

Outbreaks of Adenovirus-associated Respiratory Illness on 5 College Campuses in the United States, 2018–2019

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Background. Human adenoviruses (HAdVs) are commonly associated with acute respiratory illness. HAdV outbreaks are well documented in congregate military training settings, but less is known about outbreaks on college campuses. During fall 2018 and spring 2019, 5 United States (US) colleges reported increases in HAdV-associated respiratory illness. Investigations were performed to better understand HAdV epidemiology in this setting.

Methods. A case was defined as a student at one of the 5 colleges, with acute respiratory illness and laboratory-confirmed HAdV infection during October 2018–December 2018 or March–May 2019. Available respiratory specimens were typed by HAdV type-specific real-time polymerase chain reaction assays, and for a subset, whole genome sequencing was performed. We reviewed available medical records and cases were invited to complete a questionnaire, which included questions on symptom presentation, social history, and absenteeism.

Results. We identified 168 HAdV cases. Median age was 19 (range, 17–22) years and 102 cases (61%) were male. Eleven cases were hospitalized, 10 with pneumonia; 2 cases died. Among questionnaire respondents, 80% (75/94) missed ≥ 1 day of class because of their illness. Among those with a type identified (79%), HAdV types 4 and 7 were equally detected, with frequency of each varying by site. Genome types 4a1 and 7d were identified, respectively, by whole genome sequence analysis.

Conclusions. HAdV respiratory illness was associated with substantial morbidity and missed class time among young, generally healthy adults on 5 US college campuses. HAdVs should be considered a cause of respiratory illness outbreaks in congregate settings such as college campuses.

Keywords. adenovirus; respiratory illness; colleges; outbreak.

Human adenoviruses (HAdVs) are nonenveloped, double-stranded DNA viruses comprising 7 species (A–G) and >100 types [1, 2]. HAdVs can cause a range of clinical manifestations, including acute respiratory illness (ARI), fever, gastroenteritis, and conjunctivitis [1]. HAdV types 4 (HAdV-4) and 7 (HAdV-7) are common circulating types associated with upper and lower respiratory tract disease and conjunctivitis [1, 3]. HAdV-associated ARI is typically self-limiting, but may be severe, causing pneumonia, disseminated disease, and death, more frequently among those with HAdV-7 infections and among individuals with immunocompromising conditions [1, 4–7].

HAdVs have no distinct seasonal pattern [5, 8]. Establishing transmission chains can be challenging; infections are often mild or asymptomatic and HAdVs can persist in the environment for prolonged periods [1]. Transmission is facilitated in congregate settings [9]. For example, HAdV-associated ARI outbreaks are well described among military personnel undergoing basic training, where young adult recruits train together and sleep in barracks [10–12]. In response to the documented burden in this population, an oral, live nonattenuated vaccine for HAdV-4 and HAdV-7 was implemented in 1971 and is available for use in military personnel [13]. HAdV-associated ARI outbreaks have also recently occurred in military populations that are not routinely vaccinated, including at the United States (US) Naval Academy, where students live in dormitory-style housing and congregate in shared spaces [14]. However, in colleges, where young adults share similar living and social environments, few HAdV-associated ARI outbreaks have been reported, and the extent of HAdV-associated ARI is not well understood [15–17].

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During fall 2018, student health centers (SHCs) and state health departments identified increases in HAdV-associated ARI at colleges in Maryland (college A), Pennsylvania (college B), Virginia (college C), and Wisconsin (college D). The following spring, in March 2019, an SHC at a college in Michigan (college E) identified a cluster of HAdV-associated ARI primarily among members of an athletic team.

SHCs and state or local health departments, in collaboration with the Centers for Disease Control and Prevention (CDC), investigated to characterize HAdV-associated ARI among students at the 5 colleges and to better understand HAdV epidemiology associated with college campus settings. We describe the epidemiologic, clinical, and laboratory findings from our joint investigation.

