International Journal of Community Medicine and Public Health
Sivaranjani E et al. Int J Community Med Public Health. 2025 Apr;12(4):1965-1970
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20250953

Review Article

Human metapneumovirus: the hidden viral menace making headlines

Sivaranjani E.*, Jasmine S. Sundar, Kalpana S., Valarmathi S., Srinivas G.

Department of Epidemiology, The Tamil Nadu Dr. M.G.R Medical University, Guindy Chennai, India

Received: 27 January 2025
Accepted: 17 March 2025

***Correspondence:**
Dr. Sivaranjani E.,
E-mail: Sivaranjani.ph@gmail.com

ABSTRACT

Human metapneumovirus (HMPV) is a significant contributor to acute respiratory tract infections (ARIs), a leading global cause of morbidity and mortality, particularly in children under five years old. Discovered in 2001 in the Netherlands, HMPV is a member of the paramyxoviridae family and exists as two genotypes (A and B) with further subdivisions. Its prevalence is global, with seasonal outbreaks occurring predominantly in spring and winter. By the age of 5-10 years, most children have been exposed, but re-infections can occur throughout life due to incomplete immunity. HMPV infections primarily present as bronchiolitis, pneumonia and wheezing with more severe outcomes in infants, the elderly and immunocompromised individuals. The virus is challenging to diagnose due to its slow growth in cell culture, with RT-PCR and immunofluorescence assays being the most reliable diagnostic tools. Differential diagnosis includes other respiratory viruses such as RSV, influenza and bacterial pathogens. Treatment options remain limited to supportive care, through experimental therapies like ribavirin and fusion inhibitors show promise in preclinical studies. Prevention strategies focus on hygiene measures such as handwashing, mask usage and environmental disinfection, along with strict infection control protocols in healthcare settings. Despite its significant health burden, no licensed vaccines or antiviral treatments are available. Public health efforts emphasize the need for active surveillance, public education and research into effective vaccines and therapies. This review highlights the epidemiology, clinical manifestations, diagnostic challenges and prevention strategies of HMPV, emphasizing the need for targeted interventions to mitigate its global impact.

Keywords: Human metapneumovirus, Public health, Respiratory viruses

INTRODUCTION

Acute respiratory tract infection (ARI) is a leading cause of morbidity and mortality worldwide. Globally, ARIs were responsible for about 20% of total deaths in children less than 5 years of age in 2000 alone; moreover, about 70% of these deaths occurred in Sub-Saharan Africa and the southern regions of Asia.[1] ARIs affect children regardless of their economic status, with similar incidence rates in both developed and developing countries, but with a higher mortality rate in developing countries.[2] The risk of pneumonia is higher in children in developing countries (10–20%, compared to 3–4% in developed countries).[3] Human metapneumovirus (HMPV) was first discovered in 2001 in the Netherlands, when the virus was isolated from a paediatric patient who had symptoms similar to those of hRSV infection.[4] Since then, HMPV has been detected in 4–16% of patients with ARIs.[5] Belonging to the order Mononegavirales, the Paramyxoviridae family is divided into the subfamilies Paramyxovirinae and Pneumovirinae. The Pneumovirinae subfamily is further divided into two genera, Pneumovirus and Metapneumovirus. hRSV is placed under the genus Pneumovirus, while HMPV is placed under the genus Metapneumovirus. Whole genome analysis has shown that HMPV exists as two genotypes, A and B. Based upon the sequence variability of the attachment (G) and fusion (F) surface glycoproteins, these two genotypes are further divided into subgroups A1, A2, B1 and B2. Subgroup A2 is again subdivided into A2a and A2b.[6] The prevalence of HMPV has been documented in many countries and is considered a

leading cause of ARTIs worldwide owing to the limited prevention and control measures.[4] The clinical symptoms of HMPV infection in infants, elderly individuals and immunocompromised individuals are mainly characterized by fever, cough and gasp for breath, etc.[7] HMPV has been widely prevalent worldwide and continuously brings a significant medical burden to the local area, as effective vaccine or antiviral drug for treating or preventing HMPV infection is not licensed.[8] This review will explore the current understanding of human metapneumovirus, with a focus on its epidemiology, pathogenesis, clinical characteristics as well as strategies for prevention and control.

