ISSN: 2347-6567

International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Vol.13 | Issue 1| Jan - Mar -2025

www.ijamscr.com

DOI : https://doi.org/10.61096/ijamscr.v13.iss1.2025.1-13

Review

Emerging Respiratory Pathogens: Insights into Human Metapneumovirus (hMPV) and Bocavirus in Acute Respiratory Tract Infections

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Published on: 10 Jan 2025

Published by:
DrSriram Publications

Abstract

Acute respiratory tract infections caused by various viral pathogens remain a dominant cause of global morbidity and mortality, profoundly affecting healthcare systems and vulnerable populations. Human metapneumovirus and human bocavirus have emerged as critical agents implicated in both endemic and epidemic settings, often presenting with overlapping clinical features and significant burdens in paediatric, elderly, and immune compromised groups. Their virological diversity, capacity for coinfections, and potential for severe outcomes have led to intensified research aimed at unravelling their molecular mechanisms and clinical impact. Diagnostic modalities for these pathogens have advanced considerably, incorporating sensitive molecular assays and metagenomics-based approaches. Despite noteworthy progress in understanding their biology and epidemiology, therapeutic measures remain primarily supportive, and vaccine development continues to face challenges stemming from viral diversity and immune evasion strategies. This chapter provides a detailed and integrative review of human metapneumovirus and human bocavirus, beginning with their global epidemiological trends and delving into their virology, pathogenesis, clinical spectrum, and diagnostic complexities. It further examines emerging therapeutic and preventive paradigms, including the promise of novel antivirals and vaccine candidates. By highlighting gaps in current knowledge and exploring future research directions, this chapter underscores the necessity for comprehensive surveillance, innovative technologies, and collaborative efforts to reduce the burden of these pathogens on public health worldwide.

Keywords: Human Metapneumovirus, Human Bocavirus, Acute Respiratory Tract Infections, Virology, Pathogenesis, Diagnostics, Therapeutics, Public Health.

INTRODUCTION

Human metapneumovirus and human bocavirus have, over the past two decades, become increasingly recognized as noteworthy contributors to acute respiratory tract infections in diverse age groups and clinical settings [1,2]. These pathogens—both discovered relatively recently compared to other respiratory viruses—challenge conventional management strategies by displaying wide genetic variability and frequent coinfections that obscure clearcut clinical diagnostics. In many regions, respiratory infections present a year round burden on healthcare infrastructure, but the precise contribution of emerging pathogens is often underestimated due to suboptimal surveillance and limited diagnostic resources [3]. Heightened awareness of these agents is essential, not only because they complicate management in pediatric populations but also because they pose particular risks for the elderly and those with compromised immunity, leading to more frequent hospitalizations and worse clinical outcomes [4]. Clinicians and researchers have steadily begun to appreciate the multifaceted nature of human metapneumovirus and human bocavirus, noting that these viruses exhibit distinct patterns of seasonality, transmission, and host tropism. Human metapneumovirus, first isolated in 2001, is a negative sense RNA virus of the Pneumoviridae family, often causing symptoms comparable to respiratory syncytial virus and parainfluenza viruses [2,5]. While its infection typically manifests as a mild upper respiratory illness, severe disease can occur in immunocompromised individuals and in very young children, sometimes leading to pneumonia and bronchiolitis [5]. Human bocavirus, a small single stranded DNA virus classified in the Parvoviridae family, was discovered in 2005 and is frequently detected in children presenting with respiratory symptoms, often alongside other viral agents such as adenovirus and influenza [6,7]. This pattern of coinfection obscures clear clinical definitions of bocavirus induced disease and complicates therapeutic decision making [8]. Researchers have taken significant steps to deepen the molecular and immunological understanding of these pathogens, unearthing unique genetic features and antiviral defense evasion strategies [9]. Innovations in diagnostic techniques, particularly polymerase chain reaction–based tests, have dramatically improved detection rates, but questions remain regarding the clinical significance of asymptomatic carriage and prolonged viral shedding [10]. Parallel advancements in immunology have aided the investigation of host immune responses, unveiling key roles of cytokine cascades and innate immune pathways that shape disease progression. Nonetheless, consensus guidelines for consistent laboratory findings and robust clinical correlations remain underdeveloped, limiting the ability to firmly classify individual cases based on either virus [11].

This chapter explores human metapneumovirus and human bocavirus from an integrative viewpoint, connecting epidemiological patterns, virological mechanisms, and pathophysiological processes that govern disease. It describes the range of clinical manifestations, from mild upper respiratory illnesses to severe lower respiratory complications, and highlights diagnostic opportunities and pitfalls that arise when these viruses cooccur with other pathogens [12]. The discussion further encompasses recent developments in antiviral therapies and preventative strategies, including monoclonal antibodies, fusion inhibitors, and evolving vaccine designs [2,7]. Public health significance is underscored throughout, emphasizing how improved surveillance, coordinated research efforts, and the deployment of cutting edge diagnostic technologies can contribute to more effective containment and clinical management of these emerging pathogens. By synthesizing the current body of knowledge, this chapter endeavors to reveal critical gaps that future research must address, ensuring that global healthcare systems are better equipped to handle the ever shifting landscape of respiratory virus epidemiology.

