection. In conventional cell cultures, the hMPV reproduces ineffectively and exhibits only mild cytopathic effects [56]. Additionally, the method costs a lot of money and calls for unique steps like trypsin addition.

Tertiary monkey kidney cells, Vero cells, LLC-MK2-cells, BEAS-2B cells, A549 cells, and HepG2 cells are among the various cell lines where hMPV can be grown [57]. Tertiary monkey kidney, LLC-MK 2, and Vero cell lines exhibit cytopathic effects, but only after 10 to 21 days of incubation. A quick method for determining hMPV is the shell vial culture technique, which incorporates centrifugation, brief incubation, and fluorescent staining [58]. A rapid method for identifying hMPV is the direct immunofluorescence assay, which uses labelled

antibodies to find hMPV antigens in respiratory specimens. Microarray and ELISA techniques are also employed but are not offered commercially. The most popular and accurate method to identify hMPV is reverse transcriptase PCR assays, which amplify the viral RNA. Targets commonly used include F, N, G, L, and M. The F and N genes are considered more specific and conserved for identifying hMPV [59, 60].

6.6 Treatment for hMPV

There is currently no specific FDA-approved antiviral treatment for hMPV infection. Symptomatic care is a regular part of treatment, and when necessary, respiratory support is provided [61]. Supportive measures are the mainstays of treatment. Patients with fever are given antipyretic drugs like acetaminophen and ibuprofen. If the patient appears dehydrated and cannot tolerate oral hydration, intravenous fluid hydration is recommended [62]. In severe cases of acute respiratory failure, patients with hMPV may also need additional oxygen support, such as a high-flow nasal cannula or mechanical ventilation. This is particularly true for patients with pre-existing respiratory or cardiac disease and those who are immunocompromised. The majority of patients do recover completely. Patients with hMPV should be put on droplet precautions to prevent the spread of the disease. For hMPV, there is currently no vaccine available [63, 64]. However, several vaccines tested on rodents and non-human primates against various hMPV structures seem promising. However, none have been examined on human test subjects.

6.7 Prevention of hMPV

Emphasis should be placed on preventative measures to treat other respiratory illnesses, including covering the mouth and nose with a tissue when coughing or sneezing into the upper sleeve rather than the hands, promptly throwing away used tissues and washing hands properly. They wash their hands for at least 20 seconds with soap and water. Do not touch your mouth, nose, or eyes with unwashed hands. Avoid being close to sick people [65].

7. HUMAN BOCAVIRUS

7.1 Discovery and Classification of HBoV

Using molecular screening techniques, HBoV was identified in Sweden in 2005 from the

combined cell-free filtrates of the NPA from kids with ARTIs. HBoV is a member of the genus Bocavirus, family Parvoviridae, and subfamily Parvovirinae. Based on the sequence similarities and genomic organization of these two close relatives, the name Bocavirus was created by combining the terms bovine parvovirus (BPV) and canine minute virus (CMV) [66]. Parvovirus B19 (B 19V), a pathogenic adenovirus-associated virus, a member of the genus Dependoparvovirus, and the recently identified parvoviruses 4 (PARV4) and 5 (PARV5), members of the new genus Tetraparvovirus, are the parvoviruses linked to human infections [67, 68]. Although the latter hasn't yet been linked to clinical significance, the new genus Hokovirus has been assigned to it based on similarities [69, 70].

7.2 Genotypes of HBoV

Bovine parvovirus (BPV), canine minute virus (CMV), and HBoV are all members of the genus Bocavirus [71]. There are currently 1 to 4 different subtypes of the HBoV virus. While the other three are frequently found in gastrointestinal specimens, HBoV1 is the most frequent subtype in respiratory samples. Only vertebrates can contract HBoV genotypes, which are members of the family Parvoviridae, subfamily Parvovirinae, and genus Bocavirus [72, 73]. The subfamily Densovirinae, which infects arthropods and has no sequence homology with the other subfamily, is part of the Parvoviridae family. Eight genera of the subfamily Parvovirinae is recognized by the current classification of the International Committee on Taxonomy of Viruses database: Amdoparvovirus, Aveparvovirus, Bocaparvovirus, Copiparvovirus, Dependoparvovirus, Erythroparvovirus, Protoparvovirus, and Tetraparvovirus [74,75].

7.3 Prevalence of HBoV

In three studies, HBoV was found using PCR in the respiratory secretions of adults with respiratory tract infections in 1 of 126 (0.8%), 3 of 202 (1.5%), and 3.1% cases [76-78]. A case study of five adults with bocavirus-associated pneumonia included five patients [79]. Adults with bocavirus-associated pneumonia were the subjects of one hospital and four outpatient cases in another series. Serologic responses to HBoV infection have also been documented. The first report of HBoV and adenovirus co-infection in immune-suppressed and non-immuno-

suppressed children in Mexico were published. In a 2008 study by Lindner, 280 of 299 adults (or 94%) had an immunoglobulin G (IgG) response, while 2 of 299 cases (or 1% of the population) had an immunoglobulin M (IgM) response [80].

7.4 Clinical Manifestations of HBoV

Clinical signs and symptoms of HBoV infections are similar to those caused by other respiratory pathogens [81]. Wheezing, respiratory distress, fever, cough, rhinorrhea, bronchiolitis, and pneumonia are common respiratory symptoms in HBoV-infected people. In children with acute otitis media, HBoV has been found in the NPA and middle ear fluid [82]. Although several studies have found HBoV in stool samples from kids with acute gastrointestinal disorders, its pathogenicity is unknown [83, 84]. Like other respiratory viruses, HBoV infection is at risk for congenital heart conditions, asthma, chronic obstructive pulmonary disease, immunosuppression, maternal smoking, preterm birth, and winter birth. Infection with the HBoV may also result from daycare facilities, drinking sewage or river water, or both [85].

