

GLOBAL WATER PATHOGEN PROJECT

**PART THREE. SPECIFIC EXCRETED PATHOGENS: ENVIRONMENTAL AND
EPIDEMIOLOGY ASPECTS**

ADENOVIRUSES

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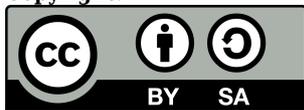
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Summary

Adenoviruses are associated with numerous disease outbreaks, particularly those involving daycares, schools, children's camps, hospitals, military settings, and other health care centres. Today, fifty-two different serotypes of adenovirus have been identified. However, several types have also recently been identified with molecular techniques and designated as genotypes. All serotypes and genotypes have been divided into seven species (A to G) that infect humans. Of all the known adenovirus types, one third are associated with human disease as gastroenteritis, respiratory infections, eye infections, acute hemorrhagic cystitis, and meningoencephalitis, while two thirds of infections are asymptomatic.

Children and immunocompromised individuals are more severely impacted by adenovirus infections. Adenoviruses have a worldwide distribution, where infections occur throughout the year causing 5 to 10% of all febrile illnesses in infants and young children. Most individuals have serologic evidence of a prior adenoviral infection by the age of 10. Although many adenovirus types are found in stool from patients with diarrhea, only enteric adenoviruses (type 40, 41 and 52) have been shown to be the causative agents of gastrointestinal disease. Enteric adenoviruses replicate in the gut to 10^{11} virions per gram of stool, but many other non-enteric viral particles (i.e. types 1,2,5,3 and 7) may persist for months and even up to years in stool after an infection. These phenomena may explain why adenoviruses are ubiquitous in the environment where contamination of human faeces or sewage occur in such areas of increased population densities.

Adenoviruses have been detected in various waters worldwide including wastewater, river water, drinking water, ocean, and swimming pools. Adenoviruses typically outnumber the enteroviruses, when both are detected in surface waters. Evidence has shown that adenoviruses survive longer in water than enteroviruses and the hepatitis A virus; this may be due to their double-stranded DNA. A majority of the results are based on PCR technology and indicate only the presence of nucleic acids and do not include infectivity data.

Adenoviruses are frequently detected in high concentrations in wastewater and wastewater-contaminated waters, so their use as potential indicators for the presence of human faeces has been suggested as a complement to bacterial indicators. It is well documented that bacteria behave differently to viruses in aquatic environments, particularly with regard to their survival times. In this respect, adenoviruses are good candidates for indicators of virus contamination with long term survival properties, high resistance to ultraviolet light, and a DNA genome which simplifies and decreases the cost of molecular detection procedures compared to the costly RNA processing.

In recent years, there have been several studies analyzing ground water samples showing the presence of

adenoviruses with no correlation between the presence of viruses and bacterial indicators (i.e. *Escherichia coli*). These results may be useful for risk assessment studies since ground water is a common source of drinking water and subsequently connected to the interest of public health. Adenoviruses are more often found in ground water than other viral types, and they have been abundant in untreated river water and finished water after conventional water treatment plant processes. The different treatment processes (conventional and alternative) for reducing concentrations of adenoviruses in water, have shown variable efficiency. In addition, environmental conditions have been reported to present variable effect on adenovirus stability.

In summary, the knowledge of adenovirus importance has increased significantly during the last decades, and adenovirus is now playing an important role in both clinical settings and in the environmental context.

Adenovirus

Both respiratory and enteric human adenoviruses (HAdV) are found in water, cause waterborne disease and are present at a higher frequency in sewage than other enteric viruses (Pina et al., 1998). These viruses have been suggested to be preferred candidates as index organisms for viral pathogens because they fit most criteria for an ideal indicator such as resistance to many chemical/physical agents and to UV light (Katayama et al., 2008; Gerba et al., 2002; Girones et al., 2014).

The first adenovirus strains were isolated in 1953 from lymph nodes and got their name from adénos, the Greek word for gland (Rowe et al., 1953). The following year it became clear that the virus caused acute respiratory infection. Thus, two basic properties of adenoviruses were detected; their ability to cause acute respiratory infection and the propensity to persist in lymphoid tissue. Today, fifty-two different serotypes of adenovirus have been identified; however, several types have also in recent years been identified with molecular techniques. All types have been divided into seven species (A to G) that infect humans. This species breakdown is affected by the receptor binding structure. Adenoviruses are a family of viruses that globally infects most children already before the age of five. High fever for a week is often seen but approximately every second adenovirus infection is non-symptomatic. Adenoviruses rarely cause life-threatening infections, except in immunodeficient individuals. It is now known however that environmental occurrence and transmission is important.

1.0 Epidemiology of the Disease and Pathogens

1.1 Global Burden of Disease

Adenoviruses have a worldwide distribution, and infections occur throughout the year (Fox et al., 1977). Adenoviruses cause 5 to 10% of all febrile illnesses in

infants and young children and most individuals in North America have serologic evidence of a prior adenoviral infection by the age of five. (Fox et al., 1977). Both respiratory and enteric adenovirus infections are prevalent in daycare centers and in households with young children but nosocomial transmission has also been documented (Liu et al., 2014; Tran et al., 2010). Adenovirus species F representing human adenovirus type 40 and 41 has been found to be associated with acute gastroenteritis and is responsible for 1 to 20% of the cases of diarrheal disease globally in both outpatients and hospitalized children (Uhnoo et al., 1984; Brandt et al., 1984; Li et al., 2004). Type 40 and 41 primarily affect young children less than 2 years of age and the infection occur throughout the year. The clinical characteristics include watery diarrhea accompanied by vomiting, low-grade fever, and mild dehydration. The burden of adenovirus infections is particularly important in immunocompromised hosts (Lion, 2014), where a variety of clinical syndromes can occur and reactivation of endogenous adenovirus plays a role in diseases in these patients.

1.1.1 Global distribution

Human adenovirus (HAdV) infections are common and ubiquitous with a worldwide distribution. Even if most HAdV species appear to circulate globally, predominant types differ between countries or geographic regions, and they change over time (Lin et al., 2004; Ishiko et al., 2008; Ampuero et al., 2012). Transmission of new strains across continents may occur and lead to replacement of hitherto dominant HAdV types (Kajon et al., 2010). The prevalence of adenovirus respiratory infections in children in North and South America ranges from 2 to 14% and may be higher during outbreaks (Fox et al., 1977; Videla et al., 1998). Many (30-70%) respiratory illnesses in unvaccinated new military recruits in USA are adenovirus associated as well (Russell et al., 2006). About 5 to 15% of acute diarrheal infections in all continents are due to enteric adenoviruses (Dey et al., 2011; Uhnoo et al., 1984; Kim et al., 1990; Barnes et al., 1998; Van et al. 1992; Moore et al., 2000).

Children are especially susceptible but elderly are also again susceptible to the enteric types 40 and 41 due to waning immunity with increasing age. Due to contamination by human faeces or sewage into the environment HAdVs seem to be more common in developing countries with poor sanitary conditions (Dey et al., 2011; Filho et al., 2007; Moyo et al., 2014). However, the incidence of all HAdV infections is higher in crowded closed settings, such as day care centers, boarding schools, geriatric facilities, military training camps, and hospitals. Intrafamilial infections are also common and HAdVs are frequent in immunocompromised patients. Every serotype can cause a unique infection, which means theoretically that it is possible to acquire more than 50 adenovirus infections to get immunity. Types 53-68 are genetically typed and antibody specificity has not yet been investigated or confirmed against these recent types. The adenoviruses most commonly reported to be associated with human disease globally are HAdVC1, -C2, -C5, -B3, -B7, -B21, -E4, and -F41 (Guo et al., 2012;

Yliharsila et al., 2013; Tabain et al., 2012; Barrero et al., 2012).