EPIDEMIOLOGY

Human metapneumovirus and human bocavirus exhibit epidemiological patterns that demonstrate their wide geographical reach and potential for seasonal outbreaks. Human metapneumovirus, first detected in the Netherlands, has since been documented on nearly every continent, underscoring its ability to spread across diverse climates and population densities [2,13]. Its incidence tends to peak in late winter and early spring in temperate regions, aligning with patterns observed for respiratory syncytial virus, although variations can occur based on local environmental factors [6]. Multiple studies have confirmed that hMPV infections are most common among young children, with the majority of individuals acquiring antibodies by early childhood. However, the virus can also manifest in older adults, particularly those who experience waning immunity or suffer from comorbidities, leading to sporadic outbreaks in long term care facilities [14]. This broad age distribution underpins the importance of sustained population level surveillance, as the collective risk profile for severe complications extends beyond just pediatric populations [14,15]. Human bocavirus has similarly been identified in countries

spanning the globe, with regional differences observed in both prevalence and strain diversity [16]. Unlike some other respiratory pathogens, HBoV frequently cocirculates and is codetected with viruses such as adenovirus, rhinovirus, and influenza, complicating interpretations of its exact disease burden [8,16]. This phenomenon has led some researchers to classify HBoV more as a bystander pathogen, but mounting evidence suggests it can independently cause significant lower respiratory tract infections—particularly in children under five years old [6,8]. Epidemiological surveys have shown that nearly half of HBoV detections occur alongside other viral agents, giving rise to questions about how synergy or antagonism between pathogens influences clinical outcomes. In low and middle income countries, diagnostic limitations have historically hampered accurate estimates of HBoV prevalence and burden, though recent advances in molecular testing have begun to shed light on its role in severe pneumonia and wheezing illnesses [17,18]. Seasonality for HBoV is less distinct than for hMPV, with reported peaks ranging from winter to spring in temperate zones, but also sporadic detection throughout the year in tropical regions [19]. This variability likely reflects complex interactions between viral biology, climate factors, and host behaviors, including school attendance and indoor crowding. Outbreak investigations have identified clusters of HBoV transmission in daycare centers, hospitals, and other communal settings, suggesting that close contact significantly enhances viral spread [16]. Age specific susceptibility also plays a notable role. Young children, especially those under two years of age, appear to be the most susceptible to symptomatic infection, possibly due to immature immune systems and higher exposure risks [20]. Although less frequently reported, cases in adults and the elderly do occur and can become clinically relevant in the presence of other risk factors like chronic pulmonary diseases or immunosuppression [14]. Longitudinal studies have tracked the evolutionary dynamics of both viruses. Human metapneumovirus exists in two major genetic lineages (A and B), each subdivided into additional sub lineages, which can cocirculate and occasionally supersede each other in different seasons [2,21]. Human bocavirus also demonstrates genetic variability, with four primary species (HBoV1–4), although HBoV1 is most commonly linked to respiratory infections [6]. These shifts in genetic makeup, including recombination events observed in HBoV and antigenic drift in hMPV, highlight the potential for these viruses to adapt and possibly escape preexisting immunity [22]. Consequently, robust and ongoing molecular surveillance is necessary to map emerging variants and correlate them with changes in clinical severity or transmissibility. Pediatric hospital admissions for lower respiratory tract infections often reveal a significant fraction of hMPV or HBoV cases, underscoring their impact on healthcare systems [5,7]. Infections in immunocompromised individuals, including transplant recipients and patients undergoing chemotherapy, can lead to prolonged viral shedding and atypical presentations that are difficult to diagnose and manage effectively [9,14]. Reports of nosocomial outbreaks in neonatal intensive care units underscore the vulnerability of hospitalized populations, where even small lapses in infection control can lead to largescale transmission events [13]. These epidemiological realities reinforce the need for comprehensive control measures, encompassing improved diagnostic testing, robust surveillance networks, and heightened awareness among clinicians and infection prevention teams. As global populations grow and travel becomes more frequent, the potential for rapid international dissemination of novel or more virulent strains increases. Lessons learned from other emerging respiratory viruses, such as Middle East respiratory syndrome coronavirus (MERSCoV) and severe acute respiratory syndrome coronavirus 2 (SARSCoV2), highlight the necessity of early detection, molecular characterization, and coordinated public health interventions. In many respects, hMPV and HBoV represent established but underrecognized threats, particularly in regions where healthcare resources remain constrained [23]. Continued investment in epidemiological research and capacity building will be essential to refine our understanding of these viruses' transmission dynamics and to implement effective prevention and control strategies. By leveraging modern molecular tools, advanced data analytics, and cross border collaboration, it may be possible to reduce the substantial burden these pathogens impose on vulnerable communities worldwide.

Virology and Genomic Insights Human metapneumovirus and human bocavirus belong to distinct virus families, each with unique genomic architectures that drive differences in replication, immune evasion, and pathogenicity [2,5]. Human metapneumovirus, a member of the Pneumoviridae family, has a single stranded, negative sense RNA genome spanning roughly 13 kilobases [2]. It encodes several structural and non structural proteins, including the fusion protein (F), the glycoprotein (G), and the matrix protein (M), which collectively mediate viral entry, replication, and release [5]. The F protein is of particular importance due to its central role in membrane fusion and syncytia formation, making it a prime target for neutralizing antibodies and vaccine development strategies [9]. Despite ongoing research, the complete mapping of how each viral protein contributes to disease pathogenesis and immune evasion remains incomplete, underscoring the complexity of hMPV biology [9,11]. Molecular epidemiology has identified two major hMPV genetic lineages, designated A and B, each further subdivided into multiple sublineages based on sequence variations in the F and G genes [2]. These lineage and sublineage shifts can influence clinical outcomes, disease severity, and patterns of reinfection. This genetic diversity stems from a gradual process of antigenic drift facilitated by selective pressures in the human host, similar to mechanisms observed in influenza viruses [21]. Advanced genomic techniques, including whole genome sequencing, have facilitated a clearer understanding of viral evolution. They have also helped define correlations between genetic markers and virulence, although consistent links between specific strains and clinical