7.5 Diagnosis of HBoV

Currently, a suitable culture method for HBoV identification needs to be developed. As a result, real-time PCR assays are frequently used to identify viruses from NPAs, typically focusing on the NS1, NP 1, and VP1/ 2 genes [86]. For the detection of HBoV, other molecular techniques are also employed [87]. Comparing real-time PCR to traditional PCR assay techniques, real-time PCR is more sensitive, specific, and time-saving. Numerous commercial multiplex assay techniques can be used to find HBoV [88]. The EIA of IgG avidity has been developed to identify primary HBoV infection and immune activation [89]. ELISA techniques can find HBoV antibodies in serum using VLPs of VP1 and VP2 viruses [90, 91]. Detecting HBoV infections can be made possible by immunofluorescence assays that look for IgG antibodies and biomarker-based assays [92-94]. As the virus will be present in the blood during the active infective stage, initial screening of clinical samples (respiratory or stool) followed by a subsequent serum sample will aid in accurately diagnosing HBoV infection.

7.6 Treatment of HBoV

No specific in vivo or in vitro antiviral treatments or vaccinations can prevent HBoV. Only

encouraging measures are in place. Standard safety measures should be taken in order to avoid the virus from spreading through contaminated aerosols [95,96].

7.7 Prevention of HBoV

Like other respiratory viruses, HBoV1 prevention and infection control measures are necessary [97]. Coughing causes these viruses to spread into the air as they infect the respiratory tract. Although contact and infectious respiratory aerosols of various sizes can also spread respiratory viruses, large droplets are the primary means of transmission for most respiratory viruses [98]. But general infection control measures for all respiratory viral infections include good hand hygiene, medical masks and gloves, and isolation precautions.

8. CONCLUSION

In adults and children around the world, ARTIs significantly increase morbidity and mortality. Novel viral infections have suddenly become more prevalent over the past 20 years. Clinicians must be guided in their decision-making regarding diagnosis and treatment by carefully considering clinical features, diagnosis, and epidemiology research. The clinical manifestations, diagnostic techniques, available treatments, and prevention of ARTIs can all be better understood with the aid of this review.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Merera A, Asena T, Senbeta M. Bayesian multilevel analysis of determinants of acute respiratory infection in children under the age of five years in Ethiopia. *BMC Pediatr.* 2022;22(1):123. DOI: 10.1186/s12887-022-03187-4. PMID: 35272658; PMCID: PMC8908561.
2. Hassen S, Getachew M, Eneyew B, Keleb A, Ademas A, Berihun G, Berhanu L, Yenuss M, Natnael T, Kebede AB, Sisay T. Determinants of acute respiratory infection (ARI) among under-five children in rural areas of Legambo District, South Wollo Zone, Ethiopia: A matched case-control study. *Int J Infect Dis.* 2020; 96: 688-695. DOI: 10.1016/j.ijid.2020.05.012. Epub 2020 May 12. PMID: 32413607.
3. Kumar P, Srivastava M. Prophylactic and therapeutic approaches for human metapneumovirus. *Virusdisease.* 2018; 29(4):434-444. DOI: 10.1007/s13337-018-0498-5. Epub 2018 Oct 20. PMID: 30539045; PMCID: PMC6261883.
4. Murgia V, Manti S, Licari A, De Filippo M, Ciprandi G, Marseglia GL. Upper respiratory tract infection-associated acute cough and the urge to cough: New insights for clinical practice. *Pediatr Allergy Immunol Pulmonol.* 2020;33(1): 3-11. DOI: 10.1089/ped.2019.1135. PMID: 33406022; PMCID: PMC7875114
5. He P, Wang J, Ke R, Zhang W, Ning P, Zhang D, Yang X, Shi H, Fang P, Ming Z, Li W, Zhang J, Dong X, Liu Y, Zhou J, Xia H, Yang S. Comparison of metagenomic next-generation sequencing using cell-free DNA and whole-cell DNA for the diagnoses of pulmonary infections. *Front Cell Infect Microbiol.* 2022; 12:1042945. DOI: 10.3389/fcimb.2022.1042945. PMID: 36439227; PMCID: PMC9684712.
6. Keleb A, Sisay T, Alemu K, Ademas A, Lingerew M, Kloos H, Chane Mekonnen T, Derso A, Adane M. Pneumonia remains a leading public health problem among under-five children in peri-urban areas of north-eastern Ethiopia. *Plos One.* 2020;15(9):e0235818. DOI: 10.1371/journal.pone.0235818. PMID: 32915807; PMCID: PMC7485761
7. NFHS-5 Factsheet; 2019-2020. Available: http://rchiips.org/nfhs/NFHS-5_FCTS/FactSheet_MH.pdf (accessed December 23, 2020).
8. Phukan I, Baruah R, Ahmed SJ, Mahanta TG, Mahanta B, Hussain FS. Sociodemographic and environmental factors influencing acute respiratory infections among under-five children of chars (riverine islands) of Tinsukia District, Assam: A community-based