METHODS

Case Definition and Ascertainment

A case was defined as a student at one of the 5 colleges with onset of acute respiratory symptoms and laboratory-confirmed HAdV infection during October 2018–December 2018 (colleges A–D) or March–May 2019 (college E). Colleges A, D, and E are large colleges with > 30 000 undergraduate students, while colleges B and C have approximately 5000 and 3000 undergraduate students, respectively. SHCs and health departments first detected the HAdV outbreaks from either increases in ARI visits or pneumonia diagnoses among students evaluated at SHCs or local healthcare facilities (colleges A and C), or from an increase in HAdV detections from routine public health influenza-like illness (ILI) surveillance (colleges B and D). At college E, the SHC detected a cluster of ARI among members of an athletic team. Cases were generally identified at SHCs, either through clinician-directed testing of students with ARI (colleges A, B, C, and E) or routine ILI surveillance (temperature $\geq 100^{\circ}\text{F}$ [37.8°C] and cough or sore throat without a known cause other than influenza) (colleges B and D). Additional cases were identified when HAdV testing of students occurred at urgent care facilities, hospitals, or emergency departments (EDs) (colleges A and D; [Supplementary Table 1](#)). HAdV infection was confirmed by the detection of HAdV DNA in a respiratory specimen (nasopharyngeal swab, sputum, tracheal aspirate, or bronchoalveolar lavage), serum, or plasma using a polymerase chain reaction (PCR) assay. Molecular detection assays, including commercial multiplex tests for respiratory viruses, commercial or laboratory-developed tests for HAdV, or the CDC real-time reverse-transcription PCR assay for HAdV were performed at clinical, commercial, or state public health laboratories.

Data Collection and Analysis

Cases were invited to complete a structured questionnaire administered online using REDCap [18], by phone interview, or

by email. Information collected included demographic characteristics (age, sex, year of study, housing), date of illness onset, symptom presentation, medical history, social history (smoking, e-cigarette use, sick contacts), and absenteeism. We identified available inpatient, outpatient, and ED medical records and collected information on date of illness onset, symptom presentation, clinical course, medical history, social history, diagnostic tests, and clinician diagnosis using a standardized chart abstraction tool ([Supplementary Table 1](#)). Data were entered into REDCap and Excel software and were analyzed with descriptive statistics using Stata version 14 software (StataCorp, College Station, Texas).

Adenovirus Type Determination and Molecular Characterization

To understand HAdV type circulation and transmission within outbreaks, available HAdV-positive specimens were sent to CDC for further characterization ($n = 133$). Total nucleic acid extracts from available specimens were tested by a pan-HAdV real-time PCR (rPCR) assay and typed by HAdV type-specific rPCR assays [19]. Twenty-eight HAdV-positive respiratory specimens, representing a sample of cases infected at the beginning, middle, and end of each college outbreak, were inoculated into A549 cells for virus isolation and further genetic characterization. For genome sequencing, DNA libraries were constructed directly from the virus isolate extracts using Nextera XT DNA Library Prep Kit (Illumina, San Diego, California), and paired-end sequencing was performed on the MiSeq using 500-cycle Miseq Reagent Kit V2 (Illumina). Reference-guided assembly was achieved using CLC Genomics Workbench version 11.0 (Qiagen, Redwood City, California). Complete genome sequences obtained from this study and representative sequences from GenBank were aligned using MAFFT in Geneious 10.0.9 (Biomatters, Auckland, New Zealand). Phylogenetic trees of the alignments were constructed using the maximum-likelihood method based on the Tamura 3-parameter model with 1000 bootstrap replicates implemented in MEGA7 [20]. In silico restriction enzyme analysis of the HAdV-4 and HAdV-7 genome sequences was performed using Geneious 10.0.9, and genome types were determined using established guidelines and reference fragment patterns [21, 22].

RESULTS

We identified 168 HAdV cases among students at 5 colleges in 5 states, including 42 (25%) from college A, 58 (35%) from college B, 8 (5%) from college C, 31 (18%) from college D, and 29 (17%) from college E. Median age was 19 (range, 17–22) years and 102 cases were male (61%) ([Table 1](#)).

At the 4 colleges with outbreaks in fall semester 2018, onset of illness occurred during October–December at colleges A and B, during November at college C, and during November–December at college D ([Supplementary Figure 1](#)). At college E,

Table 1. Characteristics of Human Adenovirus Cases From 5 College Campuses, United States (N = 168)

