Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Emergence and re-emergence of respiratory adenoviruses in the United States

Adriana E Kajon[1], Daryl M Lamson[2] and Kirsten St. George[2]

Human adenoviruses (HAdVs) are prevalent causes of acute respiratory disease (ARD) in military and civilian communities. Over the last 20 years, collaborative efforts between US public health, military and academic laboratories have gathered comprehensive data documenting the emergence and re-emergence of specific HAdV types in association with outbreaks and unrelated cases of ARD, which have attracted national attention. New or reemerging HAdVs have included genomic variants of HAdV-B14, HAdV-B7, and HAdV-E4. Detailed molecular characterizations of virus strains are essential to understand the etiology and epidemiology of HAdV infections. The continuation of such studies is important for ongoing assessment of the national and global evolution of respiratory HAdVs and to inform decisions regarding antiviral drug and vaccine development and implementation.

Addresses
[1] Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108, USA
[2] Wadsworth Center, New York State Department of Health, 120 New Scotland Avenue, Albany, NY 12208, USA

Corresponding author:
St. George, Kirsten (Kirsten.St.George@health.ny.gov)

Current Opinion in Virology 2019, **34**:63–69

This review comes from a themed issue on **Emerging viruses: inter-species transmission**

Edited by **Adolfo García-Sastre** and **Juergen A Richt**

For a complete overview see the Issue and the Editorial

Available online 14th January 2019

https://doi.org/10.1016/j.coviro.2018.12.004

Introduction

Improvements in the detection of respiratory viruses have been greatly enhanced in the last several years by more widespread use of molecular testing methods, including those with rapid, simple devices that can be readily deployed to resource-limited settings. Among the viruses more frequently detected as a result of the implementation of these methods, are human adenoviruses (HAdV), including some which have been responsible for severe respiratory disease in both sporadic cases and outbreaks. Genomic typing of isolates with more sophisticated molecular methods has been essential for etiological and epidemiological investigations, to gain an understanding of the specific HAdV types and variants involved in severe disease, as well as of the dynamics of their emergence and reemergence.

Current status of classification and designation of human adenoviruses

HAdV are non-enveloped, double-stranded DNA viruses in the family *Adenoviridae* and genus Mastadenovirus. HAdVs are currently classified into seven species designated *Human mastadenovirus* A through G (HAdV-A - HAdV-G) that exhibit distinct pathogenic characteristics [1].

Over 85 HAdV genotypes have been described and recognized to date-based on their unique genetic make-up, determined by bioinformatics analysis of whole genome sequences [2]. Fifty one of these types were originally described as serotypes-based on their unique neutralization phenotypes using horse or rabbit reference sera [1].

HAdV genotypes are designated with a number issued in chronological order of description of the virus (HAdV-1, HAdV-2, HAdV-3, etc.). Although the practice is not standardized, some authors have implemented the use of the letters A–G preceding the number, for ease of identification of the species as well as the type in the abbreviated format (e.g. HAdV-B3, HAdV-E4, etc.).

The Human Adenovirus Working Group (HADVWG, http://hadvwg.gmu.edu/) was assembled in 2011 to coordinate and standardize the process of designation of candidate novel HAdV genotypes. The group reviews whole genome sequence (WGS) data before submission to GenBank to reduce type designation conflicts and redundancies.

Genetic variability and evolution of adenoviruses

Since the early 1980s, the comparative electrophoretic analysis of endonuclease digests of viral genomic DNA, aka restriction fragment length polymorphism (RFLP) analysis, has been a powerful tool for the identification of intratypic genetic variability among HAdV types, and for the estimation of genetic relatedness of virus strains [3,4]. The use of this method since the 1980s has revealed extensive genetic variability in HAdV types associated with acute respiratory disease (ARD) and the occurrence of multiple genomic variants [5–8], forming the foundation for molecular epidemiology studies of HAdV

infection. Traditionally, genomic variants have been designated with letters and numbers denoting their distinct digestion profiles with a given enzyme compared to those of the prototype strain (designate with the letter 'p'), and to one another (p1, p2, a1, a2, etc).

Homologous recombination is widely acknowledged as a major mechanism driving the evolution of HAdV genomes [9] and the emergence of new genotypes. Many of the new genotypes described in the last decade exhibit heterotypic penton base, hexon, and fiber genes [10] and intermediate seroneutralization phenotypes.

Molecular epidemiology of adenovirus infections

Molecular epidemiology studies of viral infection require virus typing. The most widely used approach for typing HAdVs in the molecular era has been the PCR amplification and amplicon characterization for the identification of the virus at the type level. For this purpose, the hexon gene has been the most frequently targeted region of the genome, with a focus on the type-specific hypervariable regions 1–6 or 7 [11–13]. Quantitative real-time PCR assays have been recently developed for the detection and type-specific identification of the epidemic HAdV types 3, 4, 7, 14, and 21 [14], and for the detection and type-specific identification of the endemic species HAdV-C types 1, 2, 5, and 6 [15]. These assays can be used directly on clinical specimens without the need for viral isolation.