- cross-sectional study. *Indian J Public Health*. 2022;66(3):344-347.
DOI: 10.4103/ijph.ijph_1691_21. PMID: 36149119
9. Merera AM. Determinants of acute respiratory infection among under-five children in rural Ethiopia. *BMC Infect Dis*. 2021;21(1):1203.
DOI: 10.1186/s12879-021-06864-4. PMID: 34847859; PMCID: PMC8631694.
 10. Lu D. Children's immunity at risk. *New Sci*. 2021;250(3332):8-9.
DOI: 10.1016/S0262-4079(21)00716-8. Epub 2021 Apr 30. PMID: 33967369; PMCID: PMC8087417
 11. Lee HJ, Woo JH, Cho S, Oh HW, Joo H, Baik HJ. Risk factors for perioperative respiratory adverse events in children with recent upper respiratory tract infection: A single-center-based retrospective study. *Ther Clin Risk Manag*. 2020; 16:1227-1234. DOI: 10.2147/TCRM.S282494. PMID:33363377; PMCID: PMC7754252
 12. Tesema GA, Worku MG, Alamneh TS, Teshale AB, Yeshaw Y, Alem AZ, Ayalew HG, Liyew AM, Tessema ZT. Understanding the rural-urban disparity in acute respiratory infection symptoms among under-five children in Sub-Saharan Africa: A multivariate decomposition analysis. *BMC Public Health*. 2022; 22(1):2013.
DOI: 10.1186/s12889-022-14421-0. PMID: 36324089; PMCID: PMC9632025
 13. Haataja P, Korhonen P, Ojala R, Hirvonen M, Korppi M, Gissler M, Luukkaala T, Tammela O. Hospital admissions for lower respiratory tract infections after early, late, and post-term birth. *Paediatr Perinat Epidemiol*. 2020; 34(2):139-149.
DOI: 10.1111/ppe.12631. Epub 2020 Feb 3. PMID: 32010990
 14. Assane D, Makhtar C, Abdoulaye D, Amary F, Djibril B, Amadou D, Niokhor DJB, Amadou D, Cheikh L, Ndongo D, Mbayame N, Lamine F, Bouh BCS. Viral and bacterial etiologies of acute respiratory infections among children under 5 years in Senegal. *Microbiol Insights*. 2018; 11:1178636118758651.
DOI: 10.1177/1178636118758651. PMID:29467579; PMCID: PMC5815418
 15. Ghimire P, Gachhadar R, Piya N, Shrestha K, Shrestha K. Prevalence and factors associated with acute respiratory infection among under-five children in selected tertiary hospitals of Kathmandu Valley. *Plos One*. 2022;17(4):e0265933.
DOI: 10.1371/journal.pone.0265933. PMID: 35390028; PMCID: PMC8989212
 16. Murarkar S, Gothankar J, Doke P, Dhumale G, Pore PD, Lalwani S, Quraishi S, Patil RS, Waghachavare V, Dhobale R, Rasote K, Palkar S, Malshe N, Deshmukh R. Prevalence of the acute respiratory infections and associated factors in the rural areas and urban slum areas of Western Maharashtra, India: A community-based cross-sectional study. *Front Public Health*. 2021; 9:723807.
DOI: 10.3389/fpubh.2021.723807. PMID: 34765581; PMCID: PMC8576147.
 17. Savitha AK, Gopalakrishnan S. Determinants of acute respiratory infections among fewer than five children in a rural area of Tamil Nadu, India. *J Family Med Prim Care*. 2018 Nov-Dec;7(6):1268-1273.
DOI: 10.4103/jfmpc.jfmpc_131_18. PMID: 30613509; PMCID: PMC6293935
 18. Radó MK, Mölenberg FJM, Westenberg LEH, Sheikh A, Millett C, Burdorf A, van Lenthe FJ, Been JV. Effect of smoke-free policies in outdoor areas and private places on children's tobacco smoke exposure and respiratory health: A systematic review and meta-analysis. *Lancet Public Health*. 2021;6(8):e566-e578.
DOI: 10.1016/S2468-2667(21)00097-9. Epub 2021 Jul 16. PMID: 34274050
 19. Griffiths C, Drews SJ, Marchant DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. *Clin Microbiol Rev*. 2017;30(1):277-319.
DOI: 10.1128/CMR.00010-16. PMID: 27903593; PMCID: PMC5217795.
 20. Pahal P, Rajasurya V, Sharma S. Typical Bacterial Pneumonia. 2022 Aug 1. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 30485000.
 21. Ziyade N, Elgörmüş N, Kara E, Karayel F. Otopsi olgularında viral solunum yolu enfeksiyonu etkenlerinin multipleks PCR yöntemi ile araştırılması: beş yıllık bir çalışma [Investigation of viral respiratory

