



Dissecting Pandemic-Prone Viral Families

Volume 3: The Adenoviridae

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Introduction

The *Adenoviridae* viral family is divided into 6 genera, with only members of the genus *Mastadenovirus* known to infect mammals, including humans. Of note, there are more than 100 adenoviruses of various species that infect multiple vertebrate hosts, from fish to birds. Of these, 7 species are currently known to infect humans (with multiple subspecies).¹

This viral family presents pandemic concern because of the potential for zoonotic adenoviruses to establish infections in humans; the ability of current human adenoviruses to evolve enhanced virulence; and the family's ability to efficiently spread via the respiratory route. Additionally, neither a widely available or universal vaccine nor a standard antiviral therapy is available for adenoviruses.

Though the DNA-based genome of adenoviruses is thought to delimit pandemic potential due to greater genetic stability versus RNA viruses, this should not be taken as an iron-clad rule given the prolific nature of this viral family. These viruses, despite their DNA genetics, are able to cause widespread infections, explosive outbreaks, and mortality during every season. Additionally, the worldwide multi-century destruction wrought by the DNA-based smallpox virus is testament to the prowess of DNA viruses.

Adenoviruses as Common Seasonal Viruses

In humans, adenoviruses are extremely common respiratory and gastrointestinal viruses that cause both upper and lower respiratory infections as well as gastrointestinal infections. Infection is ubiquitous during childhood and causes mostly minor disease. Adenovirus infections are less likely to occur in healthy adults. Like many respiratory viruses, however, adenoviruses have the capacity to cause severe and sudden disease in people who are immunocompromised. They are also capable of fecal-oral spread and are nonenveloped viruses, the latter conferring an enhanced fomite-based transmission potential.¹

Special Risk in Military Camps

Despite being considered a pediatric infection, in certain contexts, adenovirus infections can be severe and highly infectious in healthy adult populations. Military recruit training camps are one such situation. In these closed settings, which involve the mixing of individuals hailing from various geographies, explosive and disruptive outbreaks have occurred, with the basic reproduction rate (R_0)—the epidemiologic term used to describe the infectiousness or contagiousness of infectious agents—reaching 5.^{1,2} A single case leading to potentially 5 additional cases, each of which then lead to an additional 5, and so on, is the hallmark of a highly transmissible pathogen (an R_0 value of > 1 is required to maintain an outbreak).

This risk prompted the US military to implement a vaccination program in 1971 using a vaccine against adenovirus types 4 and 7 (HAdV-4 and HAdV-7, respectively), 2 of the major culprit serotypes. The program became standard practice in the military until the vaccine became unavailable for several years beginning in 1999. Following the program's cessation, surges of infection with HAdV-4 and HAdV-7 occurred, only to be quenched again in 2011, when the military restarted its vaccination program once a second-generation vaccine was approved for military personnel aged 17–50 years. This vaccine, which is administered via the oral route, is exclusively available to the military and, though licensed by the US Food and Drug Administration (FDA), is not commercially available to the public.^{1,3}

Risk in Closed Civilian Populations

Though not as common, adenovirus outbreaks do occur in non-military populations in closed settings, with several notable events in the eastern US in 2018.

New Jersey Pediatric Long-Term Care Centers

In late 2018, at least 2 New Jersey pediatric nursing and rehabilitation facilities experienced outbreaks. In the larger outbreak, 11 children died, and dozens were sickened by HAdV-7. In the other, several nonfatal cases occurred due to adenovirus type 3 (HAdV-3).^{4,5}

University of Maryland

Around the same time, a relatively large and disruptive outbreak of HAdV-7 occurred on the University of Maryland campus in College Park, causing more than 4 dozen cases, several hospitalizations, and 1 death.⁶ Outbreaks on other college campuses occurred during that time frame as well.⁷

Such outbreaks illustrate that the adenovirus risk in closed populations is not restricted to the military. The fact that HAdV-7, a vaccine-preventable strain, was involved is especially notable because if the available vaccine had been deployed outside military populations, these outbreaks could have been prevented.

Adenovirus 14 and Adenovirus 55 Show Particular Virulence

In the mid-2000s, adenovirus 14 (HAdV-14)—mostly associated with sporadic cases since its description in the 1950s—was characterized as an epidemic threat after abruptly appearing in multiple locations in the United States during that time. HAdV-14 had not been documented in Oregon before 2005, but it soon became a significant cause of respiratory disease in the state. Of 38 cases reviewed, occurring between 2006–2007, 76% required hospitalization and 18% died. Notably, the circulating strain was genetically distinct from the original HAdV-14 strain described in the 1950s and was designated 14a. While this new strain is not always associated with severe disease in healthy individuals, it unequivocally has that trait.^{8,9}

Adenovirus 55 (HAdV-55) is also noted to have the capacity to inflict severe disease and has been involved with numerous outbreaks.¹⁰

Adeno-Associated Viruses and Hepatitis

In the immediate period following the height of the COVID-19 pandemic, clusters of severe pediatric hepatitis cases began to be noticed in multiple countries. In many of the case patients, adenoviruses (predominantly HAdV-41) were detected in the blood. As adenovirus-induced hepatitis is not a common condition in the healthy pediatric population, and the virus is constrained in infecting hepatocytes (ie, liver cells), these clusters prompted extensive investigation for etiology.

