



Dissecting Pandemic-Prone Viral Families

Volume 4: The Pneumoviridae

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Introduction

The *Pneumoviridae* viral family, formerly a subfamily of *Paramyxoviridae*, consists of 2 genera: *Orthopneumovirus*, the members of which infect mammals, and *Metapneumovirus*, which are specific for either mammals or birds.

Pneumoviridae poses a largely underappreciated pandemic threat. Only 2 known viral family members infect humans: human respiratory syncytial virus (HRSV, commonly RSV) and human metapneumovirus (HMPV).¹ These 2 endemic respiratory viruses confer substantial morbidity and mortality on the human species, particularly among older adults and young children and across different sociodemographic strata.² If a zoonotic or yet undiscovered viral family member acquired the ability to efficiently infect humans, it could spread prolifically, especially when faced with little immunity.

RSV: Considerable Burden of Illness

RSV, the most well-known member of this viral family, consists of 2 strains: RSV-A and RSV-B. As many as 80,000 children under age 5 are hospitalized with RSV infections in the US each year; the virus is the leading cause of hospitalization among infants. Children most at risk for severe disease include those born prematurely, those under 6 months old, and those with co-morbidities.^{1,3} Additionally, RSV is believed to have a causative relationship with pediatric asthma.⁴

RSV is also a significant cause of acute respiratory illness among adults, with the potential to cause severe disease. Most adult cases occur among those aged 65 years or older, with the risk of infection increasing with age.^{5,6} In some studies, mortality rates of patients aged 60 years or older hospitalized with RSV have exceeded 5%.⁶ RSV causes hundreds of thousands of hospitalizations each year. In the US alone, RSV leads to an estimated 60,000–160,000 hospitalizations and as many as 10,000 deaths among individuals aged 65 or older annually.^{7,8} Among older adults, the hospitalization and mortality rates of RSV are higher than and similar to influenza, respectively.⁹ Notably, in-hospital complications among older patients with RSV are currently higher than among those with COVID-19 or influenza.¹⁰

Medical Countermeasures

Few preventative measures were available for RSV until recently, apart from monoclonal and polyclonal antibody products to passively protect premature and other high-risk infants from severe disease.^{11,12}

The US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) in 2023 licensed and recommended 2 vaccines to protect adults aged 60 and older against RSV lower respiratory tract disease (Abrysvo and Arexvy). One of those vaccines (Abrysvo) was also approved for pregnant people during the third trimester to provide protection to newborns.⁷ Additionally, the health agencies licensed

and recommended a preventive monoclonal antibody (nirsevimab) to protect infants and some children up to age 2 from severe RSV disease.³

The antiviral ribavirin is approved in aerosol form for the treatment of pediatric patients with severe RSV; however, this route of administration is cumbersome and often costly. The drug has the potential for teratogenicity and carcinogenicity, so special precautions are advised for healthcare workers preparing the aerosol formulation and pregnant people near those being treated.¹

The off-label use of oral ribavirin is a clinical option, primarily among people who are immunocompromised, but toxicity concerns delimit its use.¹³ The intravenous formulation of ribavirin is not FDA-approved but is available as an emergency investigational new drug (eIND) in special circumstances.¹⁴

Investigational antivirals such as PC786 (nebulized) and zelicapavir (EDP-938) have demonstrated positive clinical trial results, with the latter receiving Fast Track designation from the FDA.¹

Zoonotic Potential

RSV-A and RSV-B are officially known as *human* respiratory syncytial viruses, with humans and chimpanzees as their only natural hosts. In fact, RSV was first known as chimpanzee coryza virus, as it was first isolated from chimpanzees.¹ Animal models for human RSV are available—including sheep, chimpanzees, cattle, and rodents—though they require high inoculation doses to illustrate the ability for cross-species transmission.¹

Versions of RSV that infect murine, bovine, ovine, swine, canine, and caprine species also exist.¹ No reports of animal RSV (or orthopneumovirus) have been recorded in humans to date, and studies with a murine species show humans to be resistant to infection.¹⁵

Still, the potential exists that a zoonotic RSV-like virus could emerge or recombine with human RSV strains, as animal models demonstrate that species barriers are not absolute. If such a zoonotic RSV gained the capacity to infect and spread efficiently among humans, causing disease on par with RSV in an immunologically naïve population, it would constitute a pandemic threat.