The accurate identification of any of the newly described HAdV genotypes requires WGS, as most of these viruses are intertypic recombinants with heterotypic penton base, hexon, and fiber genes.

RFLP analysis of whole genome HAdV DNA with panels of endonucleases, either by gel electrophoresis or *in silico*, remains one of the most powerful approaches for the description of HAdV intratypic genetic variability for epidemiology studies. The early work of Li *et al.* showed a marked trend for geographic segregation of HAdV genomic variants [7,16], demonstrated the circulation of certain genomic variants for extended periods of time, and the occurrence of shifts from one predominant variant to another over time [17,18].

Phylogenetic and phylogeographic analyses of HAdV WGSs have been increasingly used in the last decade for inferring evolutionary relationships between strains and assessment of transmission networks [19,20].

Adenoviruses as causative agents of community-acquired acute respiratory disease

Since their discovery in the 1950s [21,22], HAdVs have been widely recognized as prevalent causative agents of acute respiratory disease (ARD) in both civilian and military populations. Compiled data acquired worldwide have shown that HAdV infections can occur endemically throughout the year with no obvious seasonality, or in epidemics. Outbreaks of ARD appear to predominate in the winter and spring [23]. The majority of HAdV respiratory infections occur in the first five years of life. Epidemiological data suggest that 5–15% of acute upper respiratory tract infections and around 5% of lower respiratory tract infections in childhood are caused by HAdVs [24,25].

Studies conducted worldwide since the 1950s document that the HAdV types most frequently associated with respiratory disease in immunocompetent individuals are those classified within species HAdV-B (mainly types 3, and 7, and occasionally types 14, 21, and 55), species HAdV-C (types 1, 2, 5, and 6) and species HAdV-E (type 4). Types 3, 7, and particularly type 4 are also frequent causative agents of epidemic conjunctivitis and pharyngoconjunctival fever [26]. Severe disease resulting in mortality or pulmonary sequelae has been documented predominantly in association with infection by species HAdV-B types [27–29] with types 3 and 7 being reported as the most commonly detected among pediatric cases of ARD requiring hospitalization worldwide [30–32].

Epidemiology of HAdV respiratory infections in the United States

A number of observational studies were conducted in urban communities in the United States in the 1960s to investigate natural patterns of occurrence and consequences of infection by respiratory viruses [33–35]. In these studies, HAdV infections were revealed by virus isolation in cell culture and serology, and virus typing was carried out by seroneutralization. These unique studies contributed comprehensive descriptions of the behavior of HAdV in the community, and foundational information on the pathogenicity of HAdV infections in relation to type. No studies of similar magnitude or scope have been conducted in the US since.

HAdV infections have been more easily detectable and thus more frequently reported in the last several years than in previous decades, due to the increased sensitivity of PCR-based rapid viral diagnostic platforms. Jain *et al.* [36] recently reported the detection of HAdV in 11% of the examined cases of community-acquired pediatric pneumonia requiring hospitalization in the US between January 2010 and June 2012. HAdV was the 4th most frequently detected virus in the cohort after respiratory syncytial virus, human rhinovirus, and human metapneumovirus. A second study conducted by the same group in the same time period documented HAdV infection in cases of adult pneumonia with an estimated incidence of 0.4 (0.2–0.5) cases per 10 000 adults per year [37]. Virus typing was not performed in either study.

Three main population-based surveillance resources are currently active in the US to monitor respiratory virus activity:

a) The Center for Disease Control and Prevention (CDC)'s National Respiratory and Enteric Virus Surveillance System (NREVSS; https://www.cdc.gov/surveillance/nrevss) is a laboratory-based system implemented in the 1980s that monitors temporal and geographic circulation patterns of respiratory and enteric viruses including HAdVs. Participating U.S. laboratories voluntarily report weekly to the CDC the total number of tests performed that were positive for these viruses. They also report specimen type, patient location, and week of collection. However, no HAdV typing data are acquired through NREVSS' efforts.
b) Supported by the US Department of Defense (DoD), Global Emerging Infections Surveillance and Response System (GEIS), is a network established in 1997 as part of the Armed Forces Health Surveillance Branch (AFHSB) to conduct laboratory-based respiratory illness surveillance among military populations including military-dependents https://www.health.mil/Military-Health-Topics/Health-Readiness/Armed-Forces-Health-Surveillance-Branch/Global-Emerging-Infections-Surveillance-and-Response.
c) The National Adenovirus Type Reporting System (NATRS; https://www.cdc.gov/adenovirus/reporting-surveillance/natrs) was launched by the CDC in 2014 to specifically target HAdV infections. NATRS collects information on circulating HAdVs, to identify predominant types, and assess temporal trends of circulation. It is a passive surveillance system that relies entirely on voluntary reporting of virus typing data.