severity are still debated [2,9]. Such discrepancies highlight the need for broader multicentre studies that integrate genomic, clinical, and immunological data to yield conclusive insights. Human bocavirus, in contrast, is a small, nonenveloped DNA virus from the Parvoviridae family, specifically classified under the genus Bocaparvovirus [6]. Its genome is about 5.3 kilobases in length, featuring three open reading frames that encode the structural capsid proteins (VP1, VP2, VP3) and the non structural proteins (NS1, NP1) responsible for viral replication [6,8]. The NS1 protein, in particular, has been implicated in modulating cell cycle progression and inducing cytotoxic effects in infected cells [7]. Unlike hMPV, HBoV lacks a segmented genome, so it does not exhibit the same types of reassortment observed in viruses like influenza. However, recombination events, especially among different HBoV species, appear to contribute to the genetic diversity and epidemiological patterns seen in circulating strains [22]. One notable feature of HBoV is its frequent detection in coinfections, which can blur the lines between asymptomatic carriage and active disease [24]. Molecular studies have identified high viral loads of HBoV in respiratory specimens, particularly when associated with lower respiratory tract symptoms, suggesting a more direct pathogenic role in certain cases [16]. Furthermore, in vitro studies demonstrate that HBoV can replicate in respiratory epithelial cells and can elicit robust inflammatory responses [8]. The interaction of HBoV with other viruses, such as rhinovirus or respiratory syncytial virus, is an area of active investigation, as simultaneous infections might synergistically amplify lung inflammation or alter viral shedding kinetics [16]. Next generation sequencing (NGS) technologies and transcriptomic analyses have begun to elucidate key aspects of host–virus interactions, including differential gene expression in infected cells and the role of microRNAs in viral replication [25]. For hMPV, analyses of host transcriptome profiles reveal a strong induction of innate immune pathways, particularly those mediated by interferons and proinflammatory cytokines [26]. HBoV studies point to alterations in pathways related to cell cycle and DNA damage responses, reflecting the virus's dependence on actively dividing cells for productive infection [27]. These findings may pave the way for new therapeutic strategies that target host pathways rather than the virus directly, offering a potential to minimize drug resistance. Advanced molecular techniques have also aided in characterizing specific cell surface receptors used by these viruses. Evidence suggests that hMPV binds to heparan sulfate proteoglycans and other receptors on respiratory epithelial cells, initiating viral uptake via endocytosis [28]. HBoV is hypothesized to bind to sialic acid–containing molecules or specific glycan residues, though the exact identity of its primary receptor remains under investigation [6]. Understanding these receptor interactions is not only critical for elucidating tissue tropism and pathogenesis but also for guiding rational drug design aimed at blocking viral entry. Translating genomic insights into effective clinical interventions remains an ongoing challenge. Vaccines targeting the F protein of hMPV are in various stages of preclinical and clinical development, showing promise in eliciting neutralizing antibody responses, but difficulties remain in achieving broad, long lasting immunity [9,29]. Similar challenges confront HBoV vaccine research, partially because the exact correlates of protective immunity have yet to be fully delineated [8]. The complexity of these viruses' genetic landscapes, combined with the intricacies of human immune responses, underscores the necessity of comprehensive, multidisciplinary approaches that involve virologists, immunologists, clinicians, and public health experts. Further unravelling the molecular signatures and evolutionary dynamics of these pathogens will be instrumental in shaping next generation diagnostics, prophylactics, and therapies designed to mitigate their global health impact.