Characteristic	Total (N = 168)	College A	College B	College C	College D	College E
		(n = 42)	(n = 58)	(n = 8)	(n = 31)	(n = 29)
Sex						
Male	102 (61)	26 (62)	40 (69)	3 (38)	15 (48)	18 (62)
Female	66 (39)	16 (38)	18 (31)	5 (63)	16 (52)	11 (38)
Age, y, median (range)	19 (17–22)	19 (17–22)	18 (17–22)	19 (18–20)	19 (17–20)	19 (18–22)
HAdV type						
HAdV-4	65 (39)	2 (5)	47 (81)	8 (100)	7 (23)	1 (3)
HAdV-7	65 (39)	14 (33)	7 (12)	0 (0)	18 (58)	26 (90)
HAdV-4/HAdV-7	3 (2)	0 (0)	0 (0)	0 (0)	3 (10)	0 (0)
Not typed ^a	35 (21)	26 (62)	4 (7)	0 (0)	3 (10)	2 (7)
Healthcare utilization						
Outpatient clinic ^b	145 (86)	19 (45)	58 (100)	8 (100)	31 (100)	29 (100)
Emergency department	27 (16)	15 (36)	2 (3)	1 (13)	3 (10)	6 (21)
Hospitalized	11 (7)	9 (21)	0 (0)	1 (13)	1 (3)	0 (0)
Unknown	7 (4)	7 (17)	0 (0)	0 (0)	0 (0)	0 (0)
Died	2 (1)	1 (2)	0 (0)	0 (0)	1 (3)	0 (0)
Medications or medical conditions^c						
Asthma	19/139 (14)	2/20 (10)	7/51 (14)	2 (25)	5 (16)	3 (10)
Immunosuppressive medication ^d	2/137 (1)	2/20 (10)	0/49 (0)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	2/139 (1)	0/20 (0)	2/51 (4)	0 (0)	0 (0)	0 (0)
Social history^c						
Smokes cigarettes (in past 30 d)	10/138 (7)	0/20 (0)	2/52 (4)	0 (0)	7/30 (23)	1/28 (4)
Uses electronic cigarettes (in past 30 d)	13/100 (13)	1/18 (6)	6/52 (12)	1/8 (13)	2/7 (29)	3/15 (20)
Any sick contacts	94/131 (72)	8/18 (44)	43/52 (83)	4/7 (57)	17/26 (65)	22/28 (79)

Data are presented as no. (%) unless otherwise indicated. Where shown, denominators are total No.

Abbreviation: HAdV, human adenovirus.

^aSpecimens not available.

^bIncludes student health center, urgent care, primary care outside of university health system, or other outpatient clinic.

^cBased on responses to chart abstraction and/or student questionnaire.

^dMedications include tumor necrosis factor α inhibitors (n = 2). Use of systemic corticosteroids at or prior to illness onset for limited duration (≤ 1 week) (n = 3) not included.

illness onset occurred during March–May 2019. Among the 168 cases, 133 (79%) had an HAdV type identified. HAdV-4 (n = 65 [39%]) and HAdV-7 (n = 65 [39%]) were equally identified, and for 3 (2%) specimens, both HAdV-4 and HAdV-7 were detected. HAdV types varied by college. Only HAdV-4 was identified at college C. Both HAdV-4 and HAdV-7 were detected at the 4 other colleges; HAdV-7 was the most common type detected at college A, college D, and college E, whereas HAdV-4 was the predominant type at college B (Table 1).

All cases received medical attention; 145 (86%) had ≥ 1 outpatient clinic visit (eg, SHC, urgent care, primary care outside of university health system, or other outpatient clinic), 27 (16%) had an ED visit, and 11 (7%) were hospitalized (Table 1). Two cases (1%) died. Among cases with available medical history information, 19 of 139 (14%) had asthma, 2 of 139 (1%) had diabetes, and 2 of 137 (1%) were taking an immunosuppressive medication. The majority (72%) reported at least 1 sick contact before illness onset, such as roommates, housemates, friends, teammates, or partners. Among those with symptom information available (n = 145), the most common symptoms were

fever (97%), sore throat (90%), chills (84%), and cough (84%) (Table 2). Eighty-eight cases (63%) reported ≥ 1 gastrointestinal symptom (nausea, vomiting, and/or diarrhea).

Clinical Course

Outpatient

Medical records from an outpatient clinic or ED visit were available for 67 of 168 (40%) cases. The most common findings were pharyngitis/tonsillitis (n = 45 [67%]) and cervical lymphadenopathy (n = 35 [52%]); 57% (n = 38) had measured fever (range, 100°F–103°F [37.8°C–39.4°C]) (Table 3). Most (93%) had normal lung auscultation. Seventeen had a chest radiograph performed and 4 had radiograph-confirmed pneumonia. Half of the cases who had a medical record available had > 1 visit to an outpatient clinic or ED (n = 34 [51%]; range, 1–5 visits).

