International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2064-2068 www.ijprajournal.com ISSN: 2456-4494

Human Metapneumovirus (hMPV): A Comprehensive Review of Epidemiology, Clinical Management, and Emerging Challenges

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Date of Submission: 20-06-2025 Date of Acceptance: 30-06-2025

ABSTRACT: Human metapneumovirus (hMPV), first identified in 2001 but circulating globally for over 70 years, is a leading cause of acute respiratory infections (ARIs) across all age groups. This review synthesizes contemporary data on hMPV's virology, clinical impact, and public health burden, highlighting a 17% surge in pediatric hospitalizations (2023–2025) and 11% mortality in immunocompromised populations. Global epidemiology reveals regional heterogeneity, with China reporting hMPV in 6.2% of respiratory illnesses in children under 14 during winter 2024–2025. Diagnostic advances in multiplex PCR and CRISPR-based platforms contrast with the absence of licensed antivirals or vaccines. Emerging solutions include F-protein-targeted monoclonal antibodies (e.g., MPV467) and mRNA vaccines (mRNA-1653). Urgent priorities include standardized global surveillance, therapeutic trials, and prevention strategies for this resurgent pathogen.

KEYWORDS: Human metapneumovirus (HMPV), Respiratory tract infection (RTI), Adults, Children, Epidemiology, Diagnosis, Treatment.

I. INTRODUCTION

Human metapneumovirus (hMPV), a member of the Pneumoviridae family, is an enveloped RNA virus discovered in 2001 but serologically confirmed in samples dating to 19581,6. It causes upper and lower respiratory tract infections (URTIs/LRTIs), with symptom severity disproportionately affecting young children, older adults (>65 years), and immunocompromised individuals. Globally, hMPV contributes to 11.1 million annual LRTI cases in children under five, resulting in 502,000 hospitalizations and 11,300 deaths[6]. Post-COVID-19 pandemic, hMPV has resurged markedly, with a 17% increase in pediatric hospitalizations (2023–2025) linked to A2c viral variants bearing genomic duplications[6,9]. Despite this burden, hMPV remains underdiagnosed due to nonspecific symptoms overlapping with influenza and RSV, and limited routine testing[1,10]. This review examines hMPV's molecular evolution, clinical complexities, diagnostic advances, and therapeutic innovations, providing evidence-based strategies to mitigate its global health impact**.**

II. VIROLOGY AND PATHOGENESIS

VIRAL STRUCTURE AND GENETIC DIVERSITY: hMPV possesses a single-stranded RNA genome encoding nine proteins, including the fusion (F) glycoprotein—a primary target for neutralizing antibodies and vaccine development6. The virus exhibits antigenic drift at a rate of 6.95–7.12 × 10^{-4} substitutions/site/year, driven by error-prone RNA polymerase lacking proofreading activity[6]. Recent genomic surveillance has identified emerging A2c lineages with 180-nucleotide duplications in the G gene, enhancing immune evasion and transmissibility[6,9]. Unlike influenza, hMPV lacks segmented genomes, making point mutations its primary evolutionary mechanism[6].

IMMUNE EVASION AND HOST RESPONSE: hMPV evades host immunity by suppressing interferon (IFN)-α/β signaling and downregulating major histocompatibility complex (MHC) class I expression in dendritic cells[6]. Infection triggers pro-inflammatory cytokine release (e.g., IL-6, TNF-α), exacerbating tissue damage in lower airways. Immunocompromised individuals exhibit prolonged viral shedding (up to 182 days), facilitating nosocomial transmission[1,6].

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TABLE 1: COMPARATIVE VIROLOGY OF MAJOR RESPIRATORY PATHOGENS[10]

Characteristic	hMPV	RSV	Influenza A
Genome Type	ssRNA (-)	ssRNA (-)	ssRNA (-) segmented
Key Surface Protein	F glycoprotein	F glycoprotein	Hemagglutinin (HA)
Mutation Rate	6.95–7.12 × 10^{-4} /site/yr	~1 × 10^{-4} /site/yr	~3 × 10^{-3}/site/yr
Primary Immune Evasion	Antigenic drift	Antigenic drift	Antigenic shift/drift
Shedding Duration	7–14 days (immunocompetent)	8–15 days	5–7 days