Over the last 20 years, collaborative efforts between US public health laboratories, military laboratories and academic scientists have been instrumental in gathering comprehensive data sets on HAdV activity in association with outbreaks and epidemiologically unrelated cases of ARD, attracting national attention due to their impact or severity. These efforts allowed the identification of several-specific HAdV types as emerging or re-emerging pathogens in the United States which are detailed below.

Re-emergence and spread of human adenovirus type 14

Human adenovirus 14 (HAdV-B14) was first identified in 1955 in the Netherlands during an outbreak of ARD at a military recruit training facility. It was subsequently detected in association with similar outbreaks among young civilian adults in Great Britain in 1955, in Uzbekistan in 1962, and Czechoslovakia in 1963, and in an outbreak involving army recruits in Taiwan in 1960. Although historically military but also civilian surveillance efforts have used assays capable of detecting HAdV-B14, the circulation of this type was only sporadically reported during the following four decades until 2006 when cases of infection were detected at three of 8 US military recruit training facilities under continuous surveillance by DoD-GEIS. The emerging virus was characterized as a novel genomic variant, designated 14p1, distinguishable from the prototype strain de Wit by RFLP analysis and exhibiting a distinct 6-nucleotide deletion in the fiber gene, resulting in a two amino acid deletion in the knob region of the fiber protein [38].

The earliest cases of HAdV14p1 infection detected in the US were two pediatric cases of severe ARD: a 2003 case detected in California {Louie, 2008 #1559} and a 2005 case, originally diagnosed in Alaska, and transferred to San Antonio, TX, for treatment [38]. Since then, individual cases and large outbreaks of HAdV14-associated respiratory disease of variable severity affecting diverse military and civilian communities have been reported in the US [38], Canada [39], Ireland [40], Scotland, and China [41] involving children and adults.

The most recently documented activity of the virus in the US includes a cluster of cases among college students in NY State in 2015 [20] and outbreaks of infection among military recruits in basic training in 2017 (https://www.med.navy.mil/sites/nhrc/research/oid/Pages/Surveillance-Reports.aspx).

A thorough investigation of the re-emergence and dispersion of HAdV-B14 as a causative agent of ARD, will require the examination of numerous isolates with good representation of the diverse geographic locations where the virus has been detected, as well as strains isolated before 2003 to provide additional insight on the origin of 14p1.

Human adenovirus type 4 respiratory infections among civilian adults

In the absence of an active sentinel surveillance system specifically targeting HAdV infections, the assessment of the actual burden of disease attributable to human adenovirus type 4 (HAdV-E4) infection among civilians will remain difficult. The limited data published in the peer-reviewed literature from studies conducting HAdV typing, suggest that the frequency of detection of HAdV-E4 among pediatric cases of ARD is significantly lower than that of species HAdV-C or HAdV-B types and that HAdV-4 infection occurs relatively rarely among civilian [42].

We recently examined 36 cases of HAdV-E4-associated ARD documented in the northeastern US between 2011 and 2015 and conducted a detailed molecular characterization of the isolated strains [43]. Respiratory

specimens were obtained from college students, residents of long-term care facilities or nursing homes, a cancer patient, and young adults without co-morbidities. All but one of the isolated strains were identified as 'a-like' genomic variants. One prototype-like variant, distinguishable from the vaccine strain, was isolated from an 18-year-old woman visiting a physician's office in Ulster County, New York.

Data from this study suggest that HAdV-E4 may be an underestimated causative agent of ARD among civilian adults and underscores the need for inclusion of HAdV in differential diagnostic test panels to better assess the role of HAdVs as causative agents of severe respiratory illness.

HAdV-E4-associated ARD in the military environment has been successfully controlled by vaccination with a tablet oral formulation of a live non-attenuated prototype-like strain isolated in 1963 [44]. The vaccine is currently licensed for exclusive use in military personnel and has been associated with significant reductions in respiratory illness among military recruits, with notable increases in disease rates during periods when vaccination was discontinued [44]. Together with studies, showing associations between the HAdV types in the vaccine and ARD in the civilian population, suggests that a case could be made for more widespread availability of the vaccine in the general population, especially for people at increased risk for severe disease.

Re-emergence and spread of human adenovirus type 7

In a context of marked worldwide dominance of human adenovirus type 3 (HAdV-B3) as the most prevalent HAdV-B type, human adenovirus type 7 (HAdV-B7) has been detected sporadically among cases of acute respiratory infection in the United States over the past 20 years. Genomic variants 7b, 7d2, and 7h have been identified among the relatively few isolated strains [45].