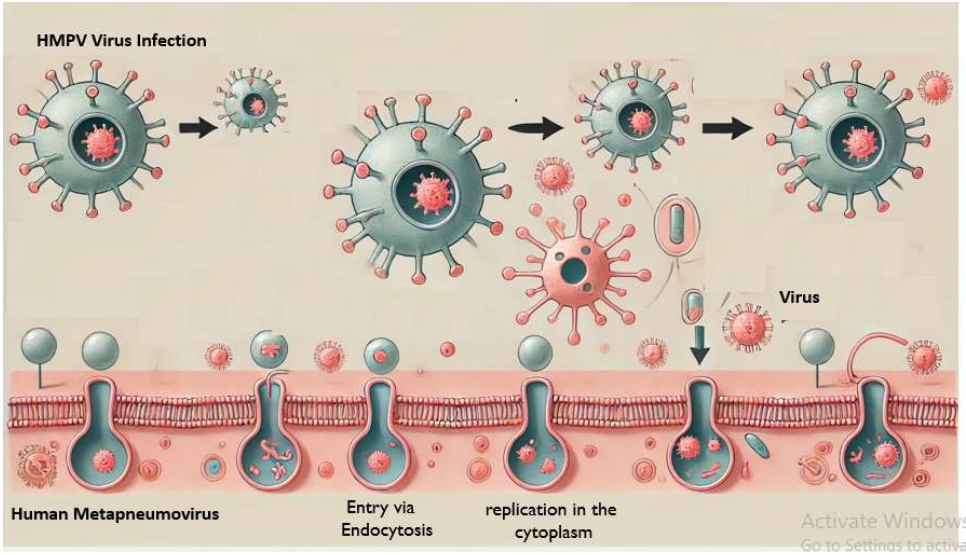

Figure 1: Proposed Mechanistic Pathway of hMPV Infection

PATHOGENESIS

Pathogenesis of human metapneumovirus and human bocavirus reflects a dynamic interplay between viral replication strategies and the host immune response in respiratory epithelial tissues [9,25]. The initial steps of hMPV infection involve binding to permissive respiratory epithelial cells through viral surface glycoproteins, especially the G protein, which facilitates attachment, and the F protein, which mediates membrane fusion [2]. Once inside the cell, hMPV undergoes replication in the cytoplasm, where its negative sense RNA is transcribed into mRNA, subsequently translated into viral proteins that orchestrate the assembly of new virions [5]. During this process, infected cells often undergo cytopathic changes, including syncytium formation, a hallmark of pneumovirus infections. Damage to epithelial layers disrupts the airway barrier, increases mucus production, and primes inflammatory pathways that lead to clinical symptoms such as cough and wheezing [9]. Inflammation triggered by hMPV infection can be extensive, involving diverse cytokines and chemokines that recruit immune cells to the site of infection [5]. Interferon signaling cascades, primarily involving type I and III interferons, play pivotal roles in restricting viral replication, but hMPV has evolved mechanisms to subvert or delay these antiviral responses [25]. Studies have shown that hMPV can interfere with host gene expression, dampening the innate immune response and enabling further replication before adaptive immunity fully engages [11,25]. This capacity to suppress or modulate the interferon response contributes to the virus's pathogenesis, particularly in severe cases where immune dysregulation leads to excessive inflammation and tissue damage. In children with developing immune systems and in immunocompromised patients, these disruptions can culminate in severe lower respiratory tract disease, including pneumonia and bronchiolitis [5,9]. Human bocavirus follows a partially different route, given its unique DNA genome and replication requirements. As a member of the Parvoviridae family, HBoV typically requires the S phase of the cell cycle for efficient replication, suggesting it preferentially infects rapidly dividing cells in the respiratory tract [6,7]. Upon attachment to unknown or partially characterized cellular receptors, the virus is internalized, and the viral DNA traffics to the nucleus, where it can hijack host DNA replication machinery [8]. The viral non structural proteins, such as NS1, are key facilitators of replication and may also contribute to cytotoxic effects, including DNA damage responses within infected cells [27]. Host cells experiencing significant DNA damage or stress often undergo apoptosis or become functionally impaired, contributing to the epithelial injury that manifests as respiratory symptoms. Inflammatory responses elicited by HBoV infection can be substantial, although the degree of inflammation may vary more widely than with hMPV, partly due to the frequency of coinfections [8]. Research indicates that coinfection scenarios involving HBoV can alter cytokine profiles, sometimes amplifying the overall inflammatory milieu and exacerbating lung injury [16]. There is also evidence that HBoV can persist subclinically in respiratory tissues for extended periods, raising questions about chronic or recurrent infections in certain individuals [6]. Such persistence might be linked to the virus's ability to establish latency or integrate into host genomes, as observed with other parvoviruses, though conclusive evidence remains limited [24]. If substantiated, such mechanisms could reshape our understanding of how HBoV contributes to chronic or relapsing respiratory symptoms. Both viruses elicit adaptive immune responses that include the production of neutralizing antibodies and Tcell–mediated immunity [9,25]. However, the durability and specificity of these immune responses can be variable. Repeated infections with different hMPV sublineages or HBoV genotypes suggest incomplete cross protection, which has significant implications for vaccine design and herd immunity [21,22]. In particular, hMPV reinfections in older children and adults illustrate that long lasting immunity may be challenging to achieve naturally, likely due to antigenic drift within viral surface proteins and the immune evasion strategies deployed by the virus [2]. HBoV's frequent coinfections also complicate the assessment of protective immunity, as a robust immune response may primarily target other concurrently infecting pathogens, leaving HBoV underrecognized or insufficiently neutralized [16]. Severe or fatal cases of hMPV or HBoV infection generally occur in immunocompromised hosts, such as transplant recipients or individuals receiving immunosuppressive therapies [9,30]. These patients may lack the immune competence required to control viral replication or may mount aberrant inflammatory responses that lead to severe pulmonary complications. In neonates and very young infants, immature immune defenses and smaller airway diameters can accelerate the progression to respiratory distress. Coexisting conditions, such as congenital heart disease or chronic lung disease, also predispose individuals to worse outcomes when infected by these emerging viruses [14]. This underscores the importance of early detection and aggressive supportive measures, including respiratory support and, where applicable, prophylactic interventions. Overall, the pathogenesis of hMPV and HBoV is multifactorial, encompassing direct cytopathic effects, immune modulation, and inflammatory cascades that drive clinical manifestations. The interplay of viral genetics and host factors—ranging from age, comorbidities, and immune status to environmental variables—dictates the spectrum of disease severity. Although our understanding of the precise molecular events governing these infections has grown, many questions remain regarding how these viruses persist, evolve, and exploit host vulnerabilities. Addressing these gaps is critical for the development of targeted therapies and vaccines that can mitigate the substantial clinical burden these pathogens impose on global healthcare systems.