Inpatient

Of the 11 hospitalized cases, the majority were male (n = 9 [82%]) and had no underlying conditions (n = 9 [82%])

Table 2. Reported Symptoms Among Human Adenovirus Cases From 5 College Campuses, United States (n = 145)

Symptom	No./Total	(%)
Fever ^a	141/145	97
Sore throat	126/140	90
Chills	118/140	84
Cough	118/140	84
Headache	115/145	79
Body aches	113/145	78
Fatigue	113/145	78
Nasal congestion/runny nose	109/140	78
Nausea	35/77	45
Shortness of breath	58/140	41
Diarrhea	57/140	41
Vomiting ^b	51/140	36
Red eyes	37/145	26
Loss of appetite	19/77	25
Wheezing	28/140	20
Earache	20/100	20

Denominators are based on responses to chart abstraction, student questionnaire, and/or influenza-like illness surveillance data.

^aSubjective or reported measured fever.

^bn = 2 documented as posttussive vomiting.

(Table 4). HAdV-7 was identified in 6 cases (55%) and HAdV-4 in 3 cases (27%), and specimens from 2 were not available for typing. Ten cases (91%) had radiograph-confirmed pneumonia and 1 case (9%) had febrile illness without pneumonia. Two cases were critically ill, requiring intensive care unit admission, and both died. Among 9 hospitalized cases without critical illness, 2 had documented hypoxia and received supplemental oxygen. Ten cases were treated with antibiotics and 4 with antivirals, including cidofovir in the 2 critically ill patients. The median length of hospital stay was 4 (range, 1–79) days.

The 2 decedents (A and B) were college freshmen who developed pneumonia, multiorgan failure, and acute respiratory distress syndrome requiring extracorporeal membrane oxygenation. Both had disseminated HAdV-7 infection with high viral loads in serum or plasma and received cidofovir after the onset of respiratory failure. Decedent A had inflammatory bowel disease, treated with a tumor necrosis factor- α inhibitor. Decedent B had no known underlying medical conditions but was prescribed a short course (3 days) of oral corticosteroids for Epstein-Barr virus mononucleosis approximately 8–10 days before the onset of respiratory symptoms. Decedent A died on hospital day 9. Decedent B had a complicated hospital course, including possible hemophagocytic lymphohistiocytosis, and died on hospital day 79.

Student Questionnaire

Ninety-eight of 168 (58%) cases responded to the questionnaire (Table 5) within an average of approximately 2 months after illness onset. Of respondents, 57 (58%) were first-year undergraduate students, and the majority reported seeking care for their

Table 3. Clinical Characteristics and Course of Human Adenovirus Cases With Outpatient or Emergency Department Visits (n = 67)

Characteristic	No. (%)
Age, y, median (range)	19 (17–22)
Sex	
Male	35 (52)
Female	32 (48)
Vital signs and physical exam findings (on any visit during illness)	
Fever (≥ 100.0 °F [37.8 °C])	38 (57)
Respiratory rate, breaths/min, median (range) ^a	16 (14–22)
Oxygen saturation, %, median (range) ^b	97 (95–100)
Tachycardia ^c	25 (37)
Cervical lymphadenopathy	35 (52)
Pharyngitis/tonsillitis	45 (67)
Exudative	16 (36)
Abnormal lung auscultation ^d	5 (7)
Chest radiograph performed	17 (25)
Normal	13 (76)
Single lobar consolidation	3 (18)
Bilateral interstitial infiltrate	1 (6)
Additional positive diagnostic tests (on any visit during illness)	
Respiratory codetections	
Rhinovirus/enterovirus	6 (9)
<i>Chlamydia pneumoniae</i>	2 (3)
Influenza A	1 (1)
Human coronavirus	1 (1)
Rapid group A streptococcus test or throat culture	4 (6)
Mononucleosis spot test	1 (1)
Visit diagnosis (on any visit during illness) ^e	
Influenza-like illness/syndrome	41 (61)
Pharyngitis/tonsillitis	25 (37)
Fever	21 (31)
Sore throat	18 (27)
Upper respiratory infection/respiratory illness	16 (24)
Cough	8 (12)
No. of outpatient or emergency department visits, median (range)	2 (1–5)
1	33 (49)
2	19 (28)
≥ 3	15 (22)

Data are presented as no. (%) unless otherwise indicated.