With no previous record of circulation in North America, the Asian genomic variant HAdV-B7d was detected for the first time in 2014, in a cluster of pediatric and adult ARD cases of variable severity in Oregon [46], and in two related adult cases in Illinois [47]. The association of this particular variant with severe and fatal ARD cases and outbreaks in different countries in Southeast Asia since 2009 is well-documented [48–50].

As with HAdV-E4 and HAdV-B14, the newly emerging genomic variant of HAdV-B7 has been detected in influenza virus-negative cases of influenza-like illness among students in college communities. We have recently generated whole genome sequences for several HAdV-B7 respiratory isolates recovered from students presenting with symptoms of acute respiratory illness in two colleges in NY State, to investigate epidemiological connections between outbreaks of HAdV-associated ARD. All isolates were identified as genomic variant 7d by RFLP and were indistinguishable from one another or from the Chinese strains isolated since 2009 using this molecular typing approach. Our phylogenetic analysis of WGSs however, distinguished two major clades of co-circulating HAdV-B7 strains. The first clade included eight strains genetically related to a strain isolated in Oregon in 2014 that had been characterized by the CDC [46]. These eight strains were isolated from students at two colleges in different counties. Interestingly, WGS distinguished the isolates from cases at the two different colleges. The second clade included four strains isolated from students at one of these two colleges that were most closely related to a 2011 Chinese strain, DG01, and to a strain isolated in 2015 in New York State (Figure 1b).

Both clades are closer genetically to a 2009 strain, isolated from a pediatric case of pneumonia in Shaanxi Province, Northwestern China (JF800905), than to the strains (KJ019887 and KJ019888) isolated from outbreak cases of ARD in 2012 and 2013 in Hubei Province in Central China. Our genetic analysis provides strong evidence of at least 2 different sources/events of introduction of the 7d genomic variant into New York State.

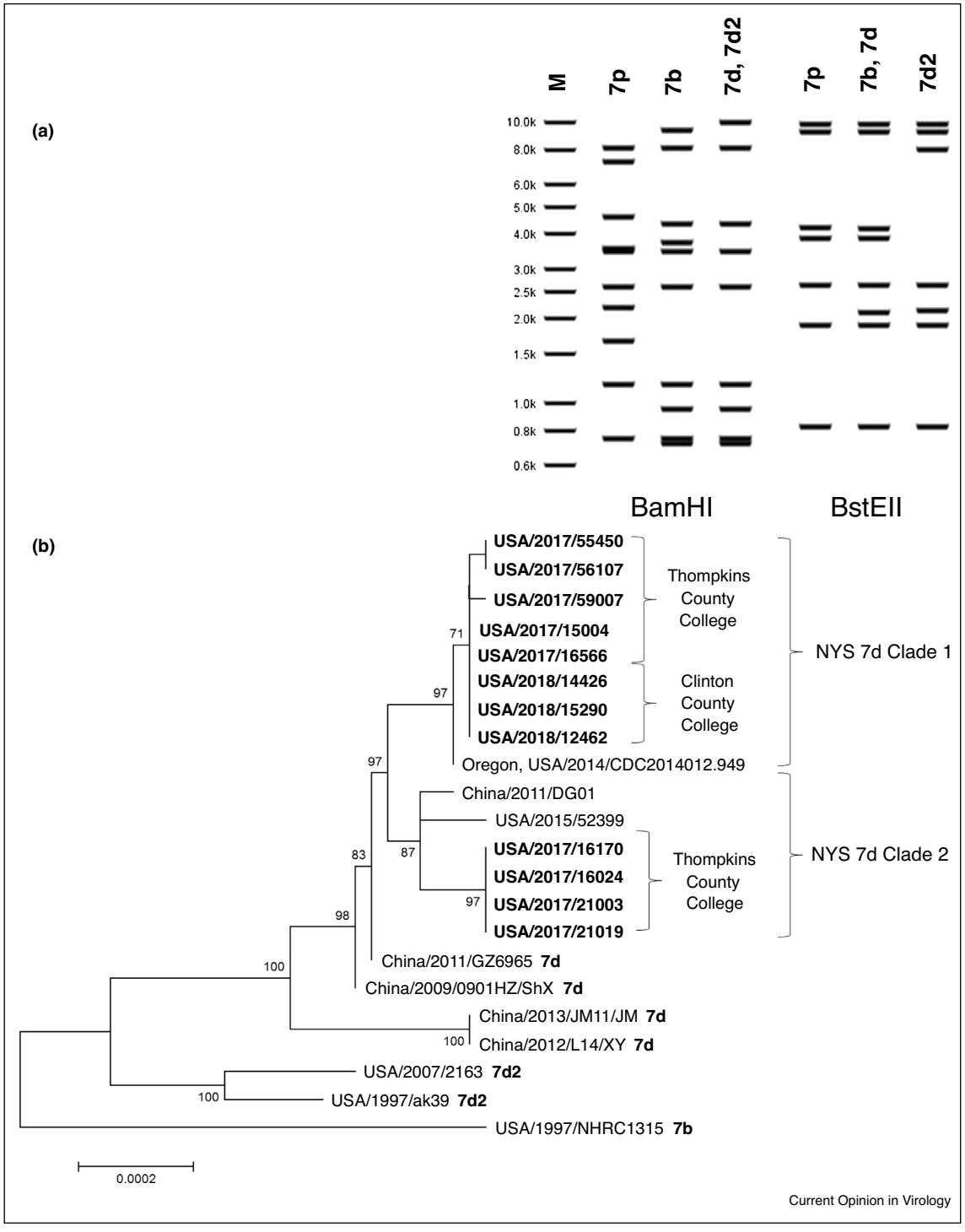
As for HAdV-E4, HAdV-B7-associated respiratory disease has been shown to be preventable by oral vaccination with a live non-attenuated tablet formulation that is currently only licensed for military use [44].

