



Dissecting Pandemic-Prone Viral Families

Volume 2: The Paramyxoviridae

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Introduction

Paramyxoviridae is a large viral family that contains many once common and well-known human pathogens, such as measles and mumps, as well as other pathogens that pose concerns for their potential to cause epidemic or pandemic disease.¹

This family of viruses infects a wide variety of species, ranging from reptiles to rodents and fish to birds. While diseases such as measles and mumps cause little morbidity and mortality in advanced societies today—because of high levels of vaccine-induced immunity—other members of this viral family have considerable burdens of infection with attendant morbidity and mortality risks. Also, within this family, there is one genus of consequence – Henipavirus - that has already been responsible for a number of serious emerging infectious diseases. The table below summarizes key genera and viruses of this family.¹

Table 1. Key genera and members of the *Paramyxoviridae* family

Genus	Key Member Viruses
<i>Respirovirus</i>	Human parainfluenza virus 1 & 3 (HPIV-1 & HPIV-3)
<i>Orthorubulavirus</i>	Human parainfluenza virus 2 & 4 (HPIV-2 & HPIV-4), mumps virus
<i>Henipavirus</i>	Hendra virus (HeV), Nipah virus (NiV), Mòjiāng virus (MojV), Langya (LayV)
<i>Morbillivirus</i>	Measles virus (MV)
<i>Pararubulavirus</i>	Menangle virus (MenPV)

The following summary outlines the aspects of several *Paramyxoviridae* member viruses that are most impactful with respect to pandemic preparedness.

Parainfluenza Viruses: Considerable Burden of Illness, No Countermeasures, Animal Counterparts

There are 4 human parainfluenza viruses (HPIVs) split between 2 genera of *Paramyxoviridae*. These are ubiquitous viruses; about 90% of adults harbor antibodies to them because infection is nearly universal during childhood. The virus is spread primarily from symptomatic individuals via respiratory droplets. Of the 4, HPIV-3 is considered the most virulent in adults and children. The various HPIVs exhibit various seasonality and interactions with each other.¹

Prior to the COVID-19 pandemic, parainfluenza was the second most common viral cause of hospitalization in children, with a rate similar to influenza. In adults, parainfluenza has been responsible for major outbreaks in nursing homes, attesting to its ability to cause reinfections, some of which are severe. In the immunocompromised, parainfluenza viruses can cause devastating and fulminant infections. In fact, during the 2009 H1N1 influenza pandemic, the second most common etiology of influenza-like illness hospitalization was parainfluenza.¹

While it may be argued that human parainfluenza viruses are part of the respiratory virus milieu and their burden of illness is relatively fixed, it is important to recognize that parainfluenza viruses of other mammalian animal species (eg, canine parainfluenza virus, bovine parainfluenza viruses, and others) could come to be human health threats if they acquire the ability to transmit efficiently between humans. There are no vaccines or antivirals for any of the human parainfluenza viruses, although vaccines exist for canine and bovine parainfluenza viruses.¹

Mumps Virus: Transmission Capacity Even With Immunity

Infection with mumps virus was once a feature of every childhood, but with the advent of vaccines, its prevalence has decreased to the point that in many countries a case of mumps is a rarity. While most notable for its ability to cause obvious swelling of the parotid glands, approximately 1-10% of cases experience meningitis and/or encephalitis—both severe, albeit now rare, manifestations of infection with this virus. Additionally, the virus can cause testicular swelling in males, which is a disruptive clinical symptom. Infection during pregnancy has been associated with fetal abnormalities and fetal demise (with first trimester infection).²

Despite the availability of mumps vaccines, large outbreaks have occurred in recent years among closed populations such as sports teams and college students. Most of the cases represented breakthrough infections despite vaccine protection. These infections occurred in the absence of any large genetic change in the culprit virus and were quenched with additional doses of vaccine. It is hypothesized that large exposure pressure in these specific populations was able to overcome the protection afforded by vaccination and not only cause infection but also spread efficiently in such an environment.²

Measles and Other Morbilliviruses: Extreme Transmissibility with Ability to Cause Severe Disease