1.1.2 Symptomatology

HAdV are most frequently associated with upper respiratory tract syndromes, such as pharyngitis or rhinitis but can also cause pneumonia. Less commonly, adenoviruses cause gastrointestinal, ophthalmologic, genitourinary, and neurologic diseases. Most adenoviral diseases are self-limiting, although fatal infections can occur in immuno-compromised hosts and occasionally in healthy children and adults, especially children with gastrointestinal infections in the developing world. The number of diarrheal deaths caused by adenovirus (HAdV-40 and HAdV-41) was estimated in 2011 to be 3-4% of all diarrheal deaths among children under 5 years of age in the world (Lanata et al. 2013). Patients who have undergone organ or hematopoietic cell transplantation together with AIDS patients and children with severe combined immunodeficiency represent a new group of patients showing a spectrum of adenovirus infections from asymptomatic shedding to fatal disseminated disease. Adenovirus infections in solid organ transplant recipients may range from asymptomatic to severe and disseminated, with prolonged viral shedding and significant morbidity and mortality, including associated graft dysfunction and rejection (Taniguchi et al., 2012). Adenovirus more frequently affects paediatric than adult solid organ transplant recipients. Despite the frequency with which they are found in stool or urine specimens, adenoviruses are an uncommon cause of morbidity or mortality in HIV-infected patients.

1.2 Taxonomic Classification of the Agents

1.2.1 Physical description of the agent

Adenoviruses (members of the family Adenoviridae) are medium-sized (90-100nm), nonenveloped viruses with an icosahedral nucleocapsid containing a double stranded DNA genome of approximately 35,000 base pairs (Figure 1). The viral capsid has the form of an icosahedron and is composed of 252 capsomers. Of these, 240 have a six-fold symmetry and are therefore called hexons. Twelve capsomers have a five-fold symmetry, pentons and produce the particle corners. From every corner an antenna like fiber is protruding. This fiber is a glycoprotein that varies in length of adenoviruses belonging to different subgroups. The fiber acts as the most important receptor-binding structure. Many of the other peptides function as cement and couple hexon and penton capsomeres to a dense capsid (Figure 2). Viral histone-like proteins mediate packing of the viral genome (Russell, 2009). In 2010, the atomic resolution structure of the complete virion appeared as a result of two structural biology techniques: X-ray crystallography and cryoEM (San Martin, 2012).

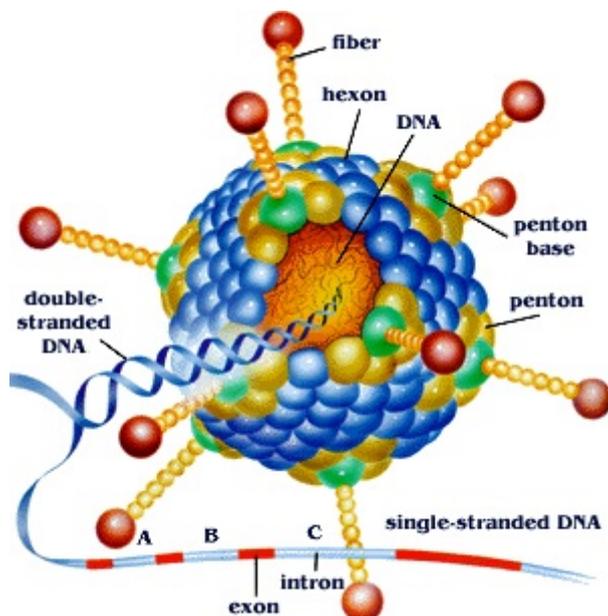


Figure 1. Schematic representation of Adenovirus
 (http://www.openwetware.org/index.php?title=Special:Cite&page=WUSM_Microbes_and_Pathogenesis_Wiki:_Adenovirus_Group_9&id=395020)

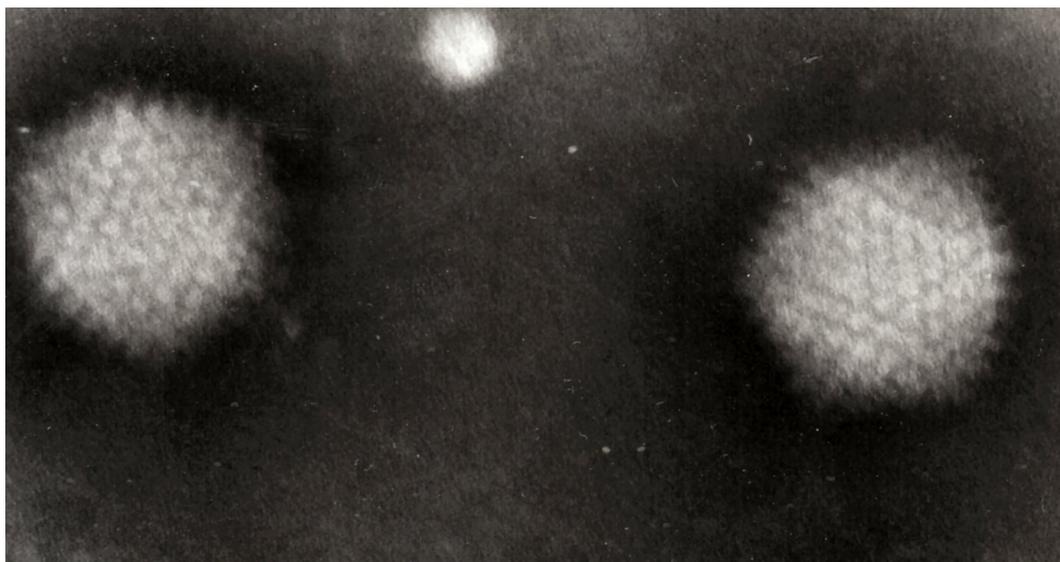


Figure 2. Transmission electron micrograph of two Adenovirus particles visualizing the dense capsid structure (<https://en.wikipedia.org/wiki/Adenoviridae>)

1.2.2 Taxonomy

Human adenoviruses (HAdVs) are classified in the genus Mastadenovirus, which contains seven known HAdV species HAdV-A to HAdV-G. Traditionally, the HAdV species were classified by hemagglutination and serum neutralization reactions into different serotypes (Rosen, 1960; Kjellen and Pereira, 1968). Today, there have been reported 68 HAdV types (Brister et al., 2013). The discovery and division of the HAdV types 52–68 are based on the genomic sequencing and bioinformatic analysis and then differ from the pre-existing 51 HAdV serotypes that

have been identified by traditional serological methods in composition and pathogenicity (Gao et al., 2014). Serotype 52 constitutes a new HAdV species (G) and has been reported after genomic sequencing and phylogenetic analysis of an isolate in the U.S. (Jones et al., 2007). New HAdV types have since been identified by several authors based on genomic data, including several emerging and recombinant viruses (Matsushima et al., 2012). A primate adenovirus from New World monkeys was detected which crossed the species barrier to infect humans (Kohl et al., 2012). The majority of new HAdV types are homologous recombination within the same subgenus, and as a result,

certain new serotypes acquire different pathogenicities. Recombination is a common evolutionary way for HAdV; however, the mechanism of recombination and the potential hazards to human beings remain unknown (Ghebremedhin, 2014).

1.2.3 Tissue Tropism/Cellular receptors/Latency

In the past few years, not just one but multiple adenovirus receptors have been identified, describing different HAdV species affinity for individual tissues. However, members of the largest species, species D, show great variability in their tropisms, with growth in tissues ranging from ocular to gastrointestinal and respiratory tissues (Pauly et al., 2014). The basis of tissue tropism is still not well established. Adenoviral keratoconjunctivitis, which is a major cause of ocular morbidity, is most commonly caused by representatives of species D, including types 8, 19, and 37, but also by human adenoviruses -E4, -C5, -B3, -B7, -B11, and -B14 (Lynch et al., 2011). Gastrointestinal manifestations are mainly associated with HAdV-F40 and -F41, but HAdV-G52 and different members of species D, including some of the most recently identified types (types 65 and 67), have also been observed (Matsushima et al., 2012; 2013). Respiratory tract involvement has been associated mainly with human adenoviruses -B3, -B7, -B16, -B21, and -E4 and various members of species C (Metzgar et al., 2010). These examples indicate that certain adenoviruses have strong tropisms for specific tissues, but the same clinical manifestations can be caused by other human adenovirus types and species, thus requiring diagnostic screening methods with broad specificity. What is known today is that the fiber protein from species A, C and F interacts with a cellular protein that belongs to the superfamily immunoglobulins. This receptor is called CAR, coxsackie adenovirus receptor because it also binds to coxsackievirus. Other types of adenoviruses utilize alternative cellular receptors such as CD46, desmoglein 2, sialic acid, or heparan sulfate (Arnberg et al., 2012).