Adenoviruses are known to be associated with historically nonpathogenic “satellite” viruses (of the *Parvoviridae* family) that require the presence of a “helper” virus in order to infect cells: adeno-associated virus (AAV). The prevalence of these viruses varies, but up to 80% of the human population carries antibodies to various AAV serotypes, with most infections occurring during childhood. Multiple research groups have since demonstrated that adeno-associated virus 2 (AAV-2) was strongly associated with most of the severe hepatitis cases in children that occurred in 2021–2022.¹¹

Limited Medical Countermeasures

Antiviral therapy for adenoviruses has been successful with intravenously administered cidofovir, though it is highly toxic and use is often precluded, except in the severely immunocompromised who have grave illness prospects. Brincidofovir—a less toxic oral version of cidofovir that has broad-spectrum activity against DNA viruses and is stockpiled by the US government for the purpose of poxvirus emergencies—is also available and has had promising results against adenoviruses in clinical trials. An orally administered vaccine for only HAdV-4 and HAdV-7 is available exclusively to military populations.¹

Zoonotic Threats

The fact that many vertebrate species harbor their own versions of adenoviruses poses a risk should the species barrier be traversed. The pandemic risk may lie in one vertebrate adenovirus breaching the species barrier and developing the ability to spread efficiently among an immunologically naïve human population. This can occur with a directly zoonotic adenovirus or with a human-animal recombinant virus that could pass from humans into another species and subsequently recombine with the native adenovirus.

There are limited reports of humans being directly infected with zoonotic adenoviruses (principally those of nonhuman primates). There is also evidence of cases of human/nonhuman primate recombinant viruses causing productive infection. For example, HAdV-B76, which has caused fatal human disease, is identical to 2 simian adenoviruses, which themselves contain genomic evidence of recombinant human, chimpanzee, and

bonobo adenoviruses. It is likely that the prolific human strain of HAdV-4 has its origin in a human recombinant simian adenovirus as well.^{12,13}

Notably, this permissive species barrier has been harnessed for use in vaccine platform technology. For example, the Oxford/AstraZeneca COVID-19 vaccine uses a recombinant, replication-deficient chimpanzee adenovirus vector engineered to encode the SARS-CoV-2 Spike protein.¹⁴

Potential for Greater Virulence

While an adenovirus-induced pandemic is less likely to occur from the known human adenoviruses, the fact that they can cause explosive outbreaks is significant. Changes in virulence, as exemplified by adenovirus 14a, raise concerns that this phenomenon was not an isolated incident but something the viral family could evolve to do more frequently in certain, yet-to-be-defined, contexts.

Additionally, the added variable of AAVs potentiating virulence merits consideration, as there are even fewer medical countermeasures (ie, zero) for AAVs, and their very nature makes diagnosis elusive.

Recommendations for Diminishing Adenoviruses' Pandemic Potential

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

1. Study the use and benefits of HAdV-4 and HAdV-7 vaccines outside the military population, particularly in closed populations such as those on college campuses and in nursing homes. Additionally, vaccines against other serotypes (such as 14a), and universal adenovirus vaccine approaches should be investigated, and where there is promise, developed.
2. Expand wastewater monitoring to track adenoviruses, including potentially zoonotic adenoviruses. Such monitoring would serve as an early warning of heavy circulation of a viral family member or the appearance of novel strains.
3. Incentivize research into and potential licensure of the use of brincidofovir against adenoviruses and build stockpiles sufficient to cover not only poxviruses but also the possibility of an adenovirus medical emergency.
4. Incentivize the research and development of other antivirals and monoclonal antibody products with distinct mechanisms of action against adenoviruses.
5. Assess adenoviruses of different animal species—including recombinant forms—for their capacity to infect humans and spread efficiently in order to target surveillance and countermeasures at the highest-risk viral species.

6. Increase routine clinical diagnosis of adenovirus through the development and use of more point-of-care (and possibly at-home) tests.
7. Undertake a specific medical countermeasure development program for AAVs, in addition to furthering basic understanding of their role in disease and their diagnosis.

Conclusion

The *Adenoviridae* family of viruses has traditionally not been viewed as a pandemic threat; however, this family's ability to cause widespread illness via respiratory spread, the existence and continued evolution of virulent human strains, its zoonotic risks, and the lack of widely available medical countermeasures confer a level of pandemic risk. As such, pandemic preparedness efforts would benefit by added focus on this important respiratory viral family.

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