CLINICAL FEATURES

Clinical presentations of human metapneumovirus and human bocavirus infections mirror many features of common respiratory viruses, often complicating differential diagnoses [2,5]. Human metapneumovirus infections can range from mild upper respiratory tract illness, characterized by symptoms such as nasal congestion, cough, and low grade fever, to severe bronchiolitis and pneumonia, particularly in young children, the elderly, and immunocompromised individuals [5,31]. The lower respiratory involvement often manifests with wheezing, tachypnea, and hypoxia, overlapping with clinical pictures of respiratory syncytial virus and influenza [2,9]. Certain patients may experience acute otitis media or exacerbations of underlying chronic conditions, such as asthma or chronic obstructive pulmonary disease. In immunocompromised patients, the disease course can be prolonged and more severe, with recurrent fever spikes and the potential for acute respiratory distress syndrome [5,9]. Nevertheless, pinpointing the virus as the singular etiological factor in severe cases can be challenging due to frequent coinfections with bacteria or other viruses [11]. Human bocavirus similarly presents a broad clinical spectrum, although controversy persists regarding how often it acts as the primary pathogen versus a coinfecting agent [6,8]. Children infected with HBoV commonly exhibit rhinorrhea, persistent cough, wheezing, and sometimes high fever [8,16]. Reports of gastrointestinal symptoms such as vomiting and diarrhea have also emerged, particularly in HBoV2–4 infections, but HBoV1 remains the main species implicated in respiratory disease [6]. Hospitalized cases often involve infants and toddlers who present with lower respiratory tract symptoms ranging from bronchitis to severe pneumonia [16,32]. Among older children and adults, HBoV is less commonly identified as the sole pathogen, though it may still play a role in exacerbating preexisting respiratory conditions. Coinfections, especially with respiratory syncytial virus, influenza, and adenovirus, can complicate the clinical picture and lead to more severe disease requiring oxygen supplementation or intensive care [8,16]. The lack of pathognomonic clinical features specific to hMPV or HBoV frequently necessitates laboratory confirmation for an accurate diagnosis [10]. Overlapping symptoms—such as cough, fever, and shortness of breath—are ubiquitous across a variety of viral respiratory pathogens, making clinical suspicion alone insufficient to guide targeted interventions [9]. In pediatrics, hMPV and HBoV infections are recognized as causes of bronchiolitis, second only to respiratory syncytial virus in some studies [14,23]. Both viruses can lead to hospital admissions in young children, highlighting their potential to place substantial burdens on pediatric wards, especially during seasonal peaks or cocirculating epidemics. Symptomatic severity can be magnified in patients with underlying lung diseases. Individuals with asthma, COPD, or cystic fibrosis may experience acute exacerbations triggered by these viral infections, requiring escalated treatments and prolonged hospitalization [31,33]. In such contexts, distinguishing the contribution of hMPV or HBoV from other potential triggers is pivotal for patient management and prognosis. Elderly patients in nursing homes or longterm care facilities represent another vulnerable demographic; outbreaks in these settings can rapidly escalate, given factors like shared living spaces and the presence of multiple comorbidities [31]. Immunocompromised hosts, such as hematopoietic stem cell transplant recipients or solid organ transplant patients, are at particular risk for atypical or severe presentations [9,30]. In these groups, hMPV or HBoV infection can manifest with protracted viral shedding, bilateral pulmonary infiltrates on imaging, and a more insidious onset of symptoms [34]. The incidence of complications, including secondary bacterial pneumonia or acute respiratory distress syndrome, may be higher, and the morbidity and mortality rates can be substantially elevated. Prompt diagnostic testing and tailored supportive care become paramount in these scenarios, often supplemented by additional measures like immunoglobulin therapy or offlabel antiviral treatments, though rigorous clinical trials remain limited [34]. Outside of the hospital setting, many mild infections caused by hMPV or HBoV go undetected or unreported, especially in resource limited areas where diagnostic testing is not routinely available [23]. These mild cases may resemble a common cold or a low grade flulike illness, leading to a cycle of underestimation of the viruses' true prevalence. School aged children and daycare attendees can be important vectors for viral transmission, disseminating these pathogens within communities [14,20]. The role of asymptomatic or minimally symptomatic carriers further complicates efforts to assess clinical burden accurately, as they can still spread the virus to susceptible individuals. Ultimately, the clinical spectrum of hMPV and HBoV ranges from mild upper respiratory complaints to life threatening lower respiratory complications, shaped by a matrix of viral, host, and environmental factors. Recognizing key risk groups—infants, the elderly, and immunocompromised patients—is critical for early diagnosis and intervention. Improved clinical awareness, combined with advanced diagnostics, can facilitate more accurate case definitions and better tailored management strategies. As our molecular and immunological understanding of these pathogens evolves, refining clinical guidelines will be essential for mitigating their considerable impact on public health.

Table 1: Summary of hMPV and HBoV with Their Main Features

Feature	hMPV (Human Metapneumovirus)	HBoV (Human Bocavirus)
Discovery	Identified in 2001 in the Netherlands	Identified in 2005 in Sweden
Family	Paramyxoviridae	Parvoviridae
Genome	Negative-sense single-stranded RNA	Single-stranded DNA
Transmission	Respiratory droplets	Respiratory droplets, fecal-oral
Primary Target Population	Infants, young children, elderly, immunocompromised	Infants, young children, elderly, immunocompromised
Seasonality	Late winter to early spring	Late winter to early spring
Symptoms	Respiratory: fever, cough, wheezing, bronchiolitis, pneumonia	Respiratory: cough, fever, wheezing; Gastrointestinal: diarrhea, vomiting
Associated Diseases	Upper and lower respiratory tract infections	Upper and lower respiratory tract infections, gastroenteritis
Diagnostic Methods	RT-PCR, serology, antigen detection	PCR, serology, antigen detection
Treatment	Supportive care	Supportive care
Vaccination/Prevention	No specific vaccine	No specific vaccine
Global Prevalence	Widespread, second leading cause of viral LRTIs in children	Widespread, co-infection with other respiratory viruses is common
Significance	Major cause of pediatric respiratory hospitalizations	Emerging pathogen with potential co-pathogen effects

DIAGNOSTICS

Accurate and timely diagnosis of human metapneumovirus and human bocavirus has been revolutionized by advancements in molecular technologies, shifting away from older methods like viral culture and serology [1,10]. Nucleic acid amplification techniques, particularly polymerase chain reaction (PCR)–based assays, remain the gold standard for detecting these viruses in clinical specimens such as nasopharyngeal swabs, bronchoalveolar lavage fluids, or sputum samples [35]. Reverse transcription PCR (RTPCR) is used for hMPV, given its RNA genome, whereas conventional or real time PCR methods target the DNA genome of HBoV [7,36]. These assays offer high sensitivity and specificity, capable of identifying viral loads even when present at relatively low levels [10]. However, one limitation is the inability of PCR to distinguish between active infection and residual viral shedding, a point particularly relevant for HBoV, which can persist asymptomatically [37]. Quantitative PCR (qPCR) has further refined diagnostic capabilities by estimating viral load, providing valuable clues about disease severity and prognosis [36]. In cases where patients present with moderate to severe symptoms, a higher hMPV or HBoV load may correlate with worse clinical outcomes or a higher likelihood of complications [38]. Even so, substantial patient to patient variability exists, and confections with other respiratory pathogens often confound interpretations of viral load data [8]. Notably, multiplex PCR panels have emerged as powerful tools for simultaneously detecting multiple respiratory viruses including hMPV and HBoV thus streamlining diagnostic workflows and improving turnaround times in busy clinical laboratories [39]. While these panels facilitate more comprehensive surveillance, they also raise the challenge of interpreting positive results for multiple viruses in a single patient. Serological methods, such as enzyme linked immunosorbent assays (ELISAs), were once central to diagnosis, but they are now used more frequently in epidemiological studies rather than routine clinical practice [40]. For hMPV, the detection of specific IgM or IgG antibodies can offer insights into recent or past exposure, though cross reactivity with related viruses can limit specificity [2,40]. Serology for HBoV is even more complicated because multiple species within the genus Bocaparvovirus can induce similar antibody profiles, and prolonged viral shedding complicates the correlation of serostatus with active disease [16,37]. Consequently, while serology can be informative at the population level helping to gauge exposure rates and immune status—it often lacks the precision needed for individual patient management.