Currently available evidence indicates that HAdVs can persist in a latent state in a variety of susceptible cells following primary infection. Latency is characterized by expression of viral proteins by the host cell without replication of a complete virus. A latent form of adenovirus infection was shown to persist in tonsillar lymphocytes in nearly 80% of children investigated, and the number of adenoviral genomes per lymphoid cell apparently declines with age (Garnett et al., 2009). Moreover, latent HAdV infections were described to occur in intestinal T lymphocytes and in lung epithelial cells, where they seem to play a role in the pathogenesis of obstructive airway disease (Hogg, 2001).

This related to the reactivation of endogenous adenovirus infections.

1.3 Transmission

1.3.1 Routes of transmission

Infections are typically transmitted by exposure to infected individuals via inhalation of aerosolized droplets or direct conjunctival inoculation, as well as by fecal-oral spread, including contact with recreational marine water, swimming pools freshwater or tap water (Wyn-Jones et al., 2011; Love et al., 2014; Bofill-Mas et al., 2010; van Heerden et al., 2005; Artieda et al., 2009). Fomite transmission can occur through exposure to infected tissue, airflow filters, or environmental surfaces (Russell et al., 2006; Soller et al., 2010). The stability of the virus at low pH is a matter of debate, but human adenoviruses are resistant to gastric and biliary secretions and can therefore be detected at high levels in feces (Matthes-Martin et al., 2013). Human adenoviruses are infrequently found in the urine of immunocompetent individuals but are present in the urine of immunocompromised patients especially in AIDS patients (Echavarria, 2008; De Jong et al., 1983; Horwitz et al., 1984). However, this secretion is probably negligible in the context of disease transmission.

1.3.2 Reservoirs

Human adenoviruses are ubiquitous in the environment where contamination by human faeces or sewage has occurred. Human adenoviruses typically are not pathogenic to animals and animal adenoviruses are only pathogenic to the species of origin. However, asymptomatic infections with human adenovirus type 12 have been documented in simian species, and antibodies to canine, bovine and simian adenoviruses have been found in humans (AWW Association, 2006). Adenoviruses have a broad range of vertebrate hosts and are known to cause respiratory infections in horses, cattle, pigs, sheep, and goats. The fowl adenoviruses are associated with many disease conditions in domestic fowl, but have also been found in wild birds, bats and reptiles (<http://www.ictvonline.org/>).

1.3.3 Incubation and duration periods

Following human adenovirus transmission, the incubation period ranges from 2 days to 2 weeks, depending on the viral type and mechanism of acquisition (Langley, 2005; Bhumbra and Wroblewski, 2010). Respiratory symptoms caused by adenoviruses are most commonly seen amongst children under the age of two and for this selected group the incubation period before the onset of symptoms is generally 4-8 days, median 5.6 days (Lessler et al., 2009). For intestinal infections the incubation period is 3 to 10 days. Fever, coryza, cough, and sore throat, usually lasting 3-5 days, are typical symptoms of adenoviral upper respiratory disease and most adenoviral infections last from a few days to a week (Tabain et al., 2012). However, severe respiratory infections may last longer and cause lingering symptoms, such as a cough. Pneumonia can last anywhere from 2 to 4 weeks and pinkeye can persist for another several days to a week. More severe keratoconjunctivitis can last for several weeks (Pihos, 2013) and enteric adenoviruses can cause diarrhea that lasts up to 2 weeks which is longer than other viral diarrhea episodes (Uhnnoo et al., 1984).

1.3.4 Period of communicability and shedding levels

The contagiousness of adenovirus is facilitated by very high levels of viral particles (100,000-1,000,000/mL) in the sputum or oral secretions of infected adults. Although many adenovirus types are found in stool from patients with diarrhoea, only enteric adenoviruses (type 40/41/52) have been shown to be the causative agents of gastrointestinal disease. A close comparison of stools from diarrheal and control patients has shown that whereas non-enteric HAdV particles are shed in stools from both diarrheal and control patients, enteric HAdV particles are found almost exclusively in diarrheal stools. As shown by several studies, up to 50% of healthy children carry non-enteric HAdV whereas enteric HAdV is rarely present in healthy children (Allard et al., 1992). Enteric adenoviruses replicate in the gut to 1.0×10^{11} virions per gram of stool and enteric HAdV carriage is about 8 times higher than non-enteric HAdV carriage in diarrheal stool samples. Moreover, as secretions of non-enteric adenoviral particles may persist for months, the presence of these adenoviruses in stools along with other viruses is common. HAdV 1, 2, 3 and 5 is reported to be excreted intermittently for up to 906 days (Fox et al., 1977). Quantitative Microbial Risk Assessment (QMRA) studies have been applied to drinking and recreational water (Chigor et al., 2014; Kundu et al., 2013) and a QMRA model associated with inhaling bioaerosols that are contaminated with HAdV at risk-prone workplaces have been presented by Carducci et al. (2016). Risk management and dose response models can be found at QMRAWiki (<http://qmrwiki.canr.msu.edu/>).

1.4 Population and Individual Control Measures

1.4.1 Vaccines and therapy

1.4.1.1 Vaccines

Vaccination and infection control measures have been applied in certain settings to prevent adenovirus infections and live oral enteric-coated vaccines directed against adenovirus serotypes 4 and 7 had been used for years in military recruits in United States since the 1971 (Top et al., 1971). In the 1999, the manufacturer of the vaccines stopped production and subsequently new outbreaks of adenovirus serotypes 4 and 7 disease in training camps occurred, including several fatalities, underscoring the continued need for the vaccines (Potter et al., 2012). In addition adenovirus serotype 14, a subtype B2 adenovirus, emerged in military recruit training sites and became the predominant strain (Binn et al., 2007; Metzgar et al., 2007). However, in 2011, a new live, oral adenovirus vaccine against adenovirus serotypes 4 and 7 was approved for use in United States military personnel aged 17 through 50 years (<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM247515.pdf>. USA TPharmaceut. 2011). During the two years following reintroduction of the vaccine, United States military trainees had a 100-fold decline in adenovirus disease burden. It was also a marked decline in the incidence of disease caused by adenovirus serotypes other than 4 and 7, including adenovirus serotype 14

(Radin et al., 2014). These data suggest that the emergence of adenovirus 14 in military recruits during the non-vaccination period was related to the discontinuation of the adenovirus serotypes 4 and 7 vaccine program, since heterotypic antibodies to adenovirus 14 were developed following adenovirus 7 immunization. Vaccines against adenoviruses have not been used in a large scale outside the United States.

Fecal shedding of adenovirus type 4 and type 7 live vaccine oral strain viruses was evaluated in a safety and immunogenicity study of 58 subjects (30 vaccine recipients and 28 placebo recipients (<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM247515.pdf>. USA TPharmaceut. 2011). Stool or rectal swabs and throat swabs were collected on Day 0, 7, 14, 21, 28 and 56. Vaccine virus strains were shed in the stool as early as day 7 following vaccination. Eight of 30 vaccine recipients (27%) tested positive at least once for adenovirus type 4 fecal shedding; 18 of 30 vaccine recipients (60%) tested positive for adenovirus type 7 fecal shedding. No adenovirus shedding was detectable in any subject by 28 days following vaccination. Vaccine strain virus was not detected in the throat of any subject.

1.4.1.2 Antiviral agents

Antiviral therapy is generally reserved for immunocompromised hosts and patients with severe adenovirus disease. There have been no controlled trials demonstrating benefit for any antiviral agent in human adenoviral disease. The antiviral agent most commonly used for adenoviral infection is cidofovir, which is currently approved for the treatment of cytomegalovirus (CMV) infections. This agent appears more active against adenovirus in vitro than other antiviral drugs such as ganciclovir (Doan et al., 2007). Antiviral drugs as ribavirin or vidarabine have no consistent activity against adenovirus in vitro (Sabroe et al., 1995).