- tract infection agents by multiplex PCR method in autopsy cases: A five-year study]. *Mikrobiyol Bul. Turkish*. 2019; 53 (2):179-191.
DOI: 10.5578/mb.67960. PMID: 31130122.
22. Moe N, Krokstad S, Stenseng IH, Christensen A, Skanke LH, Risnes KR, Nordbø SA, Døllner H. Comparing Human Metapneumovirus and Respiratory Syncytial Virus: Viral Co-Detections, Genotypes and Risk Factors for Severe Disease. *PLoS One*. 2017;12(1): e0170200.
DOI: 10.1371/journal.pone.0170200. PMID: 28095451; PMCID: PMC5240941
 23. Chu FL, Li C, Chen L, Dong B, Qiu Y, Liu Y. Respiratory viruses among pediatric in patients with acute lower respiratory tract infections in Jinan, China, 2016-2019. *J Med Virol*. 2022; 94(9):4319-4328.
DOI: 10.1002/jm.v.27875. Epub 2022 May 28. PMID: 35593042
 24. Basile K, Kok J, Dwyer DE. Point-of-care diagnostics for respiratory viral infections. *Expert Rev Mol Diagn*. 2018;18(1):75-83.
DOI:10.1080/14737159.2018.1419065. Epub 2017 Dec 26. PMID: 29251007; PMCID: PMC7103700
 25. Nabeya D, Kinjo T, Ueno S, Setoguchi M, Nishiyama N, Kami W, Arakaki W, Haranaga S, Fujita J. Characteristics of patients with viral infections of the lower respiratory tract: A retrospective study. *Medicine (Baltimore)*. 2022;101(38): e30819.
DOI: 10.1097/MD.00000000000030819. PMID: 36197196; PMCID: PMC9509109
 26. Zhang N, Wang L, Deng X, Liang R, Su M, He C, Hu L, Su Y, Ren J, Yu F, Du L, Jiang S. Recent advances in the detection of respiratory virus infection in humans. *J Med Virol*. 2020; 92(4):408-417.
DOI: 10.1002/jmv.25674. Epub 2020 Feb 4. PMID: 31944312; PMCID: PMC7166954
 27. Babaei A, Rafiee N, Taheri B, Sohrabi H, Mokhtarzadeh A. Recent Advances in Early Diagnosis of Viruses Associated with Gastroenteritis by Biosensors. *Biosensors (Basel)*. 2022;12(7):499.
DOI: 10.3390/bios12070499. PMID: 35884302; PMCID: PMC9313180.
 28. Dolskiy AA, Grishchenko IV, Yudkin DV. Cell Cultures for Virology: Usability, Advantages, and Prospects. *Int J Mol Sci*. 2020;21(21):7978.
DOI: 10.3390/ijms21217978. PMID: 33121109; PMCID: PMC7662242
 29. Charlton CL, Babady E, Ginocchio CC, Hatchette TF, Jerris RC, Li Y, Loeffelholz M, McCarter YS, Miller MB, Novak-Weekley S, Schuetz AN, Tang YW, Widen R, Drews SJ. Practical Guidance for Clinical Microbiology Laboratories: Viruses Causing Acute Respiratory Tract Infections. *Clin Microbiol Rev*. 2018;32(1):e00042-18.
DOI: 10.1128/CMR.00042-18. PMID: 30541871; PMCID: PMC6302358
 30. Dilnessa T, Zeleke H. Cell culture, cytopathic effect and immunofluorescence diagnosis of viral infection. *J. Microbiol. Mod. Tech*. 2017;2:102-110.
 31. Drews SJ, Branche AR, Falsey AR, Lee N. What is the role of rapid molecular testing for seniors and other at-risk adults with respiratory syncytial virus infections? *J Clin Virol*. 2019;117:27-32.
DOI: 10.1016/j.jcv.2019.05.010. Epub 2019 May 25. PMID: 31158780
 32. Mesquita FDS, Oliveira DBL, Crema D, Pinez CMN, Colmanetti TC, Thomazelli LM, Gilio AE, Vieira SE, Martinez MB, Botosso VF, Durigon EL. Rapid antigen detection test for respiratory syncytial virus diagnosis as a diagnostic tool. *J Pediatr (Rio J)*. 2017;93(3):246-252.
DOI: 10.1016/j.jped.2016.06.013. Epub 2016 Nov 25. PMID: 27889321.
 33. Benirschke RC, McElvania E, Thomson RB Jr, Kaul KL, Das S. Clinical impact of rapid point-of-care PCR influenza testing in an urgent care setting: A single-center study. *J Clin Microbiol*. 2019; 57(3):e01281-18.
DOI: 10.1128/JCM.01281-18. PMID: 30602445; PMCID: PMC6425177
 34. Saiki-Macedo S, Valverde-Ezeta J, Cornejo-Tapia A, Castillo ME, Petrozzi-Helasvuo V, Aguilar-Luis MA, Del Valle LJ, Cieza-Mora E, Bada C, Del Aguila O, Silva-Caso W, Martins-Luna J, Vasquez-Achaya F, Del Valle-Mendoza J. Identification of viral and bacterial etiologic agents of the pertussis-like syndrome in children under 5 years old hospitalized. *BMC Infect Dis*. 2019;19(1):75.

- DOI: 10.1186/s12879-019-3671-6.
PMID: 30665366; PMCID: PMC6341522
35. Lin CY, Hwang D, Chiu NC, Weng LC, Liu HF, Mu JJ, Liu CP, Chi H. Increased detection of viruses in children with respiratory tract infection using PCR. *Int J Environ Res Public Health*. 2020; 17(2): 564.
DOI: 10.3390/ijerph17020564. PMID: 31952364; PMCID: PMC7013517
 36. Li X, Li J, Meng L, Zhu W, Liu X, Yang M, Yu D, Niu L, Shen X. Viral etiologies and epidemiology of patients with acute respiratory infections based on sentinel hospitals in Gansu Province, Northwest China, 2011-2015. *J Med Virol*. 2018; 90(5):828-835.
DOI: 10.1002/jmv.25040. Epub 2018 Feb 22. PMID: 29388679; PMCID: PMC7166685
 37. Appak Ö, Duman M, Belet N, Sayiner AA. Viral respiratory infections diagnosed by multiplex polymerase chain reaction in pediatric patients. *J Med Virol*. 2019; 91(5):731-737.
DOI: 10.1002/jmv.25379. Epub 2019 Jan 3. PMID: 30570759; PMCID: PMC7167103
 38. Mathisen M, Basnet S, Christensen A, Sharma AK, Tylden G, Krokstad S, Valentiner-Branth P, Strand TA. Viral and Atypical Bacterial Detection in Young Nepalese Children Hospitalized with Severe Pneumonia. *Microbiol Spectr*. 2021;9(2):e0055121.
DOI: 10.1128/Spectrum.00551-21. Epub 2021 Oct 27. PMID: 34704788; PMCID: PMC8549725
 39. Zhao H, Feng Q, Feng Z, Zhu Y, Ai J, Xu B, Deng L, Sun Y, Li C, Jin R, Shang Y, Chen X, Xu L, Xie Z. Clinical characteristics and molecular epidemiology of human metapneumovirus in children with acute lower respiratory tract infections in China, 2017 to 2019: A multicentre prospective observational study. *Viol Sin*. 2022;37(6):874-882.
DOI: 10.1016/j.virs.2022.08.007. Epub 2022 Aug 22. PMID: 36007839; PMCID: PMC9797368
 40. Liu WK, Chen DH, Tan WP, Qiu SY, Xu D, Zhang L, Gu SJ, Zhou R, Liu Q. Paramyxoviruses respiratory syncytial virus, parainfluenza virus, and human metapneumovirus infection in pediatric hospitalized patients and climate correlation in a subtropical region of southern China: a 7-year survey. *Eur J Clin Microbiol Infect Dis*. 2019;38(12): 2355-2364.
DOI: 10.1007/s10096-019-03693-x. Epub 2019 Sep 5. PMID: 31489496; PMCID: PMC685846
 41. Ke Z, Strauss JD, Hampton CM, Brindley MA, Dillard RS, Leon F, Lamb KM, Plemper RK, Wright ER. Promotion of virus assembly and organization by the measles virus matrix protein. *Nat Commun*. 2018;9(1):1736.
DOI: 10.1038/s41467-018-04058-2. PMID: 29712906; PMCID: PMC5928126
 42. Kenmoe S, Vernet MA, Penlap Beng V, Vabret A, Njouom R. Phylogenetic variability of Human Metapneumovirus in patients with acute respiratory infections in Cameroon, 2011-2014. *J Infect Public Health*. 2020;13(4):606-612.
DOI: 10.1016/j.jiph.2019.08.018. Epub 2019 Sep 14. PMID: 31530440.
 43. Uche IK, Guerrero-Plata A. Interferon-Mediated Response to Human Metapneumovirus Infection. *Viruses*. 2018;10(9):505.
DOI: 10.3390/v10090505. PMID: 30231515; PMCID: PMC6163993
 44. Jesse ST, Ludlow M, Osterhaus ADME. Zoonotic Origins of Human Metapneumovirus: A Journey from Birds to Humans. *Viruses*. 2022;14(4):677.
DOI: 10.3390/v14040677. PMID: 35458407; PMCID: PMC9028271.
 45. Nao N, Saikusa M, Sato K, Sekizuka T, Usuku S, Tanaka N, Nishimura H, Takeda M. Recent molecular evolution of human metapneumovirus (HMPV): Subdivision of HMPV A2b strains. *Microorganisms*. 2020;8(9):1280.
DOI: 10.3390/microorganisms8091280. PMID: 32839394; PMCID: PMC7564156
 46. Divarathna MVM, Rafeek RAM, Noordeen F. A review on epidemiology and impact of human metapneumovirus infections in children using TIAB search strategy on PubMed and PubMed Central articles. *Rev Med Virol*. 2020; 30(1):e2090.
DOI: 10.1002/rmv.2090. Epub 2019 Dec 1. PMID: 31788915
 47. Banerjee A, Huang J, Rush SA, Murray J, Gingerich AD, Royer F, Hsieh CL,

