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MAJOR ARTICLE

Respiratory Illness Associated With Emergent Human Adenovirus Genome Type 7d, New Jersey, 2016–2017

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Background. Human adenoviruses (HAdVs) are known causes of respiratory illness outbreaks in congregate settings, but cases and clusters are less well described from community settings in the United States. During December 2016–February 2017, the New Jersey Department of Health received reports of HAdV infections from 3 sources in 3 adjacent counties. We investigated to characterize the epidemiologic, laboratory, and clinical features of this HAdV outbreak.

Methods. A case was defined as a New Jersey resident with acute respiratory illness during December 1, 2016–March 31, 2017 with laboratory identification of HAdV genome type 7d (HAdV-7d). Human adenovirus was detected by real-time and conventional polymerase chain reaction and molecular typed by partial hexon capsid protein gene sequencing. The HAdV genome type was identified by whole genome sequencing analysis. Available medical, public health, and surveillance records were reviewed.

Results. We identified 12 cases, including 3 treatment facility patients, 7 college students, and 2 cases at a tertiary-care hospital. Four cases died; all had underlying comorbidities. Nine HAdV-7d whole genome sequences obtained from all 3 sites were nearly identical.

Conclusions. Transmission of HAdV-7d occurred in community and congregate settings across 3 counties and resulted in severe morbidity and mortality in some cases with underlying comorbidities. Clinicians and local and state health departments should consider HAdV in patients with severe respiratory infection.

Keywords. acute respiratory disease; human adenovirus; outbreak; respiratory virus.

Human adenoviruses (HAdVs) comprise 7 species (A–G) and over 85 genotypes have been described [1]. Circulating types can change over time and geography. Globally, HAdV types 3, 4, 7, 14, and 21 are commonly associated with respiratory infections and outbreaks [2]. Infection can occur at any age, is usually asymptomatic or mild, but can be severe and occasionally fatal. Typical symptoms include cough, nasal congestion, and fever, with rare progression to pneumonia, respiratory failure, and death [3]. Immunocompromised individuals and older adults are thought to be at increased risk of severe disease [4–6].

Outbreaks of acute respiratory illness (ARI) associated with HAdV have been reported in community settings [7, 8], but they are more often associated with congregate settings such as military training centers, hospitals, and long-term care facilities [9–11]. In the United States, HAdV outbreaks were frequently reported among enlisted personnel at military training facilities before the introduction of a live oral HAdV-4 and HAdV-7 vaccine in 1971 [9]. Outbreaks reoccurred in military settings during 1996–2011 when vaccine use was interrupted [12], but reintroduction of vaccination in 2011 dramatically reduced the rate of febrile respiratory illness [9, 13, 14]. Currently, an oral HAdV genome type 4 (HAdV)-4 and HadV-7 vaccine is available but limited to military use [15].

Human adenovirus genome type 7 is most commonly associated with acute, self-limited respiratory tract infections. Human adenovirus genome type 7 is among the most pathogenic HAdV types [16], and infection can occasionally result in death in healthy adults [17], although more serious lower respiratory tract illness and death occurs more frequently in infants, immunocompromised individuals, and individuals with underlying respiratory disease [10]. Human adenovirus genome type 7 had not been commonly reported in the United States before 2013; 8.5% of HAdVs voluntarily reported to the National Adenovirus Type Reporting System (NATRS), administered by the Centers for Disease Control and Prevention (CDC), during 2003–2016 were HAdV-7, with HAdV-3, -2, -1, and -4 each reported more frequently [18]. During 2013–2014, a community respiratory illness outbreak associated with HAdV-7d was reported in Oregon [8]. In total, 198 cases were detected, including 136

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(69%) hospitalized cases and 5 (2.5%) deaths [8]. Although the outbreak strain had not been previously identified in the United States [8, 19], nearly identical sequences were documented in China in 2009 and 2011 [8]. In 2014, HAdV-7d was also reported in Illinois, resulting in severe illness in 2 patients [19].