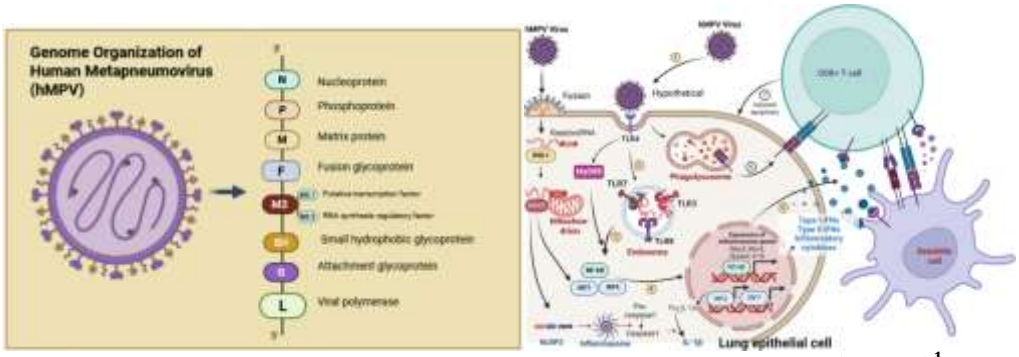

FIG 1, 2: GENOMIC STRUCTURE OF HUMAN METAPNEUMOVIRUS (HMPV)[1],MAJOR SIGNALING PATHWAYS IN HMPV PATHOGENESIS AND IMMUNE RESPONSE

III. CLINICAL MANIFESTATIONS AND HIGH-RISKPOPULATIONS

hMPV symptoms range from mild URTIs (cough, rhinorrhea, fever) to severe LRTIs (bronchiolitis, pneumonia). Risk stratification reveals three vulnerable cohorts:

1. Children <5 years: Account for 10–12% of ARI hospitalizations; 5–16% develop pneumonia[1,3].
2. Immunocompromised patients: Hematopoietic stem cell transplant (HSCT) recipients face 11% mortality from hMPV pneumonia[1,6].
3. Older adults: 40% experience COPD/asthma exacerbations; ICU admission rates parallel influenza[7,10].

Severe disease markers include hypoxia, leukopenia, and elevated C-reactive protein (>20 mg/L)[7]. Co-infections with RSV or influenza increase ICU admissions by 30% in pediatric cohorts[1,9].

IV. EPIDEMIOLOGY AND TRANSMISSION DYNAMICS

hMPV symptoms range from mild URTIs (cough, rhinorrhea, fever) to severe LRTIs (bronchiolitis, pneumonia). Risk stratification reveals three vulnerable cohorts:

Global Burden and Seasonal Trends:

hMPV circulates worldwide, with seasonal peaks in late winter to spring (February–April) in temperate regions[1,8]. The 2024–2025 Northern Hemisphere winter saw synchronized surges with influenza/RSV:

- China: hMPV detected in 6.2% of childhood respiratory illnesses (December 2024)[2,9].
- USA/India: 17% YoY rise in pediatric hospitalizations (Q1 2025)[6,9].
- Solomon Islands: Enhanced surveillance in 23 sentinel sites due to co-circulating pathogens[8].

Transmission Mechanisms:

- Community Spread: Respiratory droplets (coughing/sneezing); fomite persistence: 24–48 hours on plastic/stainless steel[1].
- Healthcare Settings: Aerosol-generating procedures (e.g., intubation) increase nosocomial risk; asymptomatic HCWs shed virus for 5–7 days[1].
- Household Attack Rates: 12.2% in high-density urban settings vs 4% rural[1].

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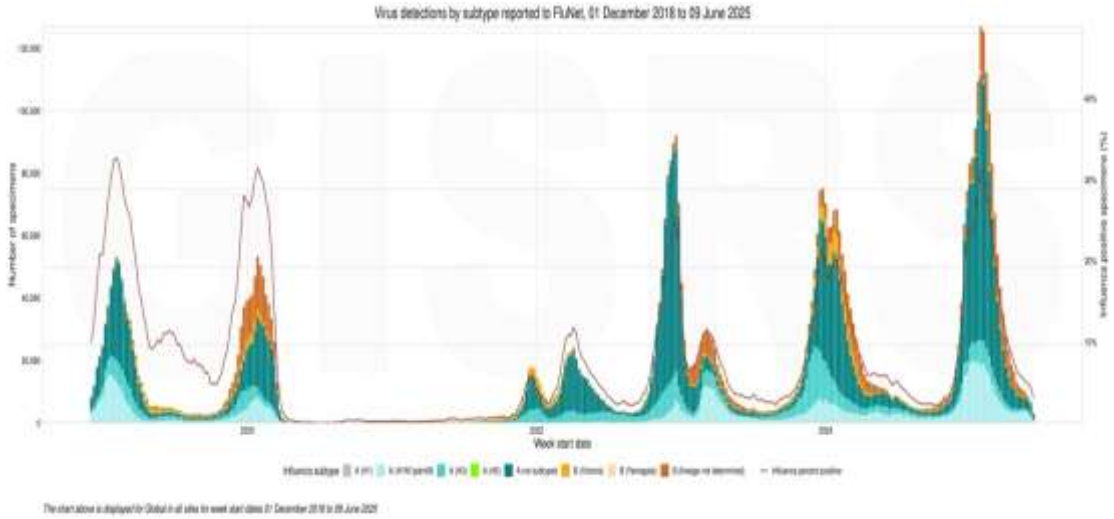
V. DIAGNOSTIC APPROACHES