- Tripp RA, McLellan JS, Mousa JJ. Structural basis for ultrapotent antibody - mediated neutralization of human metapneumovirus. *Proc Natl Acad Sci USA*. 2022;119(25):e2203326119. DOI: 10.1073/pnas.2203326119. Epub 2022 Jun 13. PMID: 35696580; PMCID:PMC9231621.
48. Malekshahi SS, Yavarian J, Shafiei-Jandaghi NZ, Mokhtari-Azad T, Farahmand M. Prevalence of Human Metapneumovirus Infections in Iran: A Systematic Review and Meta-Analysis. *Fetal Pediatr Pathol*. 2021;40(6):663-673. DOI: 10.1080/15513815.2020.1725939. Epub 2020 Feb 21. PMID: 32081050.
49. Jallow MM, Fall A, Kiori D, Sy S, Goudiaby D, Barry MA, Fall M, Niang MN, Dia N. Epidemiological, clinical and genotypic features of human Metapneumovirus in patients with influenza-like illness in Senegal, 2012 to 2016. *BMC Infect Dis*. 2019;19(1):457. DOI: 10.1186/s12879-019-4096-y. PMID: 31117983; PMCID: PMC6532257.
50. Vinci A, Lee PJ, Krilov LR. Human Metapneumovirus infection. *Pediatr Rev*. 2018;39(12):623-624. DOI: 10.1542/pir.2017-0213. PMID: 30504257.
51. Uche IK, Guerrero-Plata A. Interferon-mediated response to human metapneumovirus infection. *Viruses*. 2018;10(9):505. DOI: 10.3390/v10090505. PMID: 30231515; PMCID: PMC6163993
52. Wang X, Li Y, Deloria-Knoll M, Madhi SA, Cohen C, Ali A, Basnet S, Bassat Q, Brooks WA, Chittaganpitch M, Echavarria M, Fasce RA, Goswami D, Hirve S, Homaira N, Howie SRC, Kotloff KL, Khuri-Bulos N, Krishnan A, Lucero MG, Lupisan S, Mira-Iglesias A, Moore DP, Moraleda C, Nunes M, Oshitani H, Owor BE, Polack FP, O'Brien KL, Rasmussen ZA, Rath BA, Salimi V, Scott JAG, Simões EAF, Strand TA, Thea DM, Treurnicht FK, Vaccari LC, Yoshida LM, Zar HJ, Campbell H, Nair H; Respiratory Virus Global Epidemiology Network. Global burden of acute lower respiratory infection associated with human metapneumovirus in children less than 5 years in 2018: A systematic review and modelling study. *Lancet Glob Health*. 2021; 9(1):e33-e43. DOI: 10.1016/S2214-109X(20)30393-4. Epub 2020 Nov 26. PMID: 33248481; PMCID: PMC7783516
53. Zhao Y, Lu R, Shen J, Xie Z, Liu G, Tan W. Comparison of viral and epidemiological profiles of hospitalized children with severe acute respiratory infection in Beijing and Shanghai, China. *BMC Infect Dis*. 2019;19(1):729. DOI: 10.1186/s12879-019-4385-5. PMID: 31429710; PMCID: PMC6701130.
54. Wang C, Wei T, Ma F, Wang H, Guo J, Chen A, Huang Y, Xie Z, Zheng L. Epidemiology and genotypic diversity of human metapneumovirus in paediatric patients with acute respiratory infection in Beijing, China. *Virol J*. 2021;18(1):40. DOI: 10.1186/s12985-021-01508-0. PMID: 33602245; PMCID: PMC7890387
55. Oong XY, Chook JB, Ng KT, Chow W Z, Chan KG, Hanafi NS, Pang YK, Chan YF, Kamarulzaman A, Tee KK. The role of human Metapneumovirus genetic diversity and nasopharyngeal viral load on symptom severity in adults. *Virol J*. 2018;15(1):91. DOI: 10.1186/s12985-018-1005-8. PMID: 29792212; PMCID: PMC5966857.
56. Jeong S, Park MJ, Song W, Kim HS. Advances in laboratory assays for detecting human metapneumovirus. *Ann Transl Med*. 2020;8(9):608. DOI: 10.21037/atm.2019.12.42. PMID: 32566634; PMCID: PMC7290561
57. Feng ZS, Zhao L, Wang J, Qiu FZ, Zhao MC, Wang L, Duan S X, Zhang RQ, Chen C, Qi JJ, Fan T, Li GX, Ma XJ. A multiplex one-tube nested real time RT-PCR assay for simultaneous detection of respiratory syncytial virus, human rhinovirus and human metapneumovirus. *Virol J*. 2018;15(1):167. DOI: 10.1186/s12985-018-1061-0. PMID: 30376870; PMCID: PMC6208169
58. Nao N, Sato K, Yamagishi J, Tahara M, Nakatsu Y, Seki F, Katoh H, Ohnuma A, Shirogane Y, Hayashi M, Suzuki T, Kikuta H, Nishimura H, Takeda M. Consensus and variations in cell line specificity among human metapneumovirus strains. *Plos One*. 2019;14(4):e0215822.