During December 2016, the New Jersey Department of Health (NJDOH) noted the first of a series of HAdV clusters at a modified influenza incidence surveillance project site based at an undergraduate college. This was followed by a report on January 31, 2017 from a Pennsylvania municipal health department of 2 HAdV-associated hospitalizations involving New Jersey residents, 1 resulting in death. On February 2, 2017, a second New Jersey municipal health department notified NJDOH of a respiratory illness outbreak in an alcohol and substance use rehabilitation facility that was found to be associated with HAdV-7 [19]. All reports were of patients residing in 3 adjacent counties in New Jersey. To better understand the extent of HAdV-7 morbidity and mortality, the NJDOH, assisted by the CDC, investigated to further characterize HAdV-7 transmission associated with these settings. In this report, we describe the public health investigation, including the scope of recognized HAdV-7 strain transmission, the epidemiologic and clinical features of affected patients, and the laboratory characterization of HAdV-7 identified from patient specimens.

METHODS

A case was defined as any New Jersey resident with ARI (defined as any 2 of the following: fever ≥100°F, sore throat, cough, rhinorrhea, shortness of breath, or nasal congestion) during December 1, 2016–March 31, 2017 with laboratory identification of HAdV-7. In this report, we describe cases identified from 3 different sources: (1) a college, (2) a substance use rehabilitation facility, and (3) a tertiary-care hospital. Available medical, public health, and surveillance records were reviewed for all cases.

College Surveillance: New Jersey Department of Health Enhanced Influenza-like Illness Surveillance Network

The NJDOH conducts routine surveillance for influenza-like illness (ILI) from outpatient healthcare providers across the state as part of the CDC's US Outpatient Influenza-like Illness Surveillance Network (ILINet). The ILINet providers submit weekly numbers of patients visits and number of patients with ILI (ie, fever [100°F or greater] and cough and/or sore throat) by age group. A subset of providers (enhanced ILINet providers), which includes local universities, provides additional information on patient demographics, clinical, and laboratory information on the first 10 ILI patients seen each week. Enhanced ILINet providers also attempt to submit respiratory specimens (nasopharyngeal [NP] swab, nasal swab (anterior nares), nasal aspirate, or nasal wash from the first 10 ILI patients seen each week at the New Jersey Public Health and Environmental Laboratory (PHEL). Specimens submitted to PHEL are first tested by CDC Influenza virus real-time, reverse transcription-polymerase chain reaction (PCR) assay. A subset of specimens, including both specimens that test negative and positive for influenza, are tested for other respiratory pathogens, including HAdV, by GenMark Dx eSensor Respiratory Virus Panel (RVP) (GenMark Diagnostics, Inc., Carlsbad, CA). Available specimens testing positive for HAdV, during December 1, 2016–March 31, 2017, were submitted to the CDC for confirmation and further testing. Available demographic and clinical details of all HAdV-7 cases were reviewed.

Substance Use Rehabilitation Facility Acute Respiratory Illness Outbreak Associated With Human Adenovirus

During December 2016–March 2017, hospitalized ARI cases were identified during an ARI outbreak in a substance use rehabilitation facility [20]. Influenza testing was initially performed at the facility. The NJDOH investigated and performed an epidemiological investigation at the facility, including additional respiratory virus testing on ARI cases at the facility using GenMark Dx eSensor RVP. Human adenovirus testing was conducted by hospital laboratories or the NJDOH. Available respiratory samples from HAdV-positive patients were sent to the CDC for additional testing. Medical records were reviewed for all HAdV-7 cases.

Tertiary-Care Hospital Cases Associated With Human Adenovirus

We reviewed medical records and collected available respiratory samples from reported community-dwelling New Jersey residents hospitalized with respiratory illnesses associated with HAdV at a tertiary-care facility in Philadelphia during the study period. Available respiratory samples were sent to the CDC for HAdV confirmation and molecular typing.