Concluding remarks

Human adenoviruses are a well-documented cause of respiratory disease, causing both sporadic cases and outbreaks in multiple patient settings, with symptoms ranging from very mild to severe and fatal. The large number of types, comprehensively distinguishable only by molecular methods, are also continuously emerging and re-emerging.

Typing is currently not performed for most of the diagnosed cases of HAdV respiratory infection and only large outbreaks or cases of unusual severity have historically elicited detailed molecular, etiological, or epidemiological investigations. Molecular typing of HAdV infection is essential for an understanding of the local epidemiology of HAdV infection, the identification of newly emerging or re-emerging HAdV types and genomic variants, and for the thorough investigation of outbreaks. It is also vital for the ongoing assessment of the national and global movement of these viruses, many of which have been repeatedly documented as causative agents of severe disease. Appropriate decisions can then be made regarding future efforts for infection control including antiviral drug and vaccine development and formulation, as well as vaccination programs.

Figure 1



Molecular typing and phylogenetic analysis of whole genome sequences of HAdV-B7 strains isolated during outbreaks of ARD among college students in 2017 in NY State.
(a) RFLP analysis of BamHI and BstEII digests distinguishes genomic variants of HAdV-B7. **(b)** Phylogenetic analysis identifies two distinct clades of HAdV-B7 strains isolated from college students in NY. A phylogenetic tree was constructed from whole genome sequences of human adenovirus 7 reference and unpublished strains. The analysis was performed with MEGA6 using the Maximum Likelihood method, based on the Kimura 2-parameter model as previously described [20]. 500 Bootstrap replicates were performed; scale bar indicates the number of substitutions per site; branch lengths with values <70 are not displayed; NYS = New York State.

Conflict of interest statement

Nothing declared.

References

1. Wold MSM, Ison MG: **Adenoviruses**. In *Fields Virology*, 6th edn. Edited by David M. Knipe. Lippincott Williams and Wilkins; 2013:1732-1767.

2. Hashimoto S, Gonzalez G, Harada S, Oosako H, Hanaoka N, Hinokuma R *et al.*: **Recombinant type human mastadenovirus D85 associated with epidemic keratoconjunctivitis since 2015 in Japan**. *J Med Virol* 2018, **90**:881-889 http://dx.doi.org/10.1002/jmv.25041 PubMed PMID: 29396992.

3. Adrian T, Wigand R, Hierholzer JC: **Immunological and biochemical characterization of human adenoviruses from subgenus B. II. DNA restriction analysis**. *Arch Virol* 1985, **84**:79-89 PubMed PMID: 2985033.

4. Adrian T, Heinrich W: **COMAP: a comigrating analysis program for estimating the relationship of adenoviruses on the genome level**. *Nucleic Acids Res* 1986, **14**:559-565 PubMed PMID: 3003682.

5. Adrian T: **Genome type analysis of adenovirus type 4**. *Intervirology* 1992, **34**:180-183 http://dx.doi.org/10.1159/000150280 PubMed PMID: 1364043.

6. Adrian T, Becker M, Hierholzer JC, Wigand R: **Molecular epidemiology and restriction site mapping of adenovirus 7 genome types**. *Arch Virol* 1989, **106**:73-84 PubMed PMID: 2548461.

7. Li QG, Wadell G: **Analysis of 15 different genome types of adenovirus type 7 isolated on five continents**. *J Virol* 1986, **60**:331-335 PubMed PMID: 3018298.