DISCOVERY OF HUMAN METAPNEUMOVIRUS

In 2001, researchers in the Netherlands first identified HMPV from stored nasopharyngeal samples from 28 children with respiratory illness by using electron microscopy and random reverse transcription-polymerase chain reaction (RT-PCR) techniques. This novel virus exhibited cytopathic effect but not hemadsorption in tertiary monkey kidney epithelial cells. The genome was most closely related to avian metapneumovirus serotype C (up to 88%homology).

However, the newly discovered virus replicated efficiently in monkeys but not in birds.[9] Archived sera from the 1950s contained neutralizing antibodies against HMPV. Two retrospective Canadian studies detected HMPV in specimens collected from patients with respiratory illness between 1993 and 2001 and a US study detected HMPV in specimens from 1976 to 2001.[10-12] Collectively, these studies show that HMPV has been circulating undetected for many decades.

Epidemiology

Human metapneumovirus has been isolated on all continents and has a seasonal distribution. Outbreaks occur mainly in the spring and winter months – January to March in the northern hemisphere and June to July in the southern hemisphere.[13,14] Outbreaks of HMPV infection tend to peak in early spring over a 4–6 week period, slightly later than outbreaks of hRSV infection, which also are more spread out in time.[15] Seroprevalence studies have shown that a high percentage (90–100%) of children have been infected by the time they are 5–10 years old, but re-infection can occur throughout adulthood.[4]

This may be due to insufficient immunity acquired during the initial infection and/or due to infection by different viral genotypes. The incubation period varies from individual to individual, but is commonly between 3 and 5 days. Two studies found that both genotypes of HMPV (A and B) co-circulated during a typical respiratory virus season and frequent re-infections with different genotypes occur.[16] The annual rate of hospitalization due to hMPV infection is equal to that of influenza and parainfluenza 1, 2 and 3 combined.

Pathogenesis

Humans and animals mount neutralizing antibody responses to HMPV. In mice, neutralizing antibodies are first detected five to seven days after infection, peaking between four and six weeks after infection. In mouse models, initial infection with HMPV protects against re-infection and antibodies alone can protect in small animal models.[17,18] In contrast, when macaques were exposed to a challenge 12 weeks after their initial HMPV infection, virus replication was observed despite the presence of serum antibodies and no protection was evident when the challenge occurred 8 months after the primary infection.[19]

These findings indicate that in primates and humans, antibody levels diminish over time, allowing for re-infection. A prospective study in humans observed that older adults who later became infected had lower baseline HMPV antibody levels compared to those who remained uninfected, suggesting that antibodies provide a protective effect.[20]

Clinical manifestations

Human metapneumovirus patients are generally diagnosed with bronchiolitis, bronchitis and pneumonia. They show common symptoms like fever, cough, hypoxia, upper respiratory tract infection, lower respiratory tract infection and wheezing.[21] However, the most common causes of hospitalization are bronchiolitis and pneumonia. The average duration of fever in HMPV-positive cases is about 10 days, with a peak during the course of the illness.[22] Young adults with HMPV re-infection show mild cold and flu-like symptoms, with fever in a small proportion of infected cases.

However, in the case of elderly patients, re-infection can lead to severe symptoms (such as pneumonitis) and even to death. A study reported that HMPV infection was found in about 8% of children who came to the hospital with wheezing.[23] Wheezing is a common clinical symptom observed in multiple studies of children with HMPV-associated lower respiratory tract infections. It can lead to asthma exacerbations in small children and adults. HMPV was detected by real-time RT-PCR in asymptomatic children, but they had significantly lower viral loads that those found in symptomatic children.[24] Higher HMPV viral loads were significantly correlated with the course of illness and disease severity, irrespective of genotype.[25]

Laboratory examination may show lymphopenia, neutropenia and elevated transaminases. Studies on imaging with chest X-ray and computed tomotography (CT) show initially signs of acute interstitial pneumonia (ground glass opacity and air-space consolidation) turning into signs of bronchiolitis/bronchitis (bronchial(ar) wall

thickening or impaction).[26,27] Compared to RSV and influenza, similar rates of intensive care unit (ICU) admission, mechanical ventilation, length of stay for hospitalization and length of stay in ICU were seen for HMPV infection in adults.[28]