Centers for Disease Control and Prevention Laboratory Testing

At the CDC, respiratory specimens were tested by a generic pan-HAdV real-time (r)PCR assay [21] to confirm HAdV detection and then typed by PCR and sequencing of hexon capsid protein gene hypervariable regions 1–6 [22]. Virus isolation in A549 cells was attempted on 9 HAdV-7-positive specimens from all 3 settings that had sufficient volume. For whole genomic sequencing (WGS), deoxyribonucleic acid (DNA) libraries of the isolates were constructed using Nextera XT DNA Library Prep Kit, and paired-end sequencing was performed on the MiSeq using 500-cycle Miseq Reagent Kit V2 (Illumina). De novo assemblies were achieved using CLC Genomics Workbench version 8.5.1. Phylogenetic trees of nearly WGS obtained in this study and HAdV reference sequences from GenBank were constructed by the neighbor-joining method implemented in MEGA version 7. In silico restriction enzyme analysis of the HAdV-7 genomes was performed using Geneious 10.0.9, and genome types were determined using established guidelines and reference fragment patterns [23, 24].

In addition, a lung tissue autopsy specimen from an alcohol and substance use rehabilitation facility case was evaluated by histopathological and molecular analysis at the Infectious Diseases Pathology Branch of the CDC. Deoxyribonucleic acid was extracted from formalin-fixed, paraffin-embedded lung tissue using the QIAamp DNA mini kit (QIAGEN) and tested by a conventional HAdV group-specific PCR assay targeting the hexon gene [25]. The amplified PCR products were directly sequenced on a GenomeLab GeXP sequencer (AB SCIEX LLC, Redwood City, CA). The search for homologies to known sequences was done using the nucleotide database of the Basic Local Alignment Search Tool (BLAST).

RESULTS

College Surveillance: New Jersey Department of Health Enhanced Influenza-like Illness Surveillance Network

During December 5, 2016–April 1, 2017, 259 ILI cases presented for care at College A (Figure 1). Among these, 95 patients had samples available for testing at the PHEL, and 51 (54%) tested positive for influenza. Forty-six ILI cases were tested by RVP at the PHEL; 15 (35%) were positive for adenovirus B/E, 1 (2%) was positive for adenovirus C, and 13 (28%) were positive for other respiratory viruses including rhinovirus, human metapneumovirus, respiratory syncytial virus (RSV) A, and RSV B. Among the HAdV-positive specimens, 2 had other respiratory viruses codetected; one was positive for HAdV B/E along with influenza A and HAdV C, the other was positive for both HAdV B/E and RSV B. Among the HAdV-positive specimens, 9 were available for testing at the CDC, 7 (78%) were HAdV-7 (Figure 2), 1 (11%) was HAdV-3, and 1 (11%) was HAdV-2 (Figure 1). The HAdV-2-positive result was from a specimen from which both species, HAdV B/E and HAdV C, were detected on RVP, but HAdV-7 was not detected from this specimen.

Among the 7 HAdV-7 cases identified at College A, 5 had symptom onset dates during December 10–18, 2016 and were reported during December 17–30, 2016 (Figure 1). The remaining 2 HAdV-7-positive cases had symptom onset during February 13–14, 2017 and were reported during February 18–24, 2017. Cases were reported both before and during the peak in influenza-positive specimens collected from students at the college (Figure 1). Among the 7 HAdV-7 cases, all experienced symptoms, including 7 (100%) with fever, 7 (100%) with a sore throat, 6 (86%) with myalgia, and 5 (71%) with cough (Table 1). The median age of cases was 19 (range, 18–21). At the time of initial consultation, none required hospitalization.