Innovations in molecular diagnostics hold promise for more rapid, point of care testing options [41]. Techniques like loop mediated isothermal amplification (LAMP) and CRISPR based assays are under development, offering the possibility of detecting hMPV and HBoV within minutes rather than hours [42]. Such rapid diagnostics could be transformative in resource limited settings or during outbreak situations, enabling immediate clinical interventions and improved infection control measures. Additionally, the rise of metagenomic next generation sequencing (mNGS) allows for unbiased pathogen detection, capturing both known and novel viral entities in a single assay [43]. While cost and technical complexities currently restrict mNGS to specialized laboratories, its utility in diagnosing atypical or severe infections could expand with ongoing technological refinements and cost reductions. Laboratory protocols often emphasize sample collection best practices to ensure reliable test results. For hMPV and HBoV, nasopharyngeal swabs or aspirates are generally preferred due to higher viral loads in the upper airway, especially early in the course of infection [10]. In hospitalized patients with lower

respiratory symptoms, bronchoalveolar lavage or endotracheal aspirates may be more appropriate, particularly if upper airway swabs yield negative results despite a strong clinical suspicion [37]. Proper handling, transport, and storage of samples at appropriate temperatures are crucial for maintaining viral integrity, as RNA viruses like hMPV can degrade quickly if not managed correctly [10]. Interpretation of diagnostic results often requires correlation with clinical presentation. In cases of severe pneumonia or acute respiratory distress syndrome, a positive test for hMPV or HBoV strongly supports a causal relationship, although the potential for coinfections should be meticulously evaluated [11]. Conversely, detecting these viruses in mildly symptomatic or asymptomatic individuals does not necessarily confirm disease etiology, especially for HBoV, known for prolonged postinfection detection [8,16]. Clinicians must balance molecular findings with clinical data, imaging results, and inflammatory markers, forming a comprehensive view of the patient's condition. In pediatric settings, repeated testing might be warranted for persistent symptoms or immunocompromised states, given that viral shedding can extend over weeks [44]. At a public health level, broad based surveillance programs and well equipped reference laboratories are essential for tracking the prevalence, seasonality, and molecular evolution of these pathogens [23]. Data garnered from largescale diagnostic testing can guide infection control policies, inform vaccine design, and help identify vulnerable subpopulations. Integrating diagnostics with genotype and subtype information is particularly valuable for hMPV, as it can reveal circulating lineages and potential shifts in virulence or transmissibility [21]. The same approach can apply to HBoV, where genomic studies can uncover recombination events or emerging variants that may impact clinical outcomes. By forging a strong link between diagnostic practices and epidemiological research, healthcare systems can respond more effectively to the challenges posed by these emerging respiratory viruses.

THERAPEUTIC INTERVENTIONS

Therapeutic interventions for human metapneumovirus and human bocavirus infections remain largely supportive, reflecting the absence of widely approved, virus specific antiviral agents [9,45]. Standard care includes ensuring adequate hydration, providing supplemental oxygen when necessary, and managing fever and discomfort with antipyretics and analgesics [9,46]. In more severe cases—especially among infants, the elderly, or individuals with preexisting pulmonary disease—intensive respiratory support may be required, ranging from high flow nasal cannula oxygen to mechanical ventilation [5]. Early recognition of clinical deterioration and the prevention of secondary bacterial infections are crucial, given that bacterial coinfections can worsen outcomes and prolong hospital stays [11]. Empiric antibiotic therapy may be initiated if bacterial superinfection is suspected, but careful deescalation based on culture or diagnostic findings is vital to avoid antibiotic overuse [46]. For human metapneumovirus, experimental antiviral compounds, such as fusion inhibitors targeting the F protein, have shown promise in preclinical studies and earlyphase clinical trials [47]. These fusion inhibitors aim to block the conformational changes required for viral entry into host cells, thereby limiting viral spread [9]. Monoclonal antibodies against critical epitopes on the F protein are also under investigation, mirroring successful strategies for respiratory syncytial virus prophylaxis in highrisk infants [47]. However, no broadly licensed therapeutic for hMPV currently exists, underscoring the need for more extensive research and large scale clinical trials to confirm efficacy and safety in diverse populations [45]. Immunoglobulin based interventions, such as intravenous immunoglobulin (IVIG) enriched with neutralizing antibodies, have been explored in severe cases, particularly for immunocompromised patients who lack sufficient endogenous immunity [34]. While some case reports suggest benefits in mitigating disease progression, formal clinical trials remain limited, and the high cost of immunoglobulin products hampers widespread adoption [34]. Additionally, the varying antigenic sublineages of hMPV may reduce the efficacy of nonspecific IVIG if it lacks adequate titers against the circulating strains [21]. Convalescent plasma from individuals recently infected with hMPV could offer an alternative but requires standardized protocols for collection, testing, and administration. Therapeutic options for human bocavirus are even more constrained, partly due to ongoing debates about the virus's exact role in respiratory disease [8]. Some experimental antiviral strategies target the viral replication machinery, particularly the NS1 protein required for genome replication and packaging [48]. However, none of these approaches have progressed to advanced clinical trials. Given that HBoV often occurs as a coinfection, therapeutic interventions may primarily address other confirmed pathogens or aim to bolster overall immune function [8]. In certain immunocompromised patients experiencing severe or persistent HBoV infection, clinicians have explored experimental treatments such as cidofovir or brin cidofovir, originally developed for DNA viruses like adenovirus or cytomegalovirus [49]. While these agents exhibit in vitro activity, data on their clinical efficacy against HBoV remain anecdotal and require more robust validation. Supportive therapies that modulate the host inflammatory response, including the use of corticosteroids or other immunosuppressive agents, remain controversial [45]. In certain instances of hyperinflammatory responses, such as cytokine storm syndromes, judicious use of steroids might offer relief, although concern exists that immunosuppression could facilitate viral persistence or secondary infections [9]. Nebulized hypertonic saline and bronchodilators sometimes alleviate wheezing symptoms, especially in pediatric bronchiolitis, but their overall impact on disease course is variable [2]. Each treatment decision must be

individualized based on patient comorbidities, age, and clinical severity, emphasizing the necessity for close monitoring in an inpatient setting when respiratory compromise is evident [45].

