Emerging Adenovirus Threats: Should China Develop a Vaccine-Oriented Prevention Strategy?

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ABSTRACT

Since their discovery in 1953, human adenoviruses (HAdVs) have been noted to frequently cause outbreaks among crowded populations. Over the last decade, epidemiological studies have documented an increase in the number of such HAdV outbreaks in China. Children, the elderly, the immunocompromised, and military personnel seem to be at greatest risk of infection and the emergence of novel HAdV types have caused substantially higher morbidity and mortality among them. Vaccines against HAdV types 4 and 7 have been shown to be very safe and effective among U.S. military personnel; however, such vaccines are not readily available in China. Given China’s crowded cities and increasing elderly and military populations, HAdV outbreaks are likely to increase in the future. It seems prudent for China to study the epidemiology of HAdV infections and to consider if it may be wise to develop vaccines against the most prevalent HAdV types. This report summarizes key epidemiological characteristics of HAdVs, reviews the history of HAdV vaccine development, and discusses reasons why China should consider pursuing HAdV vaccine development.
Introduction

Human adenoviruses (HAdVs) are a frequent cause of respiratory and enteric outbreaks worldwide. China, with a population of more than 1.3 billion, has had a long history of documented HAdV circulation and outbreaks. The first Chinese HAdV infections were identified during the winter of 1958 when children 6 months to 2 years old developed an outbreak of viral pneumonia in Beijing and Changchun. It was estimated that between 16.6% to 33.3% of infected children died (1, 2). HAdV was identified as the causative agent, and soon after, similar infections were also reported in Shanghai, Shenyang, Xi’an, Lanzhou, Nanning, Taiyuan, and Xinjiang. After 1980, HAdV prevalence seemed to decrease in the general population, though outbreaks were still occasionally reported with a higher prevalence of HAdV infection observed in Northern China. Transmission remained stable for much of the last 20 years; however, more recently, there has been an increase in the number of reported cases of HAdV infection throughout China.

Outbreaks of HAdV in China are often associated with acute respiratory disease (ARD) and pharyngoconjunctival fever (3). Susceptible populations include primary and middle school students, hospital workers, community members, the immunocompromised, and military personnel. HAdV types 1-7, 11, 14, 21, 37, and 55 have all been identified in China (4). Prior to 2000, the most frequent types to cause HAdV outbreaks were HAdV-3, 7, and occasionally HAdV-2 (5), 4, 14 (6, 7), and 11 (8). Since 2000 to present, HAdV-3 has been the most prevalent type responsible for HAdV outbreaks in China. HAdV-3 in addition to HAdV-5, 7, 11, 14, and 55 types
have caused at least 7 outbreaks since 2000. These outbreaks occurred in middle schools, a military university, and within multiple military training camps (9-17). In general, the types of HAdV responsible for outbreaks in military settings have largely not been identified; however, in 2013, Yu et al. reported an outbreak of acute respiratory disease caused by HAdV-7 in a military training camp in Shaanxi, China. This was the first report of an ARD outbreak caused by HAdV-7 in military personnel in China (12).

Genetic variations, either by mutation or a recombination event, can lead to changes in the pathogenicity or virulence of a HAdV type. An emergent type of HAdV typed 14p1 has demonstrated a markedly higher virulence compared to the progenitor type HAdV-14p (18), which has caused outbreaks in the United States (19). This strain was also introduced to China, causing a 2011 outbreak of febrile respiratory illness in Chinese primary and middle schools (14). In 2012, there was also an outbreak of “unknown origin pneumonia” for which SARS, avian influenza, and bacterium agents were ruled out as causative agents. Upon further investigation, it was determined that the source of the outbreak was a HAdV type first identified in a respiratory infection outbreak in central Shanxi province during 2006. This HAdV type has since been classified as HAdV-55 and linked to multiple outbreaks in schools and military facilities (16). Studies suggest HAdV-55 has a greater propensity for transmission compared to other types of HAdV (20, 21).