Substance Use Rehabilitation Facility Acute Respiratory Illness Outbreak Associated With Human Adenovirus

The NJDOH was notified on February 3, 2017 of an outbreak involving 79 ARI cases at an alcohol and substance use rehabilitation facility during January 1–March 31, 2017, including 4 hospitalized cases [20]. Among the 79 ARI cases (59 inpatients and 20 staff), 25 cases had specimens tested for influenza, and 3 (12%) were positive. Among these 25 specimens, 4 were available for additional testing, and all 4 were positive HAdV by PCR. These 4 HAdV case-patients required hospitalization and 3 resulted in death. The 3 fatal cases included one with HAdV-7 identified from a NP specimen and one with HAdV-7 identified from lung tissue specimen at autopsy. Human adenovirus was detected by PCR from the remaining fatal case patient at the hospital, but specimens were not available for typing. This case also tested positive for influenza A. The remaining hospitalized case survived and had HAdV-7 identified from a NP specimen.

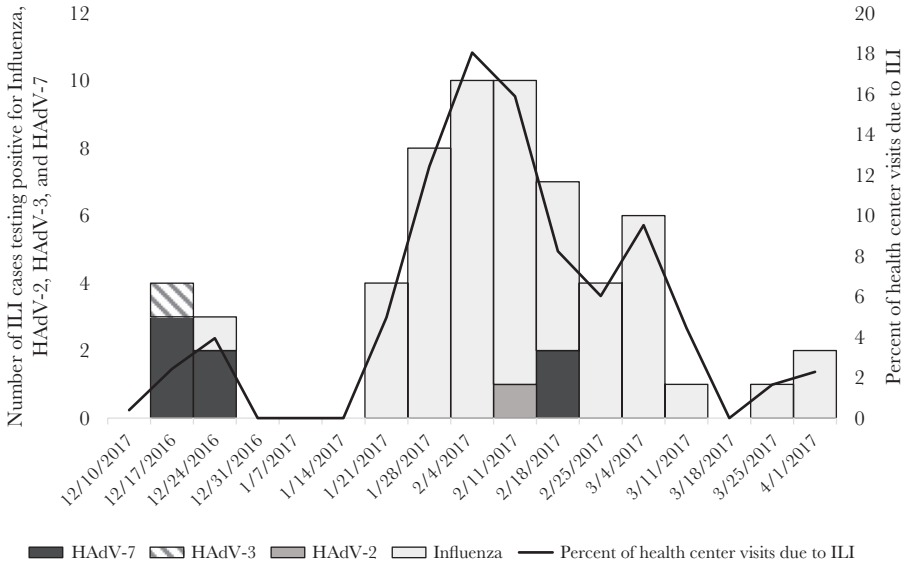

Figure 1. Number of influenza-like illness (ILI) cases, and number of cases testing positive for influenza, human adenovirus (HAdV)-B/E, and HAdV genome type 7 (HAdV-7), College A, New Jersey, December 2016–March 2017.

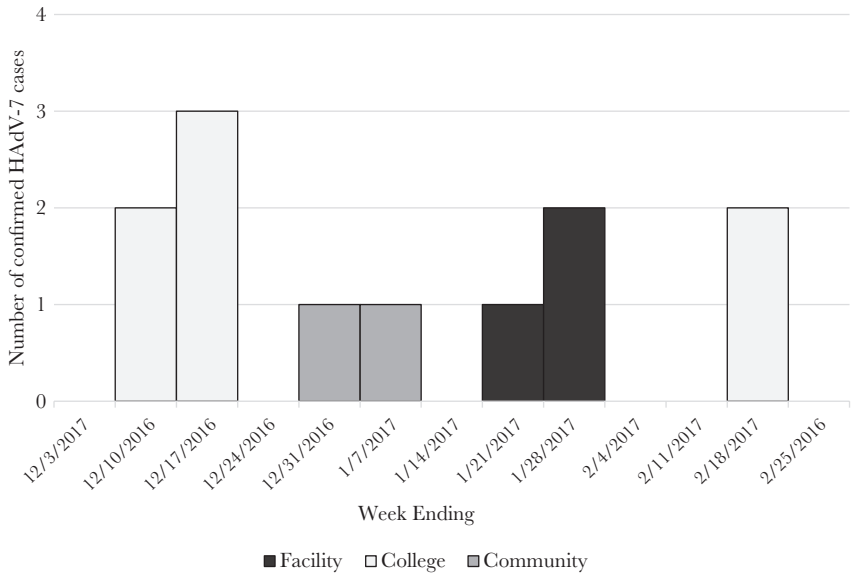

Figure 2. Counts of confirmed human adenovirus genome type 7 (HAdV-7) cases at a Substance Use Rehabilitation Facility, College, and in the Community, New Jersey, December–March 2017.