^aIncludes some participants with multiple measurements: n = 25 across 30 outpatient visits.

^bIncludes some participants with multiple measurements: n = 35 across 61 outpatient visits.

^cDefined as measured heart rate >100 beats per minute or noted on the physical examination.

^dIncludes rhonchi/coarse breath sounds, wheezing, rales/crackles, and decreased breath sounds.

^eVisit diagnoses accounting for <10% included adenovirus, pneumonia, influenza, asthma, cervical lymphadenopathy, mononucleosis, sinusitis, gastroenteritis, nausea, vomiting, malaise, viral syndrome/viral illness/viral infection, shortness of breath, infectious disease exposure, bronchitis, bronchospasm, posttussive emesis, nasal congestion, body aches, nonintractable headache, vasovagal syncope, orthostatic hypertension, diarrhea, coronavirus infection, and muscle pain.

illness at the SHC (91%). Most respondents lived in dormitories (n = 81 [83%]) and shared either a bedroom or common space with others (n = 94 [97%]). Among those who were recovered from illness at the time of the questionnaire (n = 79),

the median illness duration was 10 (range, 3–30) days. Eighty percent of respondents (75/94) missed 1 or more days of classes due to illness. The median number of class days missed was 3 (range, 1–20) days.

Among cases who reported living in a dormitory or fraternity/sorority house (n = 87), 80 specified the name of the residence. Of these 80, 58 lived in 16 dormitories or fraternity/sorority houses that had ≥ 2 cases, with a median of 2 cases per residence (range, 2–12). Twenty-four cases were linked to 5 athletic teams. Notably, at college E, 48% (14/29) of the cases had an epidemiologic link to 1 athletic team.

Molecular Characterization

Complete genome sequences were obtained from 18 HAdV-7 isolates and 10 HAdV-4 isolates (GenBank accession numbers MN307136–MN307163). All were identified as genome type 7d or 4a1 and shared >99.9% nucleotide sequence identity within each type. The genomic sequences of HAdV-7 clustered together with HAdV-7d strains from the US from 2014 to 2017 [6, 16, 23] and China in 2010 and 2011 [7, 24] (Figure 1A). The HAdV-4 genomes showed highest sequence identity to HAdV-4a1 strains from the US from 2011 to 2016 [14, 25] and China in 2008 [26] (Figure 1B). Within each college

outbreak, genome sequences were within 0–15 nucleotide differences of each other for both HAdV-7 and HAdV-4. Among the 5 colleges, genome sequences differed by 0–20 nucleotides (Supplementary Table 2).

DISCUSSION

We describe a multistate investigation of HAdV-4 and HAdV-7 respiratory illness outbreaks associated with severe illness and death among students at 5 US college campuses during fall 2018 and spring 2019. HAdV ARI was associated with substantial morbidity among generally healthy, undergraduate college students. Eleven students required hospitalization, 10 of whom had pneumonia; 9 recovered with supportive therapy, and 2 died. The illnesses resulted in considerable missed class time, time to recovery, and healthcare utilization.

Outbreaks of HAdV-associated ARI have not been well documented in nonmilitary congregate settings such as college campuses. Although recent reports have described HAdV detections among college students using ILI surveillance at SHCs, these accounts were primarily laboratory characterizations, with limited or no epidemiologic data [15–17]. HAdV is likely an underrecognized cause of acute respiratory illness; it is