In China, HAdV infection is not a reportable infectious disease and has not been incorporated into surveillance systems. Hence, HAdV infections in China are markedly underreported. As outbreaks of HAdV continue to occur, with new emergent types that exhibit increased virulence, commitments to better understand these outbreaks, and the seasonality,
population distribution, and pathogenicity of prevalent types should be made. Various methods of HAdV disease control and preventions should be aggressively pursued, one such method to consider is vaccination. In the United States, HAdV types 4 and 7 vaccines are routinely used among military personnel, and have demonstrated excellent safety and effectiveness (3). Due to the pervasive nature of HAdV in China, with the growing number of highly prevalent HAdV types observed, it seems prudent that China develop a long-term effective vaccination strategy against HAdV. In this report, we explore the most relevant literature and provide a summary of HAdV epidemiology, provide a history of HAdV vaccinations as they have been used among U.S. military personnel, and explore why China should consider developing and producing its own HAdV vaccines.

Background

Human adenoviruses (HAdVs) were first discovered in 1953 by Dr. Wallace Rowe, after he observed a unique cytopathic effect develop after serially passaging a sample of adenoid tissue-derived cell culture (22). Further investigation by Dr. Rowe and others revealed that the observed cytopathic effect was caused by a nonenveloped double-stranded DNA virus that is now classified in the family Adenoviridae (22, 23). This group of viruses are considered large compared to other viruses, and have traditionally been classified into 7 species groups (A-G), more than 55 recognized types based upon their enzymatic, biochemical, and genetic characteristics (24-26). Recently, it has been proposed that HAdVs be reclassified using an purely genetic system (27), but this has not yet been fully embraced (28, 29). HAdVs are considered relatively stable in
replication and to be resistant to environmental stressors. They are transmitted via direct contact or inhalation of aerosolized viral particles.

Infection from HAdVs can cause a variety of symptoms and conditions, the most common involving inflammation of the upper airway, the lower airway, the urinary tract, the conjunctiva, and the gastrointestinal tract. Occasionally, adenoviruses have been implicated in cardiac and neurological diseases. Manifestations of infection are usually dependent upon the tissue tropism of the specific virus. Respiratory symptoms are most often associated with HAdV species B, C, D and E infection, gastroenteritis with HAdV species F and G infection, and keratoconjunctivitis with HAdV species B and D infection. In general, HAdV does not cause severe disease, except among vulnerable populations including infants, the elderly, and immunocompromised individuals. However, some novel reassortant viruses have been recently associated with more severe disease outcomes (30, 31).

**Epidemiology**

HAdVs have a worldwide distribution with the capability of year-round transmission. Current estimates indicate HAdVs contribute to 2-5% of all global respiratory infections and are one of the most important causes of gastroenteritis among children—possibly second only to rotavirus. Additionally, HAdVs are recognized to cause markedly higher rates of severe infections among military trainees and the immunocompromised, such as HIV and transplant patients, when compared to the general population. It is among these high risk groups where a considerable amount of prior epidemiological research has been conducted.
Military Personnel

Outbreaks of ARD have long been a major health concern among military populations. This is particularly true for new recruits who are more vulnerable to infections due to crowding, poor personal hygiene, physical and psychological stressors they encounter in the training environment. Populations at military recruitment and training centers are very dynamic with the frequent introduction of new susceptible trainees causing adenoviruses to frequently become endemic. These conditions seem common worldwide among many military training populations.

Of the respiratory pathogens known to impact military personnel, HAdV is second only to influenza A as the most important. While this has perhaps been best documented among the U.S. military (31-34), other countries, including China (35), the Netherlands (36), and South Korea also report similar findings among their military trainees (37). Prior to vaccination, it is estimated that HAdV caused 70-80% of all acute respiratory disease among U.S. trainees and 90% of pneumonia hospitalizations (38-44). It is also clear that HAdV types 4 and 7 are causes of ARD among U.S. military trainees, though HAdV types 3, 11, 14, and 21 have also been prevalent (33).

Outbreaks of ARD among military populations are very costly both in terms of person-time lost during hospitalization and the associated healthcare costs. Several U.S. based studies that have been conducted in the last 2 decades have estimated the cost of one case of ARD to be between $860.00 and $3,838.00 (45, 46). This does not account for the time a trainee loses due to the need to repeat training, or the costs related to HAdV death. Given the high cost burden and limited treatment options,
vaccination against HAdV-4 and HAdV-7 among most U.S. military trainees is now routine.