The 3 case-patients who died initially developed fever and cough, which rapidly progressed to multifocal pneumonia and acute respiratory distress syndrome (ARDS), followed by acute renal failure and death. Time from symptom onset to death ranged from 4 to 37 days; 2 were male, and age range was 54–64 years. Of the 3 persons who died, 1 had hepatic cirrhosis, 1 had diabetes mellitus type 2, and 1 had both hepatic cirrhosis and diabetes mellitus type 2 (Table 1). All 3 persons who died had a reported history of alcoholism.

Tertiary-Care Hospital Cases Associated With Human Adenovirus

On January 31, 2017, the Philadelphia Department of Health reported 2 New Jersey residents to NJDOH who were admitted at an academic medical center in Philadelphia and tested positive for HAdV on a respiratory virus multiplex PCR panel. No epidemiologic links were found between the 2 cases. Case number 1 was a 53-year-old female resident of a New Jersey county neighboring Philadelphia. Her medical history was significant for non-Hodgkins lymphoma status postradiation and chemotherapy, requiring a chronic low-dose oral corticosteroid regimen, and with secondary chemotherapy-induced congestive heart failure. She had onset of sore throat, cough, rhinorrhea, and sinus pain 2 weeks preceding hospitalization and was seen in a local emergency department and urgent care at different times and treated for sinusitis and "flu". A few days before hospital admission, she developed fever (104°F), chills, worsening cough, vomiting, diarrhea, and altered mental status resulting in hospital admission on January 11, 2017. Within 4 days she required transfer to an intensive care unit (ICU), and the next day required intubation. She died on hospital day 10. Influenza testing was negative on hospital admission; HAdV-7 was confirmed at the CDC from a sample taken on January 11th.

Case number 2 was a 53-year-old male resident of a New Jersey county neighboring Philadelphia. Comorbidities included type 2 diabetes, hypertension, chronic kidney disease, past history of smoking, morbid obesity, and obstructive sleep apnea. He developed altered mental status over 2–3 days before presenting to an emergency department on January 4, 2017. He was admitted to an ICU the same day for hypoxic and hypercapnic respiratory failure secondary to pneumonia with congestive heart failure and sepsis, and he required intubation on hospital day number 3. By hospital day number 6, he required extracorporeal membrane oxygenation (ECMO) and transfer to a higher level care facility due to decompensation associated with ARDS. After a 42-day hospital course, the patient was discharged with a tracheostomy and night-time ventilatory requirements to a long-term respiratory care facility on February 14, 2017. He was discharged home on June 1, 2017 with long-term tracheostomy requirements. Human adenovirus genome type 7 was confirmed at the CDC from a sample taken on January 19th.

Genome Sequencing

Genome sequences (GenBank accession nos. MH262318–MH262326) obtained from 9 HAdV-7 isolates were nearly identical (Figure 3). However, a coinfection of wild-type and deletion variant were identified from a specimen from a college case collected on February 16, 2017. The case-patient presented with upper respiratory tract symptoms, fever, chills, myalgia, and headache, similar to other college cases. Eighty percent of raw sequence reads had a 12-nucleotide (12nt) in-frame deletion in open reading frame 2 (ORF2) of early region 4 (E4) located at position 34123–34134

Table 1. Demographic and Clinical Characteristics for HAdV-7 Case-Patients, New Jersey, December 2016–March 2017