- DOI:10.1371/journal.pone. 215822.
PMID: 31013314; PMCID: PMC6478314
59. Larsson E, Johansson S, Frøbert O, Nordenskjöld A, Athlin S. Evaluation of the ImmuView RSV Test for Rapid Detection of Respiratory Syncytial Virus in Adult Patients with Influenza-Like Symptoms. *Microbiol Spectr.* 2021;9(3): e0093721.
DOI: 10.1128/Spectrum. 00937 -21. Epub 2021 Dec 8. PMID: 34878317; PMCID: PMC8653817
 60. You HL, Chang SJ, Yu HR, Li CC, Chen CH, Liao WT. Simultaneous detection of respiratory syncytial virus and human metapneumovirus by one-step multiplex real-time RT-PCR in patients with respiratory symptoms. *BMC Pediatr.* 2017;17(1):89.
DOI: 10.1186/s12887-017-0843-7. PMID: 28347279; PMCID: PMC5368990
 61. Cong S, Wang C, Wei T, Xie Z, Huang Y, Tan J, Chen A, Ma F, Zheng L. Human metapneumovirus in hospitalized children with acute respiratory tract infections in Beijing, China. *Infect Genet Evol.* 2022;106:105386.
DOI: 10.1016/j.meegid. 2022.105386. Epub 2022 Nov 11. PMID: 36372116.
 62. González LA, Vázquez Y, Mora JE, Palavecino CE, Bertrand P, Ferrés M, Contreras AM, Beckhaus AA, Riedel CA, Bueno SM. Evaluation of monoclonal antibodies that detect conserved proteins from Respiratory Syncytial Virus, Metapneumovirus and Adenovirus in human samples. *J Virol Methods.* 2018; 254:51-64.
DOI: 10.1016/j.jviromet.2018.01.011. Epub 2018 Feb 1. PMID: 29410056
 63. Choi SH, Hong SB, Huh JW, Jung J, Kim MJ, Chong YP, Kim SH, Sung H, Koo HJ, Do KH, Lee SO, Lim CM, Kim YS, Woo JH, Koh Y. Outcomes of severe human metapneumovirus-associated community-acquired pneumonia in adults. *J Clin Virol.* 2019;117:1-4.
DOI: 10.1016/j.jc v.2019.05. 007. Epub 2019 May 15. PMID: 31128379; PMCID: PMC7106415
 64. Velayutham TS, Ivanciuc T, Garofalo RP, Casola A. Role of human metapneumovirus glycoprotein G in modulation of immune responses. *Front Immunol.* 2022;13:962925.
DOI: 10.3389/ fimmu. 2022.962925. PMID:35958551; PMCID: PMC9357950
 65. Bar-Peled Y, Diaz D, Pena-Briseno A, Murray J, Huang J, Tripp RA, Mousa JJ. A Potent Neutralizing Site III-Specific Human Antibody Neutralizes Human Metapneumovirus In Vivo. *J Virol.* 2019; 93(19):e00342-19.
DOI: 10.1128/JVI.00342-19. PMID: 31292250; PMCID: PMC6744252
 66. Kumthip K, Khamrin P, Yodmeeklin A, Ushijima H, Maneekarn N. Contamination of Human Bocavirus Genotypes 1, 2, 3, and 4 in Environmental Waters in Thailand. *Microbiol Spectr.* 2021;9(3):e0217821
DOI: 10.1128/spectrum.02178 -21. Epub 2021 Dec 22. PMID: 34937184; PMCID: PMC8694147.
 67. Lasure N, Gopalkrishna V. Molecular epidemiology and clinical severity of Human Bocavirus (HBoV) 1-4 in children with acute gastroenteritis from Pune, Western India. *J Med Virol.* 2017;89(1): 17-23.
DOI: 10.1002/jm v.24593. Epub 2016 Jul 11. PMID: 27272684
 68. Soares LS, Lima ABF, Pantoja KC, Lobo PS, Cruz JF, Guerra SFS, Bezerra DAM, Bandeira RS, Mascarenhas JDP. Molecular epidemiology of human bocavirus in children with acute gastroenteritis from North Region of Brazil. *J Med Microbiol.* 2019; 68(8):1233-1239.
DOI: 10.1099/jmm.0.001026. Epub 2019 Jun 19. PMID: 31215861
 69. Alkhalif H, Almutairi AR, Almutairi A, Almutairi RK, AlGhnam S, Aljohani S, Alqanatish JT, Babiker A. Prevalence and clinical characterization of bocavirus infection in a specialized children's hospital in Saudi Arabia. *Cureus.* 2022; 14(2): e22127.
DOI: 10.7759/cureus.22127. PMID: 35308707; PMCID: PMC8918207
 70. Piñana M, Vila J, Andrés C, Saura J, González-Sánchez A, Creus-Costa A, Saubi N, Esperalba J, Rando A, Iglesias- Cabezas MJ, Quer J, Soriano-Arandes A, Soler-Palacín P, Pumarola T, Antón A. Molecular characterization and clinical impact of human bocavirus at a tertiary hospital in Barcelona (Catalonia, Spain) during the 2014-2017 seasons. *Infection.* 2022; 1–9.