1.4.1.3 Immunotherapy

Treatment with donor lymphocytes stimulated in vitro with adenovirus can reduce the viral load and successful treatment of adenovirus disease in immuno-compromised patients has been reported (Feuchtinger et al., 2006). T-cell recovery with reconstitution of human adenovirus specific immune responses is essential for effective clearance of invasive infections, and the initial treatment step should therefore include reduction of immunosuppressive treatment whenever possible (Matthes-Martin et al., 2012).

1.4.1.4 The use of adenovirus vectors for gene therapy

There has been considerable interest and effort in developing adenovirus vectors for gene therapy. Adenoviruses have several advantages over some other viral vectors such as retroviruses and adeno-associated virus. Adenovirus vectors can infect a variety of cell types, including non-dividing as well as dividing cells, and can be prepared readily in large quantities in tissue culture (Vetrini and Ng, 2010; Chai et al., 2012)

1.4.1.5 Adenovirus-based vaccines against infectious pathogens

Another promising application for adenoviruses is their

use as vaccine vectors (Gaydos and Gaydos, 1995). As already mentioned, live, oral, enteric-coated, adenovirus serotypes 4 and 7 vaccines were safely used for years in military training camps to prevent epidemics of acute adenoviral respiratory disease. These live, oral viral vaccines have an advantage in the ability to generate both mucosal and systemic immunity. Thus, replication-competent as well as replication-defective adenovirus vectors are attractive candidates for immunization against other infectious pathogens (Tatsis and Ertl, 2004).

1.4.2 Hygiene measures

Adenoviruses can stay viable for prolonged periods on environmental surfaces such as sinks hand towels but also at medical instruments and the virus is resistant to many common disinfectants. To prevent healthcare-associated outbreaks of adenovirus infections, such as epidemic keratoconjunctivitis (EKC), health care providers should strictly follow infection control practices, including contact and droplet precautions, use proper disinfectants and promptly respond to and report clusters of cases (Threlkeld et al., 1993). Because of the stability adenoviruses can also cause significant nosocomial infections other than EKC (Swartling et al., 2015) and hand washing does not reliably remove adenoviruses from contaminated fingers (Buehler et al., 1984; Faden et al., 2005). Decontamination of environmental surfaces and instruments may be difficult since adenoviruses are very resistant to lipid disinfectants but are inactivated by chlorine or formaldehyde (Flomenberg, 2009). They can be inactivated by contact with 1:5 dilution of bleach for 1 minute or 2 minutes contact with alcohol-based hand gels (Robinson and Echavarria, 2007). Adenoviruses can be physically inactivated by heat (Flomenberg, 2009) by heating to 56°C for 30 min or 60°C for 2 min. In laboratory environments autoclaving for 30 minutes at 121°C or 250°F (15 lbs per square inch of steam pressure) is recommended (Robinson and Echavarria, 2007). In a home environment, where high-concentrated chlorine use is not recommended based on environmental grounds, surface disinfection with 10% bleach (1:10 dilution household bleach, such as Clorox) can be applied allowing a contact time of 15 minutes. For stainless steel surfaces, bleach disinfection should be

followed with 70% ethanol wipedown to avoid corrosion. Liquid waste may be treated by exposing to bleach (final volume 10%) for 15 minutes before disposing into sink.

2.0 Environmental Occurrence and Persistence

Waterborne viruses can be introduced and remain infectious in source waters used for recreational and drinking water, these pathways ultimately may result in illness in some portion of the exposed population (Kokkinos et al., 2011a; Gibson, 2014; Kotwal and Cannon, 2014).

2.1 Detection Methods

Adenoviruses (HAdV) like other viruses need to be concentrated from environmental samples and especially from water due to typically lower concentrations and their small size. Several investigators have used different methods to detect adenoviruses in various environmental samples including water (Ahmed et al., 2015; Calgua et al., 2013; Ogorzaly et al., 2013; Puig et al., 1994; Sassoubre et al., 2012; Thompson et al., 2003) and air (Ziros et al., 2011; Verani et al., 2014), based on PCR procedures. Cell cultures techniques and cell culture techniques combined with PCR have also been used (Grabow et al., 1992; Reynolds et al., 1996; Chapron et al., 2000; Ko et al., 2003; 2005). Also, recently, new metagenomics methods have been used (Aw et al., 2014).

2.2 Data on Occurrence in the Environment

2.2.1 Raw sewage, sludge and treated wastewater

Adenoviruses of several types have been detected in domestic sewage and sludge in various countries. Thirteen studies from 11 different countries have been reviewed in Table 1. Adenoviruses have also shown to be resistant to disinfection and thus have been detected in treated wastewater effluents as well, with sometimes high detection rates. In several cases, more than 80% of sewage has been found positive for adenoviruses (Prado et al. 2011, Amdioune et al. 2012, Wong et al., 2013).

Table 1. Detection of HAdV in raw sewage, treated wastewater and sludge

Area	Virus Type	Matrices Analyzed	Percent Positive (# of Samples)	Concentration Average (Range) GC/L ^a	Reference
Brasil (Florianópolis)	Untyped	Treated Wastewater Sludge	100%	50 to 1.3E+07, 4.6E+07 to 1.2E+09	Sch lindwein et al., 2010
Brazil	HAdV C, D and F (40, 41)	Raw Sewage	64.2%	1.7E+02 to 2.3+04	Prado et al., 2011
Ghana (Accra)	Untyped	Treated Wastewater	80.0% (16/20)	NR	Silverman et al., 2013

Italy (Central)	Untyped	Raw Sewage	96.0%	3.3E+09	La Rosa et al., 2010
Italy (Central)	Untyped	Treated Wastewater	76.0%	7.0E6+08	La Rosa et al., 2010
Italy (Pisa)	Untyped	Raw Sewage	100% (52/52)	6.16E+08	Carducci and Verani, 2013
Italy (Pisa)	HAdV2, HAdV31, HAdV45	Treated Wastewater	90.0% (47/52)	6.02E+06	Carducci and Verani, 2013
Japan	Untyped	Raw Sewage	100%	11E+04	He and Jiang, 2005
Japan (Tokyo)	Total HadV F	Raw Sewage	100%	8.5E+04 6.7E+04	Haramoto et al., 2007
Morocco	HAdV B and D	Treated Wastewater	45.5% samples (10/22) by ICC-PCR at two sites	NR	Amdiouni et al., 2012
New Zealand (Auckland)	HadV total HadV F	Wastewater	100%	1.87E+04 to 4.6E+06, 4.63E+03 to 2.59E+05	Dong et al., 2010
New Zealand	HAdV HAdV F	Raw Sewage	100% (37/37) at 11 sites	5.2E+04	Hewitt et al., 2013
Norway	untyped	Treated Wastewater	92.0% (59/64)	2.15E+01	Grøndahl-Rosado et al., 2014
Spain (Barcelona)	untyped	Raw Sewage	NR	0.38 to 3.87E+07	Bofill Mas et al., 2006
Sweden (Gothenburg)	untyped	Raw Sewage	NR	3.3E+05 to 1.9E+05	Hellmér et al., 2014
USA (Cincinnati)	untyped	Sludge	100%	8.5E+02 to 5.4E+04 FFUs ^b	Williams and Hurst, 1988
USA	untyped	Raw Sewage	100%	NR	Bibby and Peccia, 2013
USA	HAdV-C and -B	Sludge	100%	NR	Bibby and Peccia, 2013

NR - Not Reported

^aGC Gene copies 1 GC equals one virus; ^bFFU 1 FFU equals one virus; ^cUpflow Anaerobic Sludge Blanket (UASB reactor) and three serial anaerobic filters, activated sludge with extended aeration and final chlorination of the effluents.

Since adenoviruses are frequently detected in high concentrations in treated wastewater and wastewater-contaminated waters, their use as potential indicators for the presence of human sewage has been affirmed. Also, a correlation has been noticed between the presence of HAdV with other viruses in sewage such as human polyomavirus or norovirus (La Rosa et al. 2010; Kokkinos et al. 2011b; Hewitt et al., 2013).