Characteristics	Total (n = 12)	Facility Cases (n = 3)	College Cases (n = 7)	Community Cases (n = 2)
Female	5 (42)	1 (33)	3 (43)	1 (50)
Age Group (years)				
18–30	7 (58)	0	7 (100)	0
31–50	0	0	0	0
51–80	5 (42)	3 (100)	0	2 (100)
Symptoms				
Fever	12 (100)	3 (100)	7 (100)	2 (100)
Myalgia	7 (58)	1 (33)	6 (86)	0
SOB	4 (33)	2 (67)	0	2 (100)
Anorexia	4 (33)	0	4 (57)	0
Diarrhea	3 (25)	0	3 (43)	0
Cough	9 (75)	3 (100)	5 (71)	1 (50)
Sore Throat	8 (67)	0	7 (100)	1 (50)
Chills	9 (75)	2 (67)	6 (86)	1 (50)
Headache	6 (50)	0	6 (86)	0
Vomiting	3 (25)	1 (33)	1 (14)	1 (50)
Rhinorrhea	6 (50)	1 (33)	5 (71)	0
Illness Severity				
Hospitalized	6 (50)	3 (100)	0*	2 (100)
Died	5 (42)	3 (100)	0*	2 (100)
Comorbidities				
Any	5 (42)	3 (100)	0	2 (100)
Congestive heart failure	1 (8)	0	0	1 (50)
Chronic kidney disease	1 (8)	0	0	1 (50)
Diabetes	4 (33)	2 (67)	0	2 (100)
Hepatic cirrhosis	2 (17)	2 (67)	0	0
Alcoholism	3 (25)	3 (100)	0	0

Abbreviations: HAdV, human adenovirus; SOB, shortness of breath.

*No students were hospitalized or died at the time of presentation, follow-up information was unavailable.

based on accession number KT963081, and the consensus sequence without deletion was 100% identical to other New Jersey and Pennsylvania sequences. This deletion was also confirmed in the original specimen by direct sequencing of the deletion region. In silico analysis showed that all viruses shared identical *Bam*HI restriction profiles with HAdV-7d strains circulating in Oregon in 2014 [8] and China in 2009 and 2011 [26]. The genome sequences showed 99.9% nucleotide identity with Oregon and China HAdV-7d sequences (Genbank accession nos. KT963081 [Oregon] and KC440171 [China]) available in GenBank.

Outbreak Response

The NJDOH provided infection control recommendations to both the alcohol and substance use rehabilitation facility and College A. Recommendations included, but were not limited to, the following: (1) use of US Environmental Protection Agency-registered disinfectant with proven activity against HAdVs on common touch areas in communal gathering places and (2) frequent handwashing. Additional recommendations at the alcohol and substance use rehabilitation facility included isolation of patients with fever ≥100°F (37.8°C) lasting ≥24 hour and a 72-hour deferral for new admissions during implementation of recommended infection control measures.

A variety of sources were also investigated to determine whether HAdV detections similar to what was observed in this geographic region were being observed elsewhere in the state. These sources included National Respiratory and Enteric Viruses Surveillance System reports, military installations located in New Jersey, local laboratories conducting RVP testing, and statewide syndromic surveillance from acute care hospitals. No notable increases in HAdV detections or unusual hospital activity were reported.

DISCUSSION

We describe HAdV-7 circulation in a restricted geographic location of 3 adjacent counties in New Jersey during December 1, 2016–March 31, 2017. Circulation occurred at a range of settings including among college students, among residents at an inpatient substance use rehabilitation facility, and in 2 community cases presenting to a tertiary-care hospital. Substantial morbidity and mortality occurred among case-patients in the substance abuse facility and 2 nearby community residents. Although these cases were temporally and spatially connected, no known epidemiologic links were found between cases presenting at different locations.