Human Metapneumovirus

The second major human pneumovirus was discovered relatively recently, in 2001. Human metapneumovirus (HMPV) is a major cause of upper respiratory infection in children and adults. Like most respiratory viruses, it mostly causes mild disease, but the capacity for severe disease exists.¹⁶

A retrospective study of children who were hospitalized with laboratory-confirmed metapneumovirus found a relatively high rate of ICU utilization (18%) and need for mechanical ventilation (6%).¹⁷ In adults, a significant proportion of hospital admissions for pneumonia, asthma, and emphysema are due to HMPV infection. In one 4-year study of adults hospitalized with HMPV, the rate of ICU admission was more than 30%, with most requiring mechanical ventilation and half developing acute respiratory distress syndrome (ARDS).¹⁸

Medical Countermeasures

No standard treatment for metapneumovirus exists beyond supportive care. There are no major antivirals on the horizon, though ribavirin may exhibit some activity.¹ Vaccine development, however, is promising. At least 2 combination HMPV vaccines are undergoing clinical testing: one using an mRNA platform and another using a protein virus-like particle platform.^{19,20}

Zoonotic Metapneumoviruses

Prior to the discovery of human metapneumovirus, the only known metapneumovirus was avian pneumovirus. In fact, HMPV descended from this virus several hundred years ago, representing a zoonotic infection that has since become a permanent human pathogen.²¹ If other avian pneumoviruses exist that have not yet been identified, they could pose a zoonotic threat similar to the original avian pneumovirus.

Pneumoviruses: Post-COVID-19 Pandemic Activity

The post-COVID-19 pandemic period saw notably high activity for both human pneumoviruses, associated with the resumption of social interactions. Typically, infections with both viruses are ubiquitous in childhood, but diminished social interaction during the pandemic increased the pool of susceptible individuals. When social interaction resumed, this expanded pool experienced high attack rates from both viruses over a short period, leading to high levels of illness and stress on hospitals, particularly pediatric facilities. This disruptive event—including the associated strain on hospital capacity—shows how endemic pneumoviruses can cause significant damage and underscores the potential impact of a novel pneumovirus on a global pool of susceptible individuals.²²

Recommendations

The following recommendations should be considered given the pandemic potential of *Pneumoviridae* members.

1. Continue and accelerate the development of pneumovirus antivirals. Ideally, such compounds will have activity against both RSV and HMPV.

2. Pursue the licensure of oral ribavirin for the treatment of RSV. As this is a generic drug, incentives to pursue licensure of the oral formulation for this indication likely are needed. Similar pursuits are warranted for the intravenous formulation of ribavirin.
3. Include both the oral and intravenous formulations of ribavirin in the Strategic National Stockpile (intravenous formulations may already be stockpiled for arenavirus infections).
4. Prioritize and accelerate the development of monoclonal antibodies and vaccines against HMPV.
5. Conduct basic scientific investigations and serosurveys of adults exposed to zoonotic pneumoviruses to characterize their ability to infect humans.
6. Augment wastewater surveillance of RSV and include HMPV, as well as develop the capacity to identify zoonotic pneumoviruses present in human wastewater.
7. Promote and/or develop home tests for RSV and HMPV to increase situational awareness of this viral family and optimize linkages to care and treatment.

Conclusion

The *Pneumoviridae* viral family poses a pandemic threat not only from its known human viruses but also from zoonotic family members. As mentioned, the family includes viruses adjacent to its human viruses. While currently constrained in their ability to cause disease in humans, known or undiscovered zoonotic pneumoviruses could acquire the ability to cross species barriers and cause infection in humans, constituting a pandemic threat.

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