- DOI:10.1007/s15010-022-01955-z. Epub ahead of print. PMID: 36401674; PMCID: PMC9676756
71. Liao J, Yang Z, He Y, Wei J, Ren L, and Liu E, Zang N. Respiratory tract infection of fatal severe human bocavirus 1 in a 13- month-old child: A case report and literature review. *Front Pediatr.* 2022;10: 949817. DOI: 10.3389/fped.2022.949817. PMID: 36605757; PMCID: PMC980 8049
 72. Ljubin-Sternak S, Slović A, Mijač M, Jurković M, Forčić D, Ivković-Jureković I, Tot T, Vraneš J. Prevalence and Molecular Characterization of Human Bocavirus Detected in Croatian Children with Respiratory Infection. *Viruses.* 2021;13 (9):1728. DOI: 10.3390/ v13091728. PMID: 34578309; PMCID: PMC8473146
 73. Abozahra R, Abdelhamid SM, Khairy K, Baraka K. Detection and phylogenetic analysis of Human bocavirus in children diagnosed with acute respiratory tract infection. *Med Microbiol.* 2020;69(9):1197-1202. DOI: 10.1099/jmm.0.001243. Epub 2020 Aug 19. PMID: 32812862
 74. Mohammadi M, Yavarian J, Karbasizade V, Moghim S, Esfahani BN, Hosseini NS. Phylogenetic analysis of human bocavirus in children with acute respiratory infections in Iran. *Acta Microbiol Immunol Hung.* 2019;66(4):485-497. DOI: 10.1556/ 030. 66.2019.017. Epub 2019 May 31. PMID: 31146533.
 75. Cotmore SF, Agbandje-McKenna M, Canuti M, Chiorini JA, Eis-Hubinger AM, Hughes J, Mietzsch M, Modha S, Ogliaastro M, Péntzes JJ, Pintel DJ, Qiu J, Soderlund- Venermo M, Tattersall P, Tijssen P, Ictv Report Consortium. ICTV Virus Taxonomy Profile: Parvoviridae. *J Gen Virol.* 2019; 100(3): 367-368. DOI: 10.1099/jgv.0.001212. Epub 2019 Jan 23. PMID: 30672729; PMCID: PMC6537627.
 76. Stobnicka-Kupiec A, Gołofit-Szymczak M, Cyprowski M, Górny RL. Detection and identification of potentially infectious gastrointestinal and respiratory viruses at workplaces of wastewater treatment plants with viability qPCR/ RT-qPCR. *Sci Rep.* 2022;12(1):4517. DOI: 10.1038/s41598-022-08452-1. PMID: 35296727; PMCID: PMC8 924946
 77. Coverstone AM, Wang L, Sumino K. Beyond respiratory syncytial virus and rhinovirus in the pathogenesis and exacerbation of asthma: The role of metapneumovirus, bocavirus and influenza virus. *Immunol Allergy Clin North Am.* 2019;39(3):391-401. DOI: 10.1016/j.iac.2019.03.007. Epub 2019 May 16. PMID: 31284928; PMCID: PMC7127190
 78. Kenmoe S, Vernet MA, Njankouo-Ripa M, Penlap VB, Vabret A, Njouom R. Phylogenic analysis of human bocavirus detected in children with acute respiratory infection in Yaounde, Cameroon. *BMC Res Notes.* 2017;10(1):293. DOI: 10.1186/s13104-017-2620-y. PMID: 28716110; PMCID: PMC5514512
 79. von Mollendorf C, Berger D, Gwee A, Duke T, Graham SM, Russell FM, Mulholland EK; ARI review group. Aetiology of childhood pneumonia in low- and middle- income countries in the era of vaccination: a systematic review. *J Glob Health.* 2022;12:10009. DOI: 10.7189/jogh.12.10009. PMID: 35866332; PMCID: PMC9305023
 80. Bagasi AA, Howson-Wells HC, Clark G, Tarr AW, Soo S, Irving WL, McClure CP. Human Bocavirus infection and respiratory tract disease identified in a UK patient cohort. *J Clin Virol.* 2020;129:104453. DOI: 10.1016/j.jc v.2020.104453. Epub 2020 May 21. PMID: 32534437; PMCID: PMC7240277
 81. Madi NM, Al-Adwani A. Human bocavirus (HBoV) in Kuwait: molecular epidemiology and clinical outcome of the virus among patients with respiratory diseases. *J Med Microbiol.* 2020;69(7):1005-1012. DOI: 10.1099/jmm.0.001219. PMID: 32579103; PMCID: PMC7481742
 82. Bertrand PJ, Vázquez Y, Beckhaus AA, González LA, Contreras AM, Ferrés M, Padilla O, Riedel CA, Kalergis AM, Bueno SM. Identification of biomarkers for disease severity in nasopharyngeal secretions of infants with upper or lower respiratory tract viral infections. *Clin Exp Immunol.* 2022; 210(1):68-78. DOI: 10.1093/cei/uxac083. PMID: 36036806; PMCID: PMC9585550
 83. Christensen A, Kesti O, Elenius V, Eskola AL, Døllner H, Altunbulakli C,