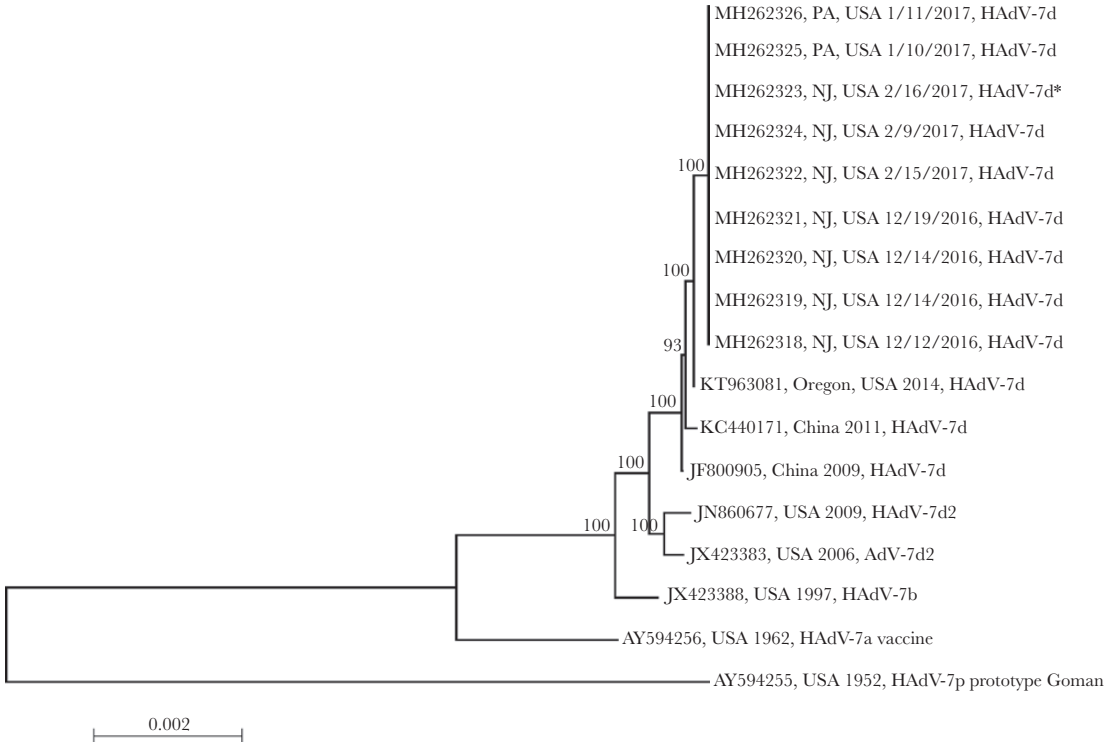

Figure 3. Phylogenetic analysis of human adenovirus genome type 7d (HAdV-7d) whole genome sequences from New Jersey (NJ) and Pennsylvania (PA), 2016–2017. The 9 sequences labeled with NJ and PA were obtained from the 9 isolates described in this manuscript. Genomic sequences were aligned using ClustalW implemented in BioEdit (version 7.2.5), and the neighbor joining phylogenetic tree was constructed using MEGA7 software. Numbers at selected nodes indicate level of support using 1000 bootstrap replicates. The scale bar indicates the estimated number of nucleotide substitutions per site. Sequence names are derived from the GenBank accession number, geographic location, and year of sample collection and virus genome type identified. The sequence obtained from the case, which had a deletion variant coinfection containing a 12-nucleotide, in-frame deletion located in early region 4 open reading frame 2, is marked with *.

Human adenovirus can affect young healthy adults living in congregate settings, such as college campuses, and was well documented among military recruits at basic military training sites before introduction of live HAdV-7 vaccine [27–29]. Civilian outbreaks in other congregate settings have been less commonly reported in the United States, and they include an HAdV-11 outbreak in a job training center with barrack style dormitories [30], HAdV-7 and HAdV-3 outbreaks in pediatric long-term care facilities [10, 31], and an HAdV-4 outbreak in a long-term care facility for older adults [6]. Community HAdV outbreaks, including an HAdV-14 outbreak in Oregon in 2006–2007 [7] and an HAdV-7 outbreak in Oregon in 2013–2014 [8], have also been reported. Kajon et al [32] recently described detections of HAdV-4 in the northeastern United States, including in a long-term care facility outbreak and in the community. Human adenoviruses are not considered to have specific seasonality, and outbreaks can occur throughout the year. These HAdV cases occurred during the 2016–2017 influenza season (October 2, 2016–May 20, 2017) in the United States [33]; however, within the college, cases were reported both before and during peak influenza activity.