8. Li QG, Wadell G: **The degree of genetic variability among adenovirus type 4 strains isolated from man and chimpanzee**. *Arch Virol* 1988, **101**:65-77 PubMed PMID: 2843149.

9. Robinson CM, Singh G, Lee JY, Dehghan S, Rajaiya J, Liu EB *et al.*: **Molecular evolution of human adenoviruses**. *Sci Rep* 2018, **3**:1812 PubMed PMID: 23657240.

10. Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D: **Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen**. *J Clin Microbiol* 2010, **48**:991-993 http://dx.doi.org/10.1128/JCM.01694-09 PubMed PMID: 20042633; PubMed Central PMCID: PMC2832463.

11. Lu X, Erdman DD: **Molecular typing of human adenoviruses by PCR and sequencing of a partial region of the hexon gene**. *Arch Virol* 2006, **151**:1587-1602 http://dx.doi.org/10.1007/s00705-005-0722-7 PubMed PMID: 16502282.

12. Sarantis H, Johnson G, Brown M, Petric M, Tellier R: **Comprehensive detection and serotyping of human adenoviruses by PCR and sequencing**. *J Clin Microbiol* 2004, **42**:3963-3969 http://dx.doi.org/10.1128/JCM.42.9.3963-3969.2004 PubMed PMID: 15364976; PubMed Central PMCID: PMC516336.

13. Okada M, Ogawa T, Kubonoya H, Yoshizumi H, Shinozaki K: **Detection and sequence-based typing of human adenoviruses using sensitive universal primer sets for the hexon gene**. *Arch Virol* 2007, **152**:1-9 http://dx.doi.org/10.1007/s00705-006-0842-8 PubMed PMID: 16957827.

14. Lu X, Trujillo-Lopez E, Lott L, Erdman DD: **Quantitative real-time PCR assay panel for detection and type-specific identification of epidemic respiratory human adenoviruses**. *J Clin Microbiol* 2013, **51**:1089-1093 http://dx.doi.org/10.1128/JCM.03297-12 PubMed PMID: 23325827; PubMed Central PMCID: PMC3666809.

15. Lu X, Erdman DD: **Quantitative real-time PCR assays for detection and type-specific identification of the endemic species C human adenoviruses**. *J Virol Methods* 2016, **237**:174-178 http://dx.doi.org/10.1016/j.jviromet.2016.05.020 PubMed PMID: 27363737.

16. Li QG, Wadell G: **Comparison of 17 genome types of adenovirus type 3 identified among strains recovered from six continents**. *J Clin Microbiol* 1988, **26**:1009-1015 PubMed PMID: 2838500.

17. Wadell G, de Jong JC, Wolontis S: **Molecular epidemiology of adenoviruses: alternating appearance of two different genome types of adenovirus 7 during epidemic outbreaks in Europe from 1958 to 1980**. *Infect Immun* 1981, **34**:368-372 PubMed PMID: 6273316.

18. Wadell G, Cooney MK, da Costa Linhares A, de Silva L, Kennett ML, Kono R *et al.*: **Molecular epidemiology of adenoviruses: global distribution of adenovirus 7 genome types**. *J Clin Microbiol* 1985, **21**:403-408 PubMed PMID: 3980690.

19. Kajon AE, Hang J, Hawksworth A, Metzgar D, Hage E, Hansen CJ *et al.*: **Molecular epidemiology of adenovirus type 21 respiratory strains isolated from US military trainees (1996–2014)**. *J Infect Dis* 2015, **212**:871-880 http://dx.doi.org/10.1093/infdis/jiv141 PubMed PMID: 25748322.

20. Lamson DM, Kajon A, Shudt M, Girouard G, St George K: **Detection and genetic characterization of adenovirus type 14 strain in students with influenza-like illness, New York, USA, 2014–2015**. *Emerg Infect Dis* 2017, **23**:1194-1197 http://dx.doi.org/10.3201/eid2307.161730 PubMed PMID: 28628451; PubMed Central PMCID: PMC5512483.

21. Rowe WP, Huebner RJ, Gilmore LK, Parrott RH, Ward TG: **Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture**. *Proc Soc Exp Biol Med Soc Exp Biol Med (New York, NY)* 1953, **84**:570-573 PubMed PMID: 13134217.

22. Hilleman MR, Werner JH: **Recovery of new agent from patients with acute respiratory illness**. *Proc Soc Exp Biol Med Soc Exp Biol Med (New York, NY)* 1954, **85**:183-188 PubMed PMID: 13134329.

23. Lion T: **Adenovirus infections in immunocompetent and immunocompromised patients**. *Clin Microbiol Rev* 2014, **27**:441-462 http://dx.doi.org/10.1128/CMR.00116-13 PubMed PMID: 24982316; PubMed Central PMCID: PMC4135893.