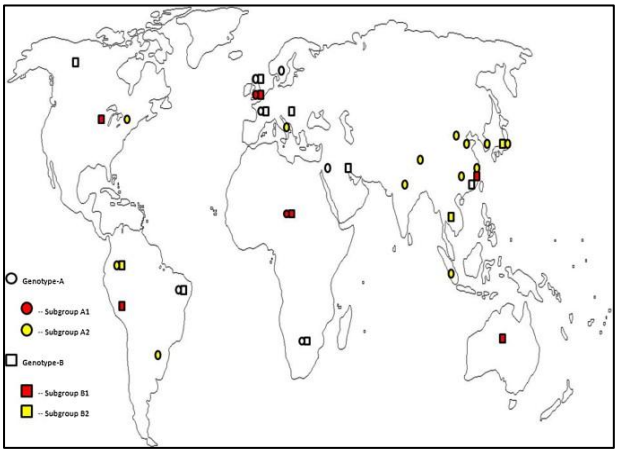

Figure 1: Geographical distribution of HMPV genotypes.

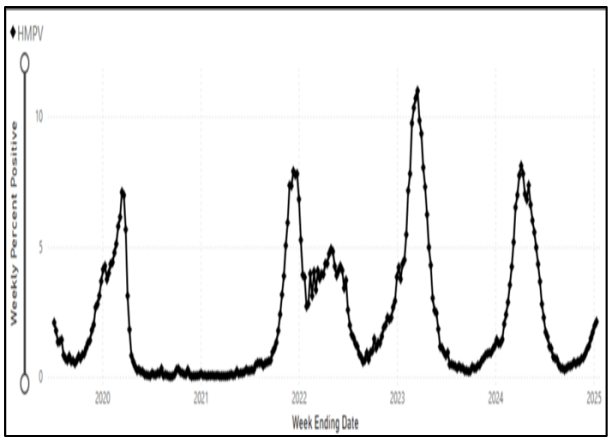

Figure 2: Trends of HMPV.

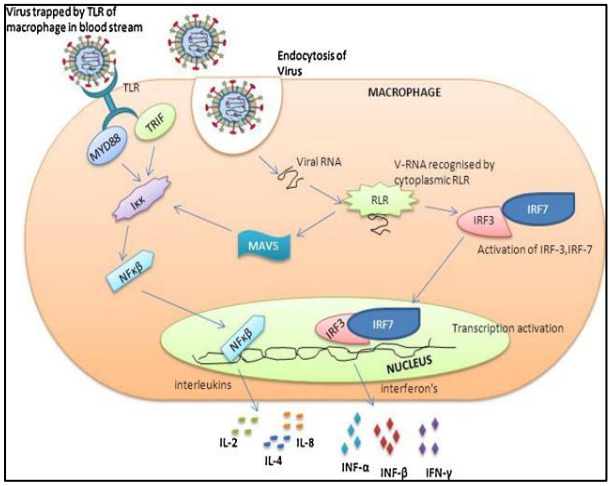

Figure 3: Pathogenesis of HMPV.

Diagnosis

HMPV growth in cell culture is fastidious; this may be one reason for its late identification. Most studies have reported reliable cytopathic effects only in tertiary monkey kidney or LLC-MK2 cells.[11] The cytopathic effect is variable, with some strains inducing hRSV-like syncytia formation and others inducing focal rounding and cell destruction.

Typically, the cytopathic effect is displayed more than 10–14 days after inoculation. Confirmation of HMPV cytopathic effect relies on RT-PCR testing of infected supernatants, particularly in the absence of commercially available antibodies.

A recent study demonstrated that HMPV can replicate more effectively in human laryngeal carcinoma (HEp-2) cells, even without exhibiting a cytopathic effect.[29] In such cases, the presence of HMPV was verified by directly testing HEp-2 cell culture supernatants using RT-PCR or by passaging the virus onto LLC-MK2 cells to observe cytopathic effects. However, many clinical laboratories do not at present have the capability to perform routine diagnostic RT-PCR for HMPV detection.