Of particular note in this report are the 4 deaths among HAdV-7 cases. All deaths occurred in patients over 50 years of age with pre-existing comorbidities, including congestive heart failure, hepatic cirrhosis, alcohol use disorder, and diabetes mellitus type 2. Human adenoviruses have been associated with severe illness and high mortality rates in immunocompromised patients [34], and patients with recent transplantation or a chronic underlying diseases have an increased risk of severe disease when infected with HAdV [35]. Human adenovirus genome type 7 has previously been shown to cause severe morbidity and mortality in outbreaks, eg, HAdV-7d has been associated with more severe illness and higher fatality rates compared with other HAdV types in children in Southern China [36]. This outbreak demonstrates that HAdV-7d associated with this outbreak, which is known to have circulated in the United States at least since 2013 [8], is also capable of substantial morbidity and mortality.

Currently, the role of HAdV as a cause of ARI in nonmilitary congregate settings is not well documented beyond individual outbreak reports. However, increasing ILI surveillance and availability of molecular testing methods has allowed for increased detection and identification of HAdVs [32]. Increased detection of HAdV-7, and other types, in civilian congregate settings and the community, as reported both here and elsewhere, provides increased evidence of the impact of HAdV infections in these

settings. Human adenovirus surveillance data currently available in the United States is limited; the CDC summarizes typed HAdV detections reported voluntarily through the NATRS to describe trends in circulating HAdV types, but the number of laboratories providing typed information is limited [18]. Increased reporting, diagnostic, and surveillance efforts could help further understand the circulation and burden of HAdVs.

Due to the documented burden in military recruits, a live oral HAdV-4 and HAdV-7 vaccine is currently available for military use [15]. In recent studies, researchers have questioned whether this vaccine may benefit other populations beyond military recruits, eg, in congregate settings such as college settings, summer camps, and long-term care facilities [32]. We describe an example of HAdV-7 circulation with substantial morbidity and mortality in these settings, and we recognize the need for additional studies to better understand the risk associated with HAdV in nonmilitary congregate settings.

Molecular analysis showed that genome sequences obtained from New Jersey and Pennsylvania HAdV-7d isolates were nearly identical and were nearly identical to the strains circulating in Oregon from 2013 to 2014 [8] and in China in 2009 and 2011 [26]. It is interesting to note that a 12nt in-frame deletion variant located in ORF2 of E4 was identified in a case that was coinfected with a wild-type strain. This case was identified at the college and presented with similar symptoms to other college case-patients. The E4-ORF2 protein produced early in infection is a soluble cytoplasmic component and not complexed with other viral or cellular proteins [37]. Predicted restriction enzyme profiles showed that this virus was related to genome type HAdV-7d, which was not identified in the United States before the 2013 Oregon outbreak [8]. The HAdV-7d was first reported from China in 1980 [24] and became the major genome type circulating in China through 1990, but then it disappeared until re-emerging 21 years later [26].

There are limitations to this report. Surveillance for HAdV is passive, and testing and typing availability is limited. In the college and substance use rehabilitation facility, not all ARI specimens were available for testing, limiting our understanding of the true extent of the outbreak. The passive nature of our surveillance may result in bias towards more severe cases who presented for clinical care and subsequent testing.

CONCLUSIONS

We describe 2 clusters of HAdV-7d-related illnesses and severe sporadic cases in community patients, including substantial morbidity and mortality in patients with underlying conditions, in a 3-county region of New Jersey during December 1, 2016–March 31, 2017. Clinicians and public health authorities should consider HAdV in patients or clusters of patients with severe respiratory infection, including during the influenza season. Further studies evaluating the risk of HAdV in nonmilitary congregate settings would provide further information on HAdV burden.

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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