Of the known human infectious diseases, measles virus possesses the greatest transmissibility, with the capacity to infect 15 people via a single infected individual. Its mode of transmission is unequivocally airborne; consequently, it can spread prolifically with a household attack rate of up to 100%. Vaccination has attenuated the morbidity and mortality of measles worldwide; however, the virus causes more than 100,000 deaths annually, mostly among under- and unvaccinated children. Before a vaccine became available in 1963, the US bore a considerable toll of hospitalization and death from this virus. Currently, vaccine hesitancy and disruptions of vaccination routines threaten measles virus control. Severe complications include meningitis, encephalitis, and pneumonia. Additionally, measles virus can erase much of the immune memory one has accrued against other pathogens, rendering individuals susceptible to myriad other infections.^{3,4}

Measles is a virus of zoonotic origin, and other members of the *Morbillivirus* genus currently circulate in other mammalian species, including canine distemper virus (CDV), peste des petits ruminants virus (PPRV), phocine distemper virus (PDV), dolphin morbillivirus (DMV), and porpoise morbillivirus (PMV). The progenitor of the measles virus is the now eradicated rinderpest virus of cattle, which likely found its way into human populations via cattle domestication. The other morbilliviruses have plasticity regarding species, and there is evidence that consequences can be severe. For example, CDV can cause fatal disease in primate species and adapt to them.⁵

The pandemic threat lies not in a resurgence of measles but of another morbillivirus entering the human population for which measles vaccination is insufficient to confer protection. A morbillivirus that could produce severe disease in even a minority of individuals coupled to anywhere near the transmissibility of measles could be catastrophic in an immunologically naïve population. If measles can still exact more than 100,000 deaths per year, a considerably higher toll could be expected if one of the zoonotic morbilliviruses becomes an efficient human pathogen.⁶

Henipavirus Genus

Of the paramyxoviruses, the *Henipavirus* genus poses particular concern. This concern is grounded in several attributes that certain members of the genus possess. Particularly, the ability of these zoonotic viruses to spill into humans, infect other mammals, spread between humans in certain contexts, and cause severe disease make this genus a subject for specific preparedness. It is important to emphasize that these are not novel viruses but viruses that have emerged due to factors that bring reservoir species in closer contact with domesticated animals and humans.⁷

Hendra

The first of the *Henipavirus* genus to be described was Hendra virus (HeV). This virus, whose ultimate reservoir is in bats, first spilled into horses and from horses to humans in 1994. Hendra virus can cause both severe pneumonia and encephalitis in humans. Human-to-human spread has not been documented. The predilection of the virus for horses, including racehorses, spurred countermeasure development, including an available equine vaccine.⁷

Nipah

The most concerning of the *Henipavirus* genus is Nipah virus (NiV), which shares more than 65% amino acid homology with Hendra virus yet is a considerably more efficient infectious agent of humans. The virus causes mortality in up to 90% of infected humans via encephalitis and pneumonia. Nipah, like Hendra, has its ultimate reservoir in bats and spills into humans either directly or via intermediate mammalian hosts such as pigs. It is unclear what triggers spillover events. In some outbreaks, human-to-human transmission has occurred, exclusively among those with close contact with blood and body fluids. In other outbreaks, including the first-ever outbreak documented in Malaysia, human-to-human spread did not occur. Contact with date palm sap

contaminated with bat urine has been a factor in outbreaks in which an intermediate host was not involved. Bangladesh (which has regular outbreaks), India, Malaysia, and the Philippines have reported cases. Outbreak control occurs when contact with the reservoir or intermediate species ceases and appropriate personal protective equipment is deployed.⁷

Mòjiāng

The Mòjiāng virus (MojV) was discovered in an abandoned mine in China. In 2012, 6 miners became ill with pneumonia caused by an unknown/unidentified pathogen; 3 of them died. Sampling of the mine revealed a henipavirus harbored in rodents and subsequently named Mòjiāng after the county where the mine is located. This virus was the first henipavirus to be associated with rodents. No definitive human cases have been reported, as the virus was never proven to be the cause of the miners' fatal infections.⁸

Langya

Langya virus (LayV), which closely resembles Mòjiāng virus, was discovered in 2018 as the cause of febrile illness in farmers in China. Since its emergence, 35 cases have been documented, although none have been fatal. Like Mòjiāng, Langya possibly has a small mammal reservoir in shrews.⁹