For rapid and accurate diagnosis of HMPV infections, a combination of immunofluorescence assays and direct fluorescent antibody methods is used as the first-line of diagnosis, followed by RT-PCR on the negative samples.[30]

Immunofluorescent staining of shell vial centrifugation culture (SVCC) has been used successfully for a more rapid detection of respiratory viruses. SVCC allows detection of viral antigen after a culture time of just 2 days. A monoclonal antibody (MAb-8) specific to HMPV is not useful for immunofluorescence assay (IFA) directly on patient specimens, but it can be used to detect HMPV when used with SVCC with several cell lines.[31] A home-brew ELISA method has also been developed using cell lysates of HMPV.[20] Clearly, simpler ELISA tests using viral proteins possibly derived from the 2 main groups are needed to conduct large serological surveys in many parts of the world.

Differential diagnosis

The clinical presentation of HMPV, encompassing both upper and lower respiratory tract infections (URTI and LRTI), closely resembles that of RSV. The differential diagnosis for HMPV includes other respiratory viruses such as influenza A and B, RSV, parainfluenza viruses, rhinoviruses and coronaviruses.

Bacterial causes of community-acquired pneumonia should also be considered. In patients with underlying asthma or COPD, acute HMPV infection may present similarly to exacerbations of these conditions.

Table 1: Differential diagnosis for syndromes resembling HMPV infection.

Differential diagnosis for syndromes resembling HMPV infection	
Viruses	RSV
	Influenza A and B viruses
	Parainfluenza viruses
	Coronaviruses
	Picornaviruses (e.g., rhinovirus)
	Adenovirus
Bacterial infection	Mycoplasma pneumoniae
	Chlamydia pneumoniae
	Bordatella pertussis
Non-infectious causes	Asthma
	COPD

Treatment

Currently, the treatments available for HMPV infection are primarily supportive. But a few reports have raised the possibility of using ribavirin, immunoglobulin, fusion inhibitors and small interfering ribonucleic acids for the treatment and control of HMPV infection.[32,33] Ribavirin is a nucleoside with broad spectrum inhibitory activity against a variety of RNA and DNA viruses, including HMPV.

Ribavirin has demonstrated in vitro inhibition of Tumor Necrosis Factor-alfa, interferon-gamma and interleukin (IL)-10, suggesting a down regulation in Th1 and Th2 cytokine production and an increase of IL-2 production by peripheral blood mononuclear cells.[34,35] Ribavirin may terminate T-cell immune-mediated damage caused by viral infections. It limits viral transcription and showed to have immunomodulatory effects. The in vitro results are confirmed by an in vivo study in BALB/c mouse.[32]

NMSO3, a sulfated sialyl lipid known to inhibit RSV replication in cell culture and in the cotton rat model, has also been shown to inhibit HMPV replication, syncytia formation and cell-to-cell virus spread in culture.[36] None of these compounds have been systematically tested in humans for the treatment of HMPV infection, although a case report describes apparently successful treatment with ribavirin of a patient who had undergone lung transplant and had severe HMPV infection.[37]

Prevention and control

Preventing HMPV infection is similar to preventing other respiratory illnesses which includes frequent handwashing with soap and water or using alcohol-based hand sanitizers, covering the mouth and nose while coughing or sneezing and wearing masks in crowded or poorly ventilated areas. In healthcare settings, infection control remains a priority, with measures such as isolating infected patients, using personal protective equipment (PPE) like gloves, gowns and masks and thoroughly disinfecting high-touch surfaces. Environmental cleaning with appropriate agents, such as diluted bleach solutions, is also encouraged. Despite ongoing research, there are currently no vaccines or antiviral treatments specifically approved for HMPV. Clinical management focuses on supportive care, including hydration, oxygen supplementation for severe cases and over-the-counter medications for symptom relief.