Quantification of adenoviruses show usually high adenovirus concentrations in raw sewage, combined sewer overflows, primary-treated effluent, secondary-treated effluent, and chlorinated effluent from wastewater

treatment plants (Fong et al., 2010). Average adenovirus DNA concentrations in sewage and CSOs could be more than 10^6 virus particles/liter. Various adenovirus types (41, 12, 40, 2, 3) have been isolated from raw sewage, sludge and primary effluents. Surface water samples impacted by wastewater show virus concentrations and may not be suitable for full-body recreational activities (Kokkinos et al., 2011a). High concentrations of adenovirus in these waters may be due to inefficient removal during wastewater treatment and to the high persistence of these viruses in the environment (Fong et al., 2010; Rodriguez et al., 2012).

2.2.2 Surface waters

Adenoviruses have been detected in several cases of surface waters around the world showing a high prevalence of viral human pathogens in surface waters. Concentrations ranged from 1 to about 100,000 genome copies per litre of surface water in 8 studies made in 5 different countries (Table 2). Most adenovirus positive samples are mainly obtained from areas of increased population densities. The number of patients with acute infectious gastroenteritis in a river basin was highly correlated with the presence of viruses, while general microbial indicator data such as turbidity and heterotrophic plate count were independent of viral concentration as suggested in previous studies (Kishida et al., 2012). Adenoviruses have been found to be prevalent in several natural and artificial water reservoirs worldwide. Free-living amoebae (FLA) have been recovered from similar water reservoirs, and it has been shown that FLA may act as reservoirs or vehicles of various microorganisms living in the same environment. It has also

been demonstrated that adenoviruses could be incorporated into *Acanthamoeba spp.*, most likely via phagocytosis (Scheid and Schwarzenberger, 2012) and viral DNA of 4 different serotypes of adenovirus (mostly adenovirus type 2) was detected within 34 of 236 (14.4%) strains of *Acanthamoeba spp.* isolated from waters of the Canary Islands (Lorenzo-Morales et al., 2007). An experimental study showed that HAdV5 internalized by *Acanthamoeba polyphaga* was protected towards 5mg/l of NaOCl for 24 hours (Verani et al., 2016). These studies also suggested that protists could be reservoirs for human enteric viruses in environmental conditions. Battistini et al. (2013) showed that the cells of the ciliated protozoan *Euplotes octocarinatus* are susceptible to persistent internalization of human adenoviruses, suggesting an important role for these protozoa in the spread of viruses and in their protection from both natural and artificial disinfectants. Ciliates of the genera *Euplotes*, is a widespread genus in most freshwater habitats, including artificial ones such as sewage treatment plants (Madoni, 2011).

Table 2. Detection of Adenoviruses in surface water

Area	Virus Type	Matrices Analyzed	Percent Positive (# of Samples)	Concentration Average (Range) GC/L ^a	Reference
Brazil (Florianópolis)	Untyped	Lagoon	96.0% (46/48)	NR	Fongaro et al., 2012
Brazil (Peri Lagoon, Santa Catarina State)	Untyped	Lagoon	70.8% summer 62.5% winter	NR	Elmahdy et al., 2016
Hungary	Untyped	River	56% (45/80) 16 sites	19.6E+03	Kern et al., 2013
Japan (Tokyo)	HAdV types 40 and 41	River	44% (23/52) 1 site	8E+03	Kishida et al., 2012
Japan	HAdV types 40 and 41	River	61.1% (11/18)	3.16E+03 to 1.38E+05	Haramoto et al., 2010
South Africa (Durban)	Untyped	River	32.0% (8/25) 5 sites	NR	Lin and Singh, 2015
South Africa (Eastern Cape)	HAdV C type 1,2,6, B1 type 7, and F types 40,41	River	31.0% (22/72) 6 sites	1E+00 to 8.5E+04	Sibanda and Okoh, 2012
South Africa (Eastern Cape)	HAdV types 21, 40 and 41	River	35.0% (25/72) 6 sites	1.2E+01 to 4.71E+03	Chigor et al., 2012
Taiwan	HAdV type 41	River	30.8% (4/13) 13 sites	6.10E+02 to 8.51E+02	Huang et al., 2015
Taiwan	HAdV types 2,5,31,41	River	34.3% (99/288)	2.8E+03	Tao et al., 2015
USA	HAdV40 and HAdV41	Surface water	48.3% (14/29)	NR	Chapron et al., 2000
USA (Michigan)	HAdV F types	Lake	24.1% (14/58) 2 sites	<500	Xagorarakis et al., 2007

NR - Not Reported

^aGC Gene copies 1 GC equals one virus

2.2.3 Groundwater

There are a few studies analyzing ground water samples for the occurrence of adenoviruses (Table 3). Human adenoviruses have been observed in groundwater from a confined aquifer, while no fecal indicators were detected (Borchardt et al., 2012). These results may be useful for

future risk assessment studies and confirm the necessity to assess groundwater sources of viral contamination and thus it is of great interest to public health (Rigotto et al., 2011). Adenoviruses were more often found in ground water than other viral types and have the most stable persistence profile and an ability to survive for a long time in groundwater (Ogorzaly et al., 2010).

Table 3. Detection of Adenoviruses in groundwater and drinking water

Area	Virus Type	Matrices Analyzed ^c	Percent Positive (# of Samples)	Concentration Average (Range) GC/L ^a	References
Brazil	Untyped	Tap water	23.3% (17/73)	NR	Kluge et al., 2014
Brazil	Untyped	Tap water	100% (36/36)	1.0E+7	Garcia et al., 2012
Brazil	Untyped	Network water	100% (6/6)	NR	Fongaro et al., 2013
Brazil	Untyped	Surface water	83.0% (10/12) virions 66.0% (8/12) infectious viruses	NR	Fongaro et al., 2012
France	Untyped	Ground water	11.7% (7/60)	NR	Ogorzaly et al., 2010
Ghana	Untyped	Tap water	16.6% (1/6)	NR	Gibson et al., 2011
Japan	HAdV 40 41	Tap water	39.0% (25/64)	NR	Haramoto et al., 2012
Korea	HAdV types 1,5,6,40,41	Tap water	39.1% (9/23) from 11 sites	<10 MPNU/L ^b	Lee and Kim, 2002
Norway	Untyped	Surface water used for Drinking water	90.4% (47/52)	NR	Grøndahl-Rosado et al., 2014
South Africa	Untyped	Surface water used for drinking water	10.0% to 30.0% (of 204)	NR	Van Heerden et al., 2003
Spain	HAdV 2	River water	100% (9/9)	1.24+04	Albinana-Gimenez et al., 2009
		Ground water	66.7% (4/6)	7.36	
		River Water	83.3% (10/12)	9.24+03	
USA (Florida)	Untyped	Ground water	32.0% (8/25) from 5 sites	NR	Futch et al., 2010
USA (Wisconsin)	HAdV types 2,5,6,40,41	Ground water	13.0% (157/1204)	0.077 to 10	Borchardt et al., 2012
West Africa	Untyped	Surface water used for drinking water	9.1% (26/287)	NR	Verheyen et al., 2009

NR - Not Reported

^aGC: gene copies= 1 viron; ^bMPNU: Most Probable Number Unit; ^cThese waters have been used for drinking water

2.2.4 Drinking water

Adenoviruses have been isolated in drinking water in several countries such as Norway (Grøndahl-Rosado et al., 2014) Japan (Haramoto et al., 2012), Brazil (Kluge et al., 2014; Garcia et al., 2012), Ghana (Gibson et al., 2011), West Africa (Verheyen et al., 2009), and Korea (Lee and Kim, 2002). Total coliforms and *Escherichia coli* assessed in drinking water samples showed a lack of correlation between bacterial indicators and the presence of human adenoviruses indicating a lack of proper public health measures in drinking water (Fongaro et al., 2013). In a year-long survey of the occurrence of adenoviruses in drinking water in South Africa, detection peaked between April and July (winter in South Africa), when up to 30% of treated surface water samples from two different sites were positive for adenoviruses (van Heerden, 2003) (Table 3).