*Immunocompromised Individuals*

Immunocompromised individuals, who have undergone blood, marrow, or solid organ transplants, are taking immunosuppressant drugs, or have other immune-compromising conditions, are highly susceptible to infection from HAdV. Characteristically, these infections last longer, are more difficult to treat, and carry a greater risk for severe health outcomes, including death (47). In addition, symptoms from infection are often nonspecific, making it difficult to diagnose until the disease has progressed into a later stage (48). Transplant patients in particular experience frequent nosocomial HAdV outbreaks, including viral dissemination during post-op recovery. Multiple studies conducted among transplant patients in years past have estimated the incidence of HAdV infection to be in the range of 3% to 21% (21, 49-52). In general, patients undergoing solid organ transplants had higher HAdV infection rates compared to blood and marrow transplant (BMT) patients. Though one study of BMTs did estimate a very high (21%) incidence of HAdV infection (50). The authors attributed this high rate to either the greater proportion of susceptible children in the sample or to their unusually sensitive detection methods (50).

*Children*

Outbreaks of HAdV commonly occur in childcare or school settings, where HAdV type 40 and 41 are a common cause of diarrhea (20). Children also often experience
infection from HAdV types 3, 4, 7, 11, 14, and 21, which are typically associated with respiratory disease. Similar to immunocompromised individuals, children may experience much more severe adenovirus-associated health outcomes, compared to an immunocompetent adult.

**Therapy**

There are currently no US Food and Drug Administration (FDA)-approved antivirals to treat HAdV infection, though some drugs have been tested for antiviral activity (53). Ribavirin has been shown to be largely ineffective in the treatment of HAdV and is thus not used. Cidofovir has shown good antiviral effect but it can be associated with renal toxicity. Considerable experimental success has been found against HAdV infections by employing a new cidofovir analog called CMX001 or brincidofovir (Chimerix, Durham, NC, USA). CMX001 has performed well using *in vitro* and animal models with lower risk of toxicity (54, 55). It has also shown promise in early human clinical trials, showing large reductions in adenoviremia and increases in survival time among symptomatic transplant patients (47, 56, 57). Additional large trials are currently underway to further evaluate the effectiveness and safety of CMX001 (56-58). Clinical trials testing CMX001 among immunocompetent individuals have not yet taken place.

**Adenovirus Vaccines**

**History**

The development of HAdV vaccines was initiated by the U.S. military soon after HAdV was characterized in the 1950’s. By 1957, a formalin-inactivated bivalent parenteral vaccine against HAdV types 4 and 7 was undergoing clinical trials at multiple
recruitment centers, which demonstrated 90% effectiveness (59). The FDA subsequently approved the vaccine, though a reduction in antigenicity due to issues encountered during the large-scale production of the vaccine, side effects causing gastrointestinal ailment, and evidence showing the seed-lot to be contaminated with Simian virus 40 (SV40), eventually led to the revocation of the license in 1963 (59, 60).

From 1963-1971, U.S. military researchers successfully developed and tested live HAdV-4 and 7 enteric-coated vaccines, from which efficacy trials showed greater than 90% effectiveness in preventing HAdV-related infections without the gastrointestinal side effects that were attributed to the previously used live oral HAdV-7 vaccine (60-62). Soon after trials were completed, the enteric-coated vaccine tablet was given FDA clearance and the U.S. military began including it in the regular vaccine regimen for all new military trainees, which virtually eliminated HAdV outbreaks in military training facilities. Due to lack of funding for upgrades in manufacturing facilities, production of these vaccines was halted in 1996. By 1999, vaccine supplies were exhausted and a large resurgence of HAdV disease occurred throughout U.S. military bases (63). After considerable morbidity (sometimes 2,000 preventable trainee medical encounters a month), U.S. military officials sought alternative production strategy for the vaccines. Once the production contracts were awarded it took 10 years of research at considerable financial investment to again make the enteric-coated HAdV-4 and -7 vaccine tablets available. The FDA granted approval for use of the vaccine among military trainees in 2011 (32, 64).
Enteric-coated Adenovirus Vaccine Tablet