Research into vaccine development for hMPV has yielded several candidates, including recombinant subunit vaccines targeting the F protein and virus like particle (VLP) platforms [29]. Early phase trials have shown immunogenicity, but challenges persist in establishing durable immunity and cross protection against multiple lineages [9]. Live attenuated vaccines are also under exploration, though concerns about safety, especially in young infants and immunocompromised populations, have tempered enthusiasm [45]. For HBoV, vaccine research remains in its infancy, hindered by uncertainties regarding the virus's antigenic determinants, correlates of protection, and the clinical significance of asymptomatic shedding [8]. Nevertheless, the success of parvovirus B19 vaccines in preventing diseases like erythema infectiosum suggests that parvovirus based immunization may be feasible if the right antigenic targets and adjuvants are identified. Genebased approaches and novel adjuvant systems may hold promise for both viruses, mirroring broader trends in vaccine innovation. The rapid development of mRNA vaccines for other respiratory pathogens points to a potential pathway for translating genomic insights of hMPV and HBoV into practical prophylactics [29]. However, significant barriers—both scientific and regulatory remain, including the need for largescale clinical trials that enroll diverse populations to confirm safety and immunogenicity. Taken together, the current landscape of therapeutic interventions for hMPV and HBoV underscores the need for a two pronged approach: continued emphasis on supportive care to manage acute symptoms and sustained research efforts to develop targeted antivirals and vaccines. With the emergence of new technologies and a growing awareness of these pathogens' clinical relevance, the potential for novel, effective therapies is promising. Achieving this goal will require robust clinical research networks, interdisciplinary collaborations, and the leveraging of genomic surveillance data to track evolving viral strains, ensuring that tomorrow's interventions can address the challenges posed by these underrecognized but significant contributors to respiratory morbidity.

PUBLIC HEALTH IMPLICATIONS

Human metapneumovirus and human bocavirus infections carry significant public health implications, largely tied to their ability to trigger substantial morbidity in diverse age groups and to strain healthcare resources during seasonal peaks [23]. Surveillance efforts for these viruses often lag behind those dedicated to more established pathogens like influenza or respiratory syncytial virus, resulting in underestimation of their true prevalence and disease burden [1]. Enhanced surveillance programs, supported by molecular diagnostics, are vital for capturing accurate epidemiological data that can inform public health policies and resource allocation. Implementing such programs in low and middle income countries is particularly urgent, given that these regions frequently suffer disproportionate mortality and morbidity from acute respiratory infections due to limited healthcare infrastructure [23,50]. In addition to identifying seasonal trends, realtime surveillance can detect sudden spikes in cases that may indicate outbreak conditions, thereby prompting quicker interventions. Community level preventive measures for respiratory pathogens typically emphasize hand hygiene, respiratory etiquette, and avoidance of crowded settings when symptomatic [46]. While these interventions can reduce transmission for hMPV and HBoV, more tailored strategies may be needed to fully curb their spread, especially in environments like daycare centers, schools, and nursing homes, where close contact is inevitable [20]. Targeted educational campaigns and prophylactic measures could be beneficial for highrisk groups, although the absence of licensed vaccines limits current prevention efforts to general infection control practices [29]. Outbreaks in specialized settings, such as longterm care facilities, can be particularly challenging, requiring rapid case isolation and rigorous disinfection protocols to protect vulnerable residents [14]. One of the most pressing public health concerns is the potential for severe disease in immunocompromised populations. Hematopoietic stem cell transplant recipients, solid organ transplant patients, and individuals with HIV/AIDS face heightened risks, often manifesting more severe or prolonged infections [9,30]. Hospitals and transplant centers can implement stricter screening and preemptive isolation protocols during known outbreak seasons to mitigate these risks. Evidence based guidelines tailored specifically to immunocompromised patients would help standardize care and reduce morbidity and mortality [34]. Because these populations often require frequent or prolonged hospitalizations, nosocomial transmission of hMPV or HBoV can be a severe setback, underscoring the importance of robust infection control strategies and staff training [13]. From an economic perspective, hMPV and HBoV infections contribute to healthcare expenditures by driving hospital admissions, necessitating advanced supportive care, and prolonging lengths of stay [14,31]. Infants with severe bronchiolitis or pneumonia and elderly individuals with exacerbations of chronic lung diseases represent substantial cost drivers. Furthermore, the indirect costs related to lost productivity, parental work absences for child care, and community based transmission underscore the broader societal impact of these infections [50]. Public health agencies increasingly recognize that investing in preventive measures and efficient diagnostic capabilities can offer substantial longterm savings for healthcare systems. Globalization and increased travel also create challenges, as emerging viral strains or novel variants of hMPV and HBoV can cross borders swiftly, potentially introducing new sublineages or recombinants into immunologically naive populations [23]. International collaboration in genomic surveillance and data sharing is essential for early