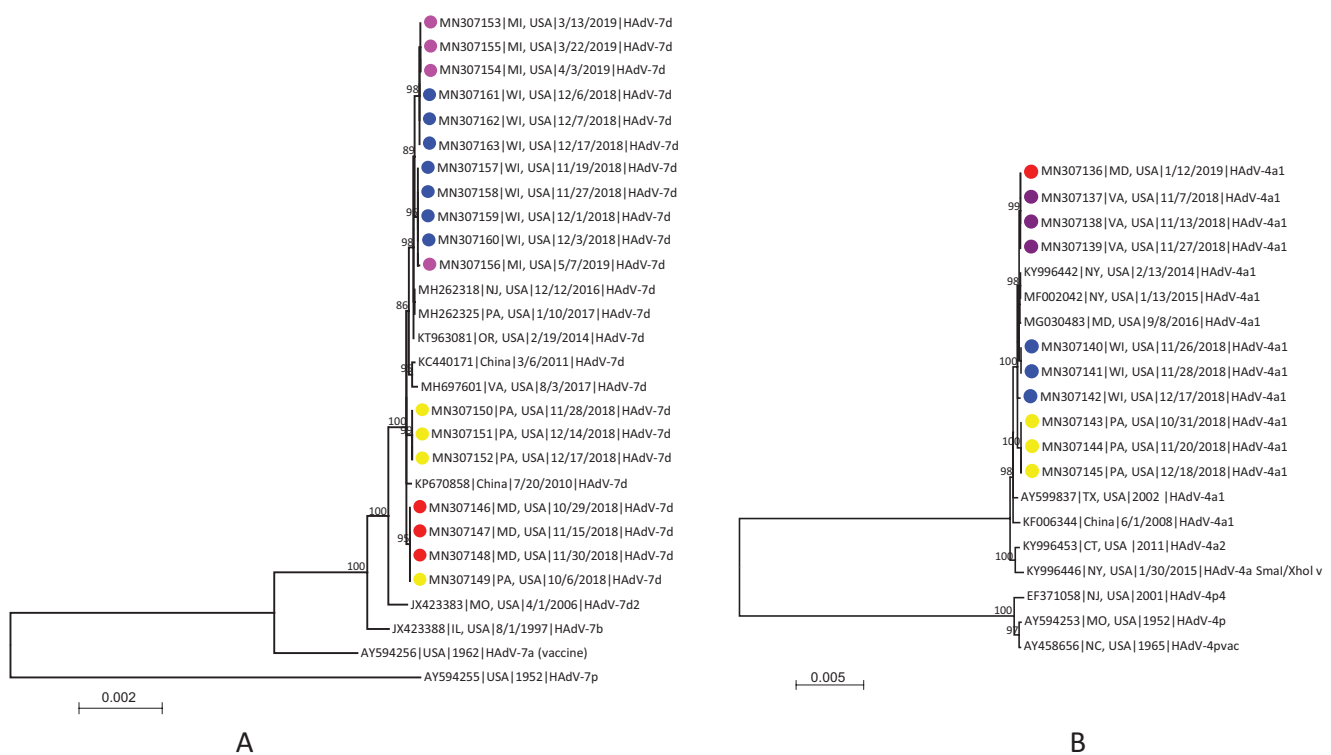


Figure 1. Phylogenetic analysis of human adenovirus 7 (A) and human adenovirus 4 (B) genomic sequences obtained from students associated with respiratory illness outbreaks in 5 college campuses and reference sequences available in GenBank. Genomic sequences were aligned by using MAFFT implemented in Geneious version 10.0.9, and the maximum-likelihood phylogenetic trees were constructed by using MEGA7 software [20] based on the Tamura 3-parameter nucleotide substitution model. Numbers at selected nodes indicate level of support using 1000 bootstrap replicates. Genomic sequences with colored dots were obtained in this study, and different colors represent sequences from different college outbreaks: red, college A; yellow, college B; purple, college C; blue, college D; pink, college E. Sequences are identified by GenBank accession number, geographic location, sample collection date or year, and virus genome type. Scale bar indicates estimated number of nucleotide substitutions per site. Abbreviations: CT, Connecticut; HAdV, human adenovirus; IL, Illinois; MD, Maryland; MI, Michigan; MO, Missouri; NC, North Carolina; NJ, New Jersey; NY, New York; OR, Oregon; PA, Pennsylvania; TX, Texas; USA, United States; VA, Virginia; WI, Wisconsin.