2.2.5 Seawater

Several researchers around the world have reported on the presence of adenoviruses in seawater Finland (Hokajärvi et al., 2013), USA, (Love et al., 2014; Jiang et al., 2001) Australia, (Ahmed et al., 2010; Kueh et al., 1989) and Japan (Haramoto et al., 2007). In a Europe-wide surveillance study that was carried out to determine the frequency of occurrence of two human enteric viruses in recreational waters (Wyn-Jones et al., 2011), adenoviruses were selected as an indicator based on their near-universal shedding and environmental survival. Researchers have also reported that the presence of adenoviruses was not statistically connected with the presence of other microorganisms in seawater (McQuaig et al., 2012; Wyer et al., 2012). In most cases the counts of faecal indicator bacteria were not able to predict the presence of adenoviruses in bathing waters. The detection of adenoviruses suggests that the presence of infectious viruses in recreational waters may constitute a public health risk upon exposure. Recent studies support the case for considering adenoviruses as an indicator of bathing water quality (Wyn-Jones, 2011).

2.2.6 Fish and shellfish

There are so far no studies on the presence of adenoviruses in fish. However, in shellfish, there are many reports since shellfish are filter feeders and concentrate the viruses in their tissues. While shellfish complying with European Regulations based on quantification of fecal bacterial indicators (FIB) are introduced into markets, several researchers confirm that current controls and depuration treatments limiting the number of FIB do not guarantee the absence of viruses in shellfish (Rodriguez-Manzano, 2013). Presence of adenoviruses were reported in Italian mussels and found no direct correlation between the presence of human pathogenic viruses and bacterial indicators (Serracca et al., 2010). In Japan enteric human adenoviruses were detected in 52% of the clams tested (Hansman, 2008). In Brazil, high loads of human

adenoviruses in the environment were connected with high numbers of viruses in shellfish (1.2xe5 per gram) (Rigotto et al., 2010). In India, high prevalence of adenoviruses (17% positive in oysters and 24% in clams) was noticed between May to December and the presence of MS-2 phage and human enteric viruses showed an association while fecal coliforms and enteric viruses showed no association (Umesha et al., 2008).

Studies have also linked illness in the community to virus types found in shellfish. In Tunisia, adenoviruses detected in shellfish were related to the types in clinical samples (Sdiri-Loulizi et al., 2010). Similar findings were reported in Morocco (Karamoko et al., 2005) and Italy (La Rosa et al., 2012). However, the detection of adenoviral genomes in shellfish exceeded the persistence of their infectivity, in most cases with 4-6 weeks (Hernroth and Allard, 2007) and it was suggested that a warning system based on PCR amplification of virus DNA might overestimate the risk for transmission of viable viruses since the presence of a PCR was not necessarily associated to viability of the virus and thus its relevance for public health.

2.2.7 Air

Many enteric viruses are present in wastewater and due to their small size, they may be transmitted in droplets. Exposure to virus contaminated droplets in several labour places mainly wastewater treatment plants (WWTP) and its consequence on workers' health have been documented. Very few studies have investigated the presence and concentrations of airborne virus in WWTP. Masclaux et al. (2014) detected that adenovirus was present in 100% of summer WWTP AIR samples and 97% of winter AIR samples. Concentrations of potentially pathogenic viral particles in WWTP air are non-negligible and could partly explain the work-related gastrointestinal symptoms often reported in employees in this sector. Concentrations reported were 2.27×10^6 genome equivalent/m³. Different concentrations have been observed also according to the plant areas: 2455 GC/m³ at the sewage entrance, 1622 GC/m³ at the biological oxidation tank, 933 GC/m³ at the sludge treatment and 589 GC/m³ at the side-entrance manhole (Carducci et al., 2016).

Wan et al (2012) evaluated the distributions of airborne adenovirus in public areas in the pediatric department of Children's Hospital in northern Taiwan and high detection rates of airborne adenovirus DNA were obtained in March with average 278.9CG/m³. Tseng et al. (2010) investigated the possibility of aerosol transmission of viruses in children in the pediatrics department of a medical center in Taipei, Taiwan. HAdV were detected in the aerosol of air samples (36% of the samples). In toilets of healthcare settings and offices HAdV were found in over 60% of samples at concentrations respectively of 6.6×10^7 GC/mL and 1.2×10^7 GC/mL in water, of 5.8×10^6 GC/m³ and 3.9×10^4 GC/m³ in air and of 483 GC/cm² and 91 GC/cm² on surfaces (Verani et

al., 2014). HAdV was detected in apartments with average in winter 2106 GC/m³ and in summer 173 GC/m³ (Moon et al., 2014).

2.3 Persistence

Data on adenoviruses have shown that their genome was more stable compared with genomes of other viruses or bacteria (El-Senousy et al., 2014). The presence of adenoviral DNA in groundwater may be misleading in term of health risk, especially in the absence of information on their infective status (Ogorzaly et al., 2010). According to a linear regression model in a year-long study in groundwater, infectivity reductions of HAdV2 ranged from 0.0076 log₁₀(10)/day (at 4°C) to 0.0279 log₁₀(10)/day (20°C). No adenoviral genome degradation was observed at 4°C, and the reduction was estimated at 0.0036 log₁₀(10)/day at 20°C (Ogorzaly et al., 2010). Adenoviruses could not be detected on produce after 24h of irrigation with water contaminated with viruses (Ward and Irving, 1987). Adenoviruses were found to be stable in biosolids for at least 60 days with no degradation (Wei et al., 2010). In a study of health risks associated with land applied biosolids no notable decline in HAdV numbers detected by PCR was observed during 6 months (T90 ≥ 180 days) (Schwarz et al., 2014).

Temperature is considered as the major factor determining virus persistence in the environment. The persistence of infectious particles, encapsidated genomes and free nucleic acids of HAdV 41 was evaluated in drinking water and surface water at 4°C, 20°C and 37°C by Prevost et al. (2016). The infectivity of HAdV 41 persisted for at least 25 days, whatever the water temperature, and for more than 70 days at 4°C and 20°C, in both drinking and surface water. Encapsidated genomes persisted beyond 70 days, whatever the water temperature. Free nucleic acids (i.e. without capsid) could persist for at least 16 days in drinking and surface water (Prevost et al., 2016).

In a review (Bertrand et al., 2012), virus persistence was found to be lower at temperatures ≥ 50°C than at temperatures < 50°C, but there was also a significant temperature-matrix effect. Virus inactivation appeared to occur faster in complex than in simple matrices. The virus genome was shown to be more resistant than infectious virus (Bertrand et al., 2012; Fongaro et al., 2013). Enriquez et al. (1995) studied the survival of poliovirus type 1, HAV and the enteric adenoviruses (types 40 and 41) in tap water at various temperatures for up to 60 days. Overall, they found that the enteric adenoviruses were more stable than the other viral types at both 4°C and 15°C and at room temperature. However, in primary and secondary sewage the enteric adenoviruses did not survive significantly longer than poliovirus at either 14°C or 15°C. El-Senousy et al. (2014) also showed that HAdV40 was more persistent than both rotavirus and hepatitis A in ground water. In spiked experiments with HAdV40 in ground water 0.05 log₁₀, 0.5 log₁₀ and 1.5 log₁₀ reduction of copy numbers at 4°C, 20°C and 35°C were shown. Infectious units reduction after 12 weeks were 0.5 log₁₀, 1.5 log₁₀ and 3.0 log₁₀ at the same temperatures. Charles et al. (2009) also showed in spiked experiments with HAdV2 that these genomes were stable ≥ 2 years in ground water with a retaining infectivity ≥ 1 year. Bofill-

Mas et al. (2006) studied the stability of HAdV during 300 days in sewage samples at 20°C resulting in T90 of 60.9 days and aT99 of 132.3 days. By cloning experiments the adenovirus types 40, 41, 31, 34, 35, 11 and 12 were detected over 105 days showing no significant differences in stability between the different types present during the experiment (Bofill-Mas et al., 2006).