Public health initiatives also play a critical role, including active surveillance to monitor HMPV outbreaks, educating the public on preventive measures and encouraging those with symptoms to stay home to prevent further spread. The World Health Organization (WHO) and other health agencies highlight the need for continued research into effective vaccines and treatments, with several vaccine candidates currently under development.[38]

CONCLUSION

Human metapneumovirus (HMPV) remains a significant cause of acute respiratory infections, particularly in vulnerable populations such as children, the elderly and immunocompromised individuals. Despite extensive research, no licensed vaccines or specific antiviral therapies are available, leaving prevention dependent on hygiene measures, infection control and supportive care. Enhanced diagnostic tools for early and precise detection, along with an integrated approach combining vaccine development, antiviral treatments and robust public health strategies, will be essential to alleviating the medical and economic impact of HMPV. Sustained investment in research and global action protocol rooted in collaboration will be the key to advancing efforts against this pervasive respiratory pathogen.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. The Lancet Infectious Diseases. 2002;2(1):25–32.
2. Shapiro: Epidemiology of acute respiratory infections. Available at: https://scholar.google.com. Accessed on 21 September 2024.
3. Human metapneumovirus: a new respiratory pathogen. J Biosci. 2008;33(4):483–93.
4. A newly discovered human pneumovirus isolated from young children with respiratory tract disease – PubMed. Available at: https://pubmed.ncbi.nlm.nih.
5. López-Huertas MR, Casas I, Acosta-Herrera B, García ML, Coiras MT. Two RT-PCR based assays to detect human metapneumovirus in

nasopharyngeal aspirates. J Virol Methods. 2005;129(1):1–7.
6. Hoogen BG, Herfst S, Sprong L, Cane PA, Forleo-Neto E, de Swart RL, et al. Antigenic and genetic variability of human metapneumoviruses. Emerg Infect Dis. 2004;10(4):658–66.
7. Makowska D, Hamelin MÈ, Boivin G. Engineering of Live Chimeric Vaccines against Human Metapneumovirus. Pathogens. 2020;19;9(2):135.
8. Ma S, Zhu F, Xu Y, Wen H, Rao M, Zhang P, et al. Development of a novel multi-epitope mRNA vaccine candidate to combat HMPV virus. Hum Vaccin Immunother. 2023;19(3):2293300.
9. Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RAM, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med. 2001;7(6):719–24.
10. Peret TCT, Boivin G, Li Y, Couillard M, Humphrey C, Osterhaus ADME, et al. Characterization of human metapneumoviruses isolated from patients in North America. J Infect Dis. 2002;1;185(11):1660–3.
11. Boivin G, Abed Y, Pelletier G, Ruel L, Moisan D, Côté S, et al. Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. J Infect Dis. 2002;186(9):1330–4.
12. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med. 2004;350(5):443–50.
13. Pilger DA, Cantarelli VV, Amantea SL, Leistner-Segal S. Detection of human bocavirus and human metapneumovirus by real-time PCR from patients with respiratory symptoms in Southern Brazil. Mem Inst Oswaldo Cruz. 2011;106(1):56–60.
14. Choi EH, Lee HJ, Kim SJ, Eun BW, Kim NH, Lee JA, et al. The association of newly identified respiratory viruses with lower respiratory tract infections in Korean children, 2000-2005. Clin Infect Dis. 2006;43(5):585–92.
15. Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis. 2003;9(6):634–40.
16. Bouscambert-Duchamp M, Lina B, Trompette A, Moret H, Motte J, Andréoletti L. Detection of human metapneumovirus RNA sequences in nasopharyngeal aspirates of young French children with acute bronchiolitis by real-time reverse transcriptase PCR and phylogenetic analysis. J Clin Microbiol. 2005;43(3):1411–4.
17. MacPhail M, Schickli JH, Tang RS, Kaur J, Robinson C, Fouchier RAM, et al. Identification of small-animal and primate models for evaluation of vaccine candidates for human metapneumovirus (hMPV) and implications for hMPV vaccine design. J Gen Virol. 2004;85(6):1655–63.
18. T lymphocytes contribute to antiviral immunity and pathogenesis in experimental human metapneumovirus infection. PubMed. Available at: https://pubmed.ncbi.nlm.nih. Accessed on 21 August 2024.
19. van den Hoogen BG, Herfst S, de Graaf M, Sprong L, van Lavieren R, van Amerongen G, et al. Experimental infection of macaques with human metapneumovirus induces transient protective immunity. J Gen Virol. 2007;88(4):1251–9.
20. Falsey AR, Hennessey PA, Formica MA, Criddle MM, Biear JM, Walsh EE. Humoral immunity to human metapneumovirus infection in adults. Vaccine. 2010;28(6):1477–80.
21. Deffrasnes C, Hamelin ME, Boivin G. Human metapneumovirus. Semin Respir Crit Care Med. 2007;28(2):213–21.
22. Hoogen BG, van Doornum GJJ, Fockens JC, Cornelissen JJ, Beyer WEP, de Groot R, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis. 2003;188(10):1571–7.
23. Jartti T, Hoogen B, Garofalo RP, Osterhaus ADME, Ruuskanen O. Metapneumovirus and acute wheezing in children. Lancet. 2002;360(9343):1393–4.
24. Bosis S, Esposito S, Osterhaus ADME, Tremolati E, Begliatti E, Tagliabue C, et al. Association between high nasopharyngeal viral load and disease severity in children with human metapneumovirus infection. J Clin Virol. 2008;42(3):286–90.
25. Peng D, Zhao X, Liu E, Huang Y, Yang X, Zhao Y, et al. Analysis of viral load in children infected with human metapneumovirus. Iran J Pediatr. 2010;20(4):393–400.
26. Franquet T, Rodríguez S, Martino R, Salinas T, Giménez A, Hidalgo A. Human metapneumovirus infection in hematopoietic stem cell transplant recipients: high-resolution computed tomography findings. J Comput Assist Tomogr 2005;29(2):223–7.
27. Kamboj M, Gerbin M, Huang CK, Brennan C, Stiles J, Balashov S, et al. Clinical characterization of human metapneumovirus infection among patients with cancer. J Infect. 2008;57(6):464–71.
28. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus and influenza virus in older adults. J Infect Dis. 2012;206(1):56–62.
29. Chan PKS, Tam JS, Lam CW, Chan E, Wu A, Li CK, et al. Human metapneumovirus detection in patients with severe acute respiratory syndrome. Emerg Infect Dis. 2003;9(9):1058–63.
30. Jokela: Detection of human metapneumovirus and respirator. Available at: https://scholar.google.com. Accessed on 19 November 2024.