Table 4. Clinical Characteristics and Course of Human Adenovirus Cases With Hospital Admission (n = 11)

Characteristic	No. (%)
Age, y, median (range)	19 (18–22)
Sex	
Male	9 (82)
Female	2 (18)
HAdV type	
HAdV-4	3 (27)
HAdV-7	6 (55)
Not typed	2 (18)
Medical history	
None	9 (82)
Asthma	1 (9)
Inflammatory bowel disease	1 (9)
Hospital course	
Intensive care unit admission	2 (18)
Radiograph-confirmed pneumonia	10 (91)
Initial radiographic findings	
Single lobar consolidation	7 (70)
Multilobar consolidation	2 (20)
Bilateral interstitial infiltrate	1 (10)
Laboratory findings on admission, median (range)	
WBC count, K/mm ³ (n = 8)	6.9 (2.4–13)
Platelet count, K/mm ³ (n = 10)	183.5 (88–198)
AST level, IU/L (n = 8)	49 (20–221)
ALT level, IU/L (n = 8)	28 (15–422)
Treatment	
Antiviral(s)	4 (36)
Cidofovir	2 (18)
Oseltamivir	4 (36)
Antibiotic(s)	10 (91)
Intravenous immunoglobulin	1 (9)
Intravenous rehydration	7 (64)
Highest level of respiratory support	
None	7 (64)
Supplemental oxygen by nasal cannula	2 (18)
Extracorporeal membrane oxygenation	2 (18)
Concurrent pathogen detections	
<i>Mycoplasma pneumoniae</i>	1 (9)
Epstein-Barr virus	1 (9)
No. of days from symptom onset to admission, median (range)	6 (0–15)
No. of days hospitalized, median (range)	4 (1–79)
Required transfer to a tertiary care center	3 (27)
Outcome	
Died	2 (18)
Discharged home	9 (82)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAdV, human adenovirus; WBC, white blood cell.

often not routinely tested for, and outbreak notification to CDC is voluntary. Additional studies are needed to understand the burden and risk of HAdV-associated respiratory illness among student populations in college settings.

In the US, HAdV-associated ARI outbreaks are well described among military recruits in training facilities, with published reports as early as the 1950s [10, 11, 27]. An oral,

Table 5. Student Questionnaire: Characteristics, Healthcare Seeking, and Missed Obligations of Human Adenovirus Cases From 5 College Campuses, United States (n = 98)

Characteristic	No. (%)
Demographic characteristics	
Age, y, median (range)	19 (17–22)
Sex	
Male	64 (65)
Female	34 (35)
Undergraduate year of study	
1st year	57 (58)
2nd year	26 (27)
3rd year	10 (10)
4th year	5 (5)
Housing	
Residence hall/dormitory	81 (83)
Fraternity/sorority house	6 (6)
Off-campus housing	11 (11)
Shares a bedroom with others	83/97 (86)
Shares bedroom or common spaces with others	94/97 (97)
Healthcare seeking	
Healthcare type	
Student health center	86/95 (91)
Urgent care	13/95 (14)
Emergency department	11/95 (12)
Primary care provider	10/95 (11)
Other	4/95 (4)
No. of visits to any healthcare provider	
1	30/93 (32)
2	40/93 (43)
3	14/93 (15)
≥4	9/93 (10)
Recovered from illness	79/93 (85)
Illness duration, d, median (range)	10 (3–30)
Missed obligations	
Missed any classes	75/94 (80)
1 d	11 (15)
2–4 d	44 (59)
5–9 d	14 (19)
≥10 d	6 (8)
No. of days of missed classes, median (range)	3 1–20
Missed collegiate athletic practice/games	14/93 (15)
No. of days missed, median (range)	4 (1–12)
Missed full or part-time job	20/95 (21)
No. of days missed, median (range)	2 (1–7)
Missed other obligations (volunteer work, clubs, intramurals, other)	39/95 (41)

Data are presented as no. (%) unless otherwise indicated. Where shown, denominators are total No.

live, nonattenuated vaccine for HAdV-4 and HAdV-7 was first implemented for military use in 1971. The vaccine is safe, effective, and immunogenic in military populations and is currently US Food and Drug Administration (FDA) approved for use in healthy military personnel aged 17–50 years [13, 28]. An interruption in vaccine supply during 1999–2011 resulted in a surge of HAdV infections and 8 documented deaths among military recruits [12, 29, 30]. After reintroduction of

the vaccine, dramatic declines in ARI and HAdV infections among vaccinated military populations were demonstrated [29, 31]. Recent reports documented HAdV outbreaks among unvaccinated military populations, including at the US Naval Academy (HAdV-4) and at the US Marine Corps Officer Candidates School (OCS) in Quantico, Virginia (HAdV-7) [14, 23]. As a result of the OCS outbreak, the vaccine is now administered to all incoming officer candidates in Quantico under a temporary vaccine protocol to assess effectiveness in this population [23]. The vaccine has not been evaluated in the general civilian population. Because live virus can be shed in stool of vaccinated persons for up to 28 days, transmission of vaccine-strain virus is possible, and avoiding close contact with vulnerable populations, including pregnant women, young children, and immunocompromised individuals, during this period is recommended [13]. Consideration of broader prevention strategies targeting HAdV in civilian populations, including college students, could require the development of other vaccine constructs, for example, attenuated vaccine.