3.0 Reductions by Sanitation Management

Adenoviruses have been detected in raw sewage throughout the world and are associated with a number of human illnesses but their occurrence and pathogenicity have not been well studied (Jiang, 2006; Mena and Gerba, 2009; Jacob et al., 2015). The continued monitoring of treated wastewater by other researchers revealed the average concentration of adenoviruses in treated wastewater (see Table 1). No correlation between the presence of viruses and *Escherichia coli* has been found (Maunula et al., 2012). Moreover, the possible treated sewage reuse in agriculture or elsewhere must be considered with concern (Crabtree et al., 1997; Kokkinos et al., 2010).

3.1 Wastewater Treatment

3.1.1 Pit Latrines, Vault Toilets, Dry Toilets

There were no data on adenovirus reductions in vault toilets, dry toilets.

3.1.2 Manure-based Composting

In the composting process of dairy manure HAdV type 41 was more stable than RNA viruses in composts with center temperatures between 65°C and 70°C. There was no reduction in DNA after one day, and about a 2.1 log₁₀ loss at 5 and 7 days (Wei et al., 2009). In the same experiment, more than a 4 log₁₀ reduction of adenoviral infectivity was noted after one day in compost. According to North American regulatory bodies total viral inactivation is expected to occur if compost particles maintain temperatures greater than 55°C for at least 3 days. This could either be the result of time-temperature requirements in ensuring that the time-temperature criteria are met by all compost particles (Wichuk and McCartney, 2007).

3.1.3 Septic tanks

No log₁₀ reduction data on adenoviruses in septic tanks are available.

3.1.4 Waste stabilization ponds

Wastewater treatment ponds (lagoons) are one of the most common types of technologies used for wastewater management worldwide, especially in small cities and towns. They are particularly well-suited for systems where the effluent is reused for irrigation. Human adenoviruses in wastewater treatment plants have been used as an indicator of the effectiveness of different treatment

processes. HAdV concentrations in wastewater were more variable in small and medium-sized WTP than in large-sized plants. HAdv concentrations were detected in influent of most WTP with a reduced median concentration in effluent. Highest culturable HAdV concentrations in effluent were from a medium-sized WWTP. No matter of treatment type, adenoviruses are likely to be present in non-disinfected effluent, with associated human health risks dependent on concentration and receiving water usage (Sidhu and Toze, 2009; Hewitt et al., 2011). Sheludchenko et al. (2016) showed a \log_{10} reduction of adenoviruses of a 1.2 \log_{10} and Jurzik et al. (2015) showed no reduction. On average, in waste stabilization ponds, one \log_{10} reduction of viruses was achieved for every 14.5–20.9 days of retention, but the 95th percentile value of the data analyzed was 54 days. (Verbyla and Mihelcic, 2015).

3.1.5 Wetlands

Wetlands, open-water cells can be used to promote sunlight disinfection and remove pathogenic viruses from wastewater. Sunlight inactivation is an important mode of disinfection for viruses in surface waters and rates for adenovirus inactivation are reported (Silverman et al., 2015). Rachmadi et al. (2016) showed an adenovirus removal of 1–2 \log_{10} in wetlands during a 9-month period. A weak negative correlation between adenovirus \log_{10} concentration and water temperature as well as pH was observed (Rachmadi et al., 2016). HAdV type 3 showed inactivation rates with one \log_{10} reduction times of more than 33 days in constructed reedbeds (Sidhu et al., 2010).

3.1.6 Aerated lagoons

The removal was found to be zero for HAdV during the wastewater treatment in aerated lagoons (O'Hara and Rubin, 2005; Jurzik et al., 2015).

3.1.7 Wastewater Treatment Facilities

3.1.7.1 Combined sewer overflows

Concentrations of adenovirus DNA in the combined sewer overflows discharges (CFOs) were not significantly different from adenovirus DNA concentrations in raw sewage showing an average concentration of 5.35×10^5 viruses/liter. Removal of adenoviruses was lower than 2 \log_{10} at the treatment plant (Fong et al., 2010). Hata et al. (2014) reported that rainfall events can introduce large amount of viral contaminants including adenoviruses into surface water by intermittent discharges from combined sewer overflows (CSOs).

3.1.7.2 By primary /preliminary treatment

Adenoviruses showed high stability in urban sewage (Silvia Bofill-Mas et al., 2006) and they were detected frequently in high concentration in raw sewage influents but were also detected less frequently in plant effluent and at much lower concentrations with removals shown to be 2–3 \log_{10} by primary sewage treatment. In this study a t_{90} of

60.9 days for HAdV was reported. In another study, the average \log_{10} removals were 2.2–3.5 for adenoviruses when using sand filters in a cold temperature climate (Kauppinen et al., 2014).

3.1.7.3 By Secondary treatment and membrane bioreactors

In a one-year quantitative survey in six different Japanese activated sludge waste-water plants adenovirus among other enteric viruses were observed. Adenoviruses were detected at the highest positive ratio among the tested viruses; almost 100% in both secondary-treated wastewater and in effluent after chlorination. The reduction of adenovirus was 2 \log_{10} and was also found to be fairly constant and independent of the concentration of viruses in the influent (Katayama et al., 2008). No removals of adenovirus across disinfection was seen in membrane bioreactors (MBR) and low median \log_{10} removals of 0.24 was detected in conventional secondary plants with a few removals of individual samples near or above the analytical variability of 1.2 \log_{10} genomic copies per liter (Francy et al., 2012).

Also, the environmental monitoring carried out at a wastewater treatment plant in Italy, showed the presence of adenovirus DNA in 100% of the raw sewage samples and in 85–100% of the effluent, an average reduction of 2 \log_{10} for adenovirus was found via activated sludge and chlorination. Moreover, this reduction was lower in rainy than in sunny weather: 1.67 \log_{10} and 2.34 \log_{10} respectively (Carducci et al., 2008; Carducci and Verani, 2013). The virus removal in a full-scale MBR have been reported between 3.9 and 5.5 $-\log_{10}$ for adenoviruses (Chaudhry et al., 2015). The greatest contribution to total removal was provided by the backwashed membrane, followed by inactivation, the cake layer, and attachment to solids. Increases in turbidity and particle counts after backwashing indicated potential breakthrough of particles, but virus removal following backwash was still high. The ability of the MBR process to provide more than 4 \log_{10} of removal for adenovirus was confirmed (Chaudhry et al., 2015). Another study was conducted to characterize effluent water qualities produced by satellite MBRs with respect to adenoviruses. They were detected in all effluent samples irrespective of membrane cleaning or breaching status (Hirani, 2013; 2014). Studies about the removal efficiencies of the viral particles in the full-scale MBR process showed that the average removal of human adenoviruses was about $5.0 \pm 0.6 \log_{10}$. The removal efficiencies for the enteric adenovirus type F species (average \log_{10} removal $6.5 \pm 1.3 \log_{10}$) were typically higher (p-value < 0.05) than those of species A and C (average \log_{10} removal 4.1 ± 0.9 and 4.6 ± 0.5 , respectively). These results demonstrated that the full-scale MBR system efficiently removed most adenoviruses from the wastewater leaving about 10^3 viral particles/L in the MBR effluent (Kuo et al., 2010).

3.1.7.4 By tertiary treatment (postsecondary)

In a research of Liu et al. (2013), HAdVs were detected in 100% of primary clarification influent, secondary

clarification effluent and granular media filtration effluent samples but only in 31.2% of membrane filtration effluent and 41.7% of final effluent samples, respectively. The average HAdVs loads were significantly reduced along the treatments but HAdVs were still present in final effluent (mean \log_{10} removals of HAdV from primary clarifier influent to second clarification, granular media filtration, membrane filtration and final effluent were 3.0, 3.2, 5.2, and 5.1, respectively). Comparison showed that membrane filtration was technically superior to granular media for the removal of HAdVs (Liu et al., 2013). Human adenoviruses were detected in 82–100% of wastewater samples in a treatment plant in Germany with median concentration of 6.8×10^3 gene copies/L. By using polishing ponds as a tertiary treatment a $2.2 \log_{10}$ reduction in bacteria and phages was achieved, but no reduction for adenoviruses was seen (Jurzik et al., 2015).