- Akdis CA, Söderlund-Venermo M, Jartti T. Human bocaviruses and paediatric infections. *Lancet Child Adolesc Health*. 2019;3(6): 418-426.
DOI: 10.1016/S2352-4642(19)30057-4. Epub 2019 Apr 1. PMID: 30948251
84. Seynaeve D, Augusseau-Rivière B, Couturier P, Morel-Baccard C, Landelle C, Bosson JL, Gavazzi G, Mallaret MR. Outbreak of Human Metapneumovirus in a Nursing Home: A Clinical Perspective. *J Am Med Dir Assoc*. 2020;21(1):104-109.e1.
DOI: 10.1016/j.jamda.2019.03.015. Epub 2019 May 14. PMID: 31101588; PMCID:PMC7105973
 85. Hansen M, Brockmann M, Schildgen V, Schildgen O. Human bocavirus is detected in human placenta and aborted tissues. *Influenza Other Respir Viruses*. 2019; 13(1):106-109.
DOI: 10.1111/irv.12609. Epub 2018 Sep 30. PMID: 30198208; PMCID: PMC6304315.
 86. Petrarca L, Nenna R, Frassanito A, Pierangeli A, Di Mattia G, Scagnolari C, Midulla F. Human bocavirus in children hospitalized for acute respiratory tract infection in Rome. *World J Pediatr*. 2020;16(3):293-298.
DOI: 10.1007/s12519-019-00324-5. Epub 2019 Nov 27. PMID: 31776891; PMCID: PMC7091143.
 87. Colazo Salbetti MB, Boggio GA, Abbiatti G, Montañez Sandoz A, Villarreal V, Torres E, Pedranti M, Zalazar JA, Moreno L, Adamo MP. Diagnosis and clinical significance of Human bocavirus 1 in children hospitalized for lower acute respiratory infection: molecular detection in respiratory secretions and serum. *J Med Microbiol*. 2022;71(10).
DOI: 10.1099/jmm.0.001595. PMID: 36301612
 88. Lin MY, Chan HC, Chi H, Chiu SC, Nora-Krukle Z, Rasa-Dzelzkaleja S, Vilmane A, Murovska M, Lin JH, Liu HF. Genetic Diversity and Phylogenetic Analysis of Human Bocavirus 2 in Pediatric Patients with Acute Gastroenteritis in Taiwan. *Int J Environ Res Public Health*. 2020; 17(3):1086.
DOI: 10.3390/ijerph17031086. PMID: 32046345; PMCID: PMC7037009
 89. Xu M, Arku B, Jartti T, Koskinen J, Peltola V, Hedman K, Söderlund-Venermo M. Comparative diagnosis of human bocavirus 1 respiratory infection with messenger RNA reverse-transcription polymerase chain reaction (PCR), DNA quantitative PCR and serology. *J Infect Dis*. 2017;215(10):1551-1557.
DOI: 10.1093/infdis/jix169. PMID: 28379530
 90. Saha S, Fozzard N, Lambert SB, Ware RS, Grimwood K. Human bocavirus -1 infections in Australian children aged < 2 years: A birth cohort study. *Eur J Clin Microbiol Infect Dis*. 2023; 42(1): 99-108.
DOI: 10.1007/s10096-022-04529-x. Epub 2022 Nov 25. PMID: 36434280; PMCID: PMC9702687
 91. Silva PE, Figueiredo CA, Luchs A, de Paiva TM, Pinho MAB, Paulino RS, da Silva DBB, de Oliveira Santos KC, Afonso AMS, de Oliveira MI. Human bocavirus in hospitalized children under 5 years with acute respiratory infection, São Paulo, Brazil, 2010. *Arch Virol*. 2018;163(5):1325-1330.
DOI: 10.1007/s00705-017-3694-5. Epub 2018 Feb 1. PMID: 29392492; PMCID: PMC7087275.
 92. Ji K, Sun J, Yan Y, Han L, Guo J, Ma A, Hao X, Li F, Sun Y. Epidemiologic and clinical characteristics of human bocavirus infection in infants and young children suffering with community acquired pneumonia in Ningxia, China. *Viol J*. 2021;18(1):212.
DOI: 10.1186/s12985-021-01682-1. PMID: 34715898; PMCID: PMC8554736
 93. Nantachit N, Kochjan P, Khamrin P, Kumthip K, Maneekarn N. Human bocavirus genotypes 1, 2, and 3 circulating in pediatric patients with acute gastroenteritis in Chiang Mai, Thailand, 2012-2018. *J Infect Public Health*. 2021; 14(2):179-186.
DOI: 10.1016/j.jiph.2020.12.007. Epub 2021 Jan 22. PMID: 33486373
 94. Korsun N, Angelova S, Trifonova I, Voleva S, Grigorova I, Tzotcheva I, Mileva S, Perenovska P. Prevalence and Genetic Characteristics of Human Bocaviruses Detected in Patients with Acute Respiratory Infections in Bulgaria. *Int J Microbiol*. 2021;2021:7035081.
DOI: 10.1155/2021/7035081. PMID: 34819956; PMCID: PMC8608525.
 95. Kumar K, Singanayagam A, Johnston SL. Respiratory Virus Infections in

- Asthma: Research Developments and Therapeutic Advances. Acta Med Acad. 2020 Aug; 49(2):130-143.
DOI: 10.5644/ama2006-124.292.
PMID: 33189119.
96. Bhat R, Almajhdi FN. Induction of Immune Responses and Immune Evasion by Human Bocavirus. Int Arch Allergy Immunol. 2021;182(8):728-735.
DOI: 10.1159/000514688. Epub 2021 Apr 19. PMID: 33873181
97. Ljubin-Sternak S, Meštrović T, Ivković-Jureković I, Tešović G, Mlinarić-Galinović G, Lukšić I, Tabain I, Tot T, Mijač M, Vraneš J. High Detection Rates of Human Bocavirus in Infants and Small Children with Lower Respiratory Tract Infection from Croatia. Clin Lab. 2019; 65(1).
DOI:10.7754/Clin.Lab.2018.180702.
PMID: 30775887
98. Wang W, Guan R, Liu Z, Zhang F, Sun R, Liu S, Shi X, Su Z, Liang R, Hao K, Wang Z, Liu X. Epidemiologic and clinical characteristics of human bocavirus infection in children hospitalized for acute respiratory tract infection in Qingdao, China. Front Microbiol. 2022;13: 935688.
DOI: 10.3389/fmicb.2022.935688.
PMID: 36033842; PMCID: PMC9399728

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Peer-review history:
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