24. Singh-Naz N, Rodriguez W: **Adenoviral infections in children**. *Adv Pediatr Infect Dis* 1996, **11**:365-388 PubMed PMID: 8718467.

25. Taylor S, Lopez P, Weckx L, Borja-Tabora C, Ulloa-Gutierrez R, Lazcano-Ponce E *et al.*: **Respiratory viruses and influenza-like illness: epidemiology and outcomes in children aged 6 months to 10 years in a multi-country population sample**. *J Infect* 2017, **74**:29-41 http://dx.doi.org/10.1016/j.jinf.2016.09.003 PubMed PMID: 27667752.

26. Li J, Lu X, Sun Y, Lin C, Li F, Yang Y *et al.*: **A swimming pool-associated outbreak of pharyngoconjunctival fever caused by human adenovirus type 4 in Beijing, China**. *Int J Infect Dis* 2018, **75**:89-91 http://dx.doi.org/10.1016/j.ijid.2018.08.009 PubMed PMID: 30144556.

27. James AG, Lang WR, Liang AY, Mackay RJ, Morris MC, Newman JN *et al.*: **Adenovirus type 21 bronchopneumonia in infants and young children**. *J Pediatr* 1979, **95**:530-533 PubMed PMID: 225460.

28. Simila S, Linna O, Lanning P, Heikkinen E, Ala-Houhala M: **Chronic lung damage caused by adenovirus type 7: a ten-year follow-up study**. *Chest* 1981, **80**:127-131 PubMed PMID: 6265156.

29. Sun B, He H, Wang Z, Qu J, Li X, Ban C *et al.*: **Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study**. *Crit Care* 2014, **18**:456 http://dx.doi.org/10.1186/s13054-014-0456-6 PubMed PMID: 25112957; PubMed Central PMCID: PMC4243941.

30. Levy Y, Nitzan M, Beharab A, Zeharia A, Schoenfeld T, Nutman J *et al.*: **Adenovirus type 3 infection with systemic manifestation in apparently normal children**. *Israel J Med Sci* 1986, **22**:774-778 PubMed PMID: 3025130.

31. Kajon AE, Murtagh P, Garcia Franco S, Freire MC, Weissenbacher MC, Zorzopulos J: **A new genome type of**

adenovirus 3 associated with severe lower acute respiratory infection in children. *J Med Virol* 1990, **30**:73-76 PubMed PMID: 2154546.

32. Yu Z, Zeng Z, Zhang J, Pan Y, Chen M, Guo Y *et al.*: **Fatal community-acquired pneumonia in children caused by re-emergent human adenovirus 7d associated with higher severity of illness and fatality rate**. *Sci Rep* 2016, **6**:37216 http://dx.doi.org/10.1038/srep37216 PubMed PMID: 27848998; PubMed Central PMCID: PMC5110970.

33. Elveback LR, Fox JP, Ketler A, Brandt CD, Wassermann FE, Hall CE: **The Virus Watch program: a continuing surveillance of viral infections in metropolitan New York families. 3. Preliminary report on association of infections with disease**. *Am J Epidemiol* 1966, **83**:436-454 PubMed PMID: 4286697.

34. Fox JP, Brandt CD, Wassermann FE, Hall CE, Spigland I, Kogon A *et al.*: **The virus watch program: a continuing surveillance of viral infections in metropolitan New York families. VI. Observations of adenovirus infections: virus excretion patterns, antibody response, efficiency of surveillance, patterns of infections, and relation to illness**. *Am J Epidemiol* 1969, **89**:25-50 PubMed PMID: 4303049.

35. Brandt CD, Kim HW, Jeffries BC, Pyles G, Christmas EE, Reid JL *et al.*: **Infections in 18 000 infants and children in a controlled study of respiratory tract disease. II. Variation in adenovirus infections by year and season**. *Am J Epidemiol* 1972, **95**:218-227 PubMed PMID: 4334623.

36. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C *et al.*: **Community-acquired pneumonia requiring hospitalization among U.S. children**. *N Engl J Med* 2015, **372**:835-845 http://dx.doi.org/10.1056/NEJMoa1405870 PubMed PMID: 25714161; PubMed Central PMCID: PMC4697461.

37. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM *et al.*: **Community-acquired pneumonia requiring hospitalization among U.S. adults**. *N Engl J Med* 2015, **373**:415-427 http://dx.doi.org/10.1056/NEJMoa1500245 PubMed PMID: 26172429; PubMed Central PMCID: PMC4728150.