Enteric-coated HAdV vaccine tablets are specifically designed with three layers: an inner core of lyophilized adenovirus, an inactive middle layer, and an outer coating that is resistant to stomach acid which allows the vaccine tablet to pass through the stomach and be dissolved and absorbed in the upper gastrointestinal tract. In a 2004 double-blind placebo controlled study of the newest bivalent HAdV vaccine delivered using the enteric-coated tablets, there were no significant differences in reported symptoms between the vaccine and placebo groups evaluated (65). Additionally, in a larger phase 3 clinical trial, seroconversion rates of 94.5% and 93.8% were observed for HAdV-4 and HAdV-7, respectively, with viral shedding detected up to 21-days post-vaccination (66). After the introduction of the new oral vaccines in 2011, US military trainees experienced a 100-fold decline in adenovirus disease burden. The vaccines have been recently estimated to prevent 1100 to 2700 hospitalization each year and 13,000 febrile illnesses (Radin et al. under journal review).

Adenovirus Vaccine in China

Currently available epidemiological data suggests endemic circulation of HAdV throughout China, causing persistent morbidity and mortality, with additional infection surges from frequent outbreaks. It seems possible to markedly reduce HAdV infections with a vaccination program targeting the most prevalent HAdV types and high risk populations, such as children and military personnel. A 2013 study of children in China with acute respiratory tract infections, revealed that 191 (8.55%) of the 2,234 respiratory samples were positive for HAdV. Of these positive samples, 72 (37.7%) and 92 (48.2%)
were typed HAdV-4 and 7, respectively (67). Inferring that were such vaccine introduced in China, a similar 80% reduction in HAdV infection could be experienced creating a long-term economic benefit related to savings in clinical care and increases in personal productivity.

Production of a HAdV vaccine is feasible given that the vaccines seed viruses are unattenuated, and the enteric coating is not difficult to develop. Diagnostic assays for the detection and typing of HAdV are also readily available to monitor effectiveness. The challenges facing successful development of the vaccine are deciding which types should be selected, which populations should receive the vaccines, and the cost of determining vaccine effectiveness.

**Conclusion**

In 2010, it was estimated that lower respiratory infections accounted for more than 6% of global mortality, translating to nearly 3 million deaths per year (68). Of these deaths, viral respiratory infections were responsible for more than half of the deaths in the general population, and higher still among children under the 5 years of age. Emerging infections have added additional complexity to this burden, as the epidemiology of viruses such as influenza A (H7N9) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) are not well understood, causing global public health concern and subsequent large reallocation of resources. Though, HAdV may not receive the same attention from the media and the health communities as the aforementioned emerging viruses have, history has shown how this group of viruses can quickly become a serious public health threat if left unchecked.
China has a long history of HAdV circulation, with significant attributable morbidity and mortality. Given China’s large and dense populations, particularly in urban settings, it seems that without intervention HAdV outbreaks will continue to occur and likely increase in the future. Hence, it seems prudent that China soon develop vaccines soon against the most prevalent HAdV types to protect the most vulnerable populations. In addition to the number of cases that would be reduced with a vaccine, the costs associated with lost productivity and treatment would also be greatly diminished, with clear evidence suggesting an actual cost-savings (46).

A useful first step to vaccine development would be to implement enhanced HAdV surveillance efforts. Such data are invaluable in determining which types and populations in a country a vaccination strategy should target, in addition to estimating the true burden of HAdV infections across the country. HAdV surveillance in the United States has proven very valuable in describing HAdV epidemiology and in identifying emergent novel HAdV epidemics (63, 69).

Overall, given the past and current epidemiological conditions of HAdV infections in China and the strong evidence supporting continual HAdV transmission, it seems that conditions are right for the development and introduction of HAdV vaccines. Through collaboration and engagement of stakeholders across multiple sectors, including government, private business, and the health community, effective new HAdV vaccines would not only vastly improve the health of one of the most densely populated countries in the world, but could also serve as a model for the mitigation of other disease threats both now and in the future. With so much at stake, perhaps now is the time for China to develop and produce HAdV vaccines.
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