3.2 Disinfection

3.2.1 Chlorine

Adenoviruses are not completely removed (100%) by tertiary treatment processes including disinfection (Lazarova et al., 1999), yet the use of chlorine disinfection is an effective strategy to control adenoviral waterborne transmission via some level of \log_{10} reductions (Girones et al., 2014). The kinetics of inactivation of human adenovirus 2 in natural and artificial seawater was studied. A $4 \log_{10}$ reduction of adenovirus viability could be achieved at a CT value of 2.6 mg Cl_2 min/L (CT; disinfectant concentration \times contact time) (Page et al., 2009). In another study, after 30 min exposure to free chlorine (2.5 mg/L), human adenovirus 2 showed 2.6 and 2.7 \log_{10} reductions and a 2.3 and 2.4 \log_{10} PFU reductions in natural and artificial seawater, respectively, although infectious viral particles were still observed (de Abreu Corrêa et al., 2012).

Inactivation of adenovirus type 2, 40 and 41 were compared after exposure to 0.2 mg/L of free chlorine or 1 mg of monochloramine per liter in buffered reagent-grade water at 5°C. Adenovirus type 2 needed 1600 mg-min/liter monochloramine for 3 \log_{10} reduction at pH 8.0. Adenovirus type 40 and 41 showed 3 \log_{10} inactivation with 5 sec contact time with 0.2 mg of free chlorine (Cromeans et al., 2010). Other investigations have reported similar time span

for chlorine inactivation of the different adenovirus types (Thurston-Enriquez et al., 2003a; Baxter et al., 2007). In another study, chlorine disinfection efficacy was investigated for human adenovirus 2 (HAdV2) in untreated groundwater source and partially treated surface waters. Chlorine disinfection of HAdV2 proceeded very rapidly (3–4 \log_{10} inactivation within 5 to 10s) in each source water and when CT values could be calculated disinfection was more effective at pH 7 than pH 8 (Kahler et al., 2010). However, water quality could play a substantial role in the inactivation of viruses and should be considered when developing chlorination plans, but more information is needed on the disinfection efficacy of chlorine for viruses in source water (Kahler et al., 2010).

3.2.2 Ozone and other oxidants

According to U.S. EPA Ground Water Rule, adenoviruses are readily inactivated by ozone with CT values as low as 0.07 mg-min/L for a 4 \log_{10} inactivation at pH 7 and 5°C (Thurston-Enriques et al., 2005). In light of this, the combined use of ozone with UV may be a viable and safe water treatment strategy that utilities could employ to achieve desired reductions in pathogenic microorganisms.

The inactivation of adenoviruses in fecal sludge at pH 8.9 and 55 mM of NH_3 resulted in a 3 \log_{10} reduction after 21 days (Magri et al., 2015). In another study, the treatment with PIX (FeCl_3) or PAX (AlCl_3) coagulants and peracetic acid (PAA) was studied and showed that both PIX and PAX flocculation reduced numbers of HAdV 40 with about 2 \log_{10} but the virus was more resistant against PAA compared to the other microorganisms such as bacteria and also Norovirus GI (Pradhan et al., 2013).

3.2.3 Ultraviolet

Adenoviruses are recognized as the most UV-resistant waterborne pathogen of concern to public health microbiologists (Meng and Gerba, 1996). Pilot experiments for the inactivation of human adenoviruses are shown in Table 4. The U.S. EPA has stipulated that a UV fluence (dose) of 186 mJ/cm^2 is required for 4 \log_{10} inactivation credit in water treatment (Gerba et al., 2002) even if lower doses have been reported with an adenovirus reduction to the limit of detection (1 TCID₅₀/100L) at UV doses of 40 to 45 mJ/cm^2 (Jacangelo et al., 2003).

Table 4. UV inactivation of Adenoviruses

Virus Type	Matrices Analyzed	Dose for (99%) 2 to 4 \log_{10} Inactivation	Reference
HAd2	Cell culture suspension	119 mJ/cm^2	Gerba et al., 2002
HAd2, 5, 41	Cell culture suspension	40 to 70 mJ/cm^2	Baxter, 2007
HAd40	BDF water	109 mJ/cm^2	Thurston-Enriquez et al., 2003b
	Treated groundwater ^a	103 mJ/cm^2	
HAd40, 41	Treated water ^a	30 mJ/cm^2	Meng and Gerba, 1996
HAd 2	Water	40 mJ/cm^2	Shin et al., 2010

HAd 1,3,4, 5, 6, 40, 41	Cell culture suspension	90 mJ/cm ²	Nwachuku et al., 2005
HAd	Treated wastewater	40 to 45 mJ/cm ²	Jacangelo et al., 2003
HAd	Spiked tertiary treated wastewater	170 mJ/cm ²	Thompson et al., 2003
HAd 41	Cell culture suspension	225 mJ/cm ²	Ko et al., 2005
HAd 2	Filtered drinking water	60 mJ/cm ²	Shin et al., 2005
HAd 2	Cell culture suspension	40 mJ/cm ²	Lee and Shin, 2011
HAd 5	Cell culture suspension	UV-OH 400 mJ/cm ^{2b}	Monteiro et al., 2015

^aTreated water: chlorinated water; ^bUV-OH:UV-electro-oxidation

A dose of approximately 170 mJ/cm² was required to achieve 4 log₁₀ inactivation in wastewater (Thompson et al., 2003). These findings suggest that UV doses effective at meeting certain wastewater regulations for total coliform bacteria may not provide suitable inactivation of the UV-resistant human adenoviruses. A comparative inactivation of different adenovirus serotypes (type 1, 3, 4, 5, and 6) by UV was done. The results of the study confirmed that adenovirus are the most resistant enteric viruses to inactivation by UV light and that adenovirus type 40 appears to be the most resistant (Nwachuku et al., 2005). Similar results have also been presented for adenovirus type 41 indicating a high resistance to UV-light (Ko et al., 2005). Median log₁₀ removal of adenoviruses during disinfection process was low in both MBR and conventional secondary plants (no removal detected and 0.24). In a few cases removal of individual samples were near or above the analytical variability of 1.2 log₁₀ genomic copies per liter (Francy et al., 2012).

By using polychromatic UV sources a significant enhancement in inactivation of adenoviruses can be achieved. As already described most adenovirus inactivation data have been based on UV disinfection experiments using UV irradiation at 253.7 nm produced from a conventional low-pressure UV source (Francy et al., 2012; Hijnen et al., 2006; Shin et al., 2005; Thurston-Enriquez et al., 2003b). By using a medium-pressure mercury lamp a complete spectrum of 200-300 nm can be produced. When full-spectrum polychromatic UV lamps were used, 4 log₁₀ inactivation of adenovirus type 40 was achieved at a UV fluence of less than 60 mJ cm⁻².

Wavelengths around 220 and 228 nm were most effective for inactivation of HAdV2 (Linden et al., 2007). Inactivation of adenovirus 2 by medium-pressure UV combined with free chlorine was considered efficient to control the contamination of drinking water by human adenoviruses within practical doses of UV and free chlorine typically used in drinking water treatment processes (Lee and Shin, 2011).

The inactivation of adenoviruses by UV irradiation is not simply predictable by the type and size of the virus or its nucleic acid genome and there is no strong correlation between virion size and genetic composition of viruses and their response to UV irradiation (Nuanualsuwan et al., 2002; Shin et al., 2005; Thurston-Enriquez et al., 2003b).

3.2.4 Thermal

Not much information on heat inactivation is available for adenoviruses in environmental waters and biosolids. A thermal inactivation study from the late sixties reported 4 log₁₀ reductions of adenovirus 12 among other viruses, in raw milk, sterilized homogenized milk, raw chocolate milk and raw ice cream mix, with minimum essential medium (MEM) as control suspending fluid (Sullivan et al., 1968). From approximately 10,000 plaque-forming units (PFU) per ml of each suspending medium, inactivation curves at 40°C - 60°C were asymptotic to the base line, showing a tailing effect indicating that small amounts of adenoviruses survived, even at the higher temperature. At 65°C, the inactivation curves approached first order reactions, indicating that temperatures near pasteurization standards were effective in inactivating adenoviruses.

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