Review Article

Human Metapneumovirus: What We Know So Far – A Mini Review

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Human metapneumovirus (HMPV) is a seasonal respiratory pathogen closely related to avian metapneumoviruses, particularly subgroup C, indicating a zoonotic origin. Retrospective data suggest it has circulated for at least half a century. HMPV poses substantial risk to young infants and vulnerable populations. During the "tripledemic," wastewater surveillance revealed overlapping peaks of influenza A, respiratory syncytial virus, and SARS-CoV-2, with localized HMPV circulation. Disease severity correlates with advanced age and chronic conditions. Although no licensed vaccine or antiviral exists, progress in neutralizing monoclonal antibodies targeting the viral fusion (F) protein highlights potential therapeutic avenues. Research from Taiwan and Indonesia shows near-year-round circulation, especially among children, with marked genetic diversity. Until specialized treatments emerge, supportive care and strengthened surveillance remain vital for managing HMPV.

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Metapneumoviruses (Pneumoviridae family) infect both birds (avian metapneumoviruses, AMPV) and humans (human metapneumoviruses, HMPV). These closely related viruses share similar genomic architectures and cause respiratory disease in their respective hosts. Although HMPV was first identified in 2001, retrospective studies indicate it has circulated in humans for at least 50 years. Among AMPV subgroups, AMPV-C is most closely related to HMPV, suggesting HMPV emerged from AMPV-C via zoonotic transmission. Over time, HMPV has become an endemic, seasonal respiratory virus in humans[1].

Wastewater monitoring yields valuable community-level insights into respiratory disease prevalence. By tracking daily RNA levels of influenza A (IAV), respiratory syncytial virus (RSV), HMPV, and SARS-CoV-2 in wastewater solids from eight treatment facilities in California's Greater San Francisco Bay

Area (July 2022–July 2023), researchers identified a "tripledemic" when IAV, RSV, and SARS-CoV-2 peaked simultaneously. Although HMPV also circulated, RSV and IAV events showed regional coherence, whereas HMPV was more localized[2].

Globally, infants under one year are at heightened risk for severe HMPV infections—on par with RSV and influenza. Within this age group, infants under six months in low- and lower-middle-income countries experience a higher mortality from HMPV-associated ALRI than older children and those in wealthier nations[3]. Europe's first COVID-19 outbreak occurred in March 2020, coinciding with the typical peak of HMPV, suggesting potential cocirculation or competition. Despite a 324% increase in HMPV testing, incidence stayed constant, with 25 (11%) ICU admissions and 14 (6%) deaths among HMPV patients. Older age, a history of myocardial infarction, and lower BMI were independent risk factors for 30-day mortality. While clinical features were similar between HMPV- and COVID-19–infected patients, HMPV was more often observed in older females with COPD or chronic heart failure, and hospital stays were slightly longer during the pandemic (7 vs. 5 days)[4].

Discovered in 2001, HMPV still lacks a specific antiviral or vaccine, unlike human respiratory syncytial virus (hRSV). Increasing attention has turned to neutralizing monoclonal antibodies (nMAbs), central to vaccine efficacy and essential as therapeutic agents. Advances in viral fusion (F) protein structural biology and lessons from hRSV and other enveloped viruses have accelerated nMAb development against HMPV[5]. High-throughput single-cell analyses of memory B cells from young and elderly donors showed that neutralizing antibodies primarily target epitopes common to both pre- and post-fusion F conformations. However, rare, highly potent, broadly neutralizing antibodies specific to pre-fusion epitopes were identified, including one targeting a vulnerable apex of the pre-fusion F trimer. Monotherapy with nMAbs recognizing three distinct antigenic sites conferred robust protection against lower respiratory tract infection in a small animal model[6].

Stabilizing the prefusion conformation of the HMPV fusion (F) protein (Pre-F) is pivotal to generating strong neutralizing antibodies. Researchers engineered a double-cleaved F protein with AI-identified stabilizing substitutions, yielding a vaccine candidate with high expression, thermostability, and structural integrity. This engineered protein induced potent cross-neutralizing responses and provided near-complete protection in cotton rats, underscoring its promise as a viable HMPV vaccine candidate[7].

HMPV in Taiwan

Using samples available from 2016 to 2018, investigators at Taipei Veterans General Hospital examined respiratory viruses (RVs) in adults with respiratory tract infections (RTIs), analyzing 2,292 samples from intensive care units (ICUs), ordinary wards, and the emergency department. The overall RV positivity rate was 22%, including 17.8% non-influenza respiratory viruses (NIRVs), which were more frequently detected in non-winter seasons. Broncho-alveolar lavage samples showed a 12.7% positivity rate, and ICU samples had a 20.5% positivity rate. Seasonal variations were noted for coronaviruses (CoV), HMPV, and parainfluenza virus (PIV), with temperature influencing the detection rates of CoV, RSV, HMPV, and PIV[8].

Another retrospective study, using community viral surveillance data from sentinel sites across Taiwan (2013-2023), investigated HMPV epidemiology. Among 114 isolated HMPV strains, fusion (F) gene sequencing indicated nearly year-round circulation, peaking in spring (March–May). Children under four years old accounted for 68.4% of infections. Penghu County showed the highest positivity rate, followed by Changhua County and Hsinchu County. Clinical symptoms were mostly nonspecific—fever (56.1%), cough (44.7%), rhinorrhea (21.1%), and sore throat (14.9%)—though severe manifestations such as central nervous system involvement (1.8%) and dyspnea (0.9%) occurred in a few cases. Phylogenetic analysis revealed significant diversity, with the A2 lineage being most common (57.9%), followed by B2 (33.3%)[9].

HMPV in Indonesia

Archived specimens that tested negative for SARS-CoV-2 by nucleic acid amplification tests (NAAT) between March 2020 and July 2021 were forwarded to the Eijkman Institute for Molecular Biology in Jakarta. These samples, obtained from Wattansoppeng city in South Sulawesi—home to a central bat park featuring Acerodon celebensis and Pteropus alecto fruit bats—were screened for influenza viruses, enteroviruses, Paramyxoviridae, Nipah virus, Coronaviridae, and Pneumoviridae. Of 210 samples tested, 19 were positive for respiratory syncytial virus (RSV)-A and RSV-B, human parainfluenza viruses 1 and 2 (HPIV-1, HPIV-2), human rhinoviruses (HRV)-A, HRV-B, HRV-C, HMPV, influenza A virus (IAV), and coxsackievirus A6 (CV-A6). HMPV strains were identified as genotypes B1 and A2a[10].

Between April and May 2020, nasopharyngeal swabs positive for SARS-CoV-2 at a COVID-19 referral laboratory in Yogyakarta were additionally screened for co-infecting viral respiratory pathogens using real-time RT-PCR. Among 125 samples tested, 59 showed co-infection with other viruses, including influenza A (32 samples), influenza B (16), HMPV (1), and adenovirus (10)[11].

Conclusion

Human metapneumovirus (HMPV) is a seasonal respiratory pathogen that circulates primarily in colder months across various regions. While there is currently no licensed antiviral or vaccine, existing supportive therapies commonly employed for respiratory infections—such as oxygen support, hydration, and, where indicated, immunomodulatory treatment—can help alleviate HMPV symptoms and complications. Promising new approaches, including the development of prefusion (Pre-F) vaccine candidates and neutralizing monoclonal antibodies (nMAbs), underscore the potential for more targeted interventions in the future. Until these become widely available, vigilant clinical surveillance and application of established supportive protocols remain the mainstay of HMPV management.

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Declarations

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