Other zoonotic henipaviruses that have been identified but not known to infect humans include the Cedar, Ghana (also known as Kumasi), Angavokely (AngV), and Madagascar viruses.^{10, 11}

Menangle Virus

Menangle virus is another zoonotic *Paramyxoviridae* family member. First identified in 1997 in Australia, the virus impacted the health of pigs, causing decreased farrowing. Subsequently, fruit bats were identified as the reservoir host of Menangle, but there is less knowledge about it compared to other bat-borne paramyxoviruses. Data on human infections is sparse; only 2 human cases described as having influenza-like illness have been documented in connection with the pig outbreak.⁷

Lack of Medical Countermeasures

Measles and mumps are the only members of *Paramyxoviridae* for which commercially available human vaccines are available, and there are no licensed treatments for any paramyxovirus. The mainstay of treatment is supportive care for severe infections (steroids may be given for parainfluenza and vitamin A for measles).^{1,3}

Experimental vaccines and monoclonal antibodies—which have been administered in emergency situations to humans—exist for Hendra and Nipah viruses and have shown success, but none are commercially available. For severe parainfluenza virus infections, predominantly occurring among immunocompromised individuals, ribavirin may be used with unclear benefit. Investigational antivirals (ie, BCX 2798, BCX 2855, DAS181)

have also been studied but have not been approved for parainfluenza virus infections, though DAS181 is in Phase 3 clinical trials.¹

It is important to recognize that the known zoonotic paramyxoviruses in the *Henipavirus*, *Morbillivirus*, and *Pararubulavirus* genera are mostly constrained in their ability to infect humans and/or transmit efficiently between them. Therefore, the pandemic threat may not arise in one of these viruses but in genetically adjacent viruses that have not yet infected humans. For example, Menangle may not itself constitute a pandemic or even an epidemic threat, but there may exist other members of the *Pararubulavirus* genus yet to be described that have enhanced human infective potential and/or could cause more severe human disease. If any of these other family members have or acquire measles-like transmissibility among humans, a large pandemic is assured.

Recommendations for Diminishing the Pandemic Potential of Paramyxoviruses

The following recommendations should be considered in light of the pandemic potential of *Paramyxoviridae* members.

1. Augment vaccine development for key henipaviruses. Currently, Nipah virus is a well-characterized threat agent that organizations like the Coalition of Epidemic Preparedness Innovation (CEPI) have targeted for vaccine development. Nipah vaccine development should consider the virus both as an official target and as a prototype pathogen for the *Henipavirus* genus, as it is unlikely that Nipah itself will be the pandemic threat that emanates from this genus. Vaccines should be tested and developed for cross-reactivity against Hendra, Mòjiāng, and other members of this genus.
2. Extend vaccine development in the *Paramyxoviridae* family beyond the *Henipavirus* genus. There is a current unmet clinical need for vaccines against parainfluenza viruses (especially in the immunocompromised), improved vaccines against mumps in the wake of breakthrough outbreaks, and potential zoonotic morbilliviruses. Additional resources and more focus should be placed on widening the lens of vaccine development to include these potential threats.
3. Advance antiviral and monoclonal antibody development to be clinically impactful and stockpiled. Though monoclonal antibodies have been used for human Hendra and Nipah infections, they remain experimental and not operational in the event of an outbreak. These monoclonal antibody products should be moved forward by manufacturers and the US Food and Drug Administration (FDA) to at least the Pre-Emergency Use Authorization (Pre-EUA) stage and be prepositioned in national and international stockpiles to provide tools for clinicians to treat cases and quell any outbreaks. Investigational antivirals, such as DAS181, should be moved as quickly as possible through clinical testing to the approval stage, while also being studied for activity against multiple members of the *Paramyxoviridae* family. Additionally, drug

repurposing—the collection of clinical data on already approved pharmaceutical ingredients for a new indication—should be conducted for members of this family.

Include human and zoonotic paramyxoviruses in wastewater and other surveillance systems. Wastewater surveillance can detect viral signals earlier than other methods. Including tests for both human and zoonotic paramyxoviruses in wastewater-based systems and other epidemiologic surveillance efforts could provide early warnings for public health and clinical responses to cases and potential outbreaks.

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