Current Standards and Limitations: RT-PCRremains the gold standard (98% sensitivity), while rapid antigen tests show poor sensitivity (52%) due to low viral loads in adults[1,5]. Multiplex assays detect co-infections but are cost-prohibitive in LMICs[1]

TABLE 2: GLOBAL HMPV ACTIVITY (2024–2025)[7]

Region	Peak Months	Case Burden	Co-dominant Pathogens
Northern China	Dec 2024–Feb 2025	6.2% of childhood respiratory illnesses	Influenza, Mycoplasma pneumoniae
USA	Jan–Mar 2025	17% ↑ pediatric hospitalizations vs 2023	RSV, SARS-CoV-2
Western Europe	Feb–Apr 2025	5.4% of ARI hospitalizations	RSV, Influenza
South Asia	Jun–Aug 2025*	Emerging outbreaks in India	Rhinovirus, Adenovirus
*Projected based on Southern Hemisphere patterns 19.			



VIRUS DETECTIONS BY SUBTYPE REPORTED TO FLUNET, 01 DECEMBER 2018 TO 16 JUNE 2025 OF ALL COUNTRIES, AS OF 26 JUNE 2025.

Source: (https://worldhealthorg.shinyapps.io/flunetchart/).

TABLE 3: DIAGNOSTIC MODALITIES FOR HMPV[4]

Method	Sensitivity	Specificity	Turnaround Time	Clinical Utility
RT-PCR	98%	100%	2–6 hours	Gold standard for acute infection
Rapid Antigen Test	52%	95%	15–30 min	Low utility in adults
Cell Culture	68%	99%	7–21 days	Research only
CRISPR-Cas13	95%*	98%*	<30 min	Emerging point-of-care solution
*Preclinical data[15].				

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TABLE 4: EXPERIMENTAL HMPV THERAPEUTICS[5]

Therapy Class	Candidate	Mechanism	Development Status
Monoclonal Antibodies	MPV467	Neutralizes F-protein epitopes	Phase I
mRNA Vaccines	mRNA-1653	Encodes prefusion F trimer	Phase I (primate data)
Host-Directed	MK-2206	AKT kinase inhibitor blocks entry	Preclinical
Viral Polymerase Inhibitors	ALS-8176	Nucleoside analog	Preclinical

Innovations: CRISPR-Cas[13] platforms and nanopore sequencing enable rapid, field-deployable diagnostics1. Chang conjunctival (1-5C4) and CRFK cell lines optimize viral isolation for research1.

VI. TREATMENT AND PREVENTION

Therapeutic Gaps and Emerging Strategies: No licensed antivirals exist. Supportive care (oxygen, hydration) is mainstay. Promising candidates include:

- Fusion inhibitors: GS-5806 (blocks F-protein-mediated entry; Phase II trials)[6].
- siRNA: ALN-RSV01 (targets nucleocapsid gene; reduces viral titers 100-fold in cotton rats)[6].
- Immunomodulators: Interferon-λ/ribavirin combinations reduce viral loads in murine models[6,7].

Prevention: Non-pharmaceutical interventions (hand hygiene, masks) reduce transmission by 40–60%[3,8]. Palivizumab (RSV mAb) is ineffective against hMPV due to F-protein structural differences[1,7].

VII. FUTURE DIRECTIONS

1. Vaccine Development: mRNA-1653 elicits robust IgA in primates; nanoparticle F-protein vaccines show preclinical promise[6].
2. Global Surveillance: WHO-integrated networks tracking hMPV genotypes (e.g., A2c variants)[2,8].
3. Point-of-Care Diagnostics: CRISPR-based tools for LMICs[1].
4. Antiviral Trials: Combination therapies (e.g., GS-5806 + interferon-Œ[a]) to curb resistance[6]

VIII. CONCLUSION

hMPV has evolved from an emerging pathogen to a persistent global threat. Its disease burden—exacerbated by antigenic drift, diagnostic limitations, and therapeutic gaps—demands coordinated action. Priorities include:

- Standardized PCR surveillance to capture true incidence.
- Accelerated vaccine trials targeting F-protein conserved epitopes.
- Tailored guidelines for immunocompromised populations.

Lessons from COVID-19 underscore that integrated respiratory virus monitoring, not pathogen-specific silos, is essential for pandemic preparedness.

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