38. Kajon AE, Lu X, Erdman DD, Louie J, Schnurr D, George KS *et al.*: **Molecular epidemiology and brief history of emerging adenovirus 14-associated respiratory disease in the United States**. *J Infect Dis* 2010, **202**:93-103 http://dx.doi.org/10.1086/653083 PubMed PMID: 20500088.

39. Girouard G, Garceau R, Thibault L, Oussedik Y, Bastien N, Li Y: **Adenovirus serotype 14 infection, New Brunswick, Canada, 2011**. *Emerg Infect Dis* 2013, **19**:119-122 http://dx.doi.org/10.3201/eid1901.120423 PubMed PMID: 23260201; PubMed Central PMCID: PMC3557982.

40. Carr MJ, Kajon AE, Lu X, Dunford L, O'Reilly P, Holder P *et al.*: **Deaths associated with human adenovirus-14p1 infections, Europe, 2009–2010**. *Emerg Infect Dis* 2011, **17**:1402-1408 http://dx.doi.org/10.3201/eid1708.101760 PubMed PMID: 21801616; PubMed Central PMCID: PMC3381588.

41. Huang G, Yu D, Zhu Z, Zhao H, Wang P, Gray GC *et al.*: **Outbreak of febrile respiratory illness associated with human adenovirus type 14p1 in Gansu Province, China**. *Influenza Other Respir Viruses* 2013, **7**:1048-1054 http://dx.doi.org/10.1111/irv.12118 PubMed PMID: 23692915; PubMed Central PMCID: PMC3933759.

42. Lynch JP 3rd, Kajon AE: **Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention**. *Semin Respir Crit Care Med* 2016, **37**:586-602 http://dx.doi.org/10.1055/s-0036-1584923 PubMed PMID: 27486739.

43. Kajon AE, Lamson DM, Bair CR, Lu X, Landry ML, Menegus M *et al.*: **Adenovirus type 4 respiratory infections among civilian adults, Northeastern United States, 2011–2015(1)**. *Emerg Infect Dis* 2018, **24**:201-209 http://dx.doi.org/10.3201/eid2402.171407 PubMed PMID: 29350143; PubMed Central PMCID: PMC5782899.

44. Radin JM, Hawksworth AW, Blair PJ, Faix DJ, Raman R, Russell KL *et al.*: **Dramatic decline of respiratory illness among US military recruits after the renewed use of adenovirus vaccines**. *Clin Infect Dis* 2014, **59**:962-968 http://dx.doi.org/10.1093/cid/ciu507 PubMed PMID: 24991024.

45. Erdman DD, Xu W, Gerber SI, Gray GC, Schnurr D, Kajon AE *et al.*: **Molecular epidemiology of adenovirus type 7 in the United States, 1966–2000**. *Emerg Infect Dis* 2002, **8**:269-277 http://dx.doi.org/10.3201/eid0803.010190 PubMed PMID: 11927024; PubMed Central PMCID: PMC2732469.

46. Scott MK, Chommanard C, Lu X, Appelgate D, Grenz L, Schneider E *et al.*: **Human Adenovirus associated with severe respiratory infection, Oregon, USA, 2013–2014**. *Emerg Infect Dis* 2016, **22**:1044-1051 http://dx.doi.org/10.3201/eid2206.151898 PubMed PMID: 27191834; PubMed Central PMCID: PMC4880082.

47. Kajon AE, Ison MG: **Severe infections with human adenovirus 7d in 2 adults in family, Illinois, USA, 2014**. *Emerg Infect Dis* 2016, **22**:730-733 http://dx.doi.org/10.3201/eid2204.151403 PubMed PMID: 26982199; PubMed Central PMCID: PMC4806933.

48. Tsou TP, Tan BF, Chang HY, Chen WC, YP, Lai CY *et al.*: **Community outbreak of adenovirus, Taiwan, 2011**. *Emerg Infect Dis* 2012, **18**:1825-1832 http://dx.doi.org/10.3201/eid1811.120629 PubMed PMID: 23092602; PubMed Central PMCID: PMC3559173.

49. Zhao S, Wan C, Ke C, Seto J, Dehghan S, Zou L *et al.*: **Re-emergent human adenovirus genome type 7d caused an acute respiratory disease outbreak in Southern China after a twenty-one year absence**. *Sci Rep* 2014, **4**:7365 http://dx.doi.org/10.1038/srep07365 PubMed PMID: 25482188; PubMed Central PMCID: PMC4258649.

50. Ng OT, Thoon KC, Chua HY, Tan NW, Chong CY, Tee NW *et al.*: **Severe pediatric adenovirus 7 disease in Singapore linked to recent outbreaks across Asia**. *Emerg Infect Dis* 2015, **21**:1192-1196 http://dx.doi.org/10.3201/eid2107.141443 PubMed PMID: 26079293; PubMed Central PMCID: PMC4480382.