detection of such changes. By linking genotypic data to clinical outcomes, researchers and public health officials can identify whether new variants carry higher transmissibility or pathogenicity, enabling pre-emptive responses such as targeted vaccination campaigns (if available) or heightened monitoring in vulnerable communities [21]. Another aspect of public health involves addressing the information gap among healthcare providers. Many clinicians and allied health professionals may be familiar with common respiratory viruses yet have limited awareness of hMPV and HBoV. Enhanced training programs and updated clinical guidelines—incorporating the latest diagnostic and therapeutic advances—could improve case detection and patient management. This is particularly pertinent during high incidence seasons or when evaluating immunocompromised patients presenting with respiratory symptoms that do not respond to standard interventions [31,34]. Professional societies and public health agencies can collaborate to disseminate updates on evolving testing methods, diagnostic criteria, and recommended management pathways. Longterm strategies will likely involve integrated disease surveillance frameworks capable of concurrently monitoring multiple respiratory pathogens, including hMPV and HBoV [39]. Such integrated approaches can optimize resource use, streamline data collection, and enhance the accuracy of disease burden estimations. The routine inclusion of hMPV and HBoV in respiratory viral panels can facilitate largescale epidemiological studies, ultimately guiding evidence based policies on vaccination, antiviral distribution, and resource allocation for outbreak control [39,42]. As vaccine development progresses, the establishment of robust immunization programs for high risk groups could further decrease the clinical and economic impact of these infections, paralleling the success of influenza and pneumococcal vaccination campaigns [29,45]. In summary, the public health challenges posed by hMPV and HBoV underscore the interconnectedness of epidemiological surveillance, clinical awareness, infection control, and research innovation. Addressing these pathogens requires not only technical expertise but also policy level commitments to strengthen healthcare infrastructures and advance preventative and therapeutic interventions. By weaving together local, national, and international efforts, the global community can better anticipate, detect, and respond to outbreaks, ultimately mitigating the toll these emerging viruses exert on populations worldwide.

FUTURE PERSPECTIVES

The trajectory of research on human metapneumovirus and human bocavirus suggests multiple avenues through which future investigations could substantially reduce disease burden. Advances in high throughput genomic sequencing, metagenomics, and bioinformatics are expected to yield more nuanced insights into how these viruses evolve over time, identifying specific mutations or recombination events that correlate with shifts in virulence or transmissibility [21,22]. This ongoing molecular surveillance will be critical for early detection of emergent lineages and guiding vaccine strategies that account for antigenic drift or novel genetic variants [43]. In parallel, improved phenotypic characterization of viral isolates in cell culture and animal models can clarify how genetic alterations affect viral replication kinetics, pathogenesis, and immunogenicity [29]. Such integrative research holds the promise of bridging laboratory findings with clinical data to inform targeted interventions and public health measures. Diagnostic innovation remains a top priority, particularly for settings with limited laboratory infrastructure. The miniaturization and cost reduction of molecular diagnostic platforms, such as microfluidic chips or CRISPR based point of care tests, could significantly expand access to timely, accurate detection of hMPV and HBoV [41,42]. Technologies enabling multiplex detection of a broad panel of respiratory pathogens, while preserving high sensitivity and specificity, will help clinicians pinpoint the primary etiological agent(s) in coinfection scenarios [39]. Automated data reporting and integration with electronic health record systems could further facilitate real time surveillance, enabling a more proactive approach to outbreak detection and management [40]. Such systems can also feed into predictive analytics models, helping to anticipate seasonal peaks and allocate healthcare resources efficiently. Therapeutic development for hMPV and HBoV faces several scientific and logistical challenges but is poised to make headway as more potent and virus specific strategies are identified. For hMPV, continued refinement of monoclonal antibody therapies and small molecule inhibitors targeting the F protein appears promising, given preliminary success in proof of concept studies [47]. Researchers are also exploring host targeted therapies that modulate immune pathways or interfere with essential host factors for viral replication, potentially reducing the likelihood of resistance [25]. Although progress is at an earlier stage for HBoV, high throughput screening of antiviral libraries could identify novel inhibitors of NS1 function or replication intermediates, laying the foundation for potential clinical trials [48]. Because viral coinfections are common, understanding the synergy or antagonism between therapies for different pathogens could optimize combination regimens, minimizing both viral replication and the overuse of antibiotics [16,46].

Vaccine research is also expected to accelerate, especially if novel technologies—such as mRNA platforms—are effectively adapted for hMPV or HBoV. Early phase clinical trials testing hMPV vaccine candidates highlight the feasibility of generating neutralizing antibodies, but challenges regarding durability, cross protection against various lineages, and safety in highrisk groups persist [9,29]. Lessons learned from these trials will shape next generation vaccine designs that incorporate conserved epitopes or utilize innovative adjuvants to enhance immunogenicity in diverse populations [9]. For HBoV, establishing clearer correlates of protection and delineating the virus's immunogenic landscape will be crucial steps toward any successful vaccination effort [6].

Should effective vaccines become available, strategies for phased implementation in pediatric populations, immunocompromised individuals, and older adults will require input from epidemiological modelling and cost effectiveness analyses. At a systems level, forging global collaborations will be paramount. Initiatives such as shared databases for genomic and clinical data, standardized research protocols, and multinational clinical trials can accelerate the pace of discoveries and broaden the applicability of findings [43]. Public–private partnerships may also play a pivotal role in bridging funding gaps and facilitating the largescale production and distribution of novel diagnostics, therapeutics, or vaccines. Educational programs that improve clinician awareness and training in detecting and managing hMPV and HBoV will amplify the benefits of scientific advances, translating research breakthroughs into tangible reductions in morbidity and mortality [31]. Ethical considerations will likewise shape future directions, particularly regarding the use of gene based interventions, the design of clinical trials in vulnerable populations, and the fair distribution of emerging technologies. Strengthening regulatory frameworks that ensure the safety and efficacy of new diagnostics and therapeutics will be indispensable, particularly for pediatric applications [49]. Continuous engagement with community stakeholders can foster trust, promote vaccine acceptance, and ensure that interventions are culturally sensitive and accessible.

CONCLUSION

Human metapneumovirus (hMPV) and human bocavirus (HBoV) illustrate how emerging viruses can become significant threats, infecting individuals across all age groups. Key challenges include high coinfection rates, overlapping symptoms, and severe risks to vulnerable populations. While advances in diagnostics have improved understanding, questions about viral shedding, asymptomatic cases, and disease severity remain. Current treatment relies on supportive care, highlighting the need for targeted antivirals and vaccines. Promising research exists, but significant hurdles, like antigenic variability, persist. Until better therapies are available, infection control and surveillance are essential. Strengthened diagnostics, genomic monitoring, and collaboration among healthcare sectors are vital to mitigating their impact and addressing future threats.

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