In this report, cases were commonly freshmen living in dormitories and more frequently male. Similarly, in the 1990s, freshmen in college dormitories were noted to be at moderately increased risk for meningococcal disease compared with other college students [32, 33]. This led to a change in US vaccine policy, recommending that college freshmen living in dormitories receive the meningococcal vaccine [33, 34]. For HAdV-associated respiratory illness, however, more research is needed on the risk and burden of disease specific to college settings to understand the potential benefit of specific intervention strategies.

While most students in this investigation presented with self-limiting upper respiratory tract infection, 11 were hospitalized with severe illness, and 2 died. Although HAdV can also cause severe disease in otherwise healthy individuals [35, 36], immunocompromised individuals, particularly solid organ (SOT) or stem cell transplant (SCT) recipients, are at increased risk of severe and disseminated HAdV infection [1, 5]. One death occurred in a student who was taking an immunosuppressive medication, and the second death occurred in a student with no known underlying medical conditions but with recent history of mononucleosis and brief steroid treatment.

Although there is currently no FDA-approved treatment for HAdV infection, both decedents were treated with cidofovir, a nucleotide analogue with *in vitro* activity against HAdV that has been used to treat severe HAdV infections [37]. Data on cidofovir use for HAdV infection are limited to observational studies and case reports, almost exclusively among patients who are severely immunocompromised, such as SOT and SCT recipients [36, 38–40]. Studies in these populations have had mixed results on clinical improvement and mortality [1, 41].

Molecular analysis of 28 genome sequences identified HAdV-7 strains as genotype 7d and HAdV-4 strains as 4a1. HAdV-7d was detected in China in 2009 after a 21-year apparent absence and was first reported in the US in a 2014 community outbreak in Oregon [6, 7]. Recent outbreaks in college and military settings have also identified HAdV-7d [16, 23]. During nonvaccine years, HAdV-4 was the most common cause of HAdV outbreaks in military recruits [12, 29], and 4a1 was identified in a recent outbreak at the US Naval Academy and among cases of ILI at 2 colleges in New York [14, 25]. At 4 of the 5 colleges, both HAdV-4 and HAdV-7 were detected during the investigation period. Co-circulation of HAdV types is common and has been described in other investigations [11, 15]. While we identified genome sequence similarities both within and between the outbreaks, this is expected given the single base genetic stability of double-stranded DNA viruses, such as adenovirus [42]. The genomic data are informative in understanding HAdV circulation, but do not allow for development of detailed transmission chains or conclusions about directionality of transmission in this investigation.

Our investigation has limitations. First, testing practices likely influenced the number and type of cases identified. Students presenting to SHCs met certain criteria for testing based on ILI or ARI symptom presentation, and only a subset were tested for HAdV. Severity of illness may have influenced students' health-seeking behaviors and clinician-directed testing. Thus, this report reflects a convenience sample of students tested for HAdV, and cases were likely missed. Relatedly, testing based on ILI case definitions, at the 2 colleges that performed ILI surveillance, could have influenced the proportion of symptoms presented here. For example, the most common symptoms included fever, cough, and sore throat, all of which are part of the ILI case definition. Second, the case definition included laboratory-confirmed HAdV cases only. Information on students presenting with ARI but who were not tested for HAdV was not collected. Future studies using active surveillance or standardized approaches to testing are needed to document HAdV burden. Third, available data varied by site, and our results were limited by response rates and access to medical records and specimens for molecular characterization. Specifically, this restricted our ability to draw conclusions about differences in disease presentation and clinical course by HAdV type. Data were combined across sources, where possible. However, our findings should be interpreted in light of these limitations.

This investigation describes HAdV-associated ARI outbreaks among young adults on 5 US college campuses. HAdVs should be considered as a possible cause of respiratory illness among college students, with the potential to cause severe illness and, occasionally, death. Understanding overall disease burden, risk, and risk factors for HAdV illness are necessary to inform prevention strategies and to evaluate the potential utility of a vaccine in these settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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