31. Landry ML, Ferguson D, Cohen S, Peret TCT, Erdman DD. Detection of Human Metapneumovirus in Clinical Samples by Immunofluorescence Staining of Shell Vial Centrifugation Cultures Prepared from Three Different Cell Lines. J Clin Microbiol. 2005;43(4):1950–2.
32. Wyde PR, Chetty SN, Jewell AM, Boivin G, Piedra PA. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res. 2003;60(1):51–9.
33. Kitanovski L, Kopriva S, Pokorn M, Dolničar MB, Rajić V, Stefanović M, et al. Treatment of severe human metapneumovirus (hMPV) pneumonia in an immunocompromised child with oral ribavirin and IVIG. J Pediatr Hematol Oncol. 2013;35(7):311-3.
34. Te Wierik MJ, Nguyen DT, Beersma MF, Thijsen SF, Heemstra KA. An outbreak of severe respiratory tract infection caused by human metapneumovirus in a residential care facility for elderly in Utrecht, the Netherlands, January to March 2010. Euro Surveill. 2012;17(13):20132.
35. Sookoian S, Castaño G, Flichman D, Cello J. Effects of ribavirin on cytokine production of recall antigens and phytohemaglutinin-stimulated peripheral blood mononuclear cells. (Inhibitory effects of ribavirin on cytokine production). Ann Hepatol. 2004;3(3):104–7.
36. Wyde PR, Moylett EH, Chetty SN, Jewell A, Bowlin TL, Piedra PA. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by NMSO3 in tissue culture assays. Antiviral Res. 2004;63(1):51–9.
37. Raza K, Ismailjee SB, Crespo M, Studer SM, Sanghavi S, Paterson DL, et al. Successful Outcome of Human Metapneumovirus (hMPV) Pneumonia in a Lung Transplant Recipient Treated With Intravenous Ribavirin. J Heart Lung Transplant. 2007;26(8):862–4.
38. Mpox detected in India. Why WHO changed the name from monkeypox-India Today. Available at: https://www.indiatoday.in. Accessed on 21 December 2024.

Cite this article as: Sivaranjani E, Sundar JS, Kalpana S, Valarmathi S, Srinivas G. Human metapneumovirus: the hidden viral menace making headlines. Int J Community Med Public Health